ANTIVIRAL COMPOUNDS

FIELD OF THE INVENTION

The invention relates generally to compounds with HCV inhibitory activity.

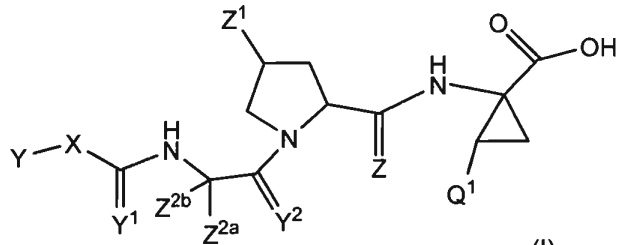
BACKGROUND OF THE INVENTION

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

There is a need for new HCV therapeutic agents.

SUMMARY OF THE INVENTION

In one embodiment the invention provides a compound of the invention which is a compound of formula I:



(I)

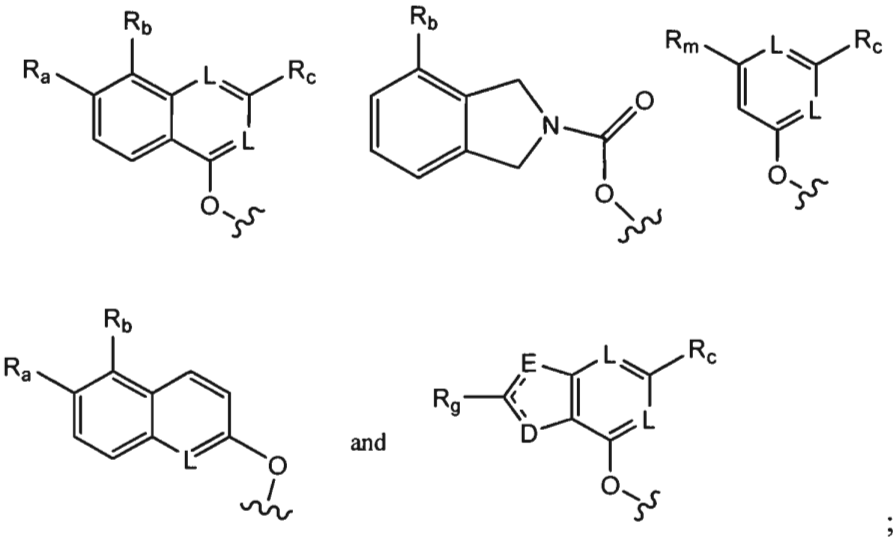
or a pharmaceutically acceptable salt, or prodrug thereof, wherein:

Y^1 is O, S, or NR^3;

Y^2 is O, S, or NR^3;

Z is O, S, or NR^3;

Z^1 is selected from the following structures:



;

each R_a is R^1, H, trifluoromethoxy, NR_sR_t, $C(=O)NR_sR_t$, $S(=O)_2NR_sR_t$ or (C1-10)alkyl, wherein one or more carbon atoms of said (C1-10)alkyl is optionally replaced by O, S, S(=O), $S(=O)_2$ or NR_g and which (C1-10)alkyl is optionally substituted with one or more hydroxy, halo, cyano, NR_nR_p, $C(=O)NR_nR_p$, (C1-10)alkoxy, carboxy, (C1-10)alkoxycarbonyl, aryl, heteroaryl, or heterocyclyl and which heterocyclyl is optionally substituted with one or more A^3; or R_a and R_b taken together with the atoms to which they are attached form a 5 or 6 membered heterocyclic ring containing one or more O, S, or NR_g;

each R_b is R^1, H, F, Cl, Br, I, CF_3, (C1-10)alkyl, or XR^3;

each R_c is R^1, H, cyano, F, Cl, Br, I, $-C(=O)NR_dR_e$, $C(=O)NR_sR_t$, NR_sR_t, $S(=O)_2NR_sR_t$, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkoxy, cycloalkyl, OR_r, SR_r, $S(O)R_r$, $S(O)_2R_r$, aryl, or heteroaryl, which (C1-10)alkyl, (C1-10)alkoxy, cycloalkyl, aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, hydroxy, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p; SR_r, $S(O)R_r$, or $S(O)_2R_r$;

R_d and R_e are each independently H or (C1-10)alkyl;

each R_f is H, hydroxy, carboxy, cyano, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p, SR_r, $S(O)R_r$, or $S(O)_2R_r$;

each R_g is H, NR_sR_t, $C(=O)NR_sR_t$, $S(=O)_2NR_sR_t$, A^2, hydroxy, carboxy, cyano, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p, SR_r, $S(O)R_r$, or $S(O)_2R_r$;

each R_h is H, A^3, $C(=O)NR_sR_t$, or $S(=O)_2NR_sR_t$;

each R_m is H, cyano, F, Cl, Br, I, $-C(=O)NR_dR_e$, (C1-10)alkoxy, cycloalkyl, or phenyl that is optionally substituted with one or more F, Cl, Br, I, (C1-10)alkyl, or (C1-10)alkoxy;

each L is independently CH or N;

one of E or D is O, S, or NR_f and the other E or D is CR_h or N;

Z^{2a} is H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, haloalkyl, (C1-10)alkyl, $-S(=O)_2$-(C1-10)alkyl, or cycloalkyl, wherein any carbon atom of Z^{2a} may optionally be replaced with a heteroatom selected from O, S or NR_g and wherein any cycloalkyl is optionally substituted with one or more (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, F, Cl, Br, or I; or Z^{2a} optionally forms a heterocycle with Q^1;

Z^{2b} is H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl;

Q^1 is (C1-10)alkyl, (C2-10)alkenyl, or (C2-10)alkynyl which Q^1 is optionally substituted with R^1 or R_c; or Q^1 and Z^{2a} taken together with the atoms to which they are attached form a heterocycle, which heterocycle may optionally be substituted with one or more oxo (=O), R^1, or A^3;

each X is independently a bond, O, S, or NR^3;

Y is a polycarbocycle or a polyheterocycle, which polycarbocycle or a polyheterocycle is optionally substituted with one or more R^1, halo, carboxy, hydroxy, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p; SR_r, $S(O)R_r$, or $S(O)_2R_r$;

each R^1 is independently $-P(Y^3)(OA^2)(OA^2)$, $-P(Y^3)(OA^2)(N(A^2)_2)$, $-P(Y^3)(A^2)(OA^2)$, $-P(Y^3)(A^2)(N(A^2)_2)$, or $P(Y^3)(N(A^2)_2)(N(A^2)_2)$;

each A^2 is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)haloalkyl, (C3-10)cycloalkyl, aryl, or heteroaryl;

each Y^3 is independently O, S, or NR^3;

each R_n and R_p is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, which (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, is optionally substituted with one or more R^1, halo, hydroxy, carboxy, cyano, or (C1-10)alkoxy; or R_n and R_p together with the nitrogen to which they are attached form a pyrrolidine, piperidine, piperazine, morpholino, or thiomorpholino ring; which ring is optionally substituted with one or more (C1-10)alkyl or (C1-10)alkoxy, and which (C1-10)alkyl or (C1-10)alkoxy is optionally substituted with one or more halo;

each R_r is independently H, (C1-10)alkyl, cycloalkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, aryl, heteroaryl, or (C1-10)alkoxycarbonyl;

each R_s and R_t is independently H, (C1-10)alkyl, cycloalkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, $S(=O)_2A^2$, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, which (C1-10)alkyl, cycloalkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, is optionally substituted with one or more R^1, halo hydroxy, carboxy, cyano, or (C1-10)alkoxy; or R_s and R_t together with the nitrogen to which they are attached form a pyrrolidine, piperidine, piperazine, morpholino, or thiomorpholino ring wherein one or more carbon atoms of said pyrrolidine, piperidine, piperazine, morpholino or thiomorpholino ring is optionally replaced by S(=O), $S(=O)_2$, or C(=O);

each A^3 is independently selected from halo, hydroxy, carboxy, cyano, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p, SR_r, $S(O)R_r$, or $S(O)_2R_r$; and

R^3 is H or (C1-10)alkyl.

The present invention also provides a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable salt or prodrug thereof, and at least one pharmaceutically acceptable carrier.

The present invention also provides for a method of treating disorders associated with hepatitis C, said method comprising administering to an individual a pharmaceutical composition which comprises a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt or prodrug thereof.

The present invention also provides a method of inhibiting HCV, comprising administering to a mammal afflicted with a condition associated with HCV activity, an amount of a compound of formula I, or a pharmaceutically acceptable salt or prodrug thereof, effective to inhibit HCV.

The present invention also provides a compound of formula I, or a pharmaceutically acceptable salt or prodrug thereof, for use in medical therapy (preferably for use in inhibiting HCV or treating a condition associated with HCV activity), as well as the use of a compound of formula I, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament useful for inhibiting HCV or the treatment of a condition associated with HCV activity in a mammal.

The present invention also provides a compound of formula I, or a pharmaceutically acceptable salt, or prodrug thereof for use in the prophylactic or therapeutic treatment of a condition associated with HCV activity.

The present invention also provides synthetic processes and novel intermediates disclosed herein which are useful for preparing compounds of the invention. Some of the compounds of the invention are useful to prepare other compounds of the invention.

In another aspect the invention provides a method of inhibiting HCV activity in a sample comprising treating the sample with a compound of formula I, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment the invention provides a compound having improved inhibitory or pharmacokinetic properties, including enhanced activity against development of viral resistance, improved oral bioavailability, greater potency or extended effective half-life *in vivo*. Certain compounds of the invention may have fewer side effects, less complicated dosing schedules, or be orally active.

DETAILED DESCRIPTION OF THE INVENTION

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

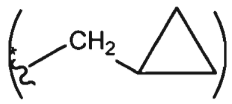
Compounds of the Invention

The compounds of the invention exclude compounds heretofore known. However it is within the invention to use compounds that previously were not known to have antiviral properties for antiviral purposes (e.g. to produce an anti-viral effect in an animal). With respect to the United States, the compounds or compositions herein exclude compounds that are anticipated under 35 USC §102 or that are obvious under 35 USC §103.

Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R^1", "L", or "A^3", then it will be understood that the groups may be the same or different, i.e., each group is independently selected.

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

methyl-2-pentyl (-$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (-$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (-$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (-$C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl (-$CH(CH_3)C(CH_3)_3$, and cyclopropylmethyl



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

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

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

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

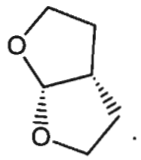
"Halo" includes F, Cl, Br, and I.

"Heteroaryl" as used herein includes 5-20 atom mono- or polycyclic ring systems wherein at least one ring is an aromatic ring comprising one or more heteroatoms (e.g. O, S, N, etc.). In one embodiment the term heteroaryl includes a radical of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(X) wherein X is absent or is H, O, (C_1-C_4)alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom,

particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto.

"Heterocycle" as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (*e.g.* 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (*e.g.* O, N, or S). The term heterocycle also includes heteroaryl ring systems as defined herein. When Q^1 and Z^{2a} taken together with the atoms to which they are attached form a heterocycle, the heterocycle formed by Q^1 and Z^{2a} taken together with the atoms to which they are attached may typically comprise up to about 25 atoms.

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



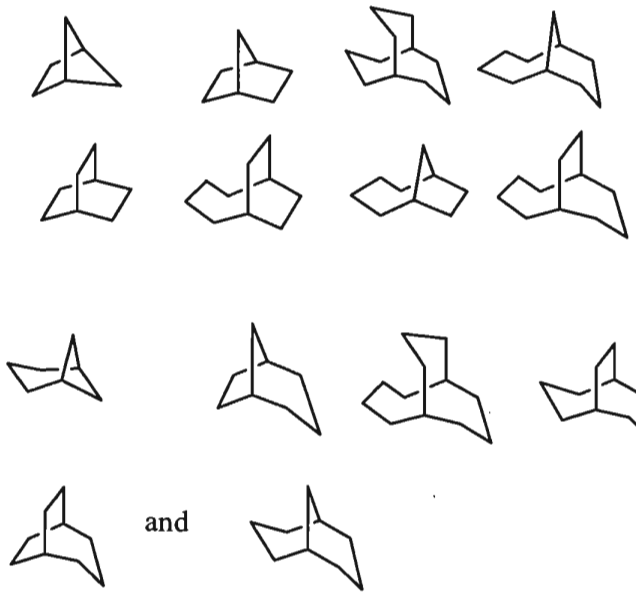
By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran,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

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

"Carbocycle" refers to a saturated, unsaturated or aromatic ring having up to about 25 carbon atoms. Typically, a carbocycle has about 3 to 7 carbon atoms as a monocycle, about 7 to 12 carbon atoms as a bicycle, and up to about 25 carbon atoms as a polycycle. Monocyclic carbocycles typically have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles typically have 7 to 12 ring atoms, *e.g.*, arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. The term carbocycle includes "cycloalkyl" which is a saturated or unsaturated

carbocycle. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl (spiro-fused rings) and naphthyl.

The term "polycarbocycle" refers to a saturated or unsaturated polycyclic ring system having from about 6 to about 25 carbon atoms and having two or more rings (e.g. 2, 3, 4, or 5 rings). The rings can be fused and/or bridged to form the polycyclic ring system. For example, the term includes bicyclo [4,5], [5,5], [5,6] or [6,6] ring systems, as well as the following bridged ring systems:



(i.e., [2.1.1], [2.2.1], [3.3.3], [4.3.1], [2.2.2], [4.2.2], [4.2.1], [4.3.2], [3.1.1], [3.2.1], [4.3.3], [3.3.2], [3.2.2] and [3.3.1] polycyclic rings, respectively) that can be linked to the remainder of the compound of formula (I) through any synthetically feasible position. Like the other polycarbocycles, these representative bicyclo and fused ring systems can optionally comprise one or more double bonds in the ring system.

The term "polyheterocycle" refers to a polycarbocycle as defined herein, wherein

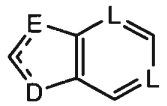
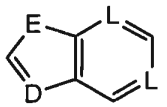
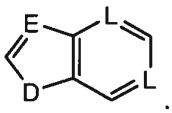
one or more carbon atoms is replaced with a heteroatom (e.g. O, S, S(O), $S(O)_2$, $N^+(O^-)R_x$, or NR_x); wherein each R_x is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, $S(O)_2NR_nR_p$, $S(O)_2R_x$, or (C1-10)alkoxy, wherein each (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, and (C1-10)alkoxy is optionally substituted with one or more halo.

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

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

The term "substituted" in reference to alkyl, alkylene, aryl, arylalkyl, alkoxy, heterocyclyl, heteroaryl, carbocyclyl, etc. , for example, "substituted alkyl", "substituted alkylene", "substituted aryl", "substituted arylalkyl", "substituted heterocyclyl", and "substituted carbocyclyl" means alkyl, alkylene, aryl, arylalkyl, heterocyclyl, carbocyclyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to, -X, -R, $-O^-$, =O, -OR, -SR, $-S^-$, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, -C(=O)R, -C(=O)NRR $-S(=O)_2-$, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(O^-)_2$, $-P(=O)(OH)_2$, $-P(O)(OR)(O^-)$, -C(=O)R, -C(=O)X, -C(S)R, -C(O)OR, $-C(O)O^-$, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, -C(=NR)NRR, where each X is independently a halogen: F, Cl, Br, or I; and each R is independently H, alkyl, aryl, arylalkyl, a heterocycle, or a protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted. Unless otherwise indicated, when the term "substituted" is used in conjunction with groups such as arylalkyl, which have two or more moieties capable of substitution, the substituents can be attached to the aryl moiety, the alkyl moiety, or both.

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

The term "-----" means that a bond is a single or double bond. In a non-limiting example,  can be  or .

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

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

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

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a

racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity. The invention includes all stereoisomers of the compounds described herein.

Prodrugs

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, *i.e.* active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically-active compound.

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

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-CH_2OC(=O)R^9$ and acyloxymethyl carbonates $-CH_2OC(=O)OR^9$ where R^9 is C_1–C_6 alkyl, C_1–C_6 substituted alkyl, C_6–C_{20} aryl or C_6–C_{20} substituted aryl. The acyloxyalkyl ester was first used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al. (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. Subsequently, the acyloxyalkyl ester was used to deliver phosphonic acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a

prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-CH_2OC(=O)C(CH_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-CH_2OC(=O)OC(CH_3)_3$.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (De Lombaert et al. (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to a phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate parent phosphonic acids. In some cases, substituents at the *ortho*-or *para*-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, *e.g.*, esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C–O bond to generate phosphoric acid and a quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell et al. (1992) *J. Chem. Soc. Perkin Trans. II* 2345; Glazier WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al. (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al. (1996) *J. Med. Chem.* 39: 4958).

Protecting Groups

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

"Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. Chemical protecting groups and strategies for protection/deprotection are well known in the art. *See e.g.*, Protective Groups in Organic Chemistry, Theodora W. Greene, John Wiley & Sons,

Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, *e.g.*, making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

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

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

the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

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

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

In one embodiment of the invention, the compound is in an isolated and purified form. Generally, the term "isolated and purified" means that the compound is substantially free from biological materials (e.g. blood, tissue, cells, etc.). In one specific embodiment of the invention, the term means that the compound or conjugate of the invention is at least about 90 wt.% free from biological materials; in another specific embodiment, the term means that the compound or conjugate of the invention is at least about 98 wt.% free from biological materials; and in another embodiment, the term means that the compound or conjugate of the invention is at least about 99 wt.% free from biological materials. In another specific embodiment, the invention provides a compound or conjugate of the invention that has been synthetically prepared (e.g., *ex vivo*).

Cellular Accumulation

In one embodiment, the invention provides compounds capable of accumulating in human hepatic cells.. Physiologically, hepatic cells are critical components of the mechanism against infection. Hepatic cells may be isolated from normal healthy donors washed (*e.g.* phosphate-buffered saline) and stored in freezing medium. Hepatic cells may be cultured in multi-well plates. At various times of culture, supernatant may be either removed for assessment, or cells may be harvested and analyzed (Smith R. et.al. (2003) *Blood* 102(7):2532-2540). The compounds of this embodiment may further comprise a phosphonate or phosphonate prodrug. More typically, the phosphonate or phosphonate prodrug can have the structure R^1 as described herein.

Stereoisomers

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

The compounds of the invention can also exist as tautomeric isomers in certain cases. All though only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole

systems and all their possible tautomeric forms are within the scope of the invention.

Salts and Hydrates

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

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

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

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

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

Methods of Inhibition of HCV

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

Compounds of the invention may act as inhibitors of HCV, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will generally bind to locations on the surface or in a cavity of the liver. Compounds binding in the liver may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compounds are useful as probes for the detection of HCV. Accordingly, the invention relates to methods of detecting NS3 in a sample suspected of containing HCV comprising the steps of: treating a sample suspected of containing HCV with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl or amino. In one embodiment the invention provides a compound of formula (I) that comprises or that is bound or linked to one or more detectable labels. Within the context of the invention samples suspected of containing HCV include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct

samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing HCV. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

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

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

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

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

Screens for HCV Inhibitors

Compounds of the invention are screened for inhibitory activity against HCV by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compounds are first screened for inhibition of HCV *in vitro* and compounds showing inhibitory activity are then screened for activity *in vivo*. Compounds having *in vitro* Ki (inhibitory constants) of less then about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably less than about 5×10^{-8} M are preferred for *in vivo* use. Useful *in vitro* screens have been described in detail.

Pharmaceutical Formulations

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

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

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

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

water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

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

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

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

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is

also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

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

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

Pharmaceutical formulations according to the present invention comprise one or more compounds of the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as

calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

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

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

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above,

and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

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

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

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

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

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

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

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

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

the treatment or prophylaxis of conditions associated with HCV activity.

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

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

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

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

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

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

Compounds of the invention can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the invention also provided

compositions comprising one or more compounds of the invention formulated for sustained or controlled release.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses), the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Routes of Administration

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

Combination Therapy

Active ingredients of the invention can also be used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination.

It is also possible to combine any compound of the invention with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a

simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

The combination therapy may provide "synergy" and "synergistic effect", *i.e.* the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, *e.g.*, in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.* serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

Suitable active therapeutic agents or ingredients which can be combined with the compounds of formula I can include interferons, e.g., pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, and albuferon; ribavirin analogs, e.g., rebetol, copegus, levovirin VX-497, and viramidine (taribavirin); NS5a inhibitors, e.g., A-831 and A-689; NS5b polymerase inhibitors, e.g., NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125; NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065; alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B; hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-84451; non-nucleoside inhibitors of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives; and other drugs for treating HCV, *e.g.*, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-

7000, civacir, GI-5005, ANA-975 (isatoribine), XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811.

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

According to the present invention, the therapeutic agent used in combination with the compound of the present invention can be any agent having a therapeutic effect when used in combination with the compound of the present invention. For example, the therapeutic agent used in combination with the compound of the present invention can be interferons, ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

In another embodiment, the present application provides pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent selected from the group consisting of pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, albuferon, rebetol, copegus, levovirin, VX-497, viramidine (taribavirin), A-831, A-689, NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, XTL-2125, SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, MX-3253 (celgosivir), UT-231B, IDN-6556, ME 3738, MitoQ, and LB-84451, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975 (isatoribine), XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811 and a pharmaceutically acceptable carrier or excipient.

In yet another embodiment, the present application provides a combination pharmaceutical agent comprising:

a) a first pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, or ester thereof; and

b) a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV, and combinations thereof.

Combinations of the compounds of formula I and additional active therapeutic agents may be selected to treat patients infected with HCV and other conditions such as HIV infections. Accordingly, the compounds of formula I may be combined with one or more compounds useful in treating HIV, for example HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

More specifically, one or more compounds of the present invention may be combined with one or more compounds selected from the group consisting of 1) HIV protease inhibitors, *e.g.*, amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, lopinavir + ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), AG1859, DG35, L-756423, RO0334649, KNI-272, DPC-681, DPC-684, and GW640385X, DG17, PPL-100, 2) a HIV non-nucleoside inhibitor of reverse transcriptase, *e.g.,* capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-

961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirine), efavirenz, BILR 355 BS, VRX 840773, UK-453,061, RDEA806, 3) a HIV nucleoside inhibitor of reverse transcriptase, *e.g.,* zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, fosalvudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, abacavir + lamivudine, abacavir + lamivudine + zidovudine, zidovudine + lamivudine, 4) a HIV nucleotide inhibitor of reverse transcriptase, *e.g.,* tenofovir, tenofovir disoproxil fumarate + emtricitabine, tenofovir disoproxil fumarate + emtricitabine + efavirenz, and adefovir, 5) a HIV integrase inhibitor, *e.g.*, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), BMS-707035, MK-2048, BA-011, BMS-538158, GSK364735C, 6) a gp41 inhibitor, *e.g.*, enfuvirtide, sifuvirtide, FB006M, TRI-1144, SPC3, DES6, Locus gp41, CovX, and REP 9, 7) a CXCR4 inhibitor, *e.g.*, AMD-070, 8) an entry inhibitor, *e.g.*, SP01A, TNX-355, 9) a gp120 inhibitor, *e.g.*, BMS-488043 and BlockAide/CR, 10) a G6PD and NADH-oxidase inhibitor, *e.g.*, immunitin, 10) a CCR5 inhibitor, *e.g.,* aplaviroc, vicriviroc, INCB9471, PRO-140, INCB15050, PF-232798, CCR5mAb004, and maraviroc, 11) an interferon, *e.g.*, pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, and albuferon, 12) ribavirin analogs, e.g., rebetol, copegus, levovirin, VX-497, and viramidine (taribavirin) 13) NS5a inhibitors, e.g., A-831 and A-689, 14) NS5b polymerase inhibitors, e.g., NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125, 15) NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, 16) alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B, 17) hepatoprotectants, e.g., IDN-

6556, ME 3738, MitoQ, and LB-84451, 18) non-nucleoside inhibitors of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, 19) other drugs for treating HCV, *e.g.*, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975 (isatoribine), XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811, 19) pharmacokinetic enhancers, e.g., BAS-100 and SPI452, 20)RNAse H inhibitors, e.g., ODN-93 and ODN-112, 21) other anti-HIV agents, e.g., VGV-1, PA-457 (bevirimat), ampligen, HRG214, cytolin, polymun, VGX-410, KD247, AMZ 0026, CYT 99007, A-221 HIV, BAY 50-4798, MDX010 (iplimumab), PBS119, ALG889, and PA-1050040.

Metabolites of the Compounds of the Invention

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

own.

Methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37 °C. Simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. The phosphonate prodrugs of the invention typically will be stable in the digestive system but are substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

Exemplary Methods of Making the Compounds of the Invention.

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

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

Generally, the reaction conditions such as temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited

therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

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

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

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

The terms "treated", "treating", "treatment", and the like, when used in connection with a chemical synthetic operation, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two. For example, treating indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100 °C to 250 °C, typically -78 °C to 150 °C, more typically -78 °C to 100 °C, still more typically 0 °C to 100 °C), reaction vessels (typically glass, plastic, metal),

solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

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

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

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

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and

sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

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

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

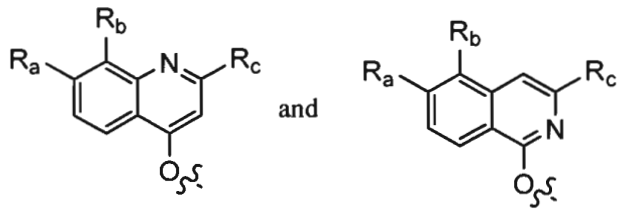
Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester, *e.g.*, (-) menthyl chloroformate in the presence of base, or Mosher

ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

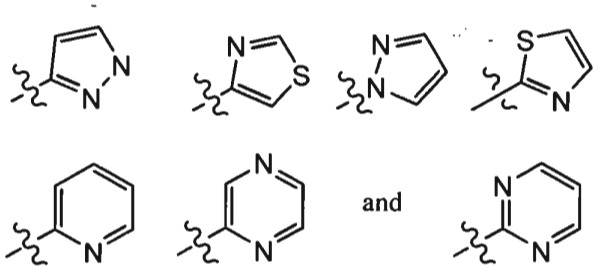
Specific Embodiments of the Invention

Specific values and embodiments identified herein for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

In a specific embodiment of the invention Z^1 is selected from the following structures:



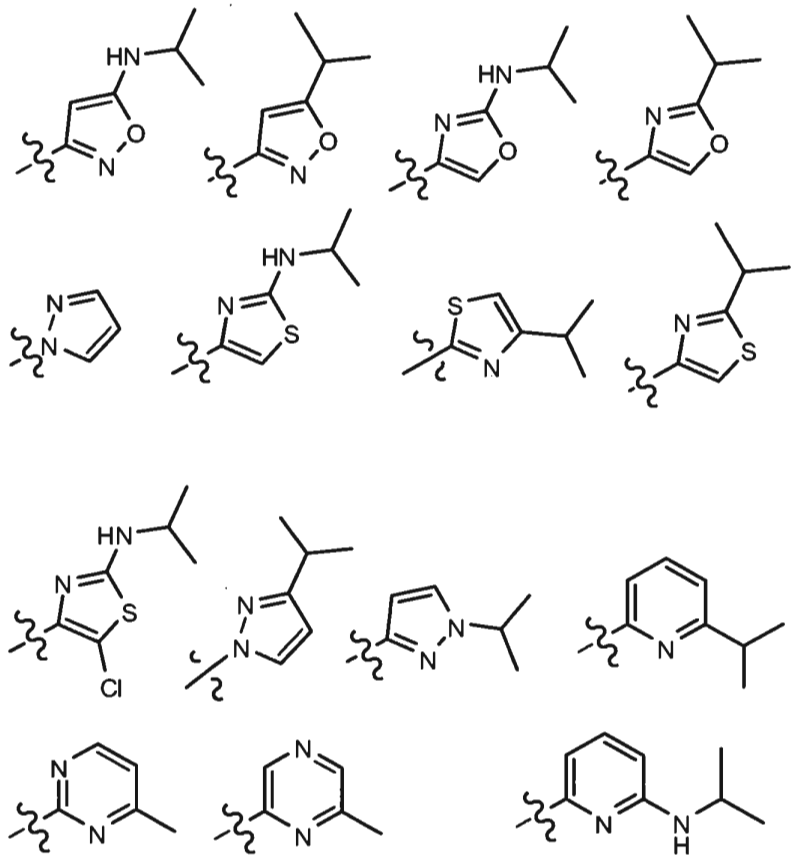
In a specific embodiment of the invention R_c is a heteroaryl ring selected from:

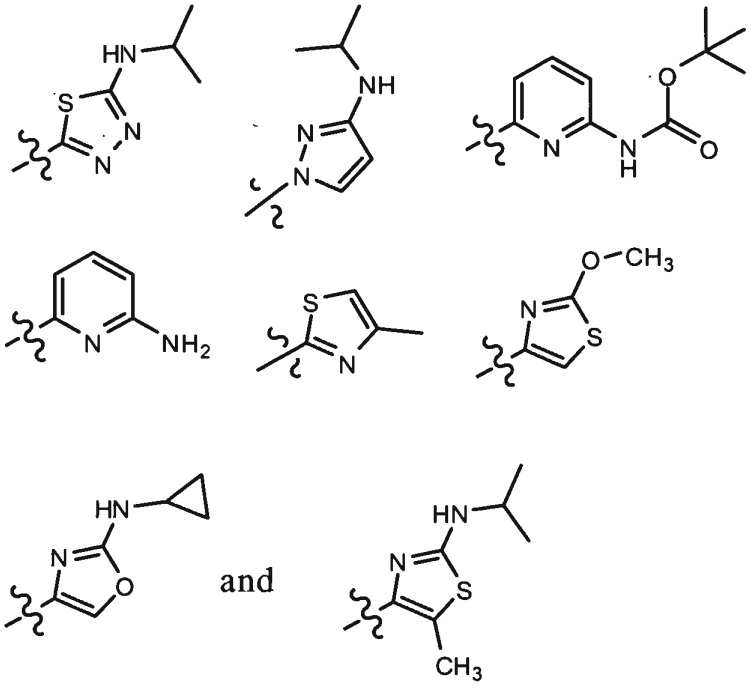


which heteroaryl ring is optionally substituted with one or more (C1-10)alkyl, halo, or NR_nR_p; wherein each R_n and R_p is independently H or (C1-10)alkyl.

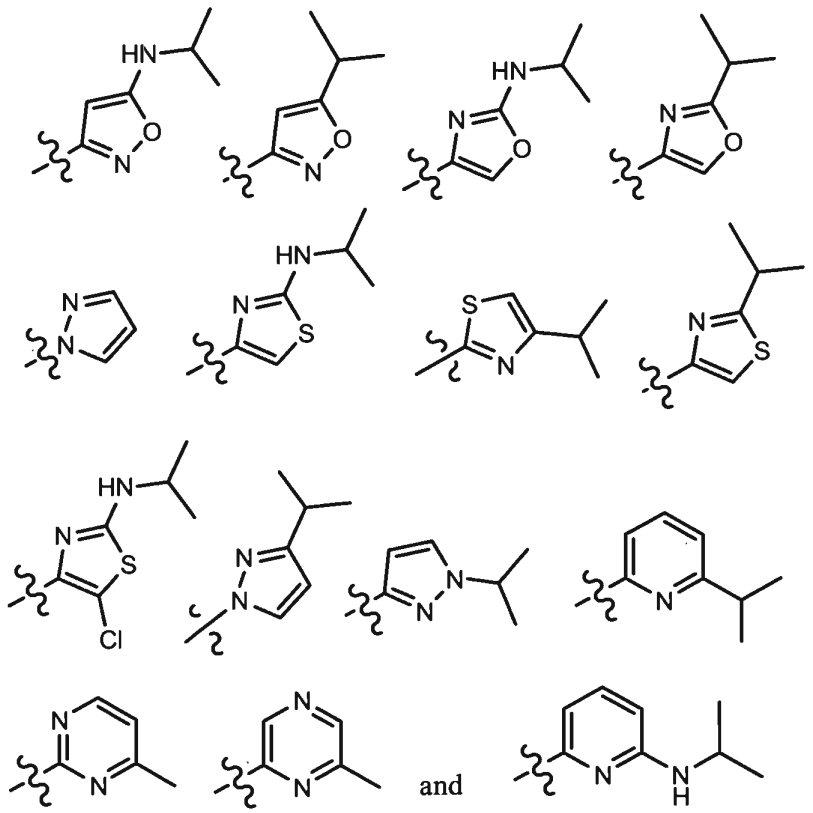
In a specific embodiment of the invention R_c is selected from:

5




HN
S
N
N
NH
N
N
O
N
N
H
O
N
NH2
S
N
O
CH3
N
S
HN
N
O
and
HN
N
S
CH3

In a specific embodiment of the invention R_c is selected from:



and

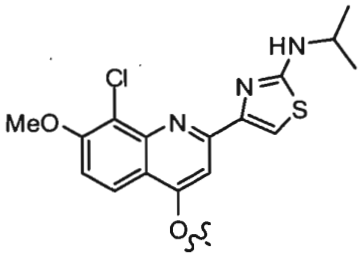
In a specific embodiment of the invention R_c is selected from ethylthio, ethoxy, 2-methoxyethyl, cyclopropylamino, 2-methoxyethoxy, cyclopropyloxy, 1,3,4-triazol-2-ylthio, 1,3,4-thiadiazol-2-ylthio, imidazol-2-ylthio, 1,3,4-triazol-2-yloxy, 1,3,4-thiadiazol-2-yloxy, or imidazol-2-yloxy.

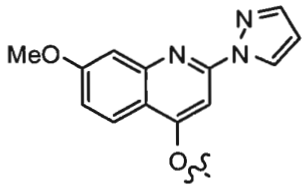
In a specific embodiment of the invention R_b is H or Cl.

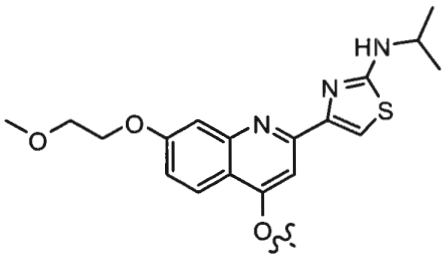
In a specific embodiment of the invention R_a is H, methoxy, N-(2-cyanoethyl)amino, N-(3,3,3-trifluoroethyl)amino, 2-methoxyethoxy, 2-hydroxyethoxy, 2-hydroxy-2-methylpropoxy, 2-amino-2-methylpropoxy, N,N-dimethylaminocarbonylmethoxy, morpholinocarbonylmethoxy, 2-[N-(2,2,2-trifluoroethyl)amino]ethoxy, 2-morpholinoethoxy, cyanomethoxy, 2-piperazin-1-ylethoxy, 2-(N,N-dimentylamino)ethoxy, 2-(3,3-dimethylmorpholino)ethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, or carboxymethoxy.

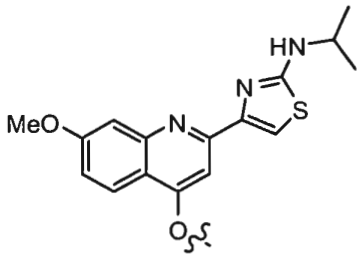
In a specific embodiment of the invention R_a is H, methoxy, N-(2-cyanoethyl)amino, N-(3,3,3-trifluoroethyl)amino, 2-methoxyethoxy, 2-hydroxyethoxy, 2-hydroxy-2-methylpropoxy, 2-amino-2-methylpropoxy, N,N-dimethylaminocarbonylmethoxy, morpholinocarbonylmethoxy, 2-[N-(2,2,2-trifluoroethyl)amino]ethoxy, or 2-morpholinoethoxy.

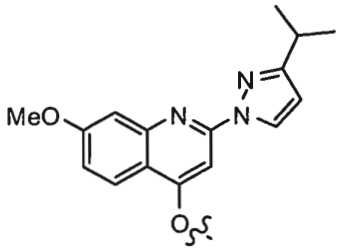
In a specific embodiment of the invention Z^1 is selected from the following structures:

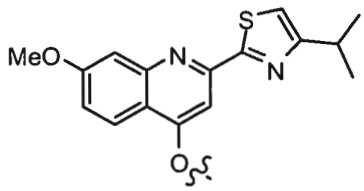


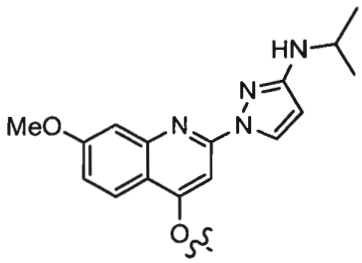


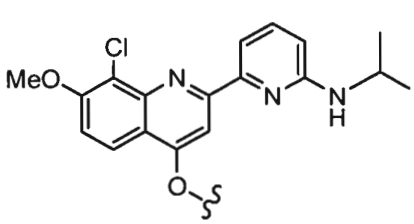


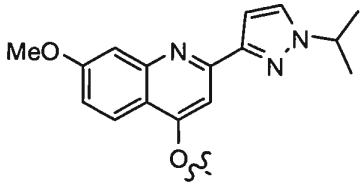


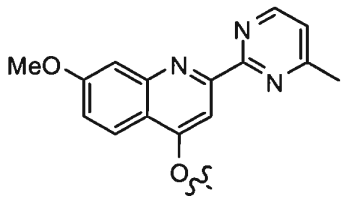


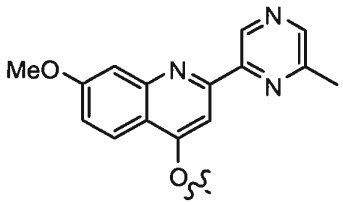


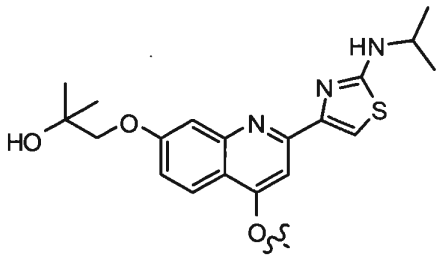




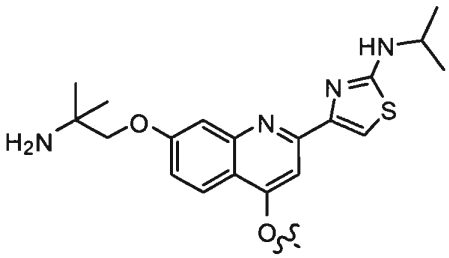


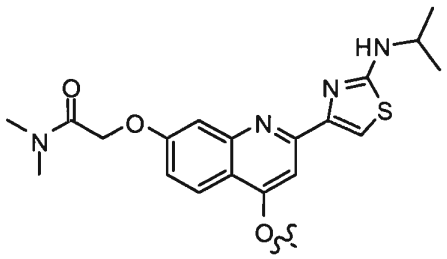


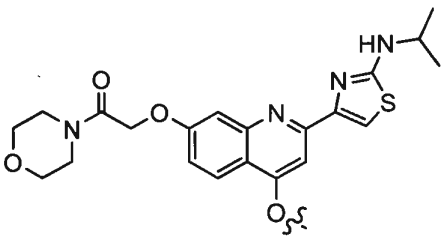


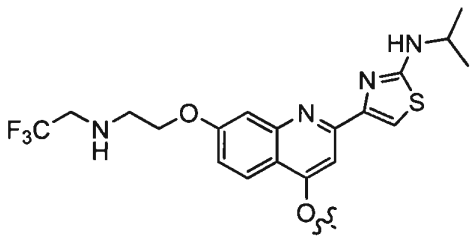


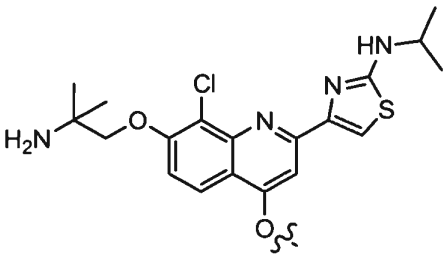
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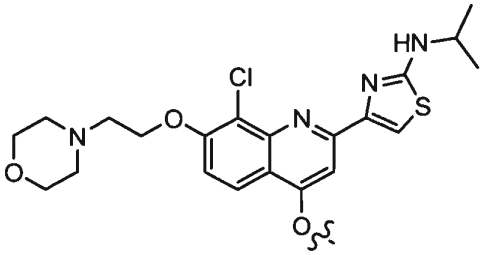


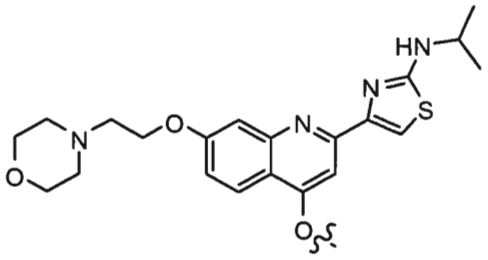


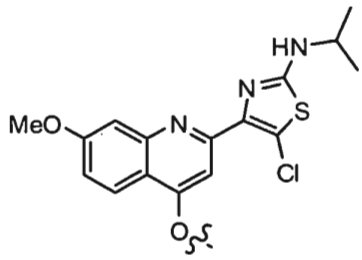


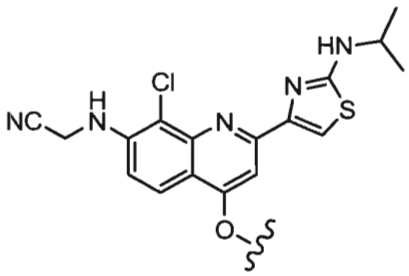


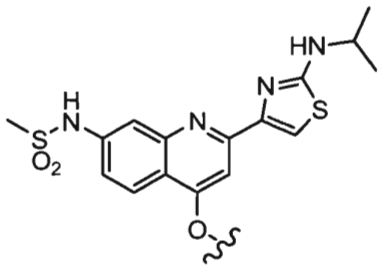


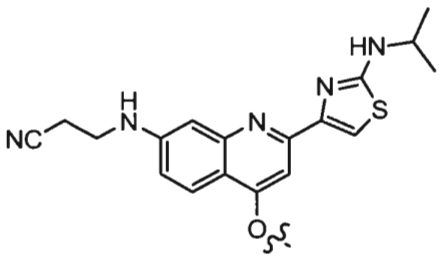


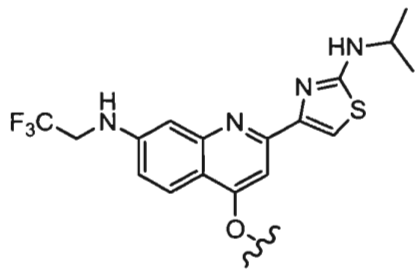


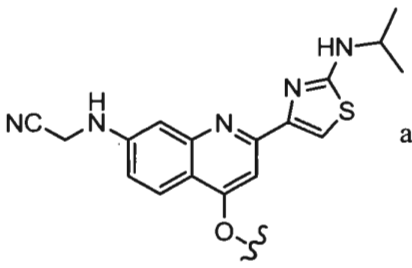




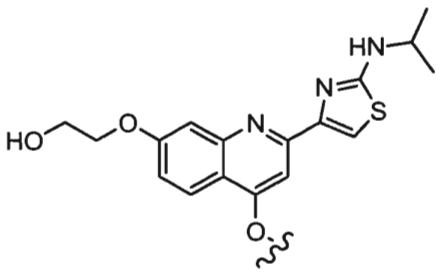








and



In a specific embodiment of the invention Z is O; Y^1 is O; and one of Z^{2a} or Z^{2b} is hydrogen.

In a specific embodiment of the invention Q^1 is vinyl or ethyl.

In a specific embodiment of the invention Q^1 and Z^{2a} taken together with the atoms to which they are attached form a 12-18 membered heterocycle, which heterocycle may optionally be substituted with one or more oxo (=O) or A^3.

In a specific embodiment of the invention Z^{2a} is *tert*-butyl.

In a specific embodiment of the invention X is a bond, O, S, or NR^3. In a preferred embodiment X is O, S, or NR^3. In another preferred embodiment X is O.

In a specific embodiment of the invention Y is a polycarbocycle.

In a specific embodiment of the invention Y is polyheterocycle.

In a specific embodiment of the invention Y is a fused carbocyclic ring system.

In a specific embodiment of the invention Y is a fused heterocyclic ring system.

In a specific embodiment of the invention Y is a fused carbocyclic ring system comprising one or more double bonds.

In a specific embodiment of the invention Y is a fused heterocyclic ring system comprising one or more double bonds.

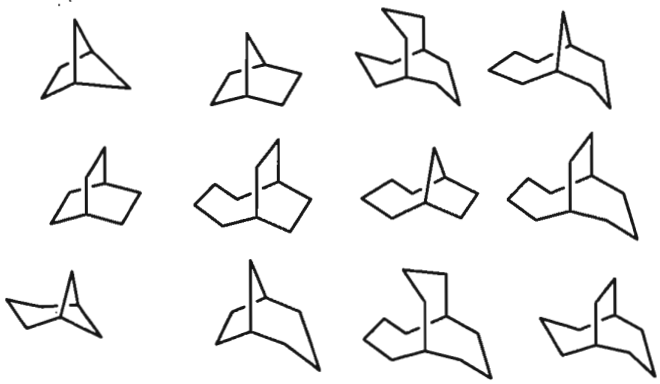
In a specific embodiment of the invention Y is a bridged carbocyclic ring system.

In a specific embodiment of the invention Y is a bridged heterocyclic ring system.

In a specific embodiment of the invention Y is a bridged carbocyclic ring system comprising one or more double bonds.

In a specific embodiment of the invention Y is a bridged heterocyclic ring system comprising one or more double bonds.

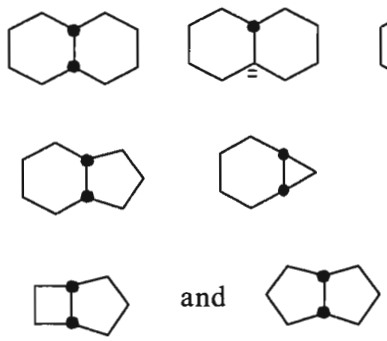
In a specific embodiment of the invention Y comprises a bridged ring system selected from:



and 

wherein one or more carbon atoms in the bridged ring system is optionally replaced with O, S, S(O), $S(O)_2$, $N^+(O^-)R_x$, or NR_x; wherein each R_x is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, $S(O)_2NR_nR_p$, $S(O)_2R_x$, or (C1-10)alkoxy, wherein each (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, and (C1-10)alkoxy is optionally substituted with one or more halo; R_n and R_p are as previously defined; and wherein the ring system optionally comprises one or more double bonds.

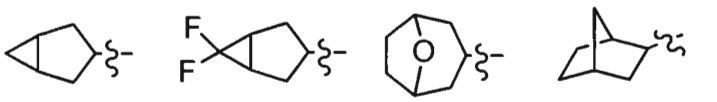
In a specific embodiment of the invention Y comprises a fused ring system selected from:



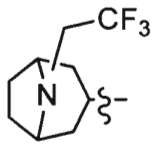
and

wherein one or more carbon atoms in the fused ring system is optionally replaced with O, S, S(O), $S(O)_2$, $N^+(O^-)R_x$, or NR_x; wherein each R_x is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, $S(O)_2NR_nR_p$, $S(O)_2R_x$, or (C1-10)alkoxy, wherein each (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, and (C1-10)alkoxy is optionally substituted with one or more halo; and wherein the ring system optionally comprises one or more double bonds.

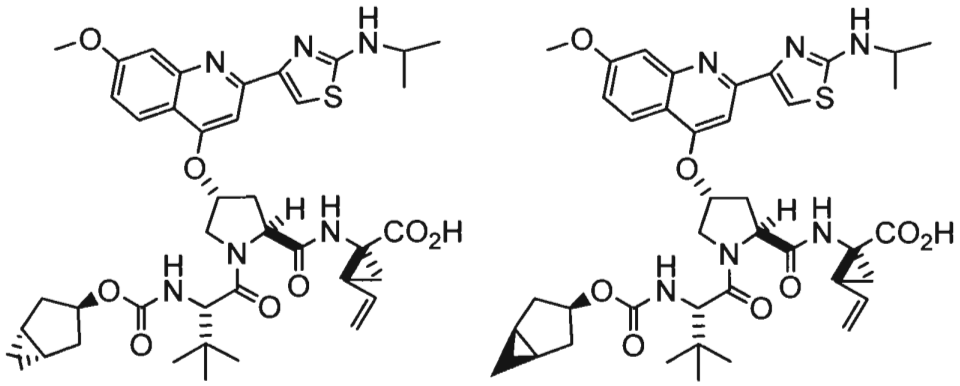
In a specific embodiment of the invention Y is selected from:

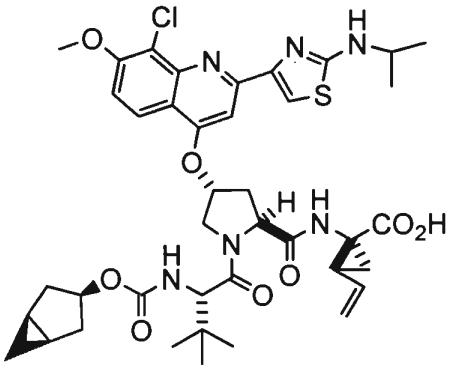


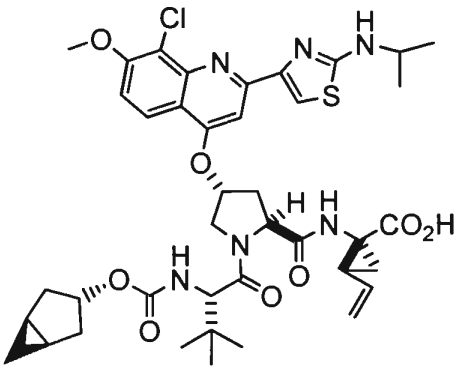


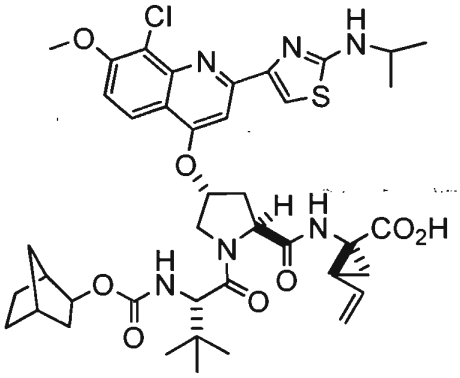
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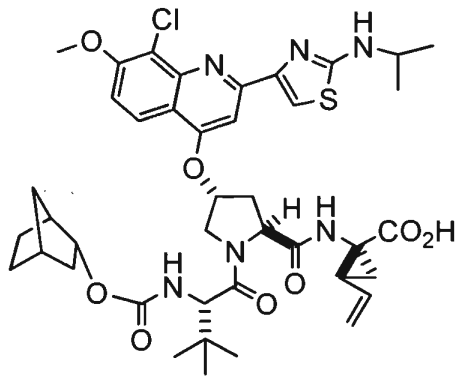
In a specific embodiment of the invention the compound of formula I is selected from:



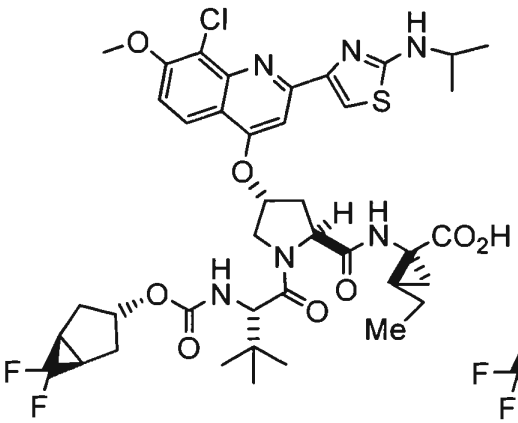


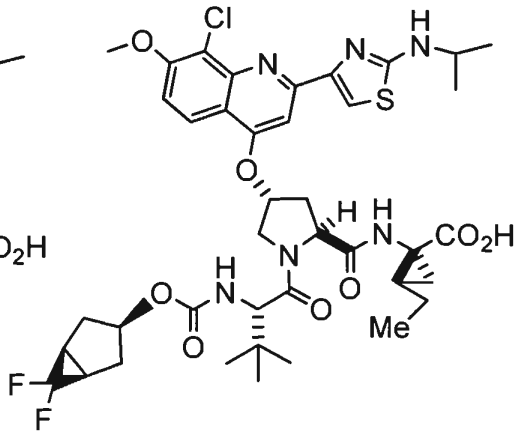


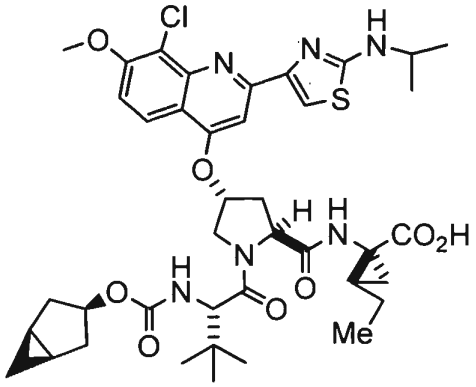


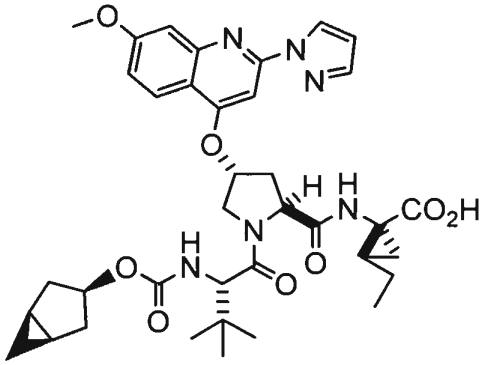


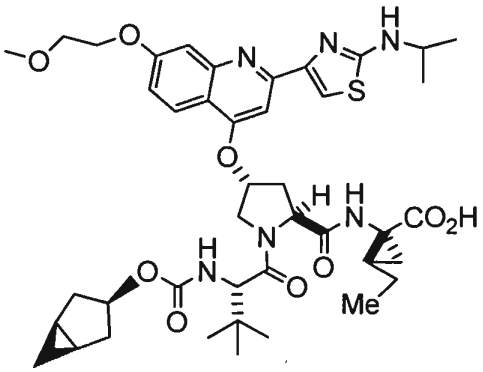
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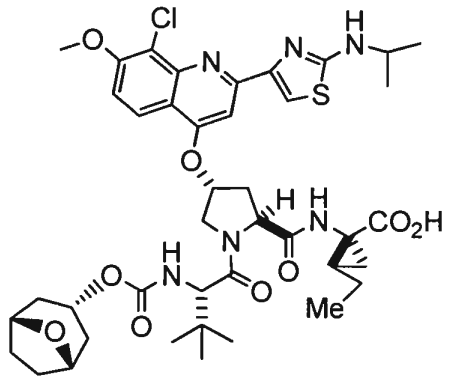


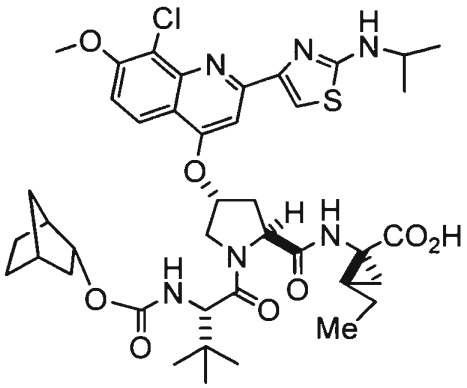


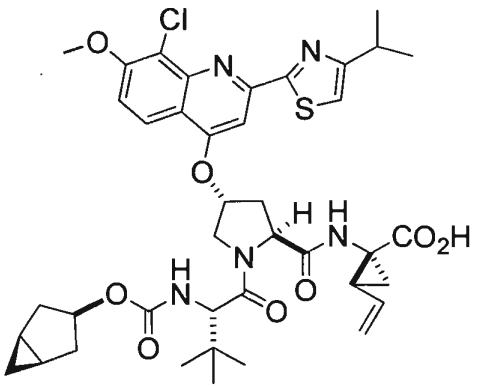


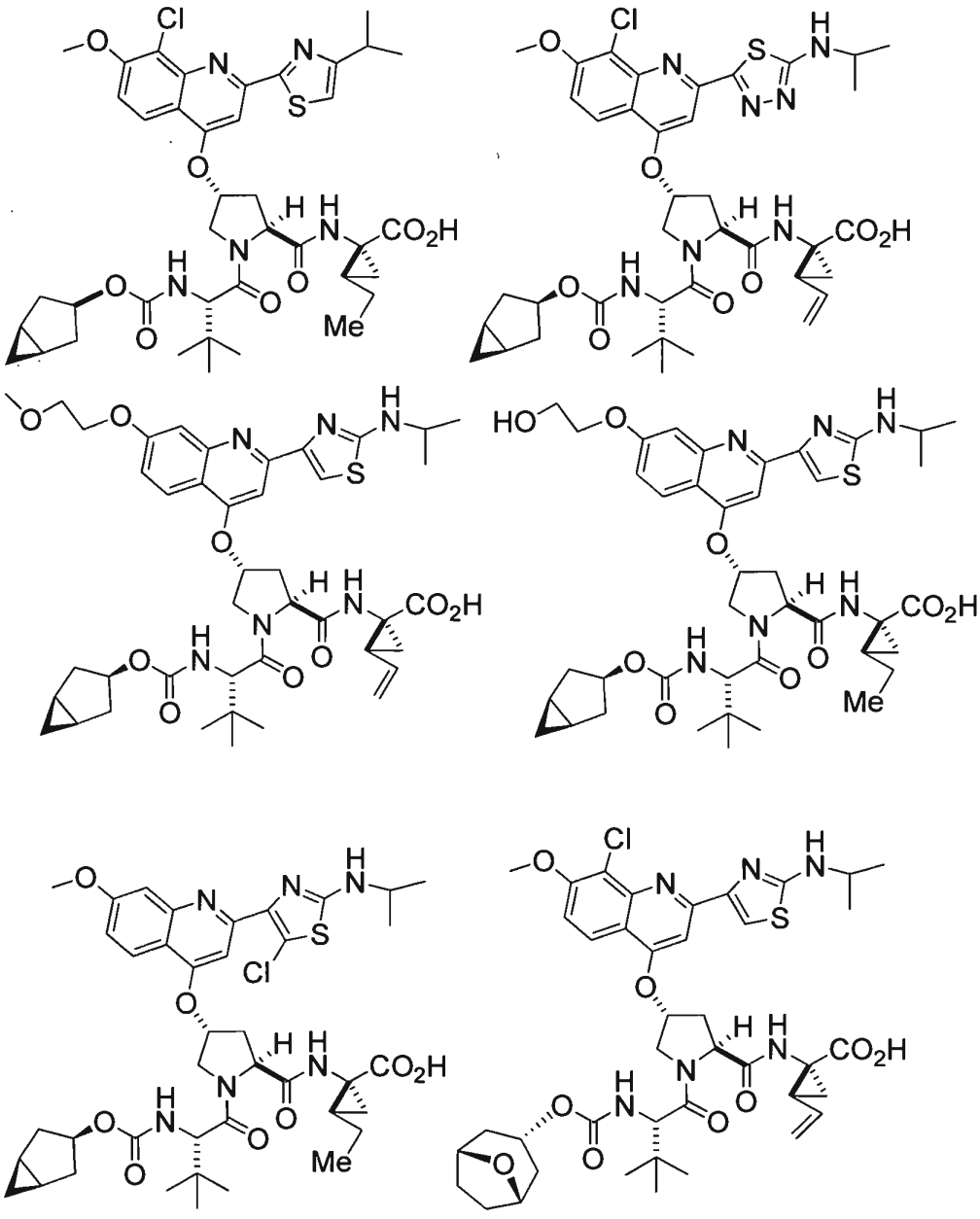




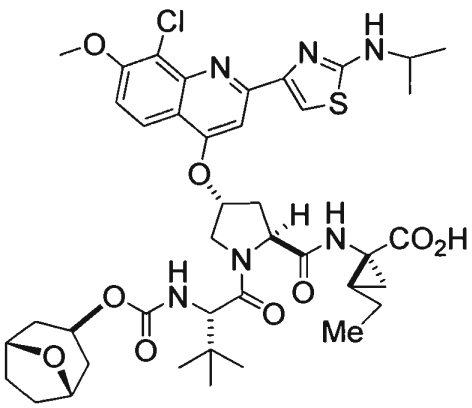
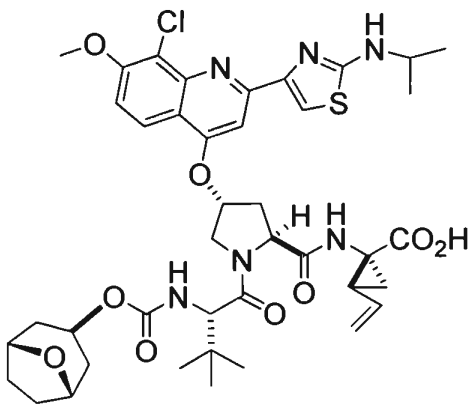
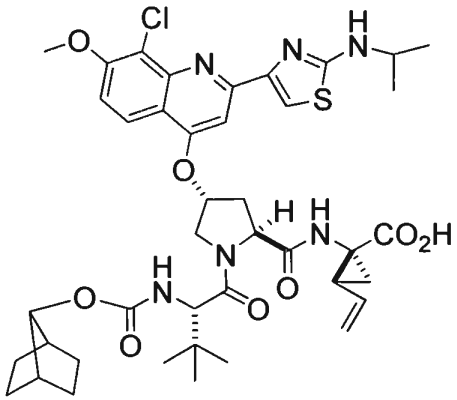
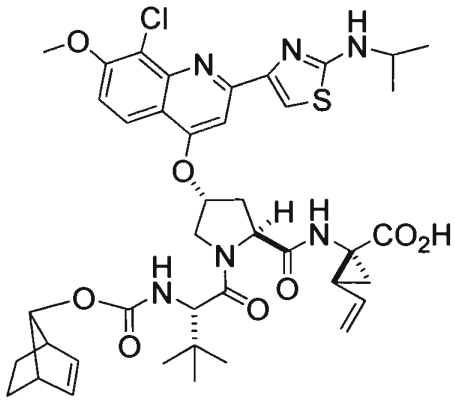
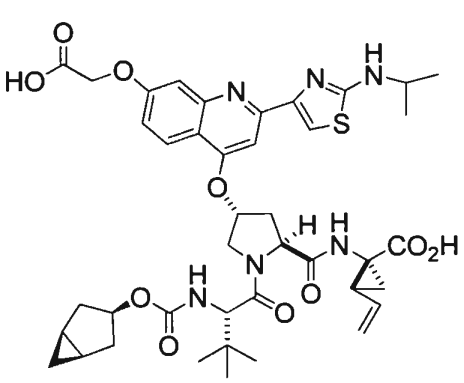
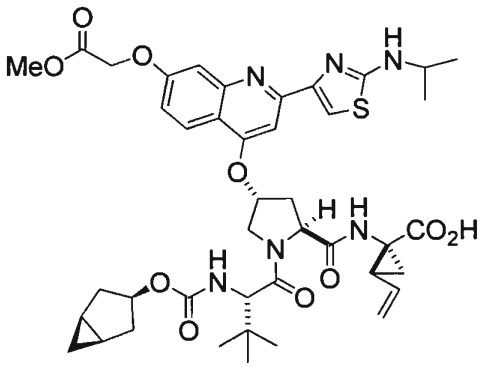






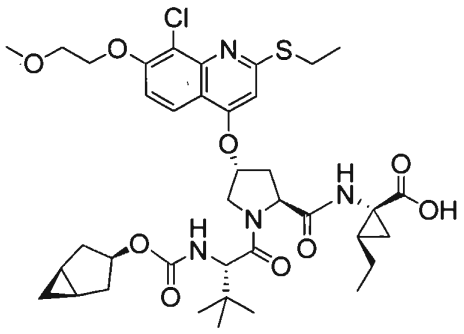


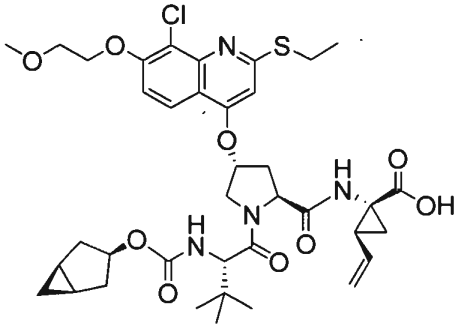
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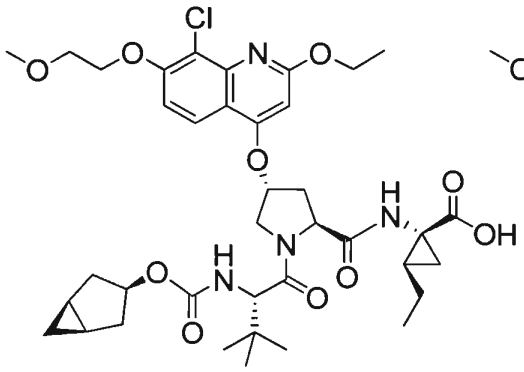







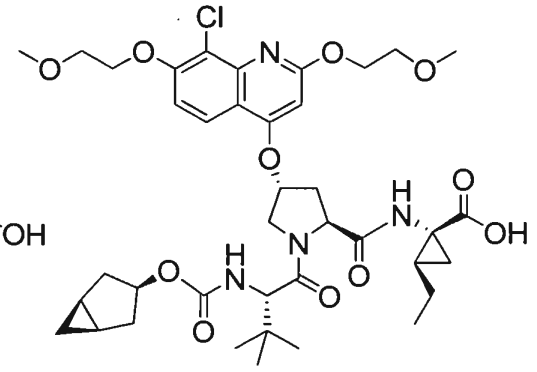
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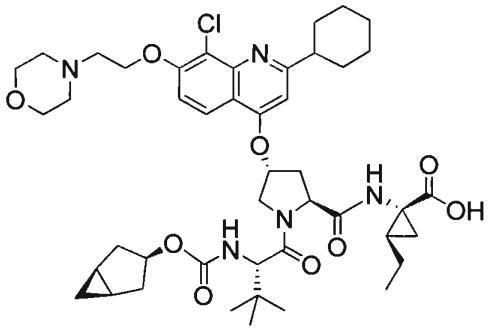
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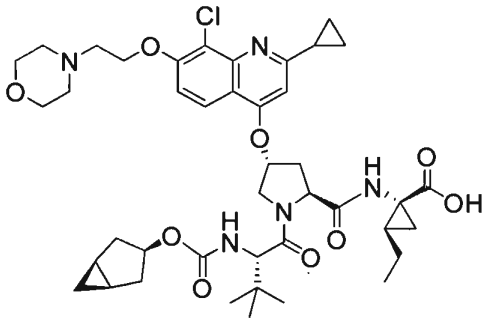




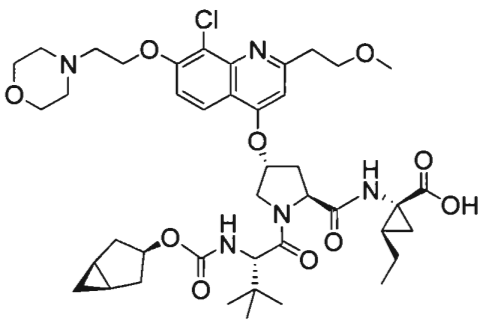


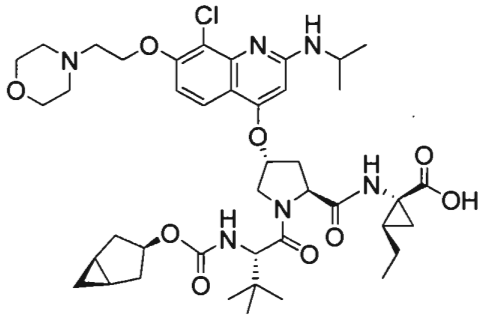


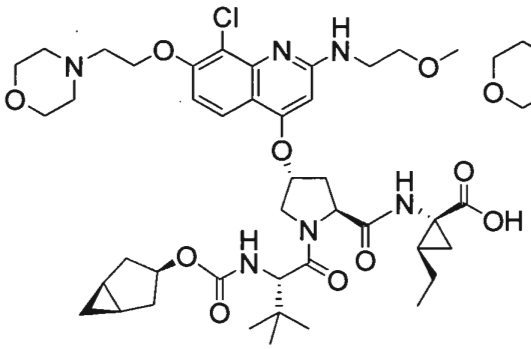


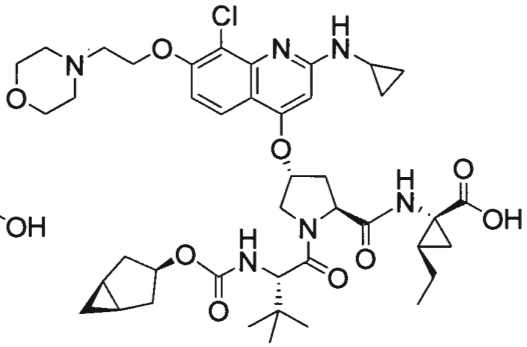


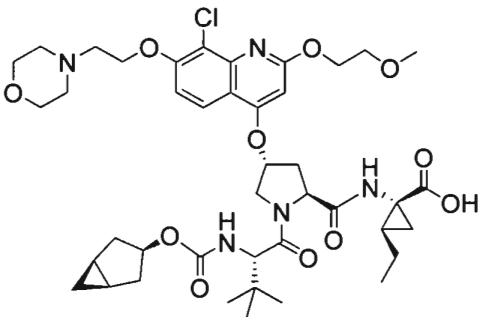
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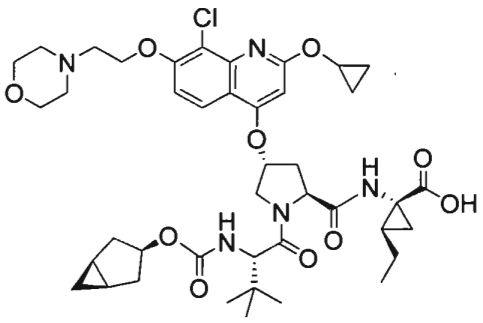


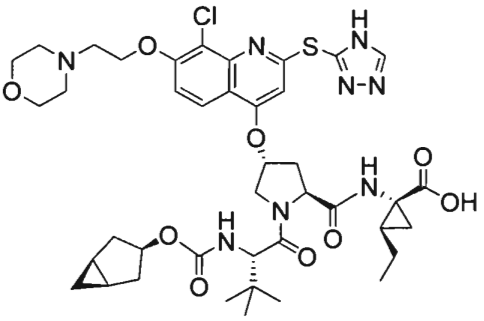


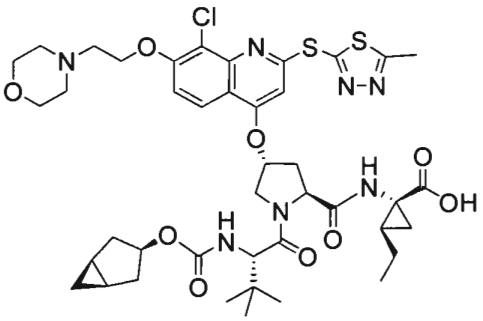


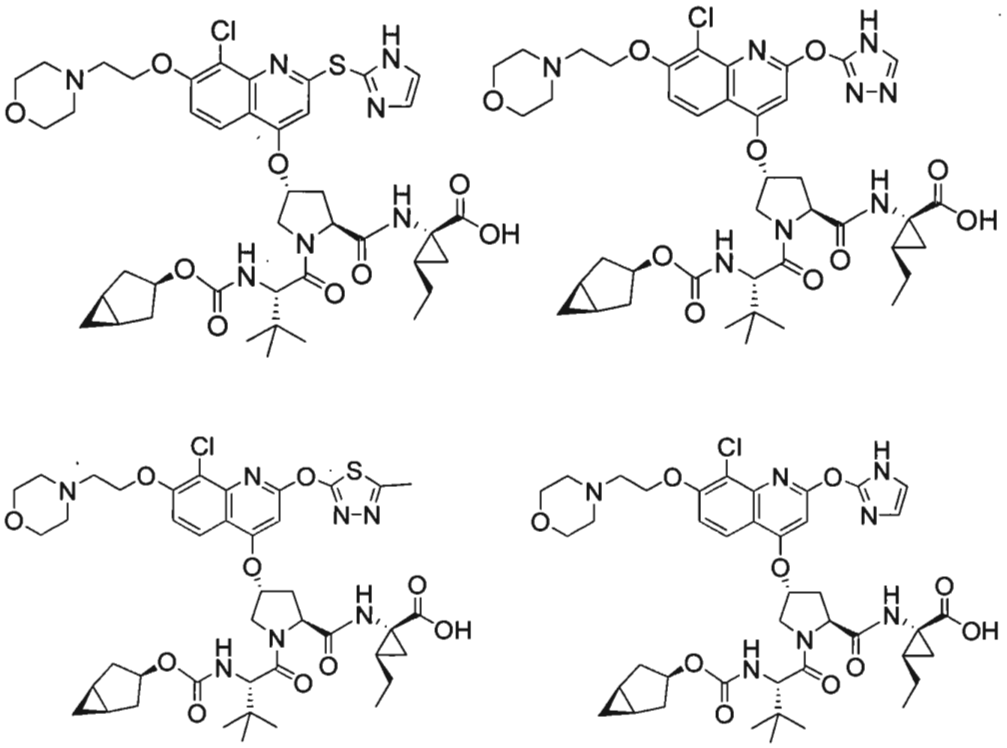




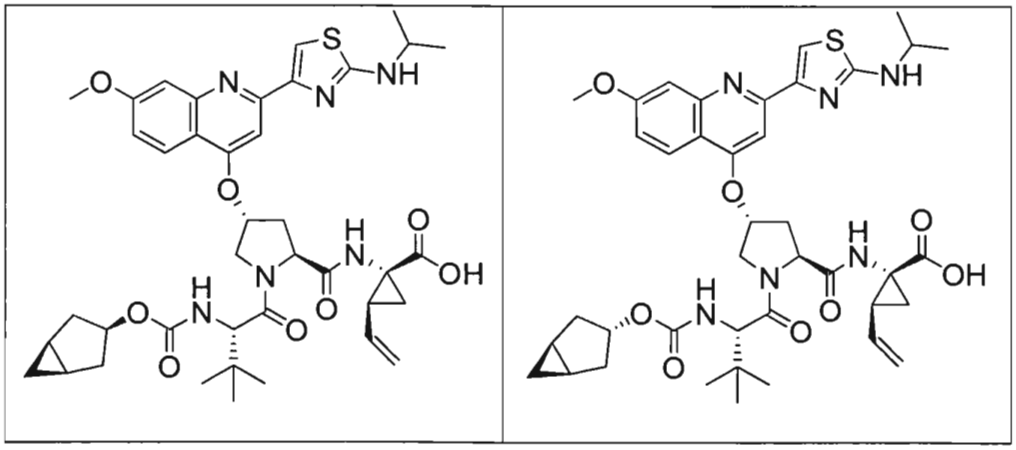


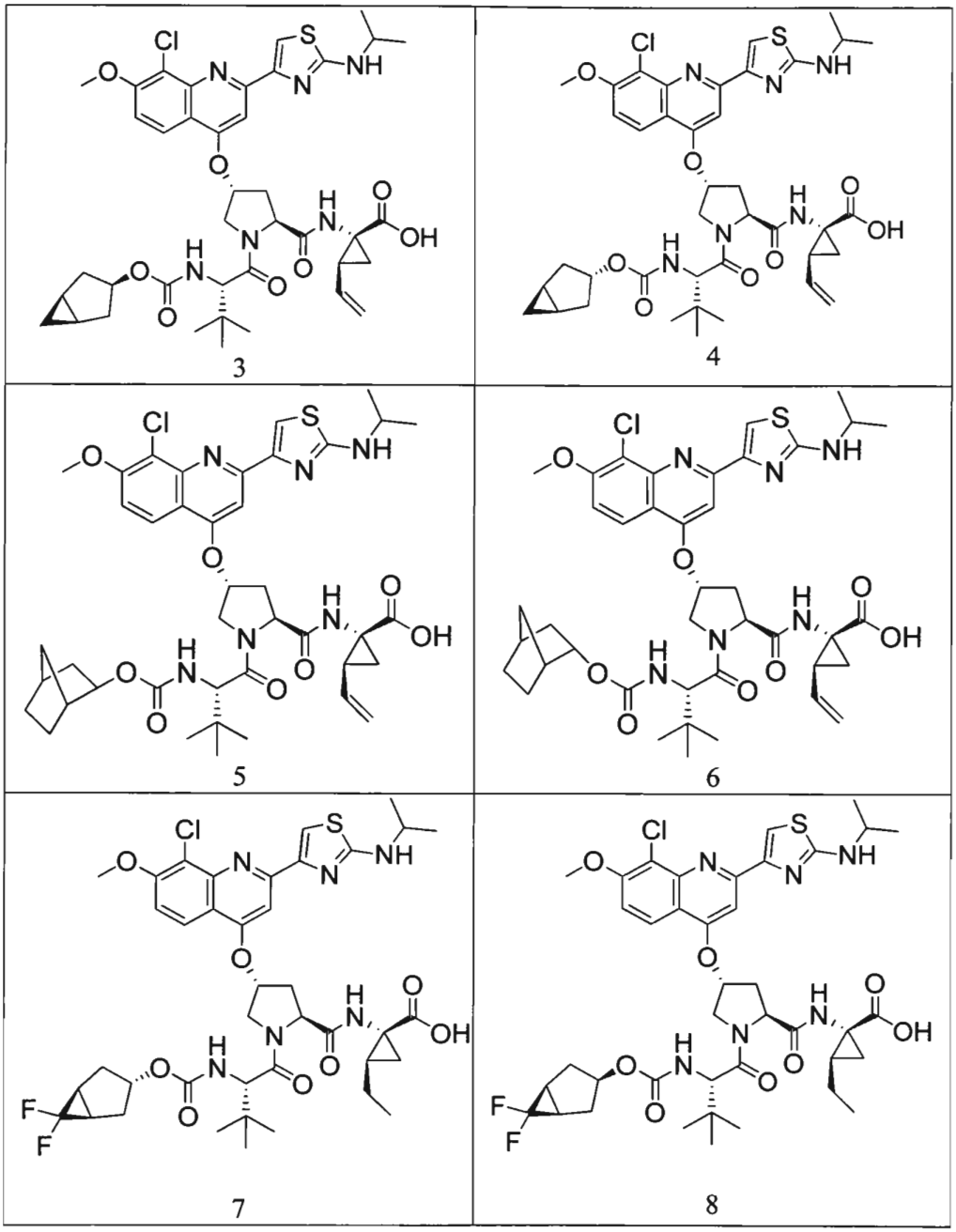


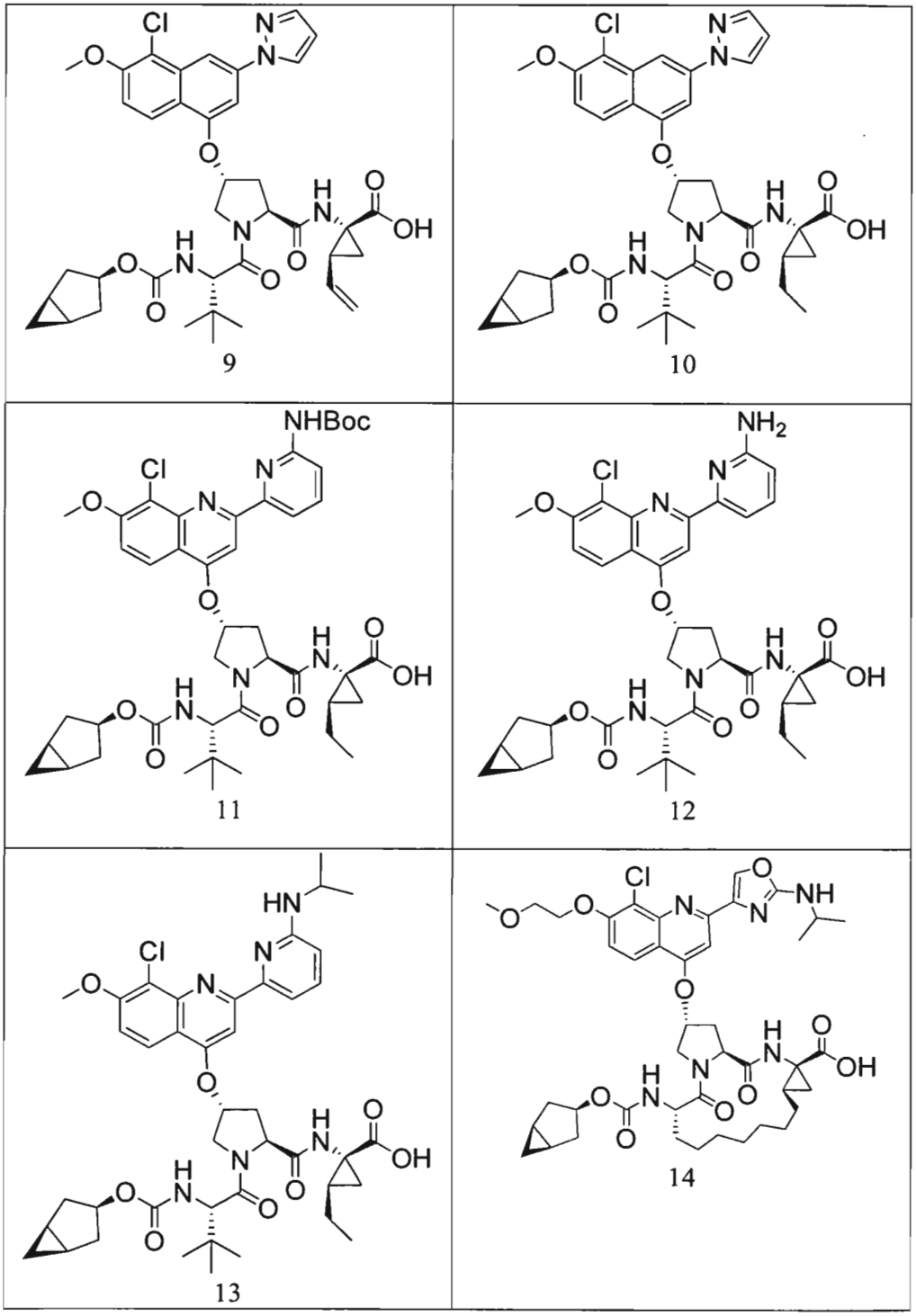


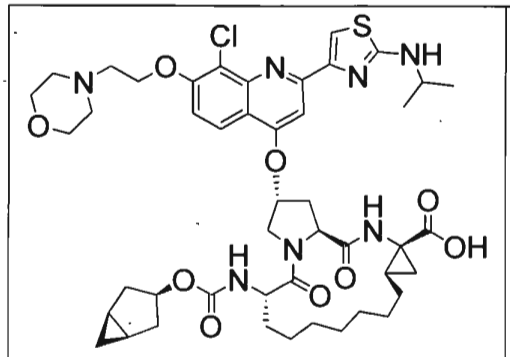


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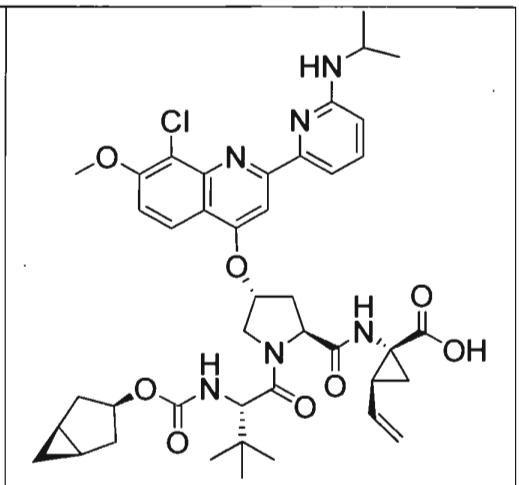



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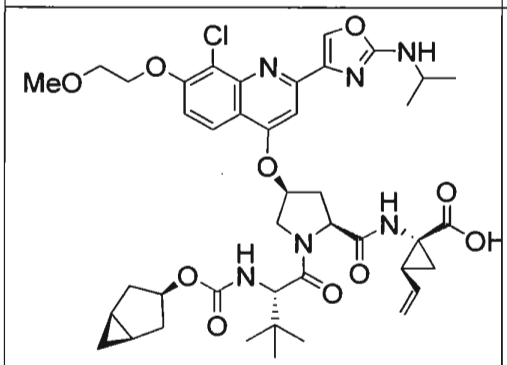

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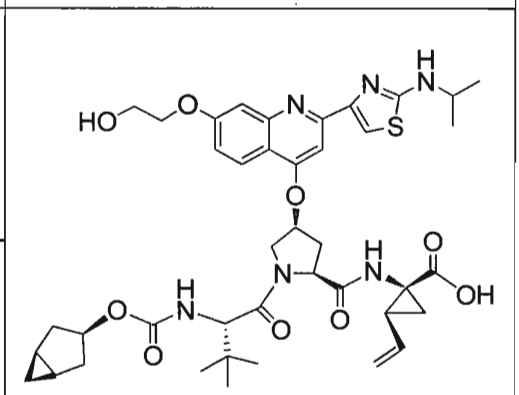
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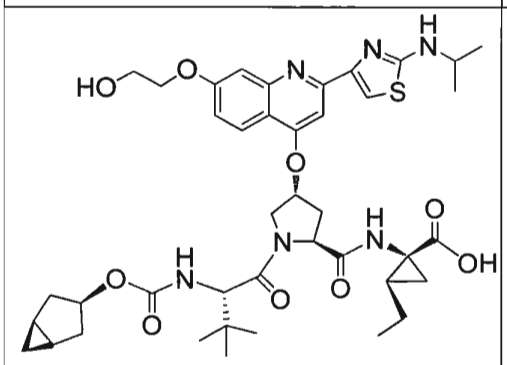
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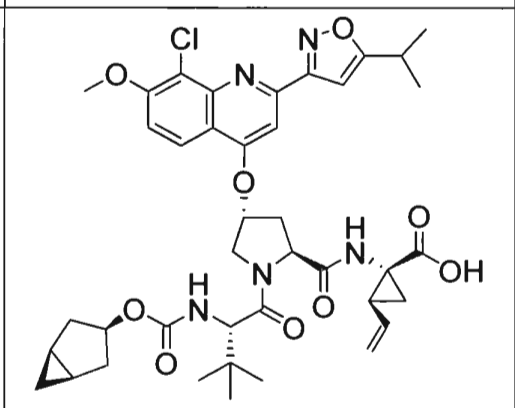
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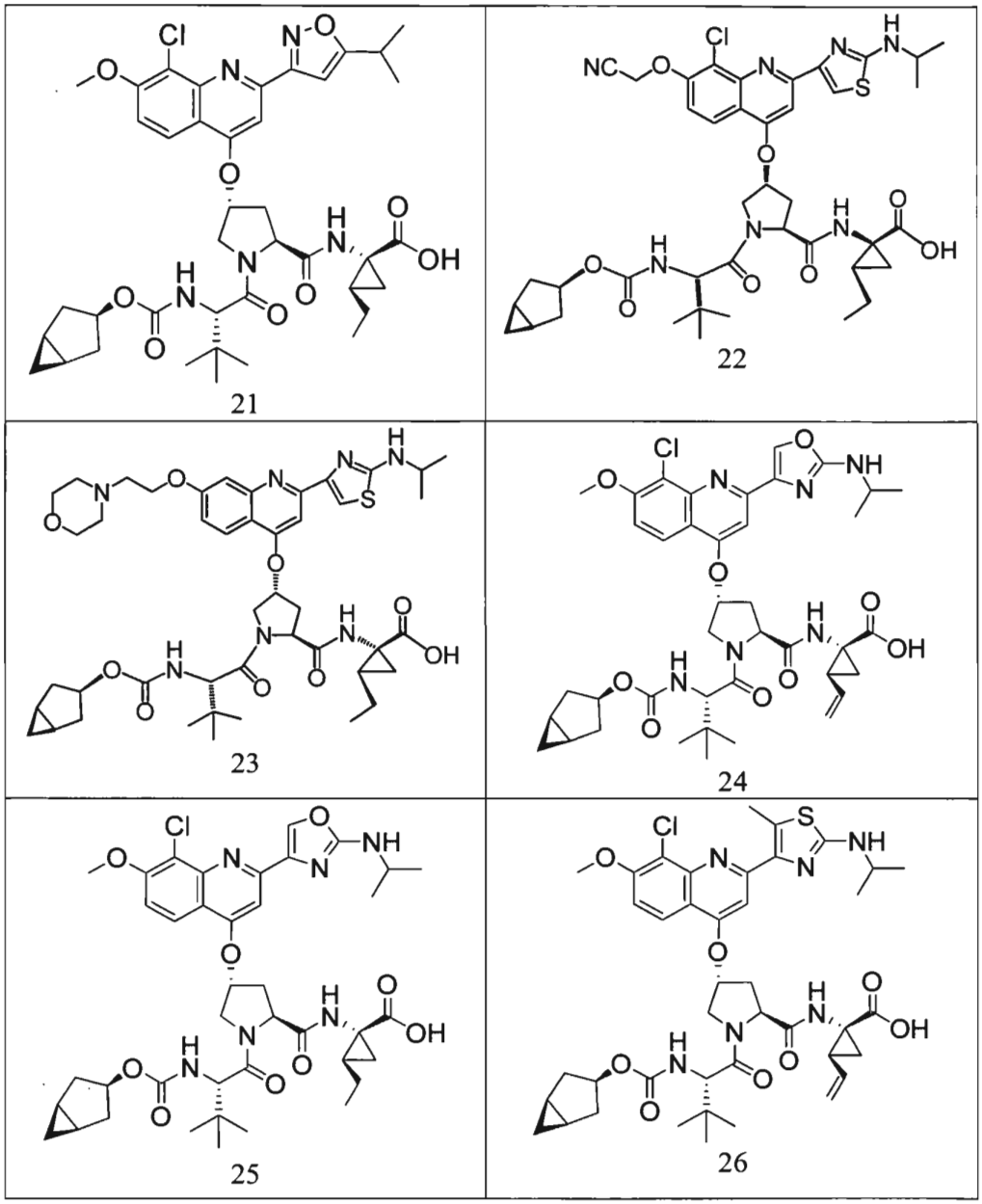
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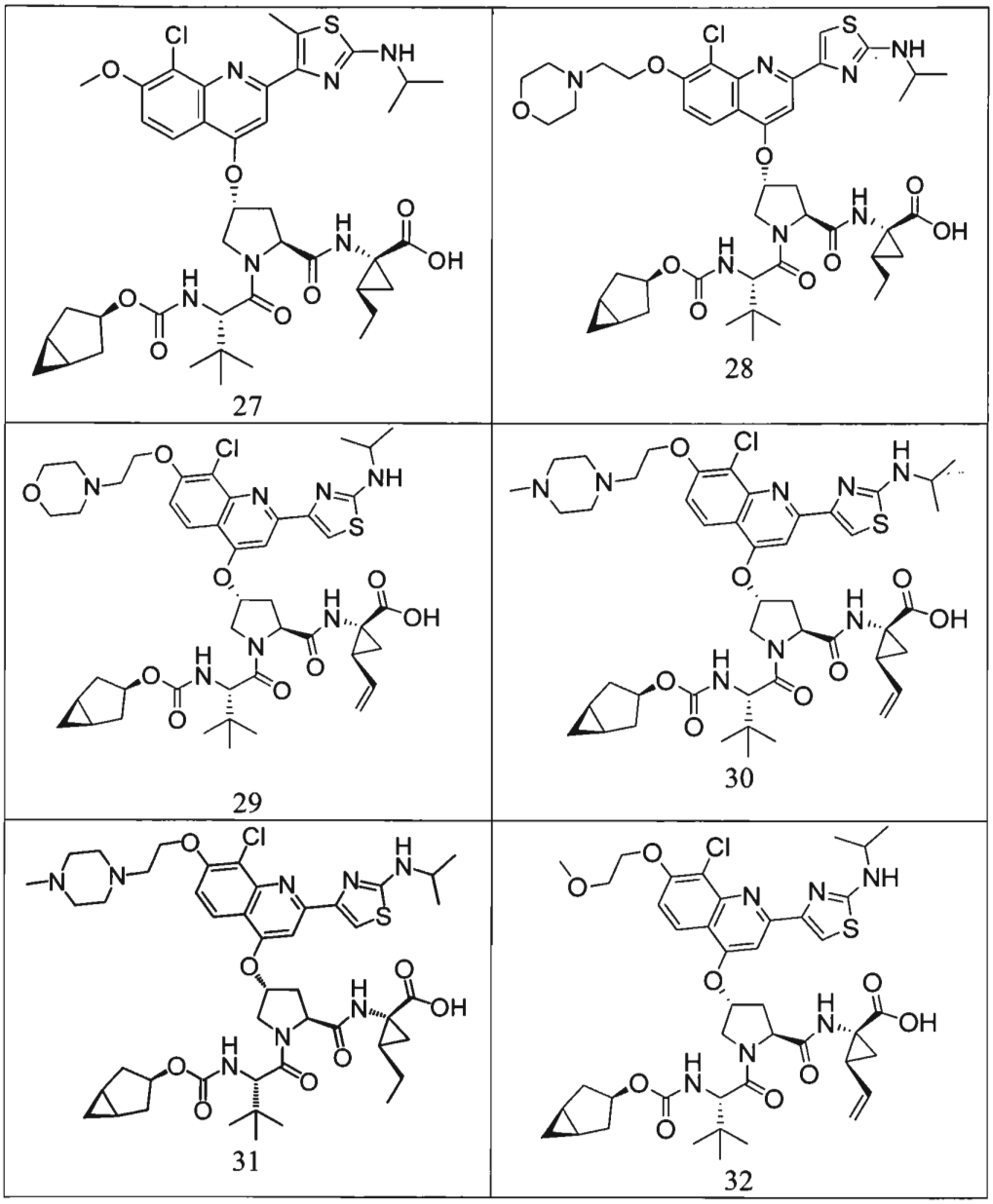


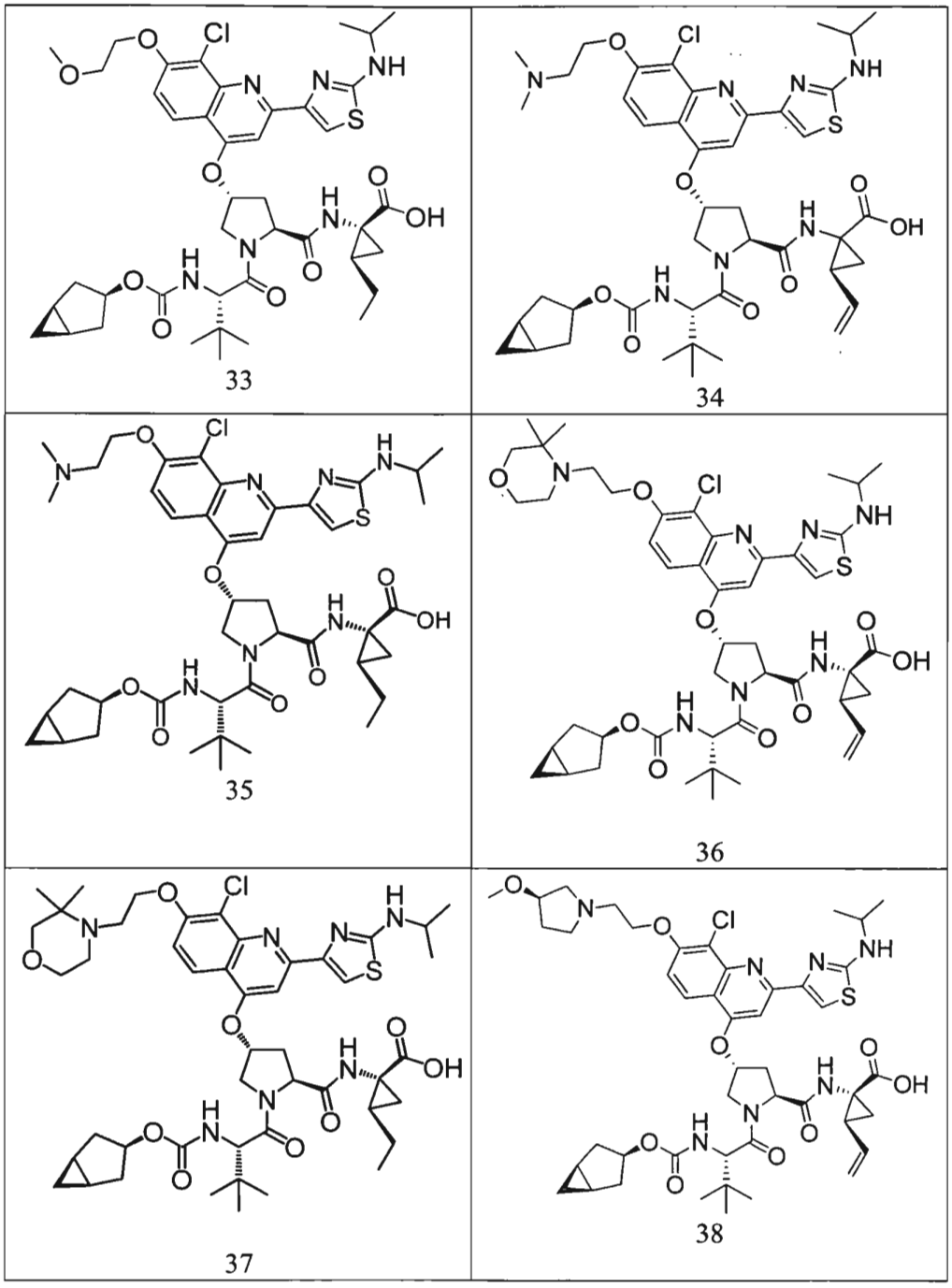
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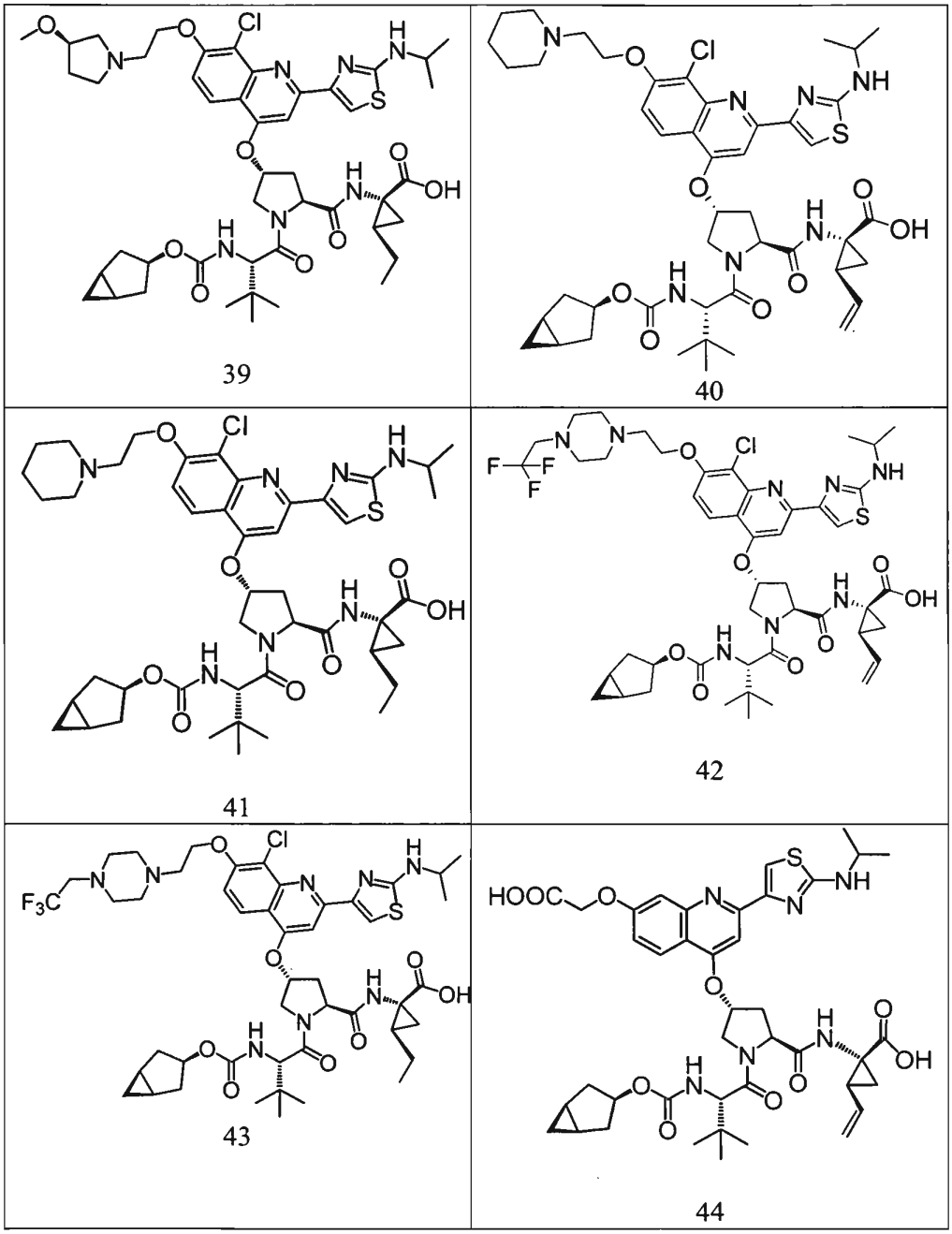


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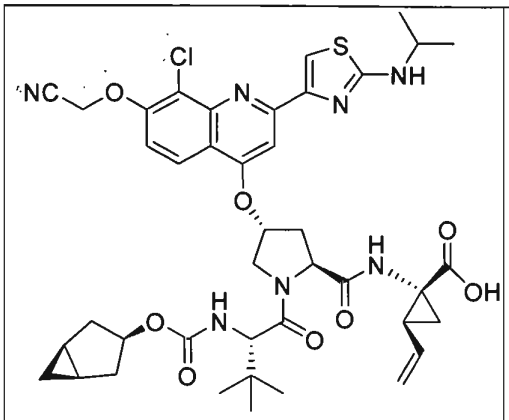
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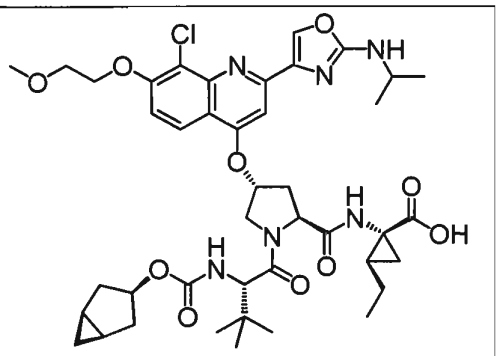
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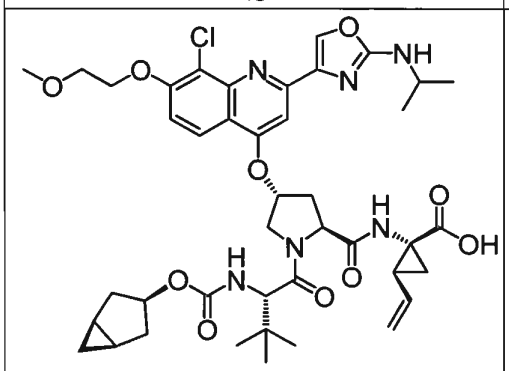
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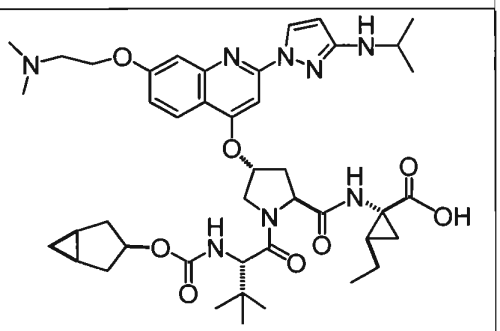
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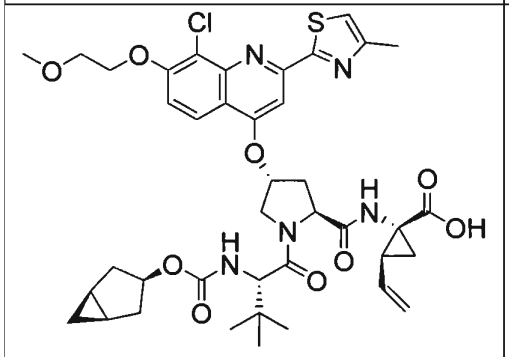
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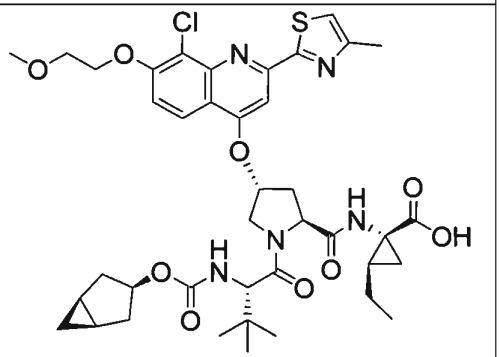
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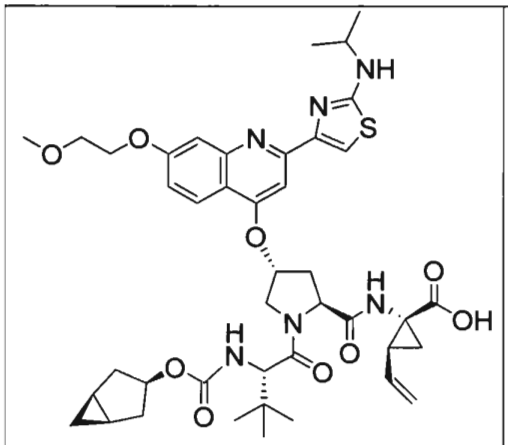
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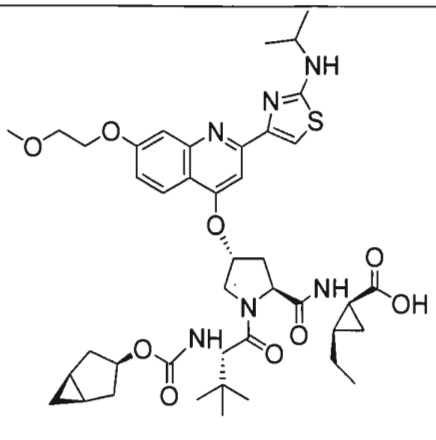
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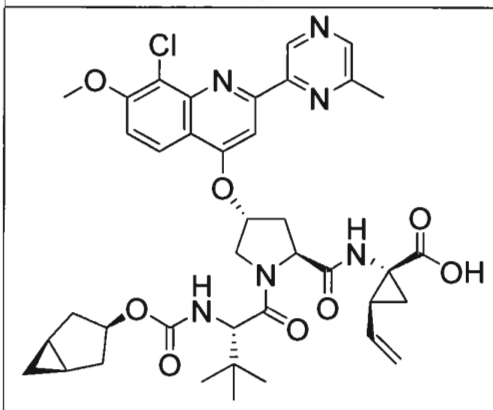
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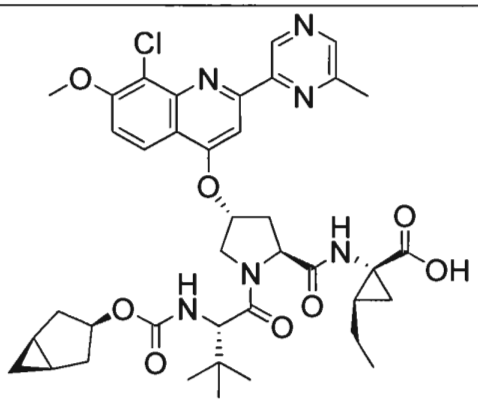
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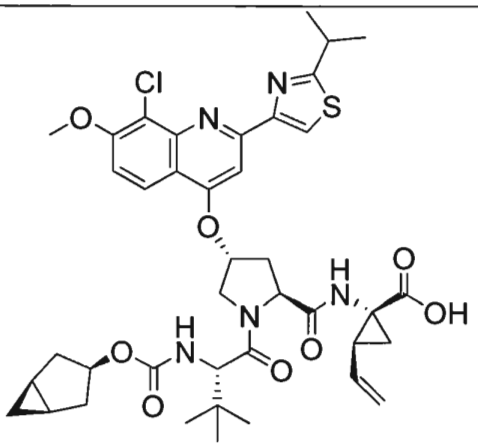
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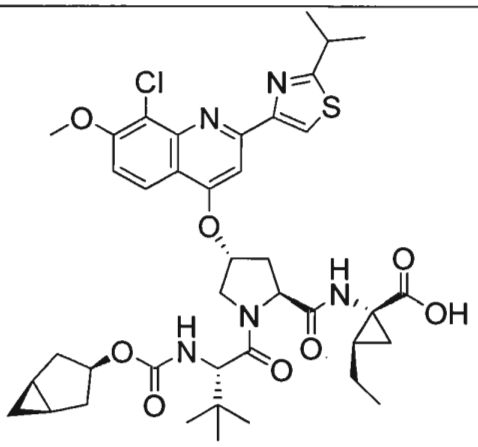
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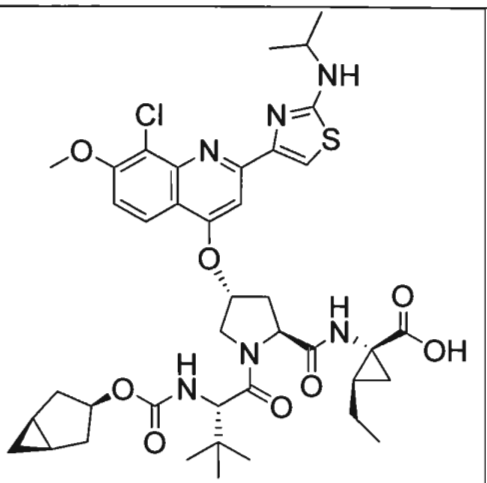
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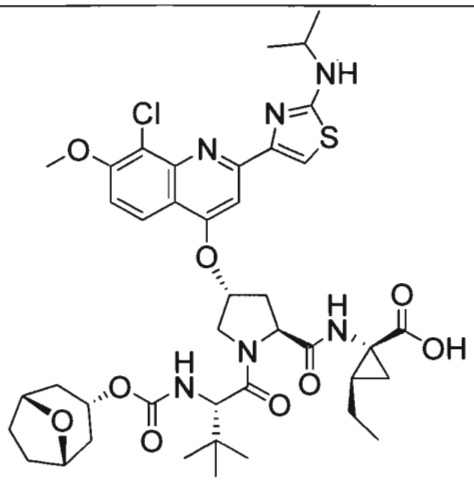
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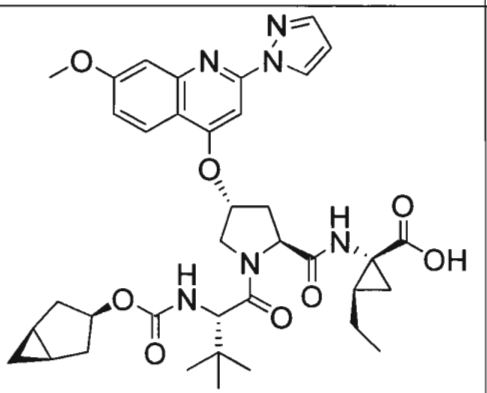
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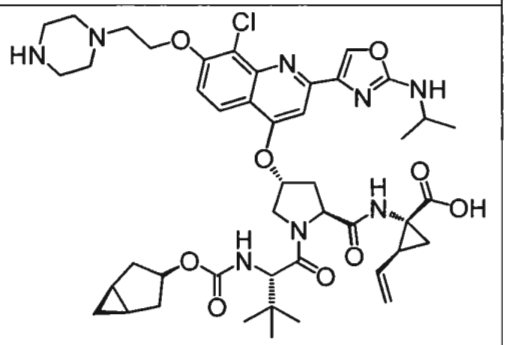
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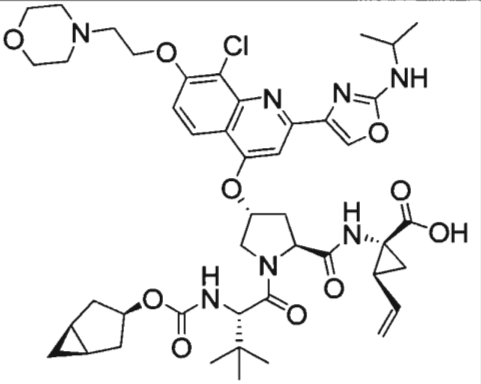
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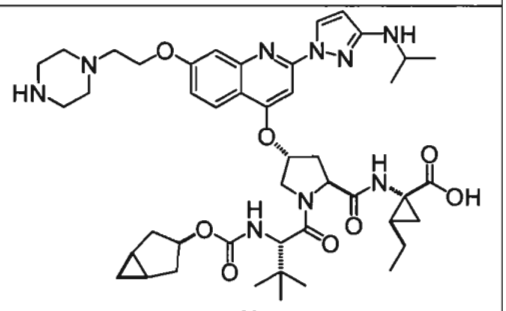
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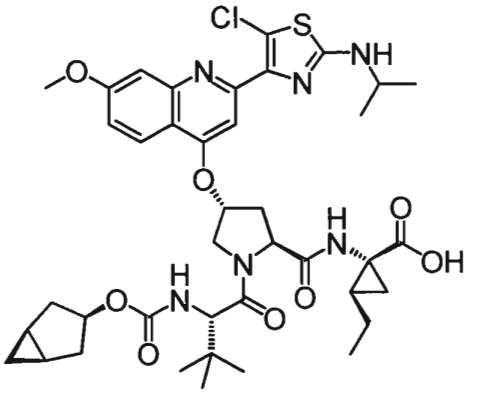
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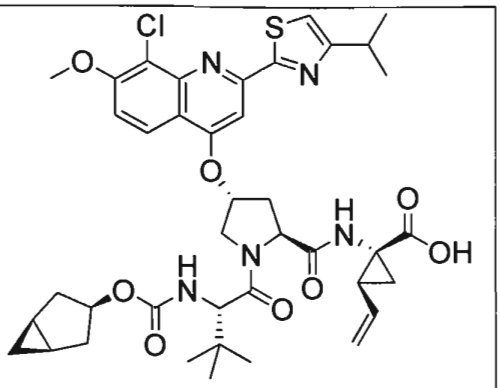
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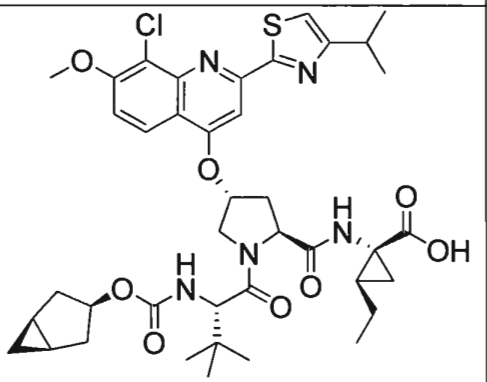
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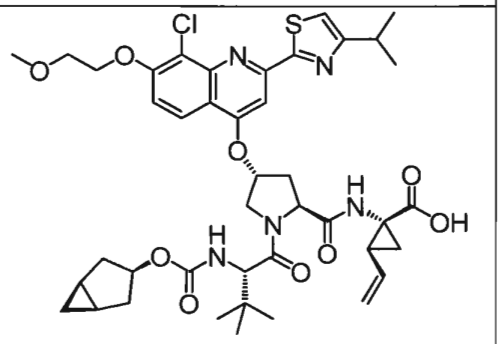
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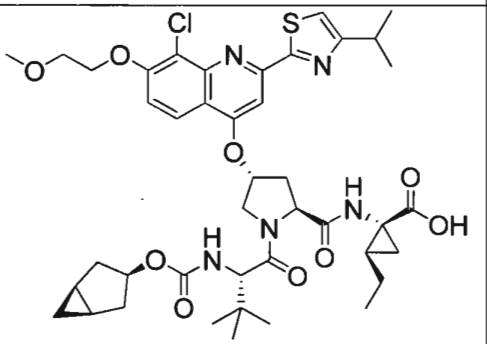
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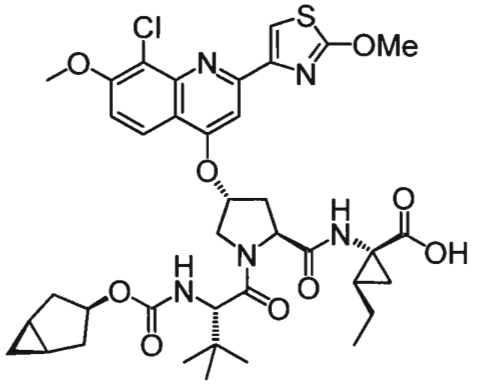
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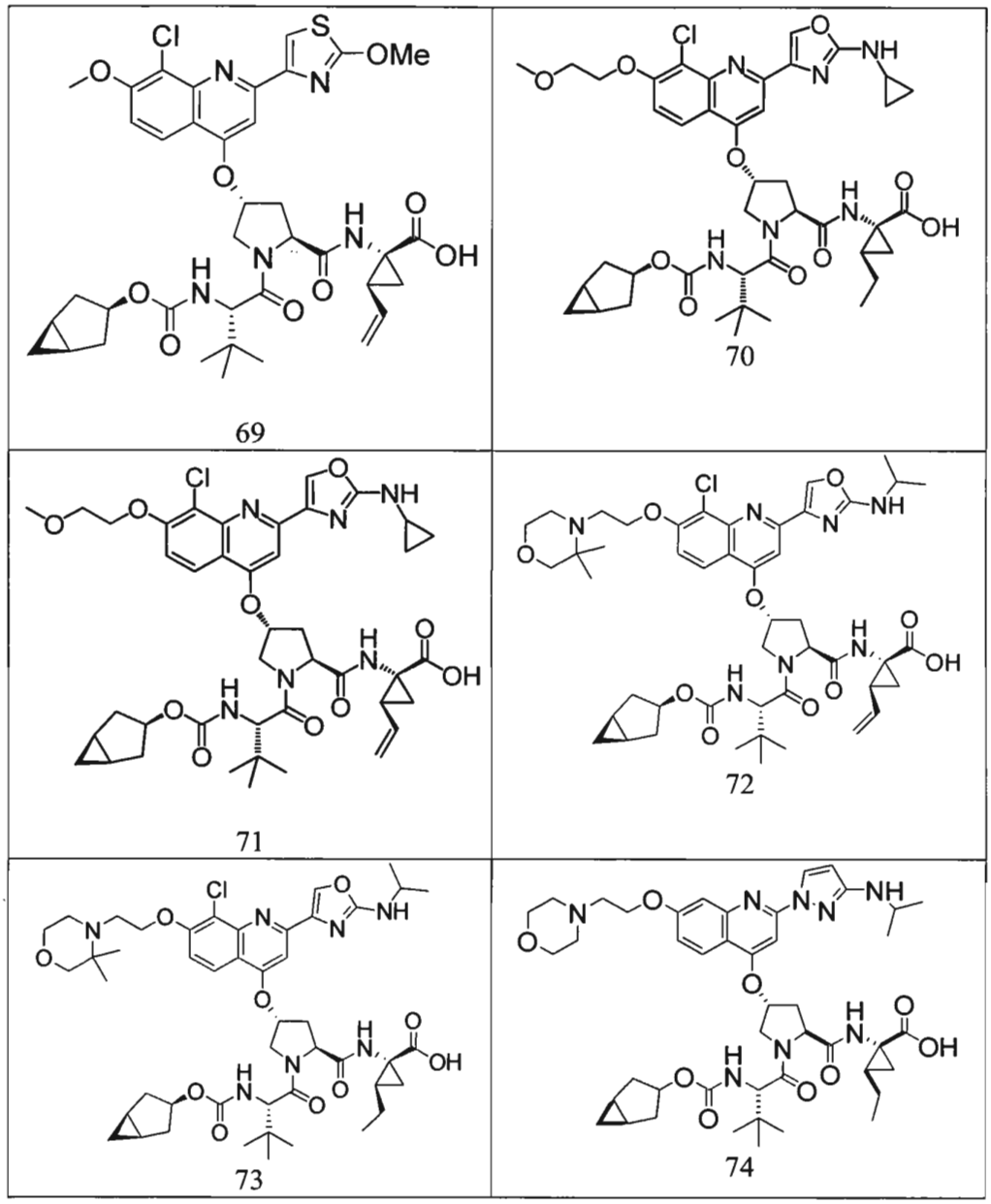
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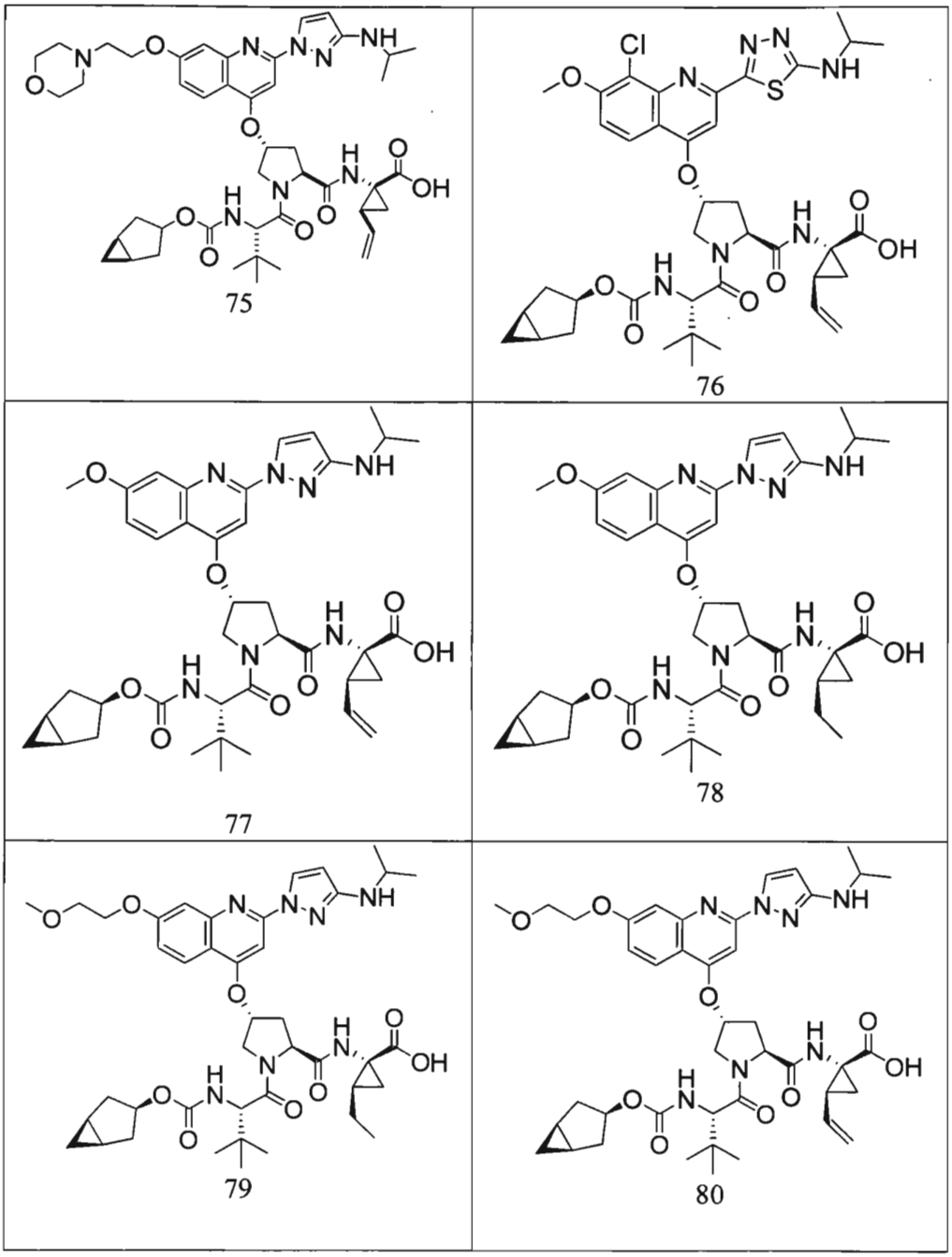
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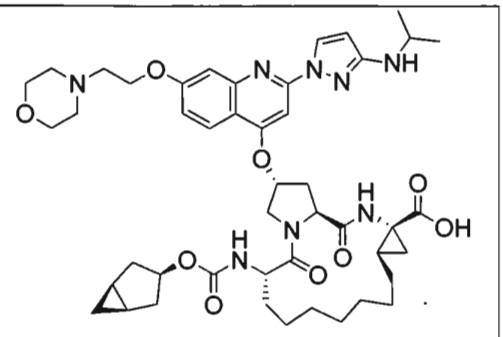
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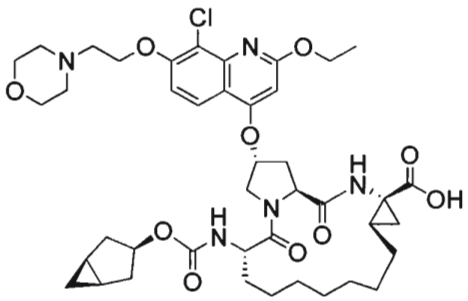
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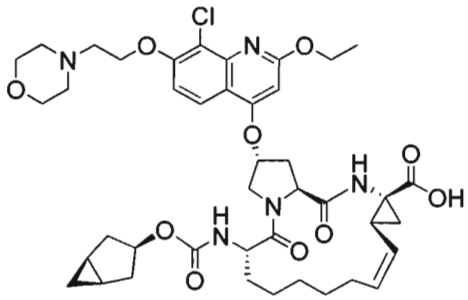
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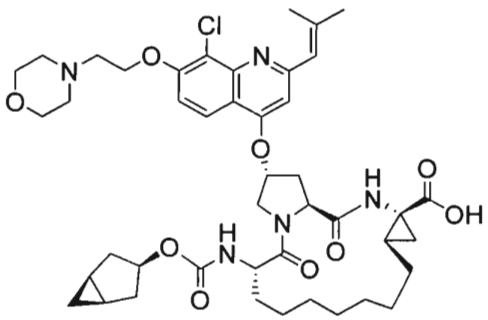

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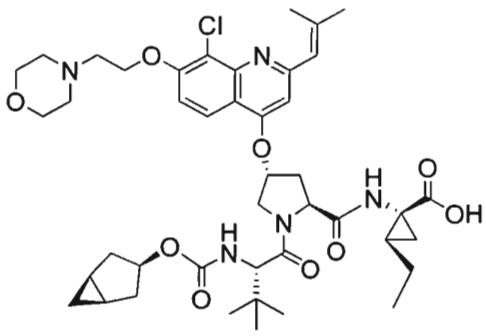
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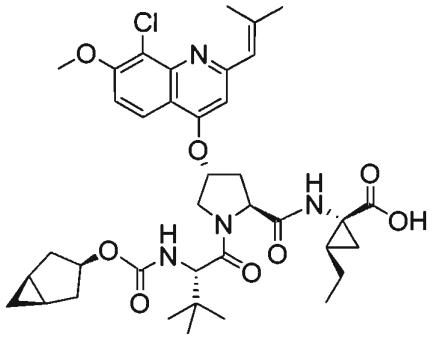
In a specific embodiment of the invention the compound of formula I is selected from:

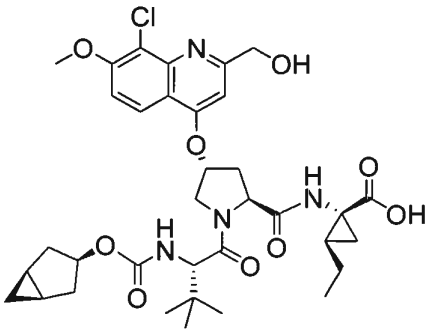


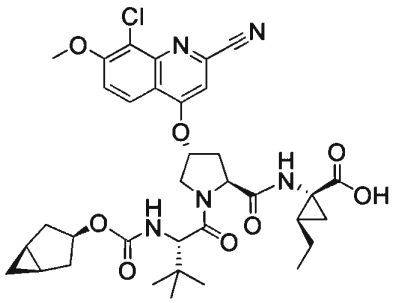


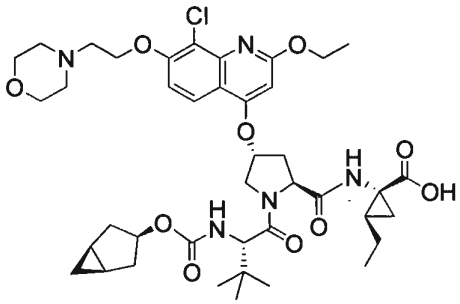




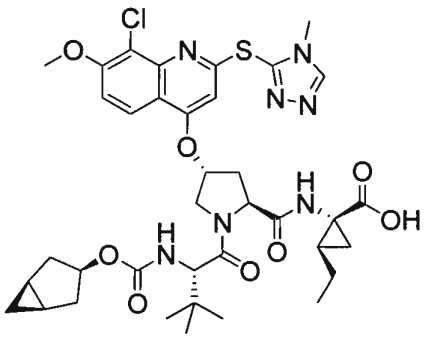


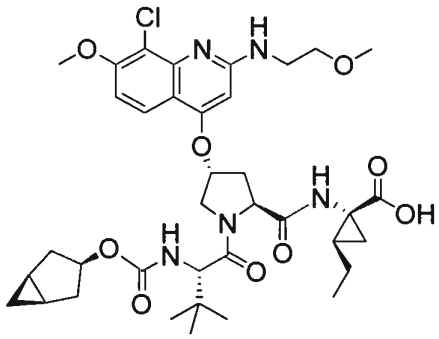


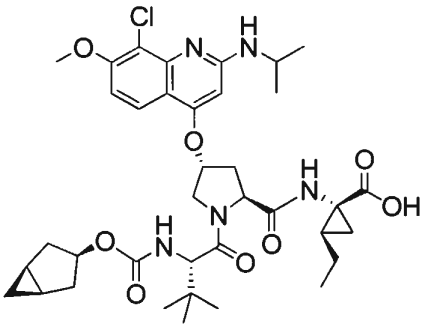


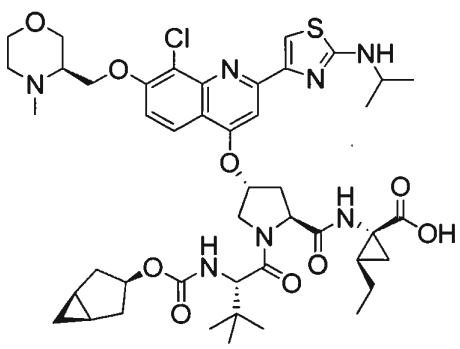


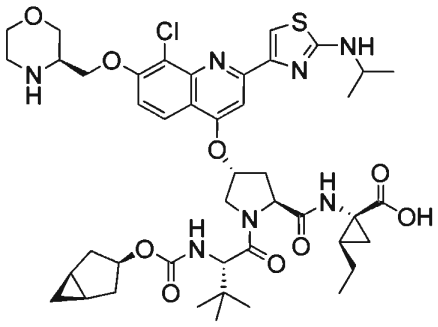
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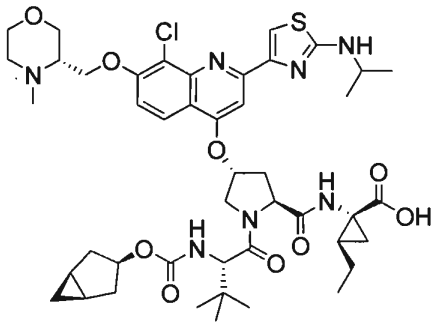


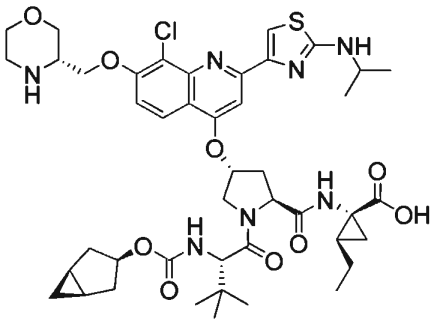


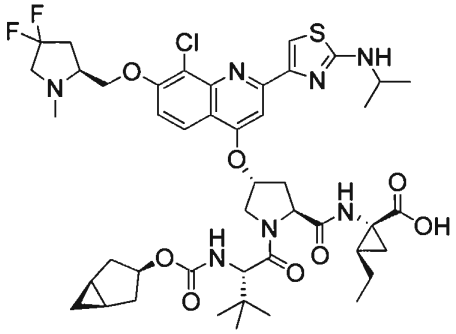


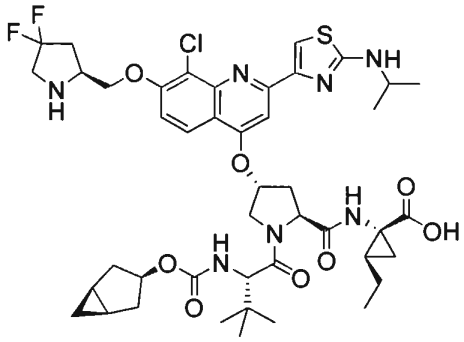


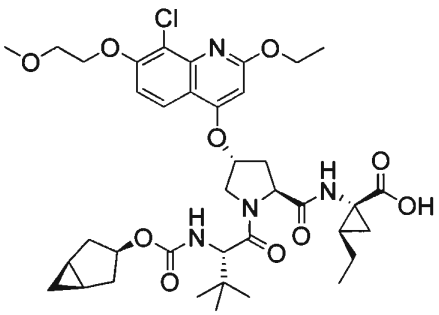


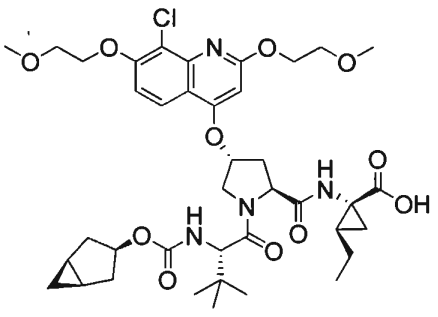


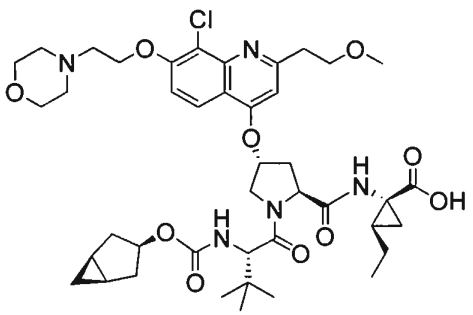


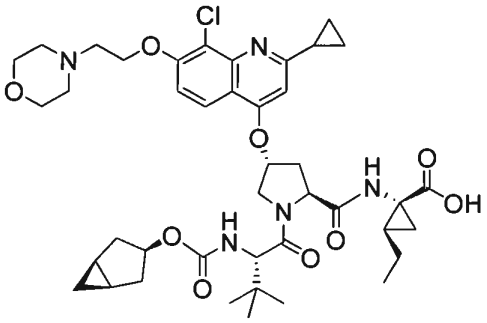


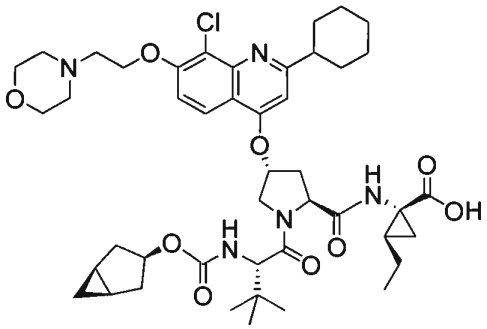


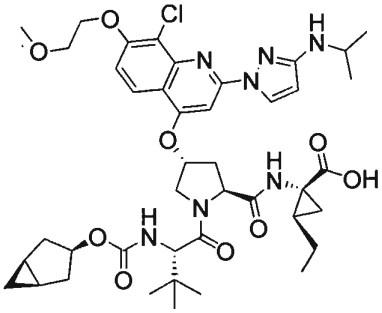


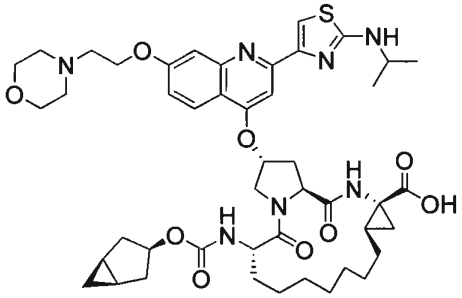


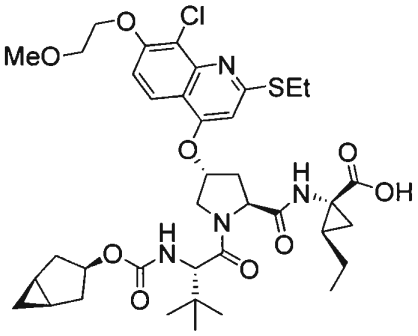


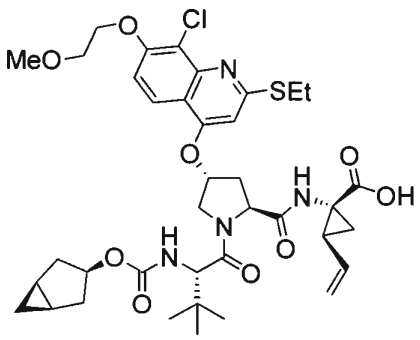


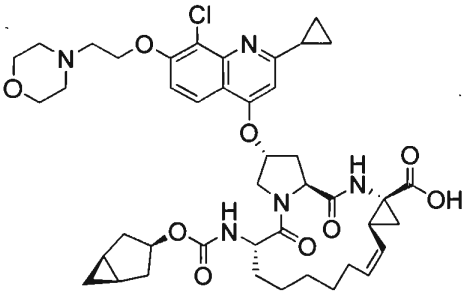


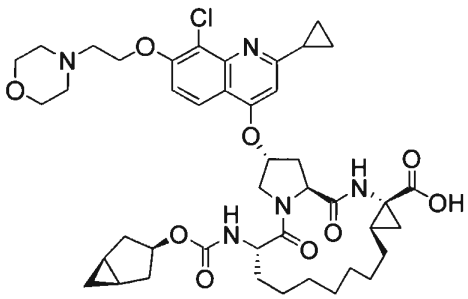


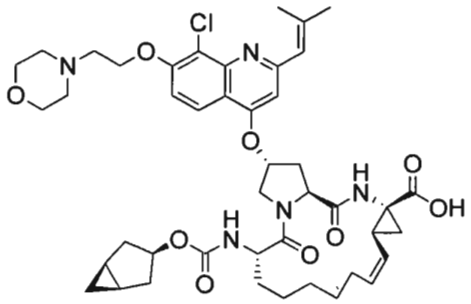




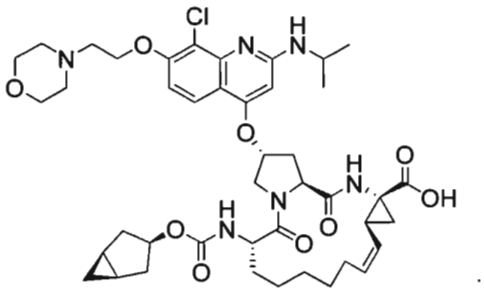




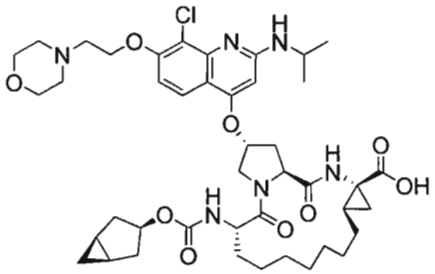


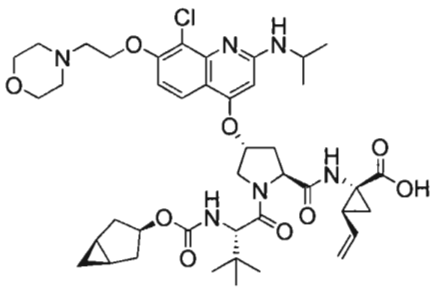


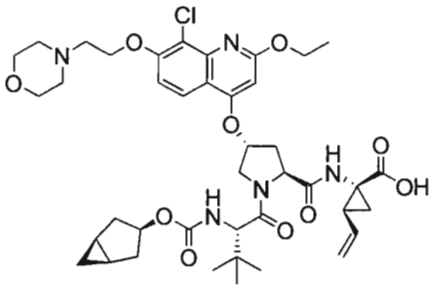
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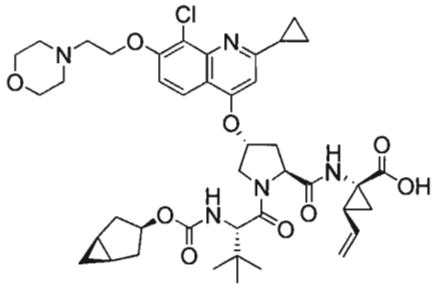


In a specific embodiment of the invention the compound of formula I is selected from:

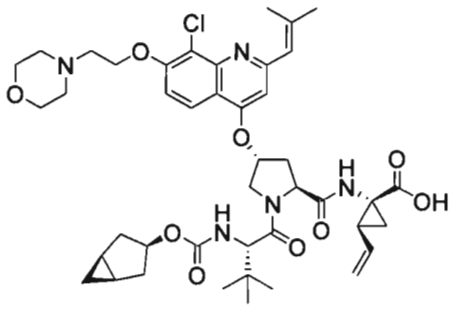




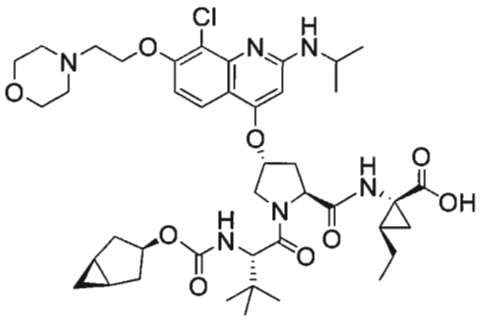


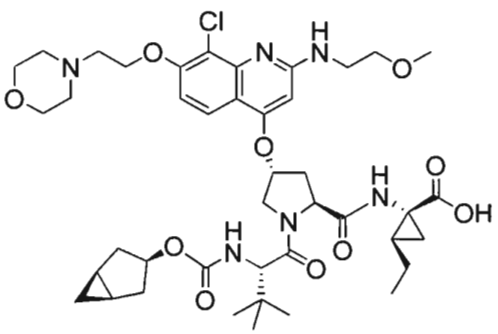


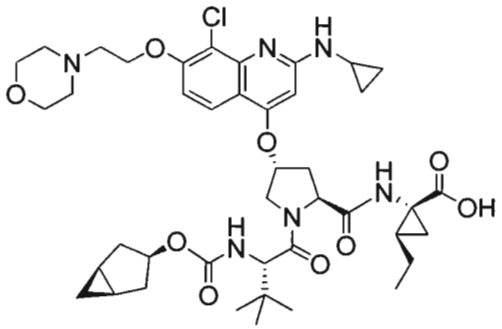
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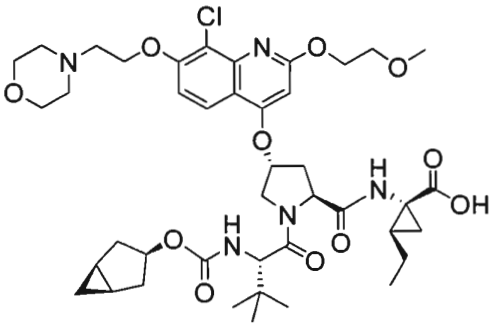


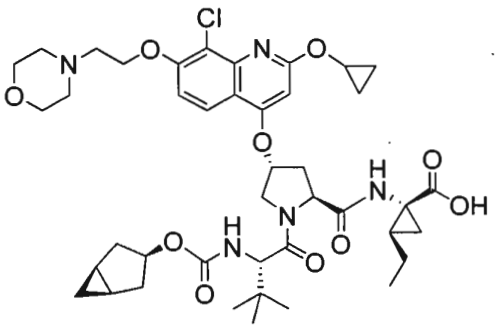
In a specific embodiment of the invention the compound of formula I is selected from:

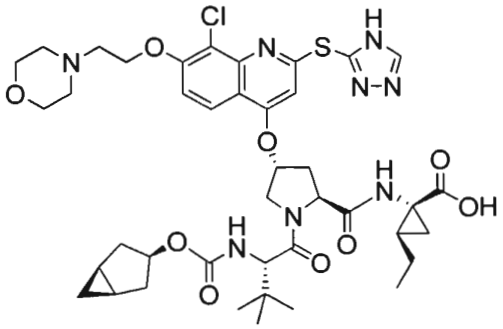


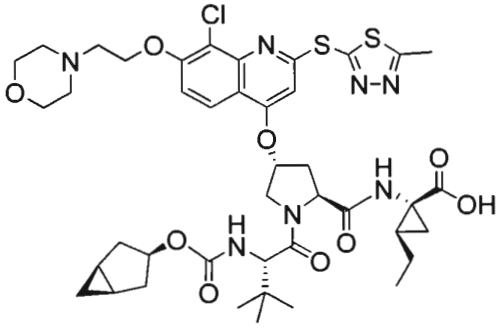


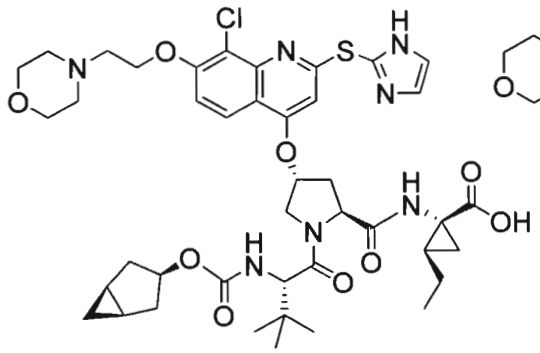


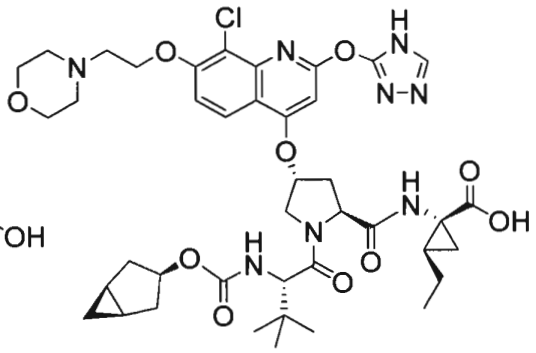




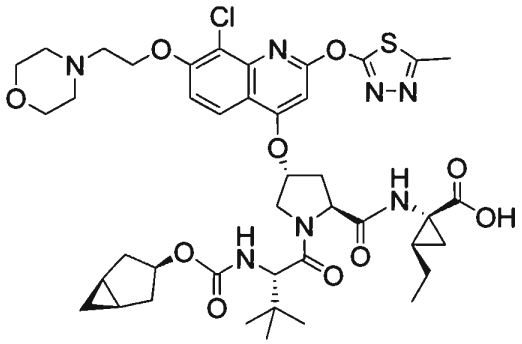




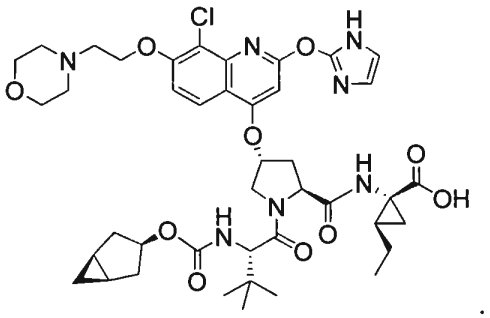




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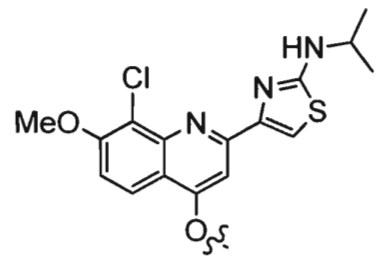
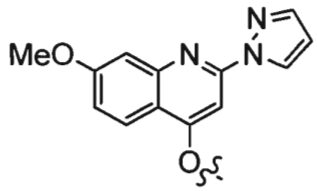
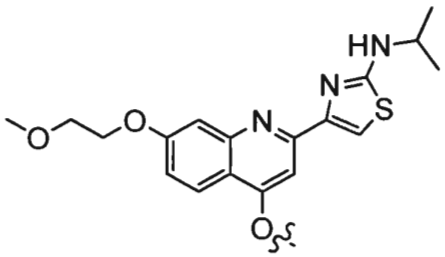
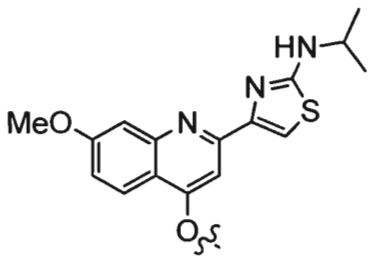
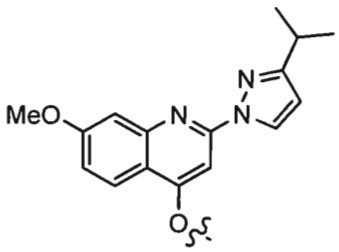
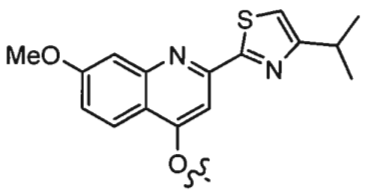
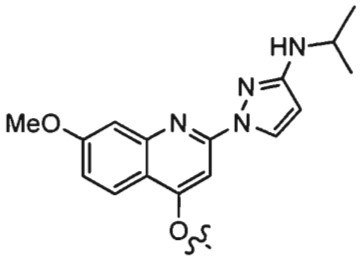
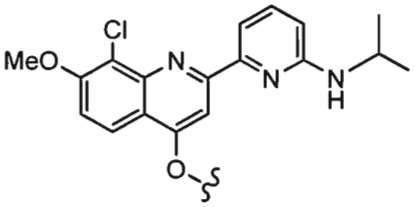


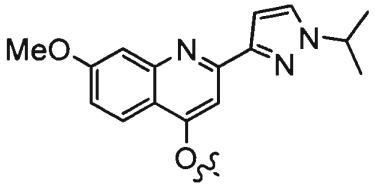
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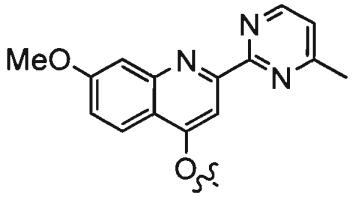


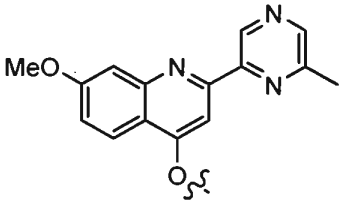
In a specific embodiment of the invention each R_n and R_p is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, which (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, is optionally substituted with one or more R^1, halo, hydroxy, carboxy, cyano, or (C1-10)alkoxy; or R_n and R_p together with the nitrogen to which they are attached form a pyrrolidine, piperidine, piperazine, morpholino, or thiomorpholino ring. In a specific embodiment of the invention R_a is H, methoxy, N-(2-cyanoethyl)amino, N-(3,3,3-trifluoroethyl)amino, 2-methoxyethoxy, 2-hydroxyethoxy, 2-hydroxy-2-methylpropoxy, 2-amino-2-methylpropoxy, N,N-dimethylaminocarbonylmethoxy, morpholinocarbonylmethoxy, 2-[N-(2,2,2-trifluoroethyl)amino]ethoxy, 2-morpholinoethoxy, cyanomethoxy, 2-piperazin-1-ylethoxy, 2-(N,N-dimethyl)ethoxy, 2-(3,3-dimethylmorpholino)ethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, carboxymethoxy, methoxycarbonylmethoxy, .

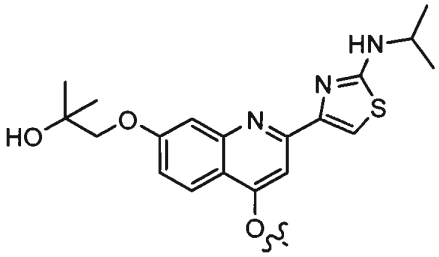
In a specific embodiment of the invention Z^1 is selected from the following structures:

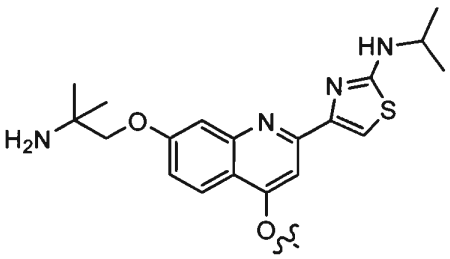









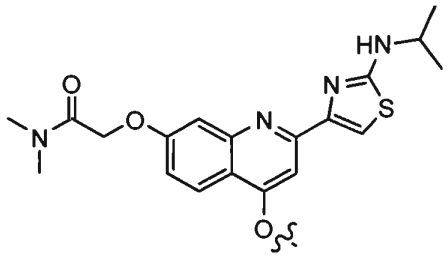




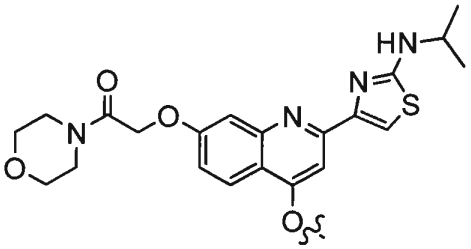


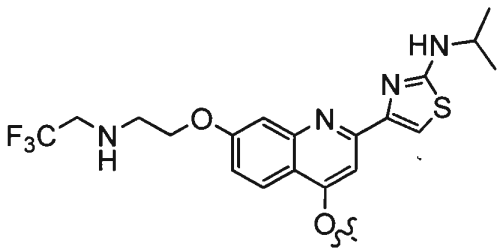


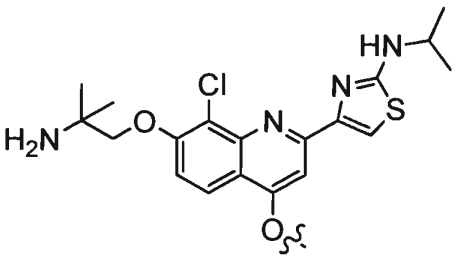


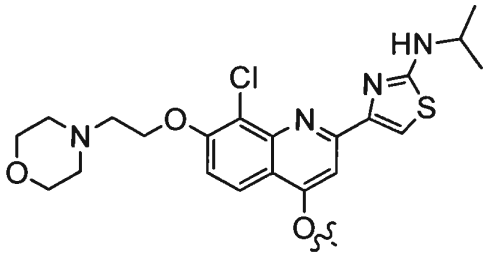


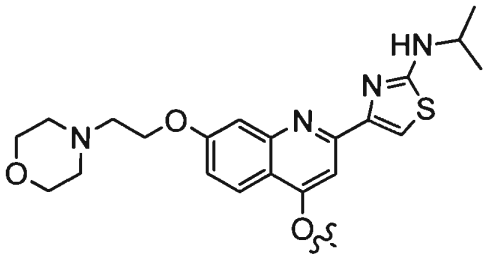
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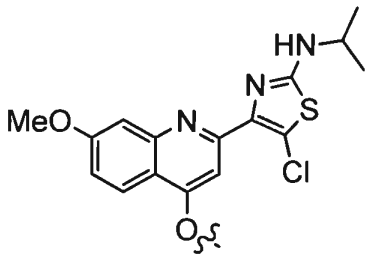


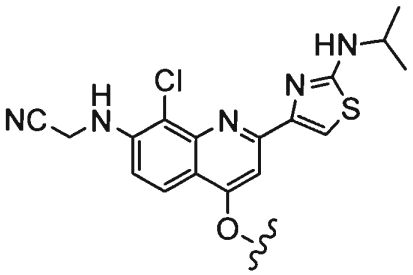


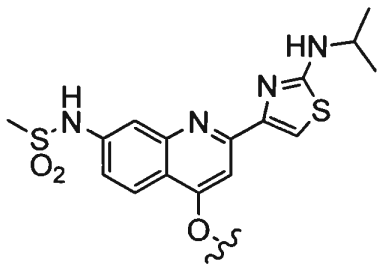


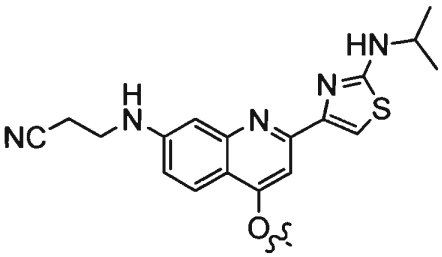


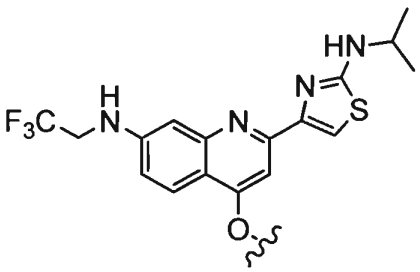




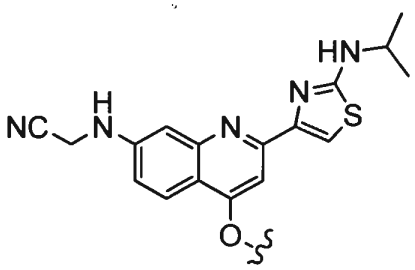


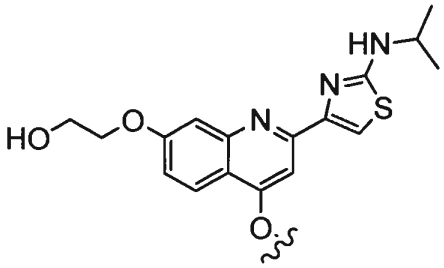


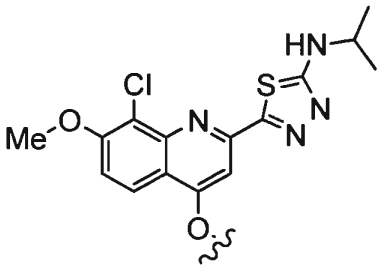


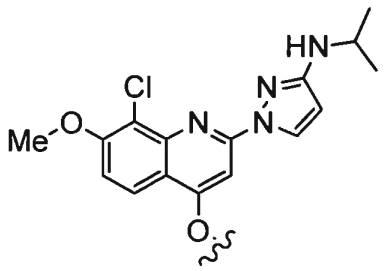


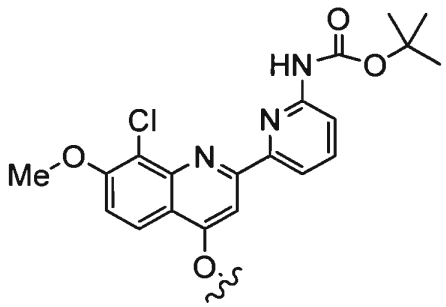
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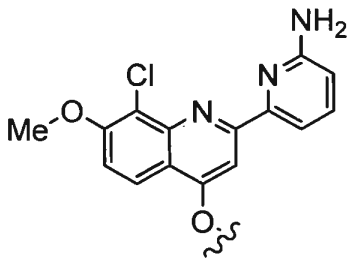


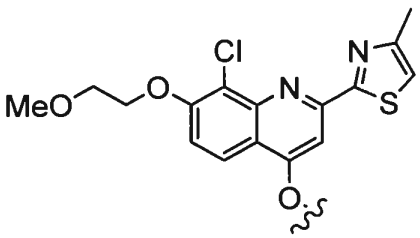




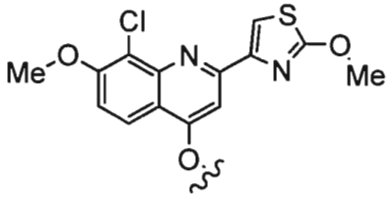


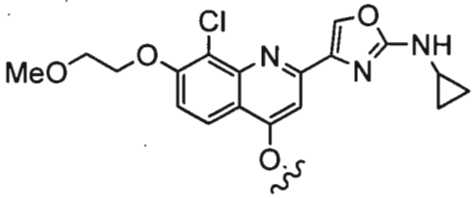


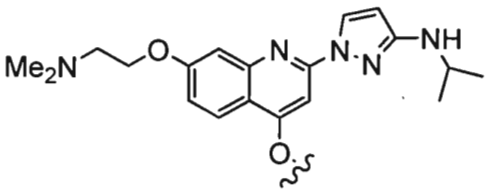


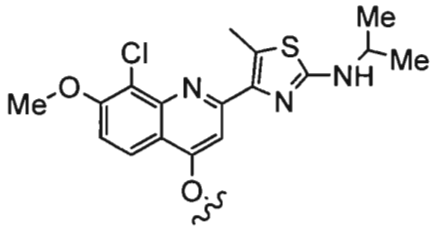


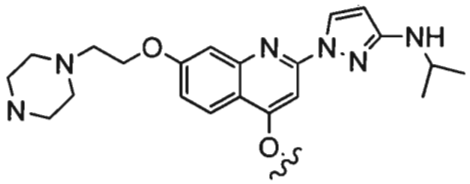
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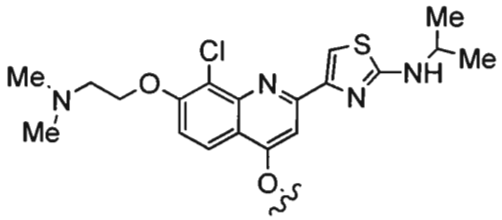


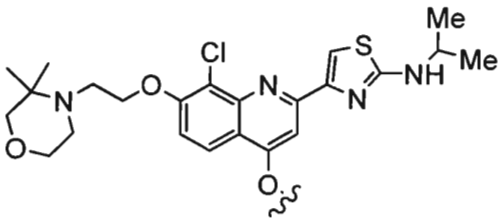


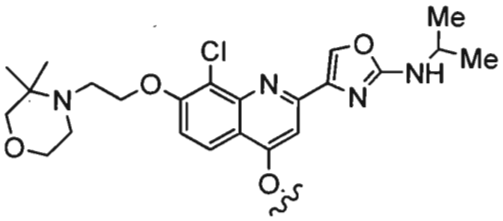


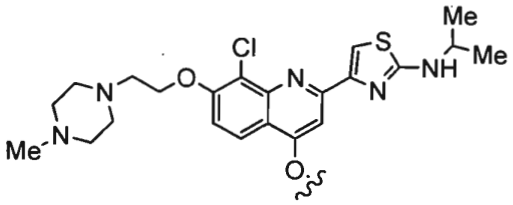


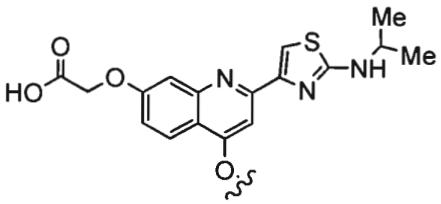


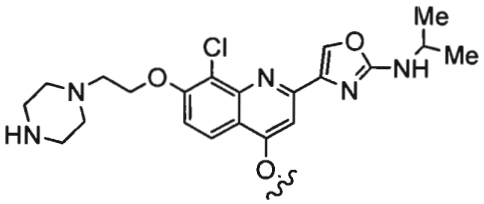


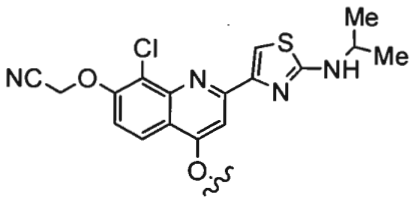


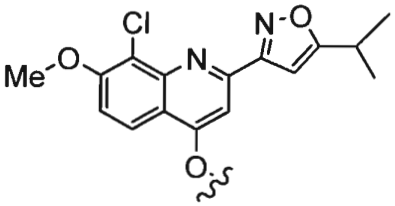


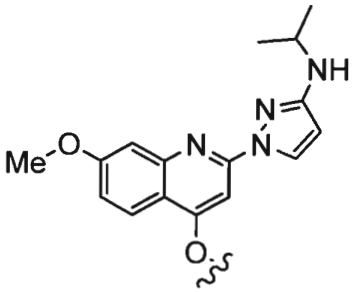


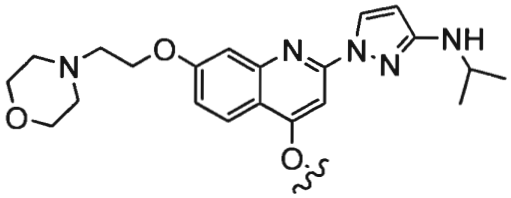


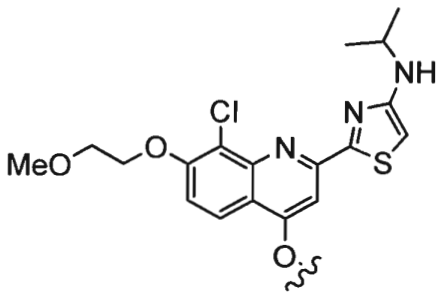


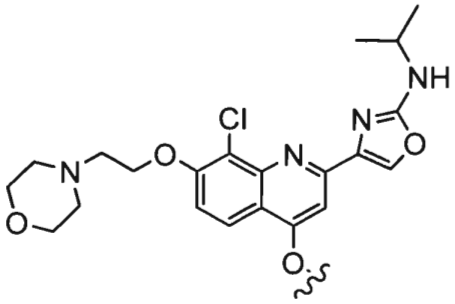


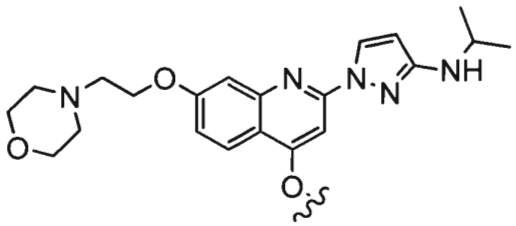


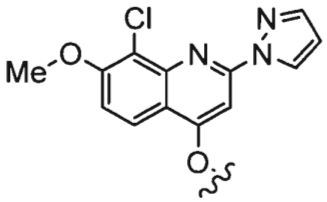


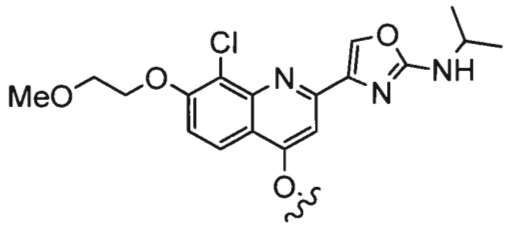


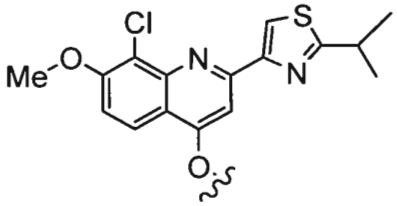


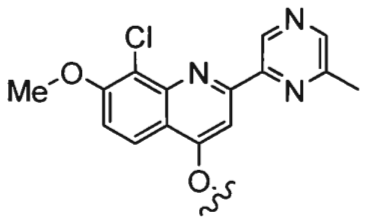


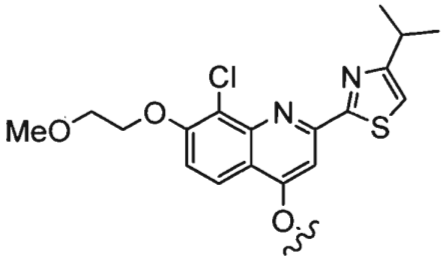


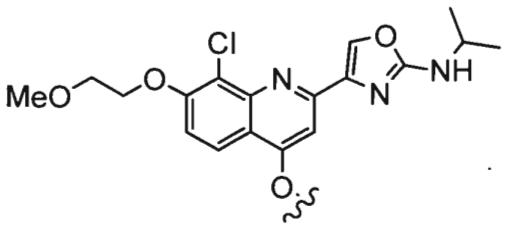


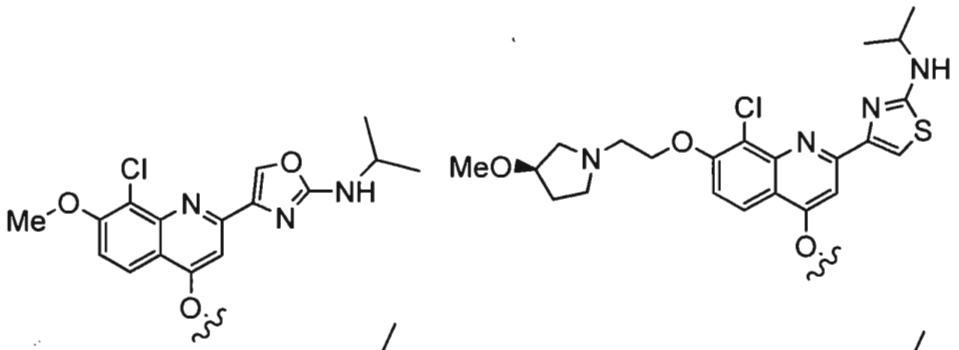


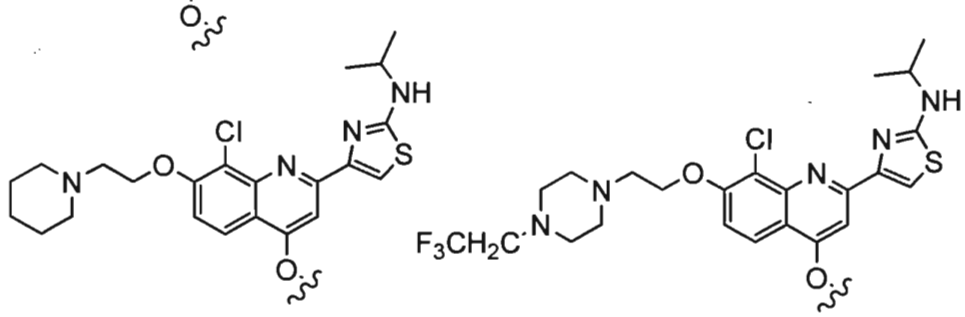


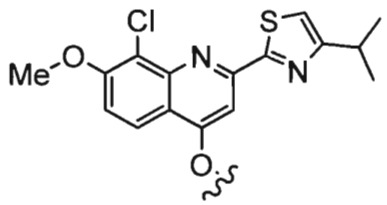




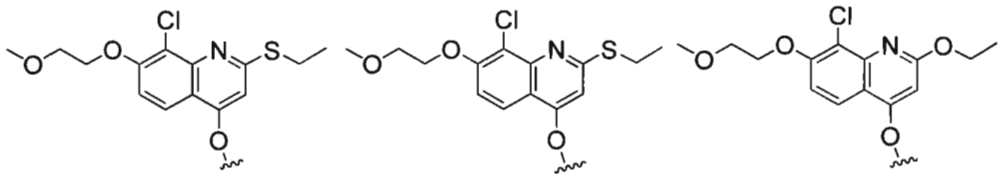


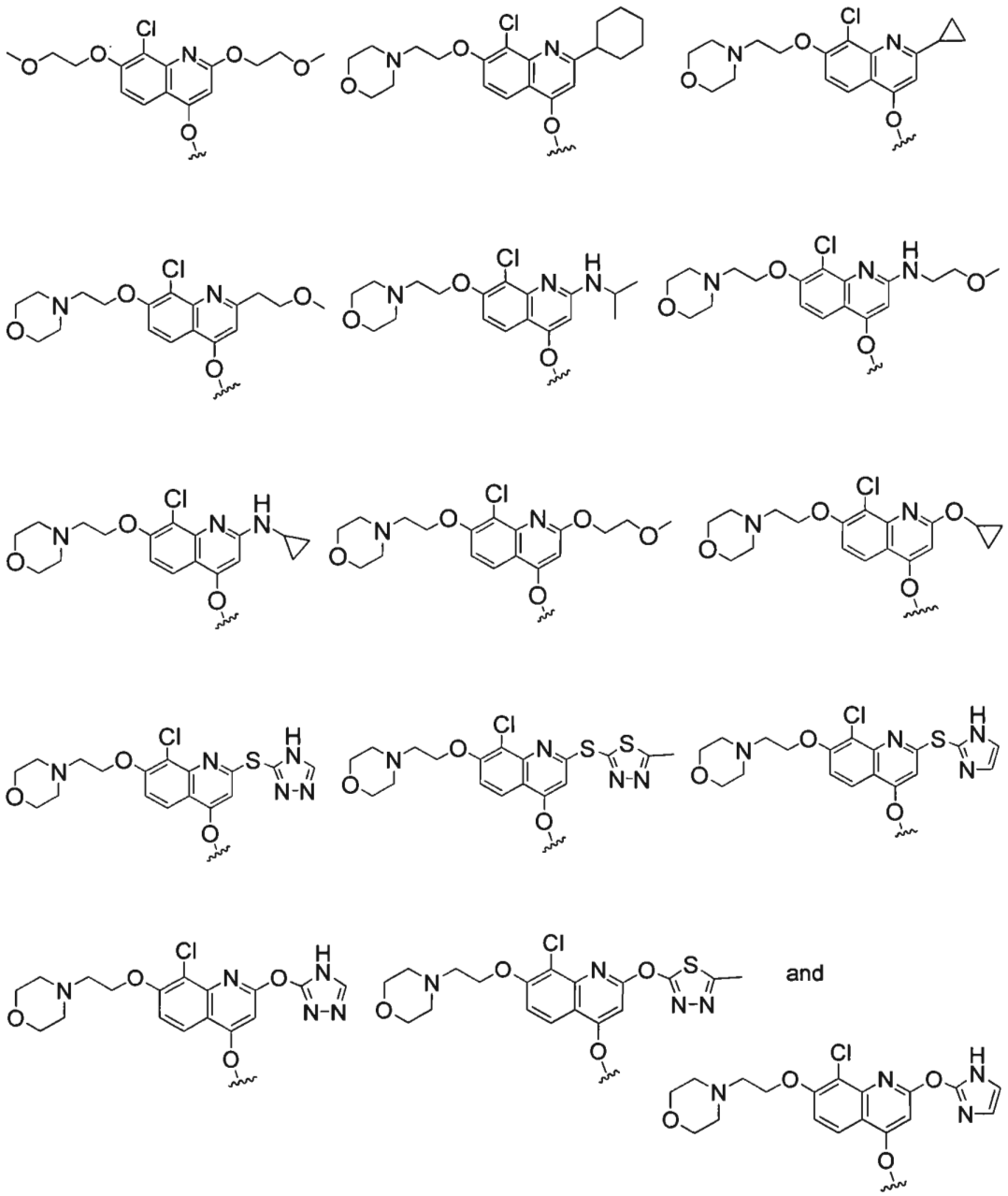




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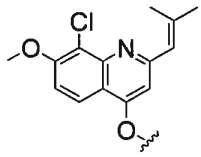
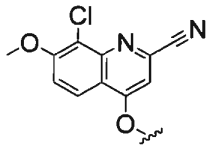
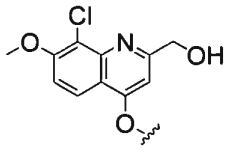
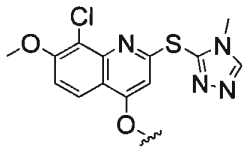
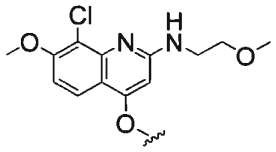
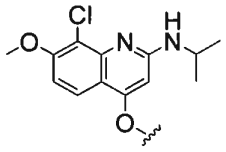
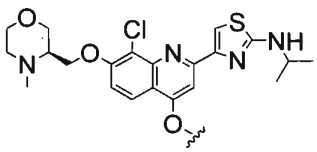
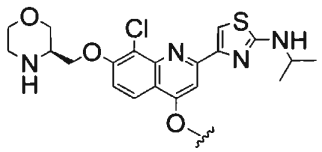
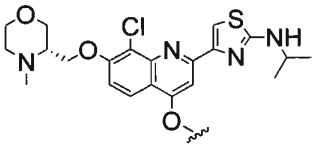
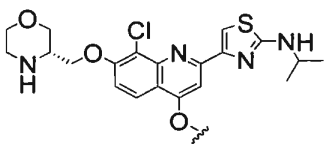
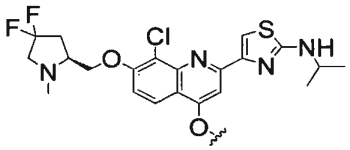
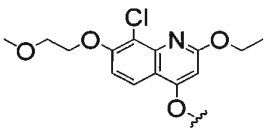
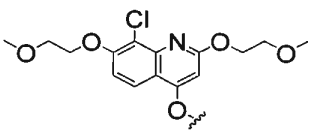
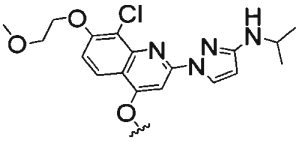
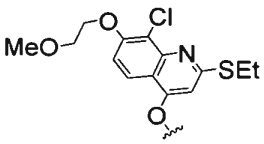
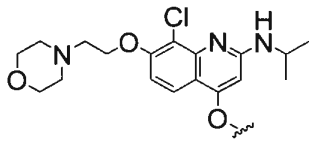
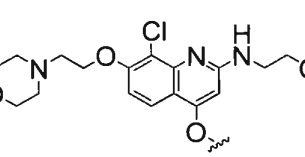
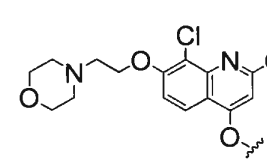
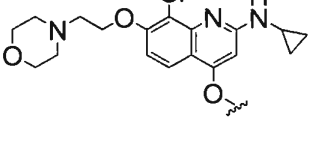
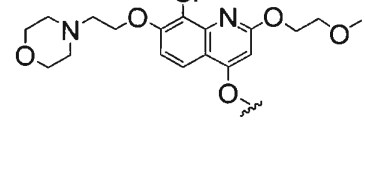
In a specific embodiment of the invention Z^1 is selected from the following structures:



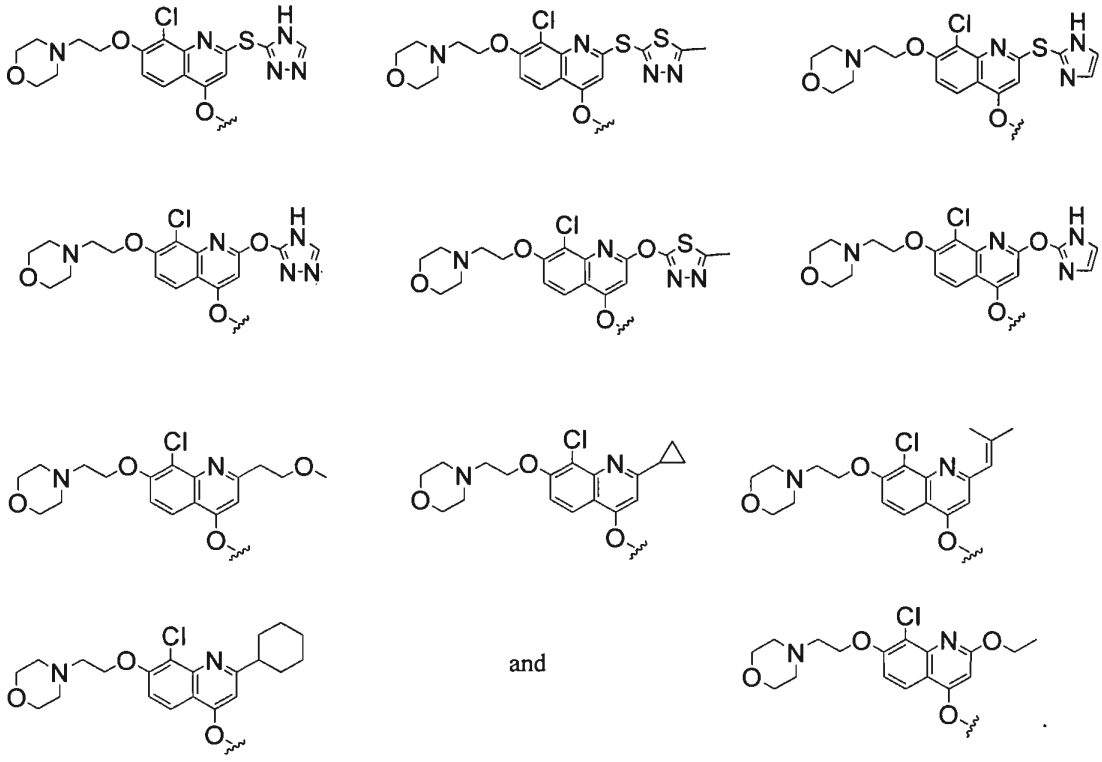


and

In a specific embodiment of the invention Z^1 is selected from the following structures:

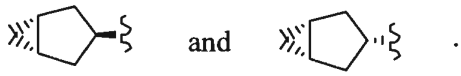





















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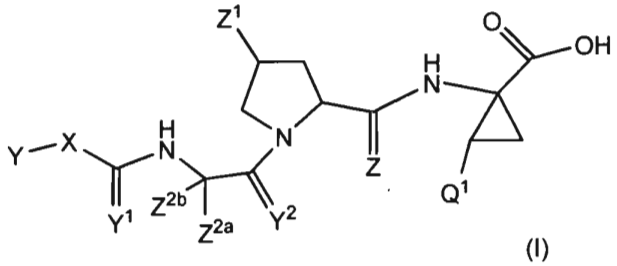
and

In a specific embodiment of the invention Y is selected from:



and

In a specific embodiment the invention provides a formula I:



(I)

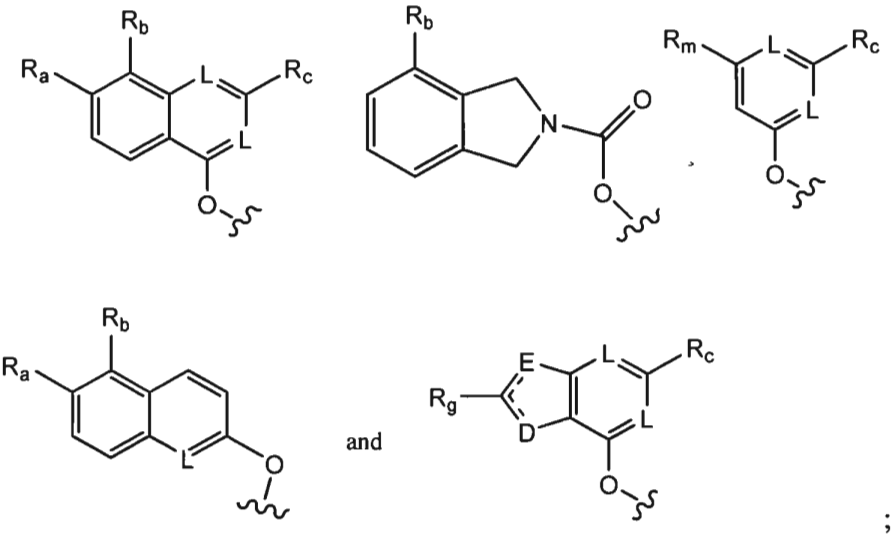
or a pharmaceutically acceptable salt, or prodrug thereof, wherein:

Y^1 is O, S, or NR^3;

Y^2 is O, S, or NR^3;

Z is O, S, or NR^3;

Z^1 is selected from the following structures:



and

;

each R_a is R^1, H, trifluoromethoxy, NR_sR_t, $C(=O)NR_sR_t$, $S(=O)_2NR_sR_t$ or (C1-10)alkyl, wherein one or more carbon atoms of said (C1-10)alkyl is optionally replaced by O, S, S(=O), $S(=O)_2$ or NR_g and which (C1-10)alkyl is optionally substituted with one or more hydroxy, halo, cyano, NR_nR_p, $C(=O)NR_nR_p$, (C1-10)alkoxy, carboxy, (C1-10)alkoxycarbonyl, aryl, heteroaryl, or heterocyclyl; or R_a and R_b taken together with the

atoms to which they are attached form a 5 or 6 membered heterocyclic ring containing one or more O, S, or NR_g;

each R_b is R^1, H, F, Cl, Br, I, CF_3, (C1-10)alkyl, or XR^3;

each R_c is R^1, H, cyano, F, Cl, Br, I, $-C(=O)NR_dR_e$, $C(=O)NR_sR_t$, NR_sR_t, $S(=O)_2NR_sR_t$, (C1-10)alkoxy, cycloalkyl, aryl, or heteroaryl, which aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, hydroxy, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p; SR_r, $S(O)R_r$, or $S(O)_2R_r$;

R_d and R_e are each independently H or (C1-10)alkyl;

each R_f is H, hydroxy, carboxy, cyano, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p, SR_r, $S(O)R_r$, or $S(O)_2R_r$;

each R_g is H, NR_sR_t, $C(=O)NR_sR_t$, $S(=O)_2NR_sR_t$, A^2, hydroxy, carboxy, cyano, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p, SR_r, $S(O)R_r$, or $S(O)_2R_r$;

each R_h is H, A^3, $C(=O)NR_sR_t$, or $S(=O)_2NR_sR_t$;

each R_m is H, cyano, F, Cl, Br, I, $-C(=O)NR_dR_e$, (C1-10)alkoxy, cycloalkyl, or phenyl that is optionally substituted with one or more F, Cl, Br, I, (C1-10)alkyl, or (C1-10)alkoxy;

each L is independently CH or N;

one of E or D is O, S, or NR_f and the other E or D is CR_h or N;

Z^{2a} is H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, haloalkyl, (C1-10)alkyl, $-S(=O)_2$-(C1-10)alkyl, or cycloalkyl, wherein any carbon atom of Z^{2a} may optionally be replaced with a heteroatom selected from O, S or NR_g and wherein any cycloalkyl is optionally substituted with one or more (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, F, Cl, Br, or I; or Z^{2a} optionally forms a heterocycle with Q^1;

Z^{2b} is H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl;

Q^1 is (C1-10)alkyl, (C2-10)alkenyl, or (C2-10)alkynyl which Q^1 is optionally substituted with R^1 or R_c; or Q^1 and Z^{2a} taken together with the atoms to which they are

attached form a heterocycle, which heterocycle may optionally be substituted with one or more oxo (=O), R^1, or A^3;

each X is independently a bond, O, S, or NR^3;

Y is a polycarbocycle or a polyheterocycle, which polycarbocycle or a polyheterocycle is optionally substituted with one or more R^1, halo, carboxy, hydroxy, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p; SR_r, $S(O)R_r$, or $S(O)_2R_r$;

each R^1 is independently $-P(Y^3)(OA^2)(OA^2)$, $-P(Y^3)(OA^2)(N(A^2)_2)$, $-P(Y^3)(A^2)(OA^2)$, $-P(Y^3)(A^2)(N(A^2)_2)$, or $P(Y^3)(N(A^2)_2)(N(A^2)_2)$;

each A^2 is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)haloalkyl, (C3-10)cycloalkyl, aryl, or heteroaryl;

each Y^3 is independently O, S, or NR^3;

each R_n and R_p is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, which (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, is optionally substituted with one or more R^1, halo, hydroxy, carboxy, cyano, or (C1-10)alkoxy; or R_n and R_p together with the nitrogen to which they are attached form a pyrrolidine, piperidine, piperazine, morpholino, or thiomorpholino ring, which ring is optionally substituted with one or more (C1-10)alkyl or (C1-10)alkoxy, and which (C1-10)alkyl or (C1-10)alkoxy is optionally substituted with one or more halo;

each R_r is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, or (C1-10)alkoxycarbonyl;

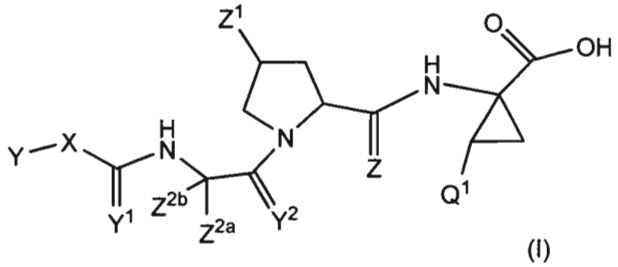
each R_s and R_t is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, $S(=O)_2A^2$, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, which (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, is optionally substituted with one or more R^1, halo hydroxy, carboxy, cyano, or (C1-10)alkoxy; or R_s and R_t together with the nitrogen to which they are attached form a pyrrolidine, piperidine, piperazine, morpholino, or thiomorpholino ring wherein one or more carbon atoms of said

pyrrolidine, piperidine, piperazine, morpholino or thiomorpholino ring is optionally replaced by S(=O), $S(=O)_2$, or C(=O);

each A^3 is independently selected from halo, hydroxy, carboxy, cyano, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p, SR_r, $S(O)R_r$, or $S(O)_2R_r$; and

R^3 is H or (C1-10)alkyl.

In one embodiment the invention provides a compound of the invention which is a compound of formula I:



(I)

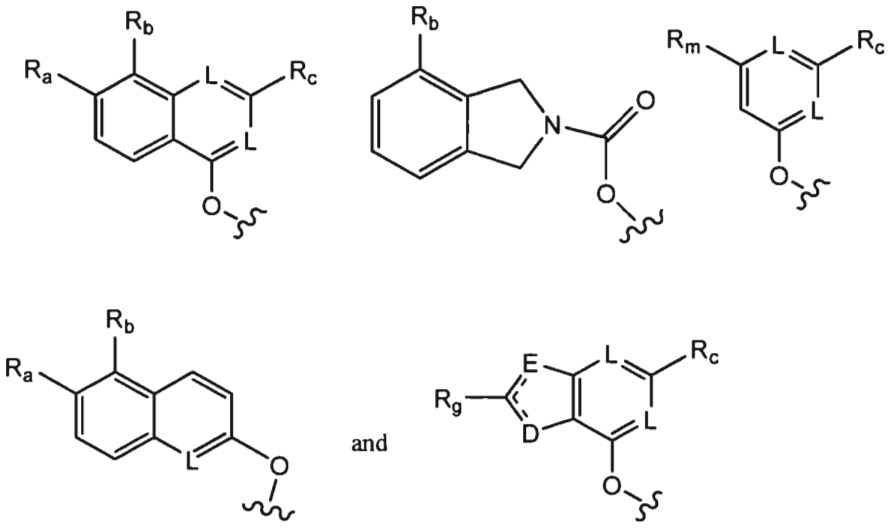
or a pharmaceutically acceptable salt, or prodrug thereof, wherein:

Y^1 is O, S, or NR^3;

Y^2 is O, S, or NR^3;

Z is O, S, or NR^3;

Z^1 is selected from the following structures:



;

each R_a is R^1, H, trifluoromethoxy, NR_sR_t, $C(=O)NR_sR_t$, $S(=O)_2NR_sR_t$ or (C1-10)alkyl, wherein one or more carbon atoms of said (C1-10)alkyl is optionally replaced by O, S, S(=O), $S(=O)_2$ or NR_g and which (C1-10)alkyl is optionally substituted with one or more hydroxy, halo, cyano, NR_nR_p, $C(=O)NR_nR_p$, (C1-10)alkoxy, carboxy, (C1-10)alkoxycarbonyl, aryl, heteroaryl, or heterocyclyl; or R_a and R_b taken together with the atoms to which they are attached form a 5 or 6 membered heterocyclic ring containing one or more O, S, or NR_g;

each R_b is R^1, H, F, Cl, Br, I, CF_3, (C1-10)alkyl, or XR^3;

each R_c is R^1, H, cyano, F, Cl, Br, I, $-C(=O)NR_dR_e$, $C(=O)NR_sR_t$, NR_sR_t, $S(=O)_2NR_sR_t$, (C1-10)alkyl, (C1-10)alkoxy, cycloalkyl, OR_r, SR_r, $S(O)R_r$, $S(O)_2R_r$, aryl, or heteroaryl, which (C1-10)alkyl, (C1-10)alkoxy, cycloalkyl, aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, hydroxy, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p; SR_r, $S(O)R_r$, or $S(O)_2R_r$;

R_d and R_e are each independently H or (C1-10)alkyl;

each R_f is H, hydroxy, carboxy, cyano, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p, SR_r, $S(O)R_r$, or $S(O)_2R_r$;

each R_g is H, NR_sR_t, $C(=O)NR_sR_t$, $S(=O)_2NR_sR_t$, A^2, hydroxy, carboxy, cyano, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p, SR_r, $S(O)R_r$, or $S(O)_2R_r$;

each R_h is H, A^3, $C(=O)NR_sR_t$, or $S(=O)_2NR_sR_t$;

each R_m is H, cyano, F, Cl, Br, I, $-C(=O)NR_dR_e$, (C1-10)alkoxy, cycloalkyl, or phenyl that is optionally substituted with one or more F, Cl, Br, I, (C1-10)alkyl, or (C1-10)alkoxy;

each L is independently CH or N;

one of E or D is O, S, or NR_f and the other E or D is CR_h or N;

Z^{2a} is H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, haloalkyl, (C1-10)alkyl, $-S(=O)_2$-(C1-10)alkyl, or cycloalkyl, wherein any carbon atom of Z^{2a} may optionally be replaced with a heteroatom selected from O, S or NR_g and wherein any cycloalkyl is optionally substituted with one or more (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, F, Cl, Br, or I; or Z^{2a} optionally forms a heterocycle with Q^1;

Z^{2b} is H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl;

Q^1 is (C1-10)alkyl, (C2-10)alkenyl, or (C2-10)alkynyl which Q^1 is optionally substituted with R^1 or R_c; or Q^1 and Z^{2a} taken together with the atoms to which they are attached form a heterocycle, which heterocycle may optionally be substituted with one or more oxo (=O), R^1, or A^3;

each X is independently a bond, O, S, or NR^3;

Y is a polycarbocycle or a polyheterocycle, which polycarbocycle or a polyheterocycle is optionally substituted with one or more R^1, halo, carboxy, hydroxy, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p; SR_r, $S(O)R_r$, or $S(O)_2R_r$;

each R^1 is independently $-P(Y^3)(OA^2)(OA^2)$, $-P(Y^3)(OA^2)(N(A^2)_2)$, $-P(Y^3)(A^2)(OA^2)$, $-P(Y^3)(A^2)(N(A^2)_2)$, or $P(Y^3)(N(A^2)_2)(N(A^2)_2)$;

each A^2 is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)haloalkyl, (C3-10)cycloalkyl, aryl, or heteroaryl;

each Y^3 is independently O, S, or NR^3;

each R_n and R_p is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, which (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, is optionally substituted with one or more R^1, halo, hydroxy, carboxy, cyano, or (C1-10)alkoxy; or R_n and R_p together with the nitrogen to which they are attached form a pyrrolidine, piperidine, piperazine, morpholino, or thiomorpholino ring; which ring is optionally substituted with one or more (C1-10)alkyl or (C1-10)alkoxy, and which (C1-10)alkyl or (C1-10)alkoxy is optionally substituted with one or more halo;

each R_r is independently H, (C1-10)alkyl, cycloalkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, aryl, heteroaryl, or (C1-10)alkoxycarbonyl;

each R_s and R_t is independently H, (C1-10)alkyl, cycloalkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, $S(=O)_2A^2$, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, which (C1-10)alkyl, cycloalkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, is optionally substituted with one or more R^1, halo hydroxy, carboxy, cyano, or (C1-10)alkoxy; or R_s and R_t together with the nitrogen to which they are attached form a pyrrolidine, piperidine, piperazine, morpholino, or thiomorpholino ring wherein one or more carbon atoms of said pyrrolidine, piperidine, piperazine, morpholino or thiomorpholino ring is optionally replaced by S(=O), $S(=O)_2$, or C(=O);

each A^3 is independently selected from halo, hydroxy, carboxy, cyano, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p, SR_r, $S(O)R_r$, or $S(O)_2R_r$; and

R^3 is H or (C1-10)alkyl.

In a specific embodiment of the invention the compound is a prodrug or a pharmaceutically acceptable salt thereof.

Schemes and Examples

General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processes is optionally separated,

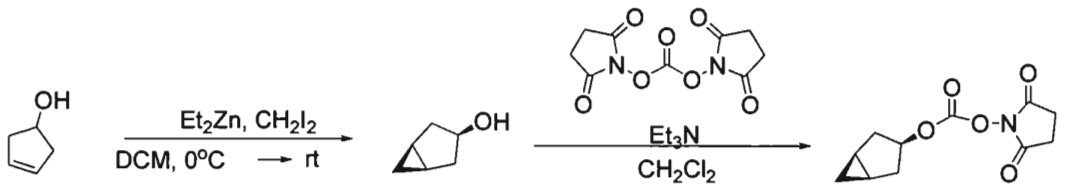
isolated, and/or purified prior to its use in subsequent processes.

A number of exemplary methods for the preparation of compounds of the invention are provided herein, for example, in the Examples herein below. These methods are intended to illustrate the nature of such preparations and are not intended to limit the scope of applicable methods. Certain compounds of the invention can be used as intermediates for the preparation of other compounds of the invention.

EXAMPLES

Section A: Preparation of Intermediates:

1. Preparation of Intermediate I:



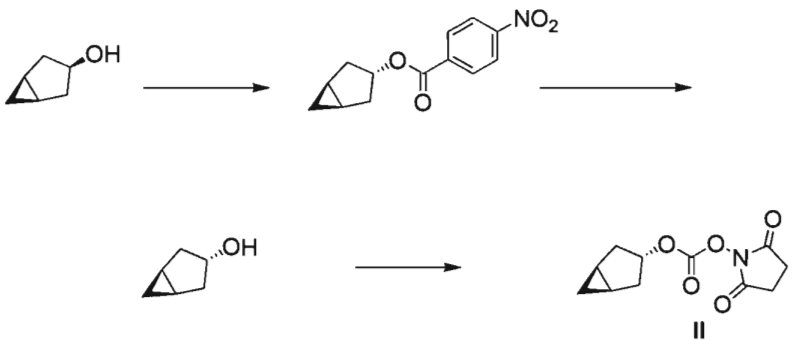
I

Step 1: To a dry, argon purged three-neck round bottom flask (1000 mL) were added anhydrous dichloromethane (100 mL) and Et_2Zn (28 mL, 273 mmol) at 0 °C. (CAUTION: Source of argon can not be from needle. Use appropriate glass adapter only. A second bubbler can also be attached to the flask to prevent excessive pressure build up.) Cyclopenten-3-ol (10.0 mL, 119 mmol) was then added dropwise (large quantity of ethane gas was produced) to the flask and the reaction mixture was allowed to stir until the evolution of gas had ceased. Diiodomethane (22 mL, 242 mmol) was then added dropwise over a period of 30 min. The reaction was allowed to warm to room temperature and continued to stir overnight under a positive flow of argon, at which point TLC analysis had indicated complete disappearance of the starting alcohol. The reaction was then diluted with CH_2Cl_2 and quenched with 2M HCl (white precipitate should be completely dissolved). The biphasic mixture was poured into a separatory funnel and the organic layer was collected. The solvent was removed under reduced pressure until 100 mL of material remained.

Step 2: Anhydrous dichloromethane (525 mL) was added to the flask followed by the dropwise addition of triethylamine (34 mL, 245 mmol). The reaction continued to stir at room temperature under a positive flow of nitrogen at which point, disuccinimidylcarbonate (40.7 g, 159 mmol) was added to the flask portion wise. The

reaction was allowed to stir until TLC analysis indicated complete disappearance of the starting material (2-3 days). Upon completion, the reaction mixture was quenched with 1M HCl (200 mL x 2) and washed with H_20 (200 mL x 2). The desired material was extracted using CH_2Cl_2 and the combined organic layers were dried using anhydrous $MgSO_4$ and passed through a silica plug. The solvent was removed under reduced pressure and the crude material was purified using flash chromatography (R_f = 0.33, 1:1 Hex/EtOAc) to provide intermediate **I** (22 g, 75%): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5. 24 (t, 1H), 3.82 (s, 4H), 2.24 (m, 2H), 2.03 (d, 2H), 1.38 (m, 2H), 0.48 (m, 1H), 0.40 (m, 1H).

2. Preparation of Intermediate II:



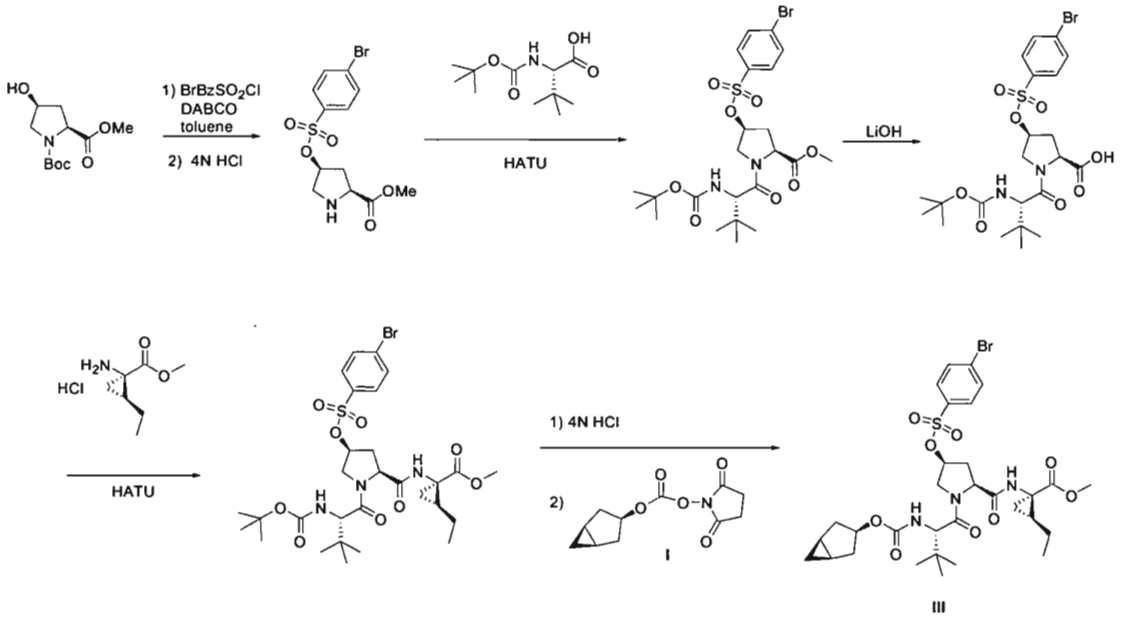
II

To a solution of *cis*-3-hydroxybicyclo[3.1.0]hexane (980 mg, 10 mmol), 4-nitrobenzoic acid (2.0 g, 12 mmol) and triphenylphosphine (3.0 g, 12 mmol) in THF (20 mL) was added diisopropyl azodicarboxylate (2.58 mL, 12 mmol) at 0 °C. The mixture was stirred for 16 h at room temperature, and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate / hexanes), affording 2.2 g (0.96 g, 77%) of the ester. LC/MS = 775.4 (M^++1).

This ester was dissolved in THF (40 mL) and aqueous lithium hydroxide solution (2 g/ 20 mL) was added. The mixture was stirred for 16 h at room temperature, and then diethyl ether (30 mL) was added. The organic layer was washed with brine, dried over sodium sulfate, and concentrated to a volume of ~10 mL. Dichloromethane (40 mL) was added

and dried over sodium sulfate again. The resulting solution of the product alcohol was concentrated to a volume of ~20 mL, which was used for the next reaction directly. Following procedures similar to those for preparation of **I**, intermediate **II** was obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.80 (t, 1H), 3.82 (s, 4H), 2.38 (m, 2H), 2.01 (d, 2H), 1.40 (m, 2H), 0.45 (m, 1H), 0.02 (m, 1H).

3. Preparation of Tripeptide Intermediates:



Step 1: N-*t*-Boc-cis-4-Hydroxy-L-Proline methyl ester (100.0 g, 407.7 mmol) and DABCO (1.5eq, 68.6g, 611.6 mmol) were dissolved in anhydrous toluene (200 mL) in a 2 L three necked round bottom flask with a mechanical stirrer and an addition funnel. After cooling the solution to 0 °C under N_2, A solution of 4-Bromo-benzenesulfonyl chloride (1.3eq, 135.6g, 530.0 mmol) in 300 mL of toluene was added through addition funnel over 60 minutes. The reaction mixture was stirred and warmed to room temperature overnight (16 hours). The mixture was slowly poured into 2L 1M $Na_2CO_{3\,(aq.)}$, and the product was extracted with EtOAc (2L). After the organic phase was washed by 0.5 N HCl (2L), H_2O

(1L), and brine (1L), it was dried ($MgSO_4$), concentrated to give 195.45 g of a yellow oily brosylate product.

To a solution of the above brosylate (407.7 mmol) in dichloromethane (300 mL) was slowly added 4.0 M HCl in dioxane (500 mL, 5eq) and the resulting solution was allowed to stir at room temperature for 2 hours. After ether (500mL) was added to the reaction mixture, the mixture was stirred for 15 min and the white precipitate was collected by filtration. The solid was washed with ether and hexane and then dried under vacuum overnight to obtain 153.0 g of the HCl amine salt, 381.8 mmol, in 94% yield for two steps.

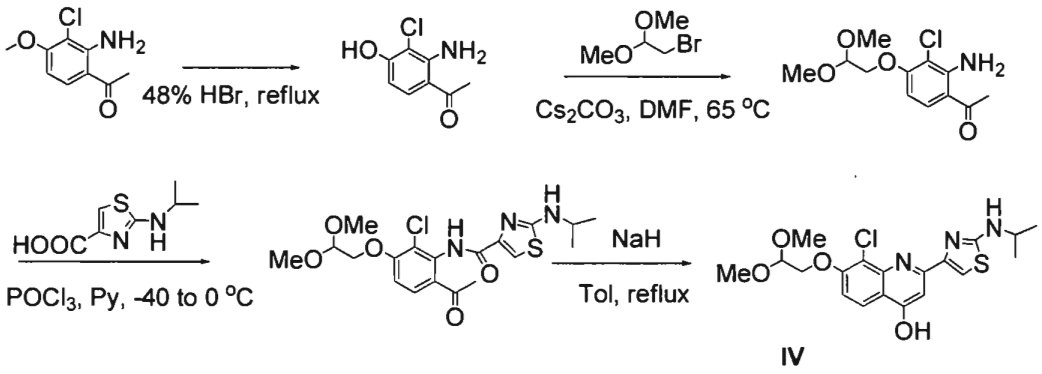
Step 2: To a solution of Boc-*tert*-butyl-glycine (97.0g, 420.0 mmol) in DMF (200mL) and DCM (200mL) were added HATU (217.76g, 572.7 mmol) and Hunig's base (126 mL, 1145.4 mmol) at room temperature. After the mixture was stirred for 20 min at room temperature, a solution of the previous HCl salt (153.0 g, 381.8 mmol) and Hunig's base (126 mL, 1145.4 mmol) in DMF (200mL) and dichloromethane (200mL) was added to the above acid mixture in one portion. The reaction mixture was stirred at room temperature for 3h, with monitoring by LCMS. The reaction mixture was concentrated to remove dichloromethane under reduced pressure and the white solid that formed was filtered off. The remaining DMF solution was diluted with ethyl acetate (1L), washed successively with 3% LiCl (aq) (3x650mL), sat'd NH_4Cl (2x500mL), 0.5N HCl (aq) (2x600mL), brine (500mL), sat'd $NaHCO_3$ (3x500mL), and brine (500mL). The resulting organic fraction was dried ($MgSO_4$) and concentrated to afford crude tripeptide (111g).

Step 3: To a solution of the methyl ester (120 g, 207.8 mmol) in THF (300 mL), MeOH (75 mL) was added a solution of LiOH (26.18 g, 623.4 mmol) in H_2O (150 mL). The solution was allowed to stir at room temperature for 4 hours. The mixture was cooled in an ice-bath while acidifying with 3N HCl to pH about 5.5, stirred for 10min, and the resulting white solids were collected by filtration. The solids were washed with more water, ether and hexane. The solids were dried under vacuum at 40°C overnight to give 95.78g (82%) of the acid.

Step 4: To a solution of the carboxylic acid (81.4 g, 144.27 mmol) in DMF (200mL) and dichloromethane (200mL) was added HATU (82.3g, 216.4 mmol) and Hunig's base (47.5 mL, 432.8 mmol) at room temperature. After the mixture was stirred for 20 min at room temperature, a solution of amine (158.7 mmol) and Hunig's base (47.5 mL, 1145.4 mmol) in DMF (200mL) and dichloromethane (200mL) was added to the above acid mixture in one portion. The reaction mixture was stirred at room temperature for 3h and monitored by LCMS. After the mixture was concentrated under reduced pressure to remove dichloromethane, the white solids that formed were filtered off. The remaining DMF solution was diluted with ethyl acetate (600mL) and successively washed with 3% LiCl (aq) (2x550mL), sat'd NH_4Cl (500mL), 1N HCl (aq) (500mL), sat'd $NaHCO_3$ (500mL), and brine (300mL). The resulting organic fraction was dried (Na_2SO_4) and concentrated to afford crude tripeptide (111g).

Step 5: The crude tripeptide was dissolved in 4N HCl in dioxane (300 mL) at room temperature and stirred for 2h. It was then concentrated under vacuum, and co-evaporated with dichloromethane (2 x 200mL) to dryness. The residue was dissolved in EtOAc (600mL) and sat'd aq. $NaHCO_3$ (1L). It was stirred vigorously. After 10 min, carbonic acid bicyclo[3.1.0]hex-3-yl ester 2,5-dioxo-pyrrolidin-1-yl ester (intermediate **I**, 41.4 g, 173.1 mmol) was added in one portion. After the resulting mixture was stirred for another 30 min, the organic layer was collected and washed with brine (500mL), dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography on silica gel with ethyl acetate/hexane to afford 94.44 g (92%) of the tripeptide intermediate **III**.

4. Preparation of Quinoline Intermediate IV:



IV

Step 1: 1-(2-Amino-3-chloro-4-hydroxy-phenyl)-ethanone (70.7 g, 354 mmol) was stirred in 48% aq. HBr (500 mL) at 110 °C for 72 h. After the mixture was cooled to 0 °C with stirring, the solids were filtered and washed with water. The resulting solids were triturated with a saturated $NaHCO_3$ solution (~350 mL), filtered, washed with water, and dried under vacuum to give ~ 40 g (61%) of crude product as a dark brown solids. LC/MS = 186 (M^++1).

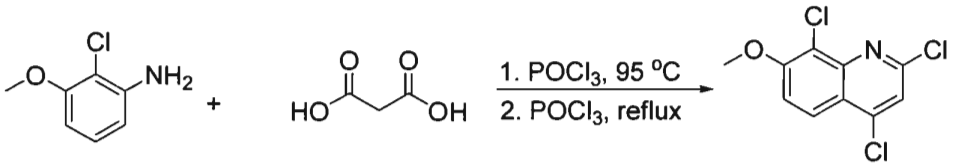
Step 2: 1-(2-Amino-3-chloro-4-hydroxy-phenyl)-ethanone (40 g, 215 mmol) was dissolved in DMF (360 ml). Cesium carbonate (140 g, 430 mmol) was added, followed by bromoacetaldehyde dimethyl acetal (54.5 g, 323 mmol). The mixture was then vigorously stirred at 65 °C for 24 h. Upon cooling to room temperature, EtOAc (1 L) and H_2O (1 L) were added to the mixture. The organic layer was extracted with EtOAc (1 x 400 ml). The combined organic layer was washed with aqueous 3% LiCl solution (2 x 1L), brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give the desired product as a white solid (39 g, 67%).

Step 3: To a mixture of 1-[2-Amino-3-chloro-4-(2,2-dimethoxy-ethoxy)-phenyl]-ethanone (13 g, 47.5 mmol) and isopropylaminothiazole-4-carboxylic acid hydrobromide (12.64 g, 47.5 mmol) in pyridine (150 ml) was slowly added phosphorus oxychloride (9.47 g, 61.8 mmol) at -40 °C. The mixture was then stirred at 0 °C for 4 h. Upon completion of the reaction, H_2O (30 ml) was added dropwise to the mixture. The mixture was then stirred at 0 °C for another 15 min. The mixture was concentrated *in vacuo*. The residue was diluted with EtOAc, washed with a sat. $NaHCO_3$ aqueous solution. The organic layer was dried

(Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, hexanes was added slowly to the solution, and a yellow solid started to crash out. More hexanes were added until not much product was left in the mother liquid (18 g, 85%).

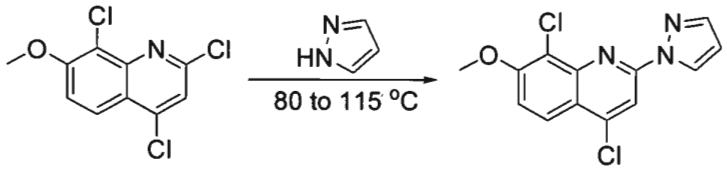
Step 4: 2-Isopropylamino-thiazole-4-carboxylic acid [6-acetyl-2-chloro-3-(2,2-dimethoxy-ethoxy)-phenyl]-amide (18 g, 40.7 mmol) was suspended in toluene (400 ml). NaH (2.4 g, 61 mmol) was added to the vigorously stirred mixture while monitoring H_2 evolution. The mixture became a clear solution during heating to reflux. The reaction was complete after refluxing for 3 h. The mixture was cooled to room temperature. A solution of AcOH (69.2 mmol) in H_2O (3 vol) was added to the mixture. After vigorous agitation for 1h at 0 °C, the solids were collected by filtration, rinsed forward with H_2O. The wet cake was dried under high vacuum to a constant weight to provide intermediate **IV** (15 g, 86%).

5. Preparation of Quinoline Intermediate V:

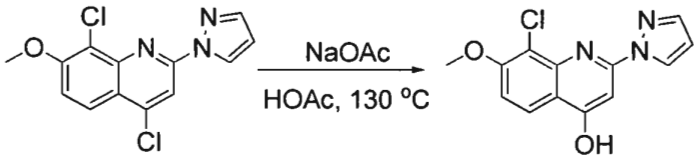


To a mixture of solids 2-chloro-3-methoxy-phenylamine (3.98 g, 25 mmol) and malonic acid (2.63 g, 25 mmol) in a 250-ml round bottom flask was added phosphorus oxychloride (2.5 ml, 27.5 mmol). The mixture was heated to 95 °C. foaming slowly occurred during vigorous stirring and stopped in 1.5 h. The mixture was then cooled to room temperature. Phosphorus oxychloride (30 ml) was added to the dark brown tar-like material, heated to 115 °C. Upon heating, all material dissolved. After 3 h of refluxing, the mixture was concentrated *in vacuo*. The residue was diluted with chloroform and poured into ice-water. 3 N aqueous NaOH was added to adjust pH to 10. The aqueous layer was extracted with chloroform. The combined organic layer was washed with brine, dried over sodium

sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate / hexanes), affording the product as a white solid (2.75 g, 46% over 2 steps). LC/MS = 261.9 (M^++1).



The mixture of pyrazole (3.1 g, 45.7 mmol) and trichloro compound (1.2 g, 4.57 mmol) was heated in a sealed microwave tube. After all solids melted at 80 °C, house vacuum was applied to the tube to remove residual moisture and the mixture was left stirring at 115 °C for 18 h. Ethyl acetate and H_2O were added to dissolve all the solids. The organic phase was washed with 0.5 N aqueous HCl, and brine. The organics were then dried over sodium sulfate, and concentrated *in vacuo*. The solids were triturated with ethyl acetate/hexanes and collected by filtration, and further dried under high vacuum to give pyrazole as a pale yellow solid (1.28 g, contaminated with a small amount of bis-addition adduct). LC/MS = 294.0 (M^++1).

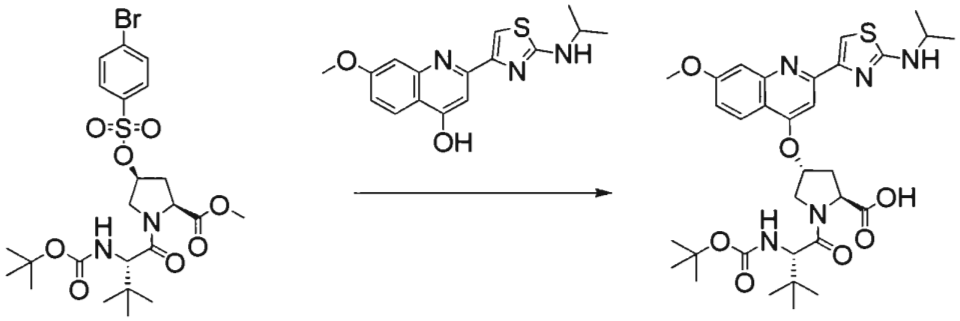


Product (650 mg, 2.2 mmol) from the previous step was suspended in acetic acid (7 ml) with sodium acetate (2.2 g, 27 mmol). The mixture was heated at 130 °C for 3 days in a sealed microwave tube. The mixture solidified during cooling to room temperature. Ethyl acetate and H_2O were added to dissolve the mixture. Sat. aqueous sodium bicarbonate was added to the organic layer and stirred for 5 min. The organic layer was then washed with brine, and concentrated *in vacuo*. The residue was then triturated with ethyl

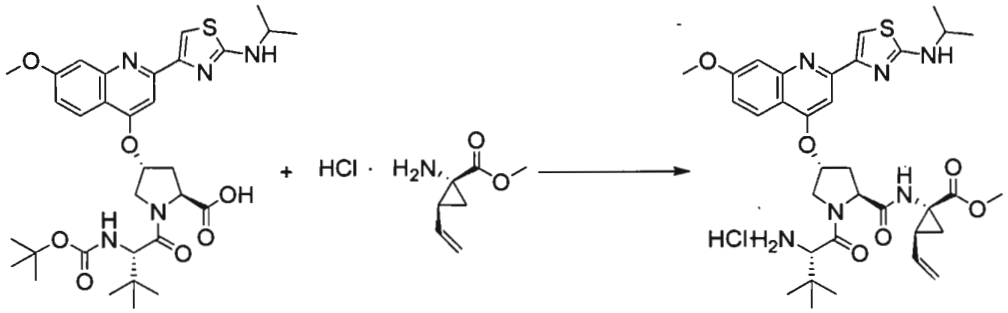
acetate/hexanes. The intermediate **V** (pure by HPLC) was collected by filtration (300 mg, 50% over 2 steps). LC/MS =276.0 (M^++1).

Section B:

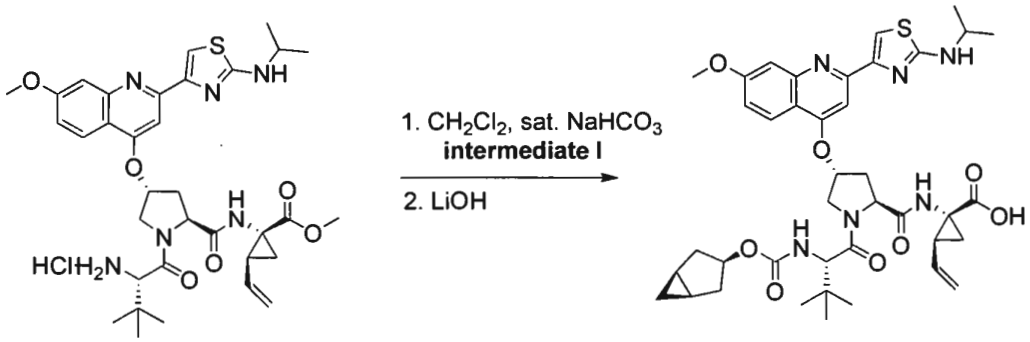
Example 1: Preparation of Compound 1.



A mixture of the methyl ester (0.62 g, 1.1 mmol), the hydroxyquinoline (0.34 g, 1.1 mmol) and cesium carbonate (0.39 g, 1.2 mmol) in NMP (6 mL) was stirred at 65 °C for 16 h. The mixture was partitioned between ethyl acetate (50 mL) and 3% aqueous LiCl (50 mL). The organic layer was washed with 3% aqueous LiCl (50 mL), and then with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate / hexanes), affording the coupled product (0.45 g, 64%) as a red-brown solid. A solution of the above product in THF (2 mL) and MeOH (2 mL) was treated with lithium hydroxide in water (0.29 mg /2 mL) for 3 h at room temperature, and neutralized with 4 N HCl. After removal of volatile solvents, the mixture was extracted with dichloromethane and the extract was concentrated to dryness, affording acid product. LC/MS = 642.3 (M^++1).



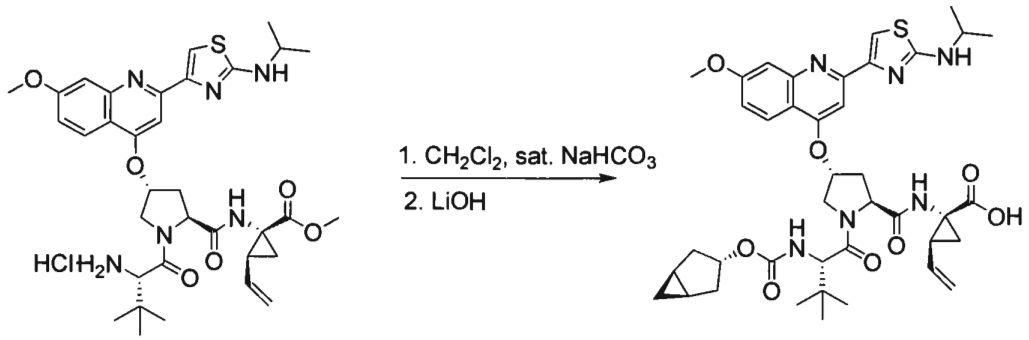
To a solution of the acid (440 mg, 0.69 mmol), (1R,2S)-1-amino-2-vinyl-cyclopropanecarboxylic acid methyl ester hydrochloride (147 mg, 0.82 mmol) and diisopropyl ethyl amine (0.48 mL, 2.8 mmol) was added HATU (390 mg, 1.0 mmol) at 0 °C, and stirred for 30 min. Ethyl acetate (50 mL) and 3% aqueous LiCl (50 mL) were added to the mixture while stirring. The organic layer was taken and washed with 3% aqueous LiCl (50 mL), and then with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate / hexanes), affording the coupled product (0.35 g, 66%) as a red brown solid. LC/MS = 765.5 (M^++1). A solution of the above product in dichloromethane (3 mL) was treated with 4N HCl in dioxane (8 mL) for 2 h at room temperature and concentrated to dryness, affording amine.



To a biphasic solution of the amine (38 mg, 0.054 mmol) in dichloromethane (20 mL) and 5% aqueous sodium bicarbonate (20 mL) was added a solution of intermediate **I** in dichloromethane in four portions, until the starting material was completely consumed (30

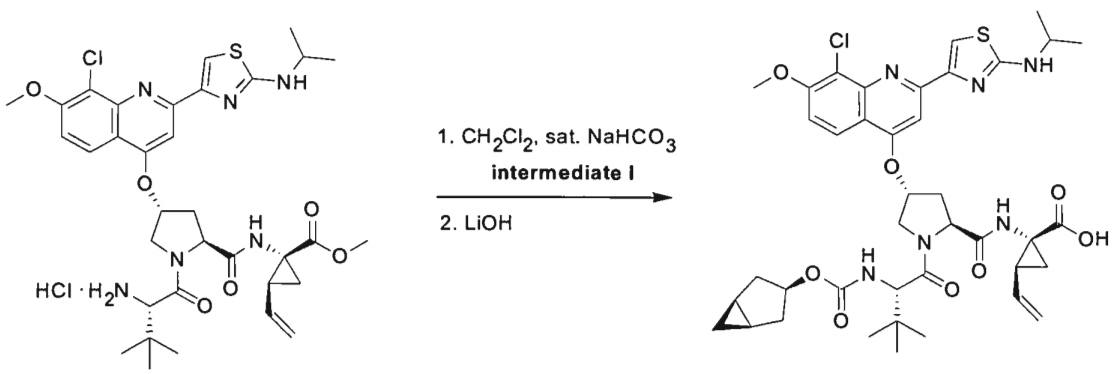
min. apart, a total of ~25 mg / 1 mL). The dichloromethane layer was taken and concentrated. The residue was purified by preparative HPLC using water / acetonitrile (0.05% TFA) as eluents. The methyl ester product was then dissolved in MeOH / water (20 mL / 2 mL). Excess lithium hydroxide (100 mg) was added and stirred at room temperature for 24 h. Dichloromethane (40 mL) and 1 N HCl (20 mL) were added sequentially. While stirring, saturated aqueous sodium bicarbonate was dropwise until the aqueous pH became ~7. The dichloromethane layer was concentrated, and the residue was purified by preparative HPLC using water / acetonitrile (0.05% TFA) as eluents, which afforded 14 mg (33%) of the Compound **1**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.75 (s,1H), 8.24 (d, J = 9.6 Hz, 1H), 8.18 (s, 1H), 7.75 (m, 2H), 7.34 (d, J = 9.6 Hz, 1H), 5.87 (dd, 1H), 5.77 (brs, 1H), 5.28 (d, J = 17.1 Hz, 1H), 5.11 (d, J = 10.5 Hz, 1H), 4.74 (t, 1H), 4.64 (d, 1H), 4.51 (t, 1H), 4.20 (m, 2H), 4.09 (m, 1H), 4.05 (s, 3H), 2.78 (m, 1H), 2.59 (m, 1H), 2.20 (q, 1H), 1.95 (dd, 1H), 1.85 (dd, 1H), 1.72 (m, 2H), 1.43 (m, 2H), 1.34 (d, 6H), 1.19 (m, 2H), 1.04 (s, 9H), 0.38 (m, 2H). LC/MS = 775.4 (M^++1); LC/MS R_t = 2.45 min.

Example 2: Preparation of Compound 2



Compound **2** was obtained by following procedures similar to those for preparation of Compound **1** except using the carbonate **II**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.75 (s,1H), 8.28 (d, J = 9.6 Hz, 1H), 8.18 (s, 1H), 7.77 (s, 1H), 7.73 (s, 1H), 7.34 (d, J = 9.6 Hz, 1H), 5.86 (dd, 1H), 5.77 (brs, 1H), 5.28 (d, J = 17.1 Hz, 1H), 5.11 (d, J = 10.5 Hz, 1H), 4.72 (t, 1H), 4.64 (d, 1H), 4.18 (m, 1H), 4.12 (m, 2H), 4.06 (s, 3H), 2.78 (m, 1H), 2.58 (m, 1H), 2.20 (q, 1H), 1.93 (dd, 1H), 1.4-1.4 (m, 4H), 1.34 (d, 6H), 1.30 (m, 2H), 1.22 (m, 2H), 1.04 (s, 9H), 0.38 (q, 1H), -0.14 (m, 1H). LC/MS = 775.4 (M^++1); LC/MS R_t = 2.33 min.

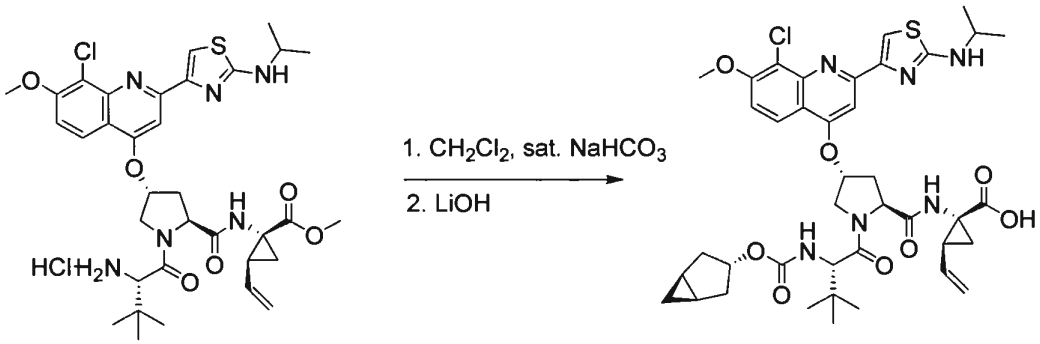
Example 3: Preparation of Compound 3



Compound **3** was obtained by following procedures similar to those for preparation of Compound **1**, except using tripeptide intermediate that was obtained by following procedures similar to those for preparation of Compound **1** except using 8-chloro-2-(2-

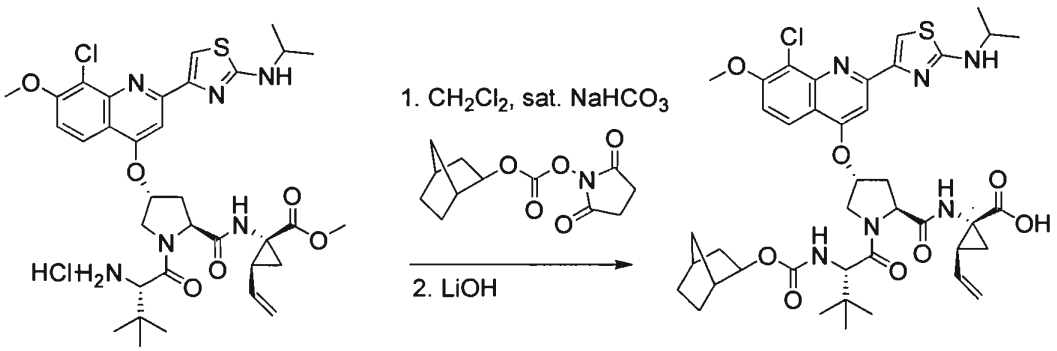
isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-ol. LC/MS = 809.5 (M^++1); LC/MS R_t = 4.42 min (6 min. run).

Example 4: Preparation of Compound 4



Compound **4** was obtained by following procedures similar to those for preparation of Compound **2** except using tripeptide that was obtained by following procedures similar to those for preparation of Compound **1** except using 8-chloro-2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-ol. LC/MS = 809.5 (M^++1); LC/MS R_t = 4.38 min (6 min. run).

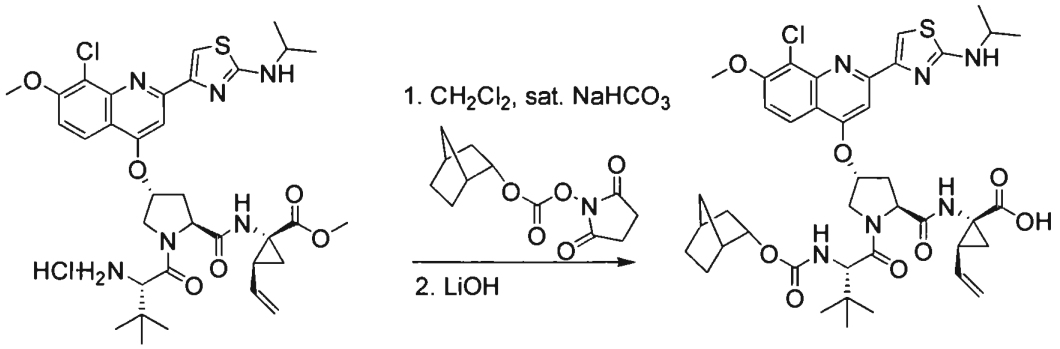
Example 5: Preparation of Compound 5



Compound **5** was obtained by following procedures similar to those for preparation of Compound **3** except using carbonate which was obtained by following procedures similar

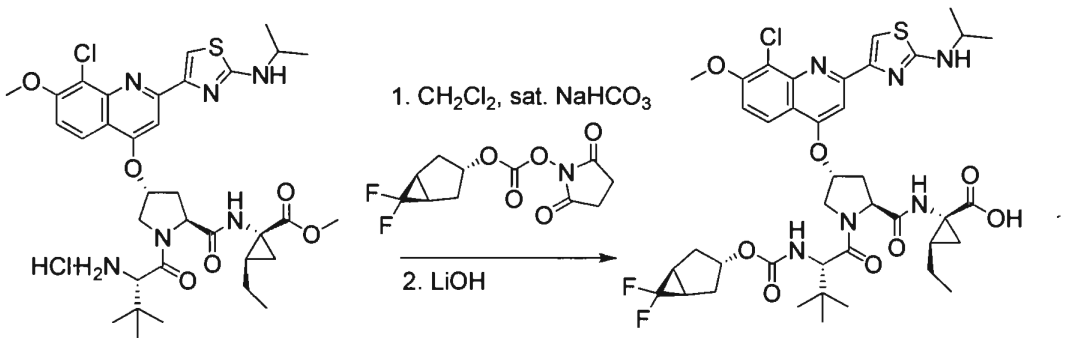
to those for preparation of Compound **1** except using *exo*-bicyclo[2.2.1]heptan-2-ol. LC/MS = 823.3 (M^++1); analytical HPLC R_t = 5.40 min (7 min. run).

Example 6: Preparation of Compound 6



Compound **6** was obtained by following procedures similar to those for preparation of Compound **3** except using carbonate which was obtained by following procedures similar to those for preparation of Compound **1** except using (+)-*endo*-bicyclo[2.2.1]heptan-2-ol. LC/MS = 823.3 (M^++1); analytical HPLC R_t = 5.41 min (7 min. run).

Example 7: Preparation of Compound 7

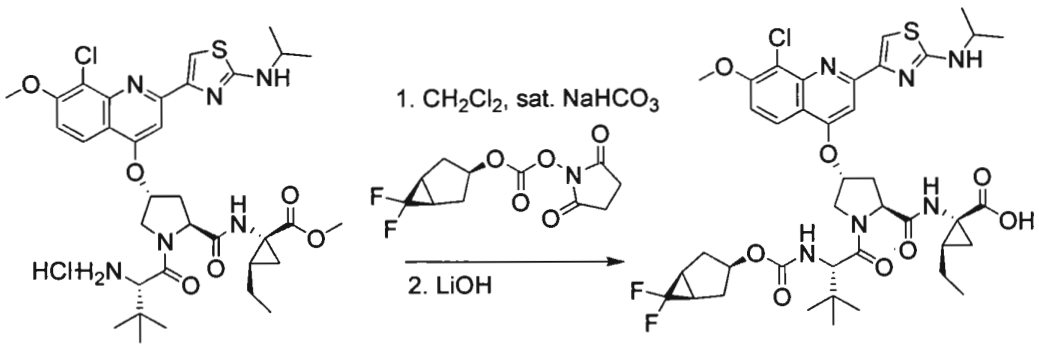


Compound **7** was obtained by following procedures similar to those for preparation of Compound **3** except starting with tripeptide that was obtained by following procedures

similar to those for preparation of Compound **1** except using (1R,2S)-1-amino-2-ethyl-cyclopropanecarboxylic acid methyl ester hydrochloride.

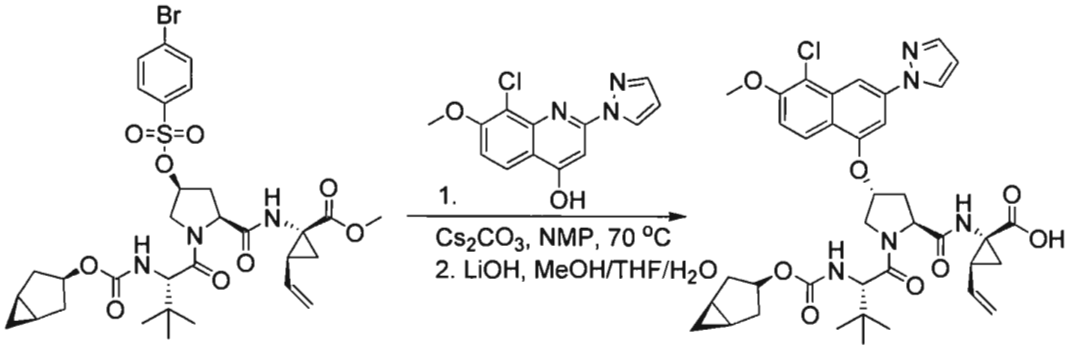
The carbonate was obtained by following procedures similar to those for preparation of Compound **1** except using *trans*-6,6-difluoro-bicyclo[3.1.0]hexan-3-ol (obtained according to WO266640558, followed by silica gel chromatographic separation of the *cis* and *trans* isomers). LC/MS = 847.5 (M^++1); LC/MS R_t = 2.76 min.

Example 8: Preparation of Compound 8



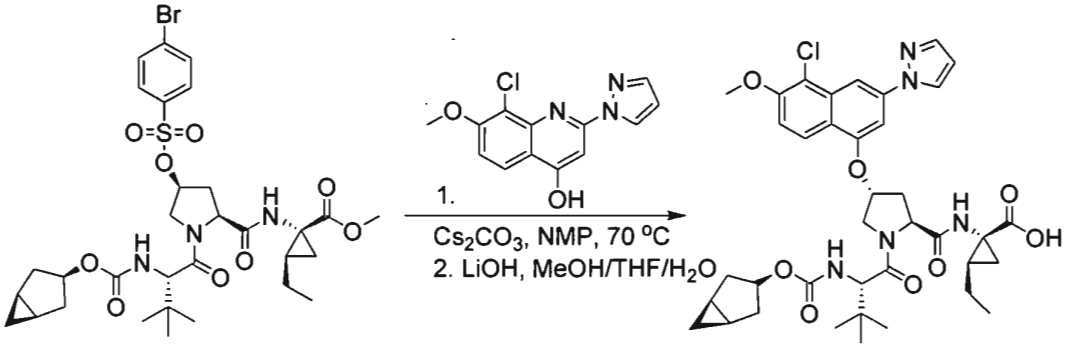
Compound **8** was obtained by following procedures similar to those for preparation of Compound **7** except using the carbonate which was obtained by following procedures similar to those for preparation of Compound **1** except using *cis*-6,6-difluoro-bicyclo[3.1.0]hexan-3-ol. LC/MS = 847.5 (M^++1); LC/MS R_t = 2.73 min.

Example 9: Preparation of Compound 9



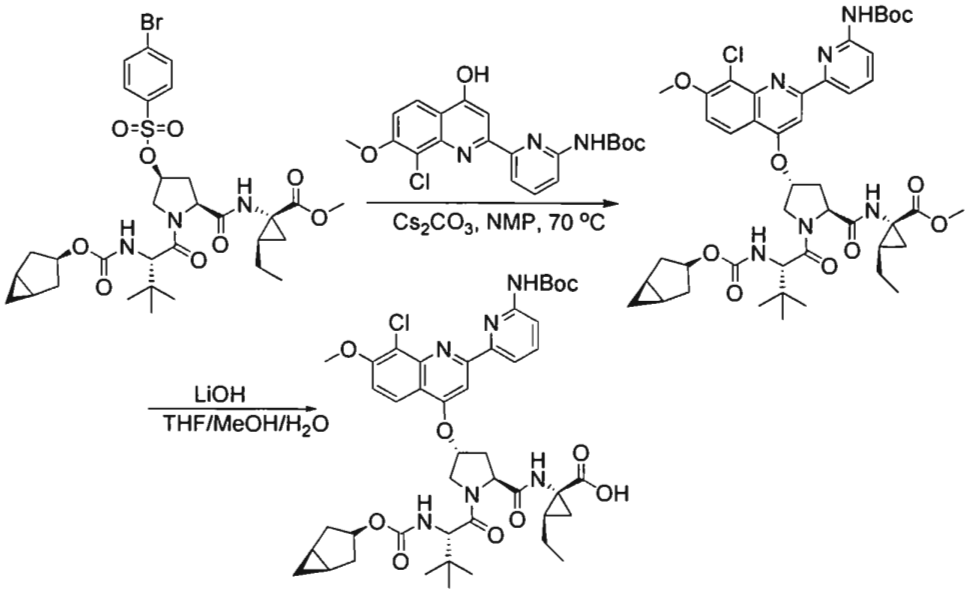
Tripeptide (391 mg, 0.55 mmol) and intermediate **V** (150 mg, 0.55 mmol) were dissolved in NMP (3 ml). Cesium carbonate (352 mg, 1.08 mmol) was added to the mixture and the mixture was heated at 70 °C for 4 h. Ethyl acetate and 3% aqueous LiCl were added to the residue. The organic layer was washed with 3% aqueous LiCl (x1), and brine. The organic phase was dried over sodium sulfate, and concentrated *in vacuo*. The residue was dissolved in THF (1.5 ml). Aqueous LiOH (5.5 mmol, 1.5 ml) was added to the mixture, followed by addition of MeOH (2 ml). The reaction was complete after vigorously stirring for 1.5 h at room temperature. 4 N aqueous HCl was added to adjust pH to 5. Ethyl acetate and brine were added to the residue, and the organic layer was concentrated *in vacuo*. The residue was purified by preparative HPLC using water / acetonitrile (0.05% TFA) as eluents, which afforded Compound **9** (120 mg, some product was lost during the purification due to poor solubility). ^{1}H NMR (300 MHz, DMSO-d6): δ 8.78 (s,1H), 8.56 (s,1H), 8.04 (d, J = 9.3 Hz, 1H), 7.91 (s, 1H), 7.51 (s, 1H), 7.40 (d, J = 9.3 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.67 (s, 1H), 5.64-5.77 (m, 1H), 5.58 (brs, 1H), 5.20 (d, J = 17.7 Hz, 1H), 5.05 (d, J = 11.4 Hz, 1H), 4.59 (t, 1H), 4.44 (t, J = 8.4 Hz, 1H), 4.33 (d, 1H), 3.94-4.07 (m, 2H), 4.02 (s, 3H), 2.48-2.60 (m, 1H), 2.20-2.35 (m, 1H), 1.85-2.11 (m, 2H), 1.72-1.85 (m, 1H), 1.50-1.51 (m, 2H), 1.05-1.35 (m, 4H), 0.93 (s, 9H), 0.39 (q, 1H), 0.25-0.38 (m, 1H). LC/MS = 735.4 (M^++1).

Example 10: Preparation of Compound 10



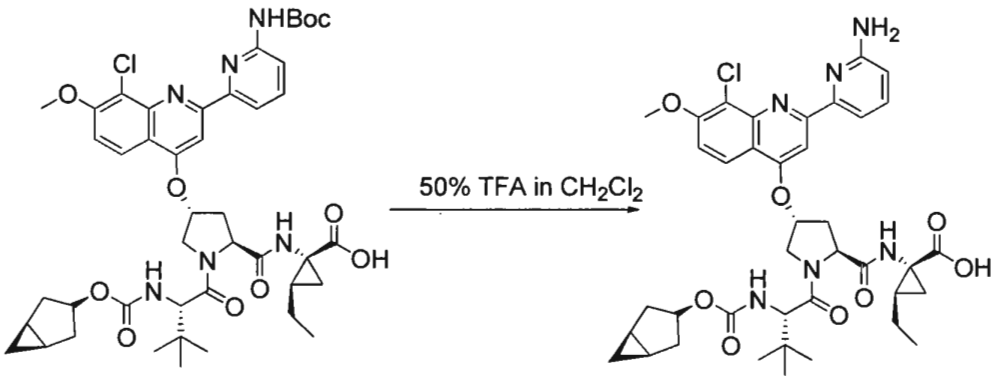
Compound **10** was obtained by following procedures similar to those for preparation of Compound **9**. ^{1}H NMR (300 MHz, DMSO-d6): δ 8.78 (s,1H), 8.31 (brs,1H), 8.04 (d, J = 9.6 Hz, 1H), 7.91 (s, 1H), 7.50 (s, 1H), 7.38 (d, J = 9.3 Hz, 1H), 6.98 (d, J = 9.9 Hz, 1H), 6.66 (s, 1H), 5.56 (s, 1H), 4.59 (t, 1H), 4.44 (t, J = 8.4 Hz, 1H), 4.33 (d, 1H), 3.94-4.07 (m, 2H), 4.02 (s, 3H), 2.48-2.60 (m, 1H), 2.20-2.35 (m, 1H), 1.85-2.11 (m, 2H), 1.40-1.60 (m, 2H), 1.06-1.30 (m, 4H), 0.93 (s, 9H), 0.90-1.05 (m, 4H), 0.39 (q, 1H), 0.25-0.38 (m, 1H). LC/MS = 737.4 (M^++1).

Example 11: Preparation of Compound 11



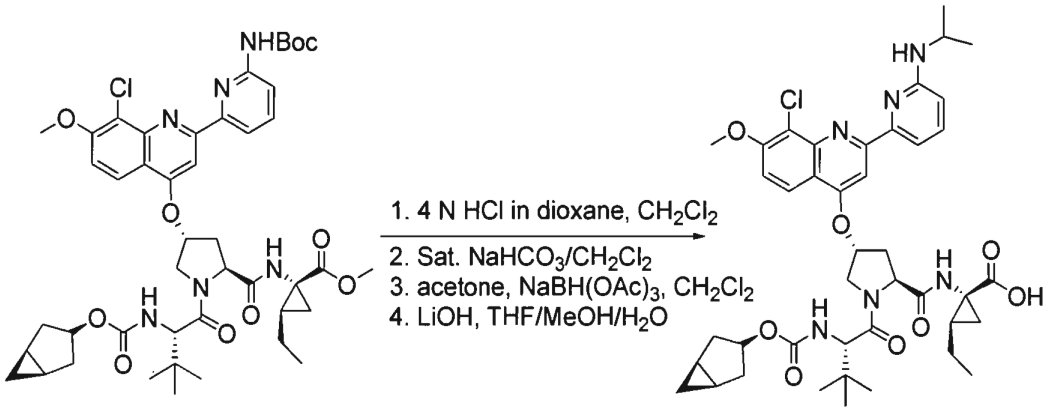
Compound **11** was obtained by following procedures similar to those for preparation of Compound **9**. LC/MS = 863.5 (M^++1).

Example 12: Preparation of Compound 12



Compound **11** (25 mg) was dissolved in 50% TFA in CH_2Cl_2. The reaction was complete after stirring for 2 h at room temperature. The mixture was concentrated *in vacuo*. The residue was dissolved in CH_3CN and H_2O, frozen and put on the lyophilizer to give Compound **12** as a pale yellow solid (20 mg). LC/MS = 763.5 (M^++1).

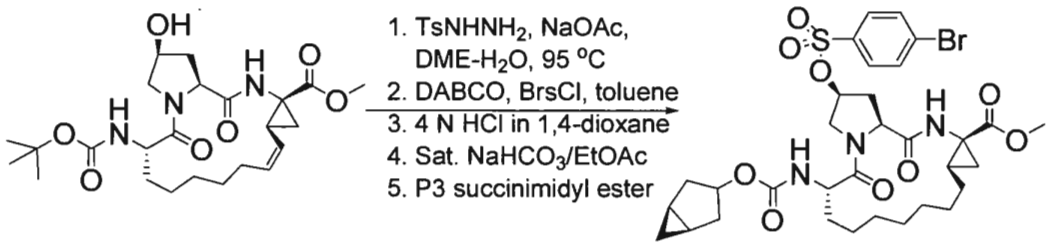
Example 13: Preparation of Compound 13



Methyl ester (0.95 g, 1.08 mmol) was dissolved in CH_2Cl_2 (10ml), and 4 N HCl in 1,4-dioxane (30 ml) was added. The reaction was complete after stirring at room temperature for 4 h. The mixture was concentrated *in vacuo*. Saturated sodium bicarbonate aqueous solution (80ml) and CH_2Cl_2 (80 ml) were added to the residue. Vigorous stirring was continued until the entire residue dissolved. The organic layer was washed with brine, dried over sodium sulfate, and concentrated *in vacuo* 250 mg (0.322 mmol) of the material was dissolved in CH_2Cl_2 (2 ml), and then acetic acid (56 µl, 0.967 mmol) and acetone (72 µl, 0.967) were added. After stirring at room temperature for 20 min, the mixture was cooled to 0 °C, and sodium triacetoxyborohydride (102 mg, 0.483 mmol) was added in one portion. After stirring at room temperature for 10 h, saturated sodium bicarbonate aqueous solution and CH_2Cl_2 were added to the mixture. The organic layer was washed with brine, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate / hexanes) to give the product as a pale yellow solid (180 mg). The solid was dissolved in THF (4 ml), and LiOH (184 mg, 44 mmol) in H_2O (4 ml) was added followed by MeOH (4 ml). The reaction was complete in 2 h. The mixture was concentrated *in vacuo*. TFA was added to adjust the pH to 2. The mixture was concentrated in *vacuo*. The residue was purified by preparative HPLC using water /

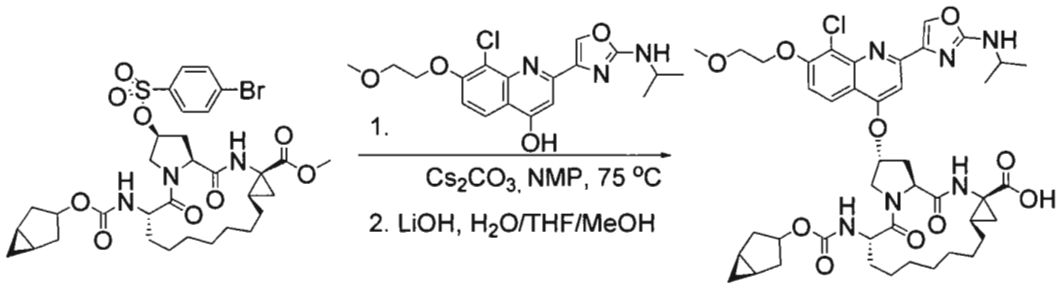
acetonitrile (0.05% TFA) as eluents, which afforded Compound **13** as a bright yellow solid (128 mg). ^{1}H NMR (300 MHz, CD_3OD): δ 8.66 (s,1H), 8.22 (d, J = 9.3 Hz, 1H), 8.00 (m, 1H), 7.94 (d, J = 7.5 Hz, 1H), 7.79 (s, 1H), 7.58 (d, J = 9.3 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 5.70 (s, 1H), 4.72 (t, J = 8.4 Hz, 1H), 4.54 (d, J = 12.3 Hz, 1H), 4.39 (t, J = 6.6 Hz, 1H), 4.01-4.25 (m, 2H), 4.13 (s, 3H), 2.73-2.83 (m, 1H), 2.50-2.62 (m, 1H), 1.85-1.92 (m, 1H), 1.60-1.80 (m, 5H), 1.45-1.60 (3H), 1.47 (d, 6H), 1.10-1.30 (m, 3H), 1.00 (s, 9H), 0.32-0.40 (m, 1H), 0.25-0.35 (m, 1H); LC/MS = 805.5 (M^++1).

Example 14: Preparation of Compound 14



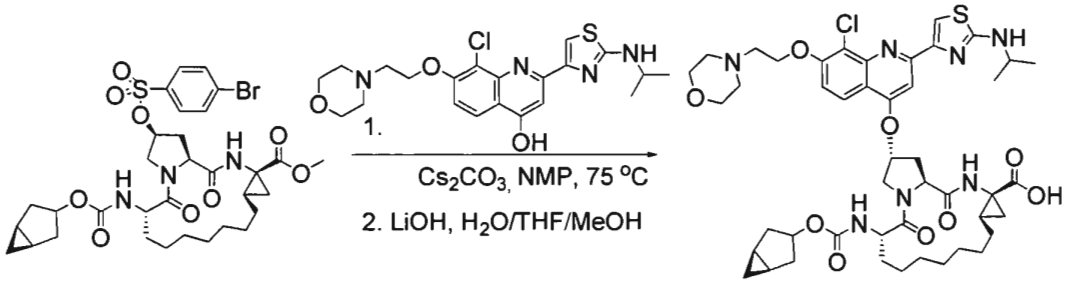
Cyclic tripeptide (5g, 10.4mmol) and *p*-toluenesulfonyl hydrazide (14.6 g, 78.2 mmol) were dissolved in ethylene glycol dimethyl ether (90 ml). Sodium acetate (12.8 g, 156 mmol) was added, followed by H_2O (10 ml). The suspension was then heated to 95 °C. The mixture was cooled to room temperature after 8 h stirring. Ethyl acetate and saturated aqueous sodium bicarbonate were added to the mixture. The organic layer was washed with 0.5 N aqueous HCl, brine and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate /hexanes) to give the desired product as a white solid (4.2 g, 84%). This solid (4.2 g, 8.7 mmol) and DABCO (3.2 g, 27.9 mmol) were dissolved in toluene (12 ml). 4-bromobenzenesulfonyl chloride (7.1 g 27.9 mmol) in toluene (12 ml) was added dropwise to the mixture. The reaction was left stirring at room temperature overnight. 5% aqueous sodium carbonate and ethyl acetate were added to the mixture and left vigorously stirring for 20 min. The aqueous layer was extracted with ethyl acetate (x1). The combined organic layer was washed with 5% aqueous sodium

carbonate (x2), 1 N aqueous HCl (x1), brine, dried over sodium sulfate and concentrated *in vacuo* to give the crude as an off-white solid. The crude was dissolved in CH_2Cl_2, and 4 N HCl in 1, 4-dioxane was added. The reaction was complete after 2 h of stirring at room temperature. The mixture was concentrated *in vacuo* and further dried under high vacuum overnight. To the 2.5 g of the crude residue (~3.9 mmol) was added ethyl acetate and aqueous saturated sodium bicarbonate. The mixture was vigorously stirred until all solids dissolved (keeping pH of the aqueous layer > 8). P3 succinimidyl ester (1.13 g, 4.7mmol) in ethyl acetate was added to the mixture. The reaction was complete in 30 min. The aqueous layer was extracted with ethyl acetate (x1). The combined organic layers were concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate /hexanes) to give brosylate as a white solid (2.5 g, 88% over 4 steps). LC/MS = 724.3 (M^++1).



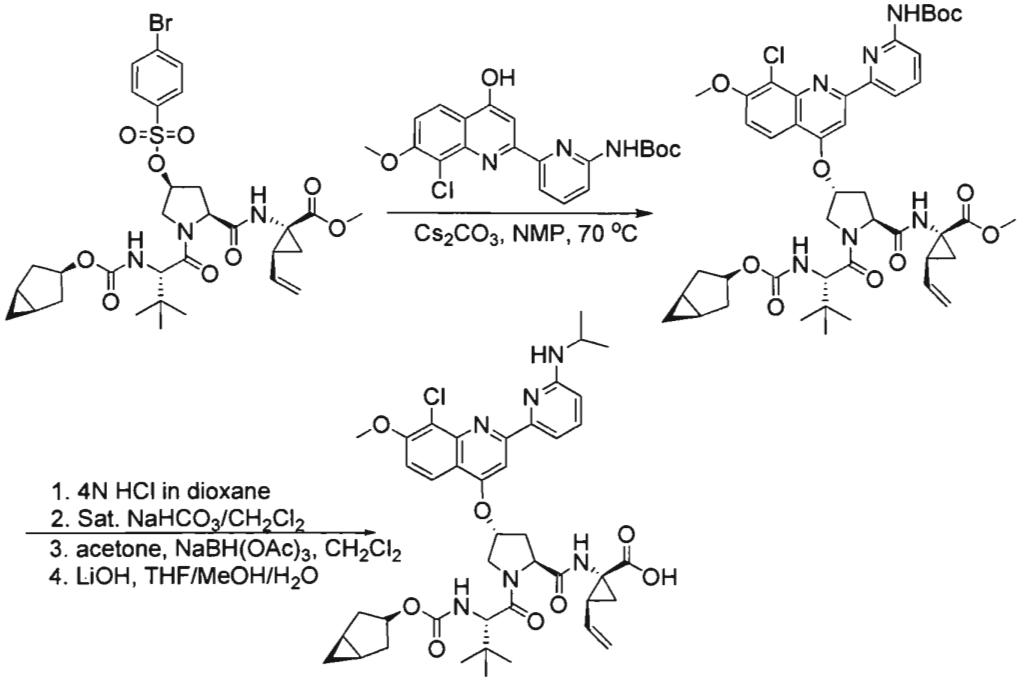
Compound **14** was obtained by following procedures similar to those for preparation of Compound **9** except using macrocyclic tripeptide and quinoline as shown. ^{1}H NMR (300 MHz, CD_3OD): δ 8.65 (s,1H), 8.29 (d, J = 9.3 Hz, 1H), 7.69 (s, 1H), 7.64 (d, J = 9.6 Hz, 1H), 5.71 (s, 1H), 4.78 (d, J = 8.1, 1H), 4.72 (d, 1H), 4.40-4.52 (m, 3H), 4.25 (d, 1H), 4.00-4.18 (m, 2H), 3.85-3.89 (m, 1H), 3.47 (s, 3H), 2.63-2.80 (m, 2H), 1.10-2.00 (m, 23H), 1.35 (d, J = 6.3 Hz, 6H), 0.30-0.39 (m, 2H). LC/MS = 851.5 (M^++1).

Example 15: Preparation of Compound 15



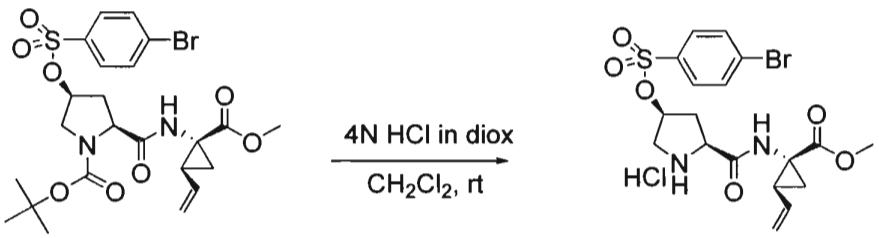
Compound **15** was obtained by following procedures similar to those for preparation of Compound **9** except using macrocyclic tripeptide and quinoline as shown. ^{1}H NMR (300 MHz, CD_3OD): δ 8.65 (s,1H), 8.33 (d, J = 9.6 Hz, 1H), 8.20 (s, 1H), 7.76 (s, 1H), 7.60 (d, J = 9.3 Hz, 1H), 5.72 (s, 1H), 4.75-4.82 (m, 3H), 4.58-4.70 (m, 2H), 4.30 (d, 1H), 4.09 (d, 1H), 3.92-4.06 (brs, 4H), 3.81 (t, 2H), 3.59 (brs, 4H), 2.60-2.80 (m, 2H), 1.10-2.00 (m, 23H), 1.38 (d, J = 5.4 Hz, 6H), 0.32-0.42 (m, 2H). LC/MS = 921.5 (M^++1).

Example 16: Preparation of Compound 16

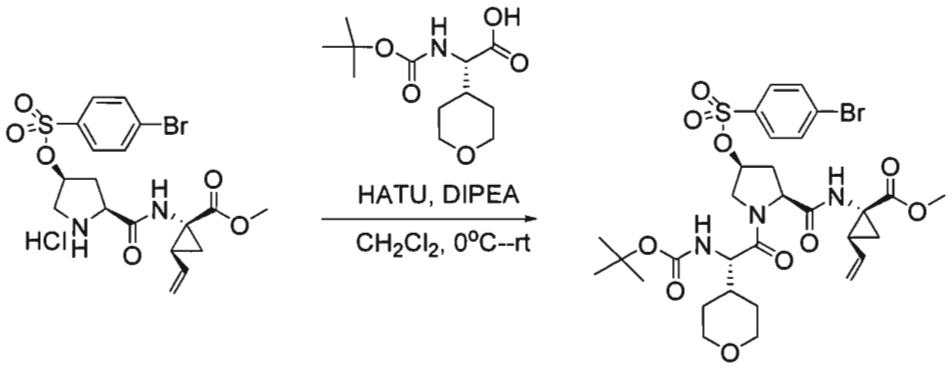


Compound **16** was obtained by following procedures similar to those for preparation of Compound **9**. ^{1}H NMR (300 MHz, DMSO-d6): δ 8.59 (s,1H), 8.11 (d, J = 9.3 Hz, 1H), 7.80-7.96 (m, 4H), 7.51 (d, J = 9.3 Hz, 1H), 7.04 (d, 1H), 5.65-5.78 (m, 1H), 5.58 (s, 1H), 5.18 (d, 1H), 5.06 (d, J = 10.5 Hz), 4.62 (t, 1H), 4.45 (t, 1H), 4.32 (t, 1H), 3.90-4.20 (m, 2H), 4.04 (s, 3H), 2.50-2.65 (m, 1H), 2.22-2.38 (m, 1H), 1.78-2.10 (m, 3H), 1.42-1.60 (m, 3H), 1.10-1.38 (3H), 1.47 (d, 6H), 1.10-1.30 (m, 3H), 0.94 (s, 9H), 0.23-0.48 (m, 1H); LC/MS = 803.5 (M^++1).

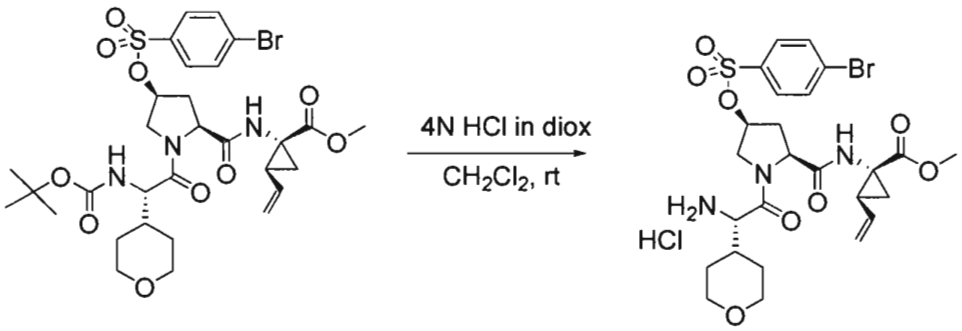
Example 17: Preparation of Compound 17



To a dry, nitrogen purged round bottom flask (250 mL) was added the Boc-protected dipeptide. Anhydrous CH_2Cl_2 (15 mL) was then added to the flask and the resulting clear yellow mixture was stirred until completely homogeneous. Lastly, HCl (5 mL, 4N in dioxane) was added dropwise to the flask and the reaction mixture was stirred at room temperature until complete disappearance of the starting material (1.5 h, as indicated by LC/MS). The solvent was removed under reduced pressure and the amine salt was used in the next step. LC/MS = 473.0 (M^++1).

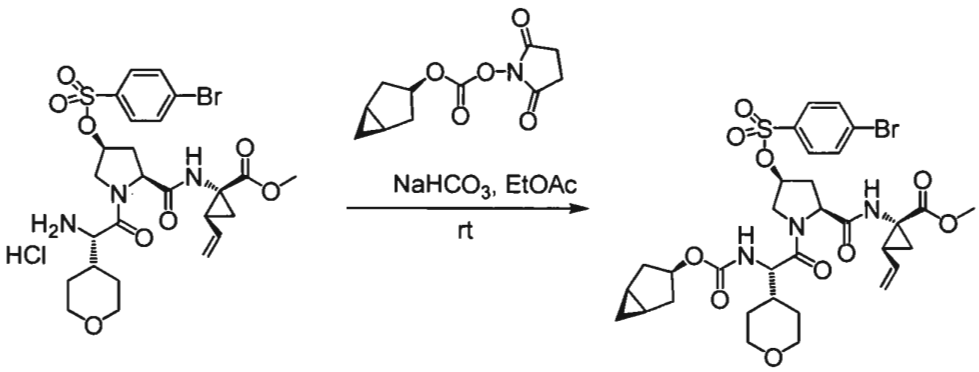


To a round bottom flask (500 mL) containing the amine salt were added the amino acid (951.63 mg, 3.67 mmol) and CH_2Cl_2 (150 mL). DIPEA (2.56 mL, 14.68 mmol) was then added and the homogeneous mixture was cooled to 0 °C. HATU (3.49 g, 9.18 mmol) was then added to the flask and the reaction mixture was allowed to warm to room temperature. The reaction continued to stir at room temp until complete disappearance of the starting material. After stirring overnight, TLC and LC-MS analysis indicated the reaction was complete. The solvent was removed under reduced pressure and the tripeptide was used in the next step as obtained. LC/MS = 714.2 (M^++1).

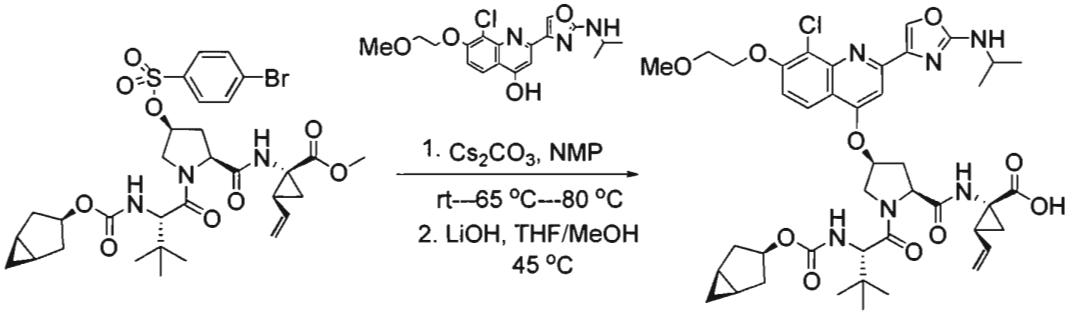


To a round bottom flask (100 mL) containing the tripeptide was added anhydrous CH_2Cl_2 (15 mL). The mixture was allowed to stir for a few minutes. HCl (9.18 mL, 4N in dioxane) was added dropwise. The reaction continued to stir at room temperature for 1.5 h at which point LC-MS indicated complete disappearance of the starting material. The

solvent was removed under reduced pressure and the amine salt was used in the next step as obtained. LC/MS = 614.1 (M^++1).



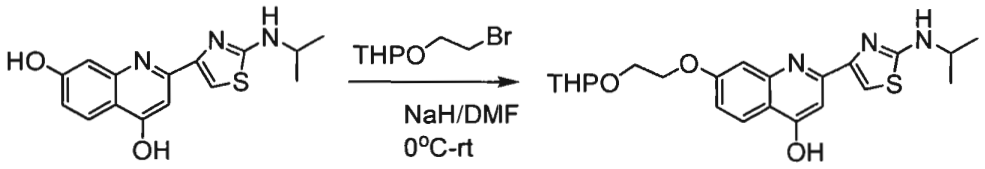
To the round bottom flask (250 mL) containing the amine salt was added EtOAc (65 mL). Sat. $NaHCO_3$ (60 mL) was then added and the biphasic solution was stirred vigorously for 1 h, at which point both phases were homogeneous. A solution of the carbonic ester (1.05 g, 4.40 mmol) and EtOAc (15 mL) was made in a separate round bottom flask (50mL) and this solution was added to the reaction flask via cannula. The reaction stirred at room temperature for 1h at which point LC-MS indicated complete disappearance of the starting material. The organic layer was separated and the solvent was removed under reduced pressure. The crude material was purified using flash chromatography (EtOAC/ 1:1 EtOAc/MeOH). 1.0 g (37 % over 4 steps) of the tripeptide was obtained. LC/MS = 710.2 (M^++1).



To a dry, argon purged pear shaped flask (50 mL) were added quinoline (500 mg, 1.32 mmol), tripeptide (1.00 g, 1.35 mmol), and anhydrous NMP (4 mL). The flask was mildly

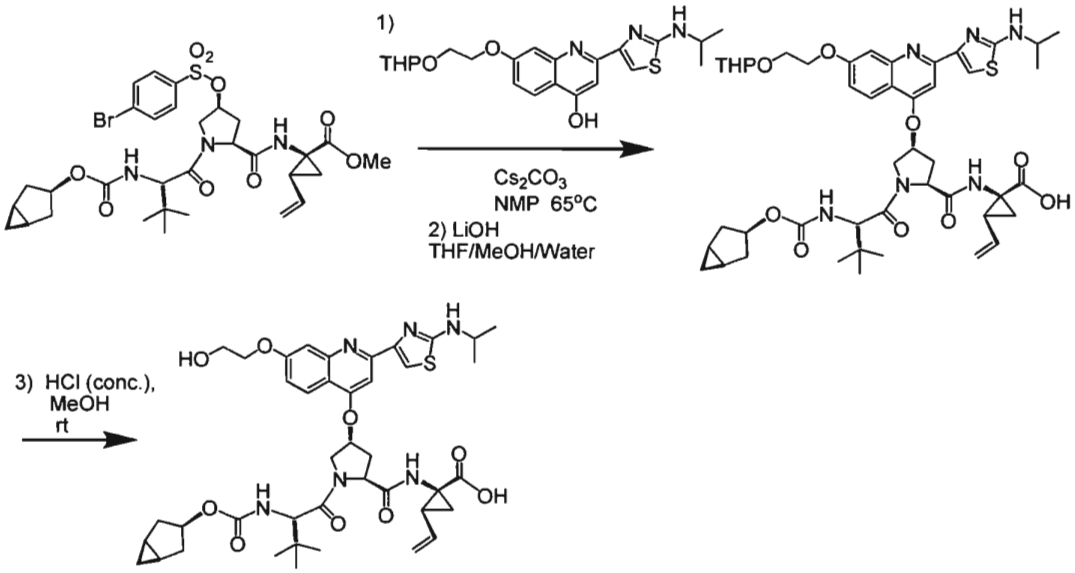
warmed to increase dissolution. Cs_2CO_3 (531.24 mg, 1.63 mmol) was then added and the flask was placed in a preheated 65 °C oil bath. After 2.5 h of stirring, LC-MS indicated 50 % conversion of the starting material to desired product. The temperature of the oil bath was increased to 80 °C and the reaction continued to stir for an additional 2 h. The flask was then cooled to room temperature and a solution of LiOH in H_2O (10 mL, 25 mmol) was added, followed by a 1:1 solution of MeOH/THF (40 mL). The flask was then placed into a pre-heated oil bath set at 45 °C and was allowed to stir until complete disappearance of the starting material. After 3.5 h, the solvent was removed under reduced pressure. The crude material was diluted with EtOAc and neutralized with 1M HCl. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organic layers were washed with 2% LiCl (3 x 10 mL) and brine (3 x 10mL), and then dried with $MgSO_4$. The solvent was removed under reduced pressure and the crude material was purified using preparative HPLC (water / acetonitrile (0.05% TFA). 400 mg (35 % over 2 steps) of the Compound **17** was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.62 (s, 1H), 8.28 (m, 1H), 7.67 (m, 2H), 5.82 (m, 1H), 5.30 (m, 1H), 5.13 (m, 2H), 4.72 (m, 1H), 4.50 (s, 1H), 4.37 (s, 1H), 4.03 (m, 7H), 3.92 (m, 6H), 3.47 (s, 2H), 3.32 (s, 2H), 2.83 (m, 2H), 2.61 (m, 2H), 1.92 (m, 2H), 1.72 (m, 4H), 1.56 (m, 4H), 1.18 (m, 6H), 0.27 (m, 2H).

Example 18: Preparation of Compound 18



Bis-phenol (2.0 g, 6.58 mmol) was dissolved in DMF (50 ml) at 0 °C and NaH (589 mg, 14.73 mmol) was added portion wise. The reaction was stirred for 30min.30 min 2-(2-

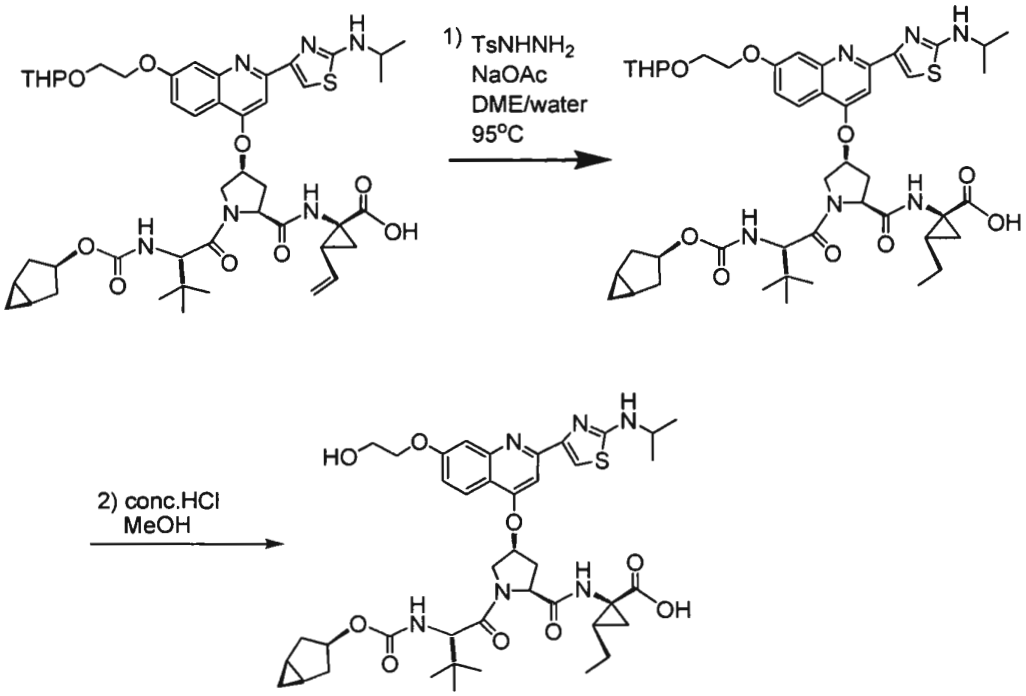
bromo-ethoxy)-tetrahydropyran (1.05 mL, 6.95 mmol) was then added to the mixture. The mixture was then vigorously stirred at room temperature and monitored by HPLC, LC/MS. After 18 hrs the reaction was diluted with EtOAc and aqueous 3% LiCl solution, and acidified to pH 6. The layers were separated and the aqueous layer was extracted with EtOAc again. The organic layers were combined and washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the desired product (2.61 g, 92%). LC/MS = 430 (M^++1).



Step 1 & 2: Used the same procedure as described before. LC/MS = 890 (M^++1).

Step 3: The acid (503.5 mg, 0.566 mmol) was dissolved in MeOH (1.80 mL) and cooled to 0 °C. Concentrated HCl (1.8mL) was added to the solution. The mixture was stirred at for 2 h. Upon completion of the reaction, the mixture was concentrated to remove the solvents. The crude product was purified by prep-HPLC to give Compound **18** as a yellow solid (159.2 mg), LC/MS = 805 (M^++1).

Example 19: Preparation of Compound 19

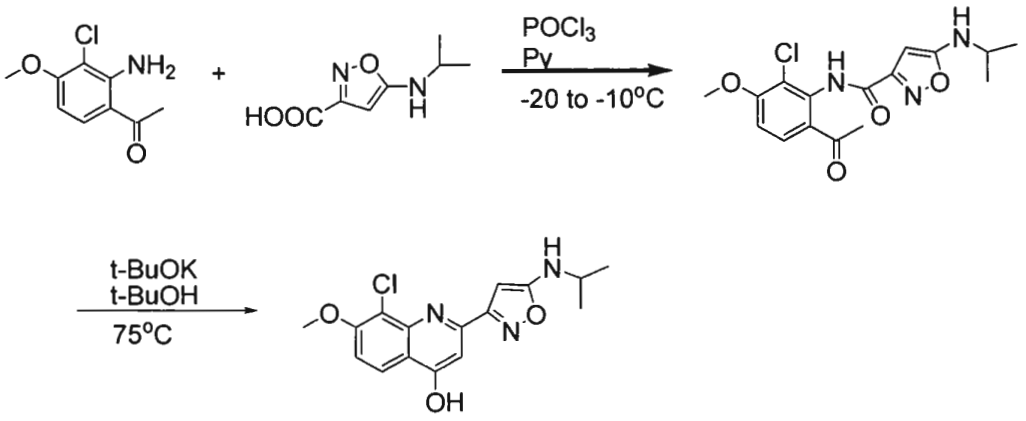


Step 1: The mixture of acid, p-$TsNHNH_2$, and NaOAc in DME (10 mL)/H_2O (1 mL) was heated to 95°C for 2h. Upon the completion of the reaction, it was cooled to room temperature, diluted with EtOAc (100mL) and 1N HCl (to pH about 3). After separated layers, the aq. Layer was back extracted with EtOAc. The organic layers were combined and concentrated. The crude product was purified by prep-HPLC to give a yellow solid. LC/MS = 892 (M^++1).

Step 2: The acid was dissolved in MeOH (3 mL) and cooled to 0 °C. Concentrated HCl (3 mL) was added to the solution. The mixture was stirred at for 2 h. Upon completion of the reaction, the mixture was concentrated to remove the solvents. The crude product was purified by prep-HPLC to give desired Compound **19** as a yellow solid (187.7 mg). LC/MS = 807 (M^++1). ^1H NMR (300 MHz, $CDCl_3$): δ 8.80 (b, 1H), 8.20 (d, 1H),7.9 (m, 1H), 7.50 (m, 1H), 7.30 (d, 1H), 5.90-5.80 (m, 2H), 5.10 (m, 1H), 4.80-4.40 (m,4H), 4.3 (m, 3H), 4.05 (m, 3H), 3.20 (m, 1H), 3.00-2.70

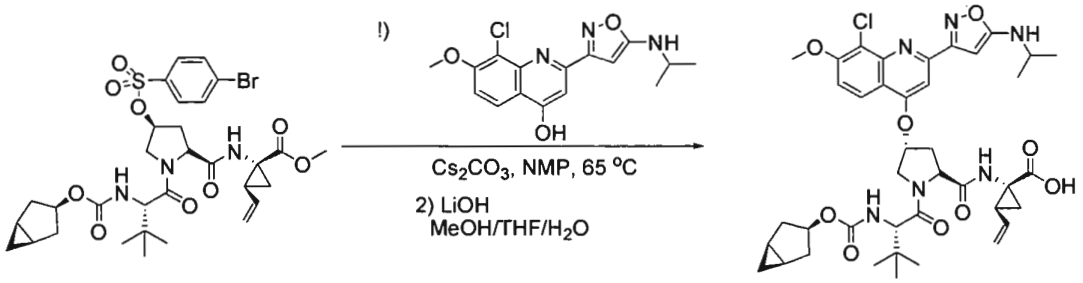
(m, 1H), 2.20 (m, 2H), 1.80-1.60 (m, 6H), 1.50 (m, 2H), 1.3 (m, 9H), 1.10-0.90 (m, 14H), 0.50 (m, 2H).

Example 20: Preparation of Compound 20



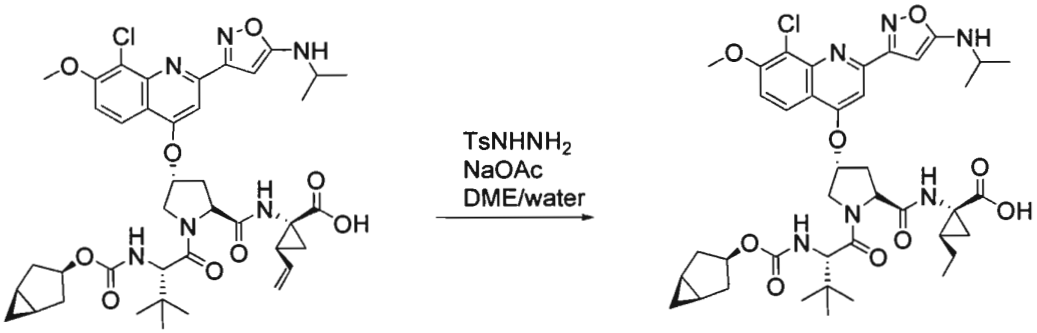
Step 1: The same procedure was used as mentioned before; starting from aniline (1.877g) gave 2.56 g of product. LC/MS = 337 (M^++1).

Step 2: The amide compound (1.50 g, 4.45 mmol) was dissolved in t-BuOH (12.5 ml). t-BuOK (9.3mL, 4.45 mmol) was added to the vigorously stirred mixture. The reaction was complete after 6 h at 75°C. The mixture was cooled to room temperature. It was acidified with 4N HCl (5mL). The slurry was treated with NaH_2PO_4 (0.5N) and filtered. The cake was washed with water and ether and then dried to give the desired product, (1.256g, 89%). LC/MS = 319 (M^++1).



Compound **20** was synthesized using procedure described before. LC/MS = 779 (M^++1). ^{1}H NMR (300 MHz, CD_3OD): d 8.13 (d, 1H), 7.51 (s, 1H), 7.47 (d, 1H), 6.91 (s, 1H), 5.90-5.78 (m, 1H), 5.53 (b, 1H), 5.31-5.09 (dd, 2H).4.68-4.49 m, 3H), 4.21 (s, 1H), 4.07 (b, 5H), 3.22 (m, 1H), 2.72 (m, 1H), 2.51 (m, 1H), 2.20 (m, 1H), 1.97 (m, 1H), 1.85 (m, 1H), 173-1.63 (m, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 1.36-1.14 (m, 4H), 1.01 (s, 9H), 0.97 (s, 2H), 0.33 (m, 2H).

Example 21: Preparation of Compound 21

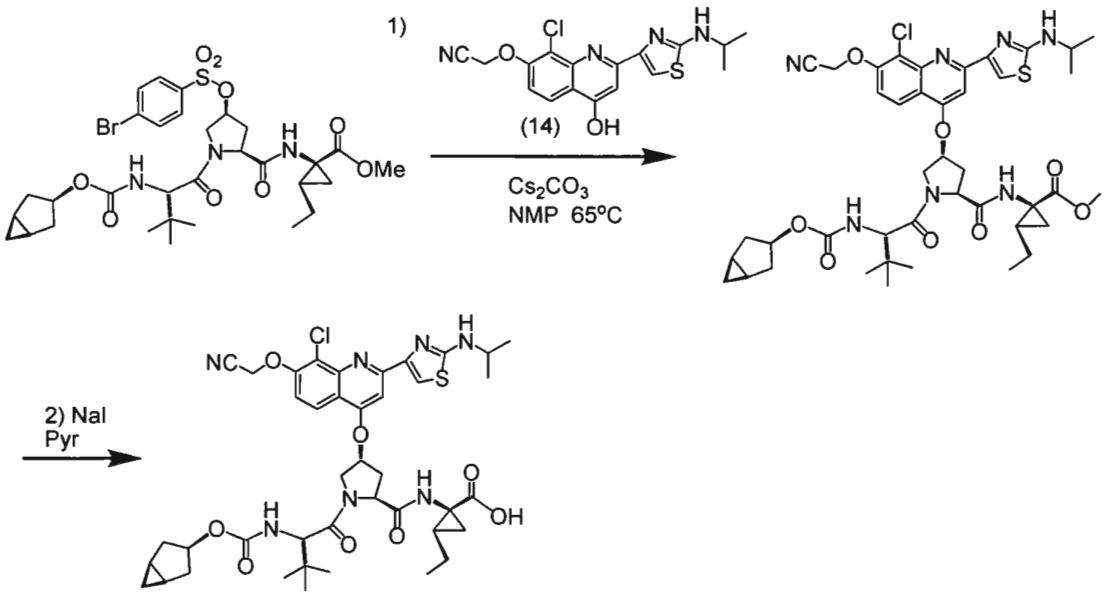


Compound **21** was synthesized using procedure described before. LC/MS = 781 (M^++1). ^{1}H NMR (300 MHz, CD_3OD): d 8.13 (d, 1H), 7.51 (s, 1H), 7.47 (d, 1H), 6.91 (s, 1H), 5.53 (b, 1H) 4.70- 4.40 (m, 3H), 4.21 (s, 1H), 4.07 (b, 5H), 3.67 (b, 2H), 2.72 (m, 1H), 2.52 (m, 1H), 2.20 (m, 1H), 1.97 (m, 1H), 1.85 (m, 1H), 173-1.63 (m, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 1.36-1.14 (m, 4H), 1.01 (s, 9H), 0.97 (s, 2H), 0.33 (m, 2H).

Example 22: Preparation of Compound 22



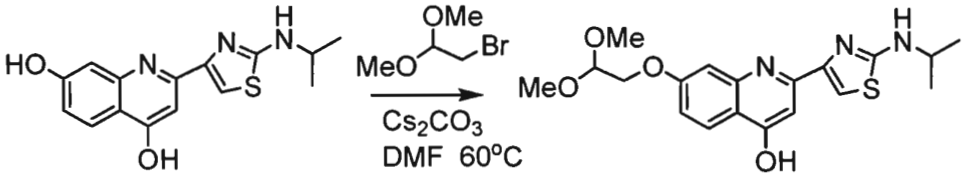
Bis-phenol (600 mg, 1.79 mmol) was dissolved in DMF (18 ml) at 0 °C and Cs_2CO_3 (584mg, 1.79 mmol) was added to the mixture, followed by bromo-acetonitrile (0.15 mL). The mixture was heated to 65°C and monitored by HPLC and LC/MS. After 4 hrs the reaction was diluted with EtOAc and aqueous 3% LiCl solution. The layers were separated and the aqueous layer was extracted with EtOAc again. The organic layers were combined and washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product (536 mg, 80%). LC/MS = 375 (M^++1).



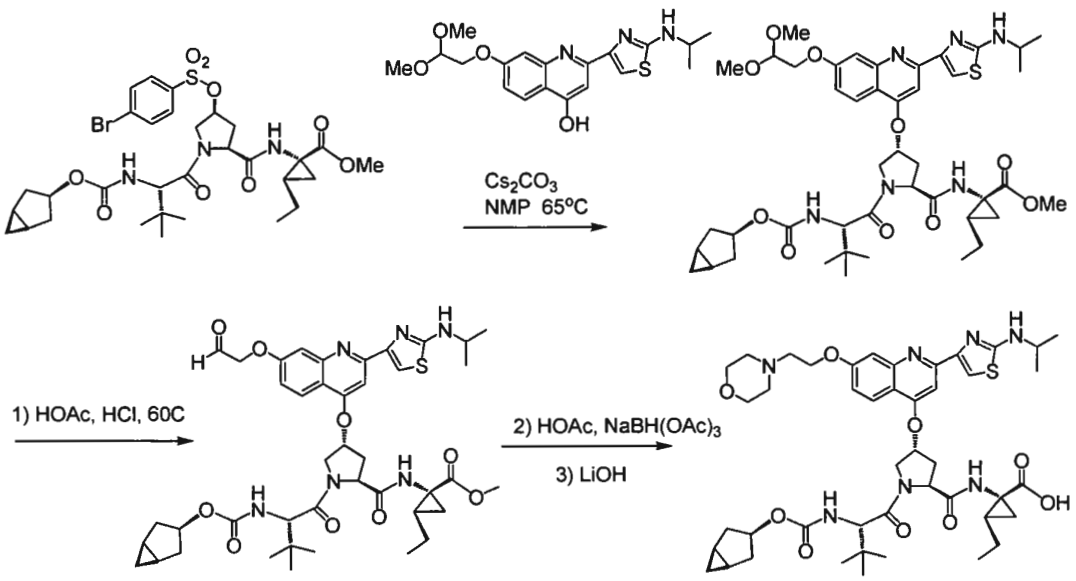
Step 1: Use the same procedure as described before. 508 mg of intermediate II gave 491 mg of product. LC/MS = 851 (M^++1).

Step 2: The methyl ester (491 mg, 0.578 mmol) and NaI (1.738g) were mixed in pyridine and heated to 115 °C for 19h. Upon completion of the reaction, the mixture was cooled to room temperature, diluted with EtOAc and acidified to pH 4 with 0.5 N HCl. Extracted with EtOAc (3x), and the organics were combined and dried over $MgSO_4$. The concentrated crude product was purified by prep-HPLC to give the desired Compound **22** as a yellow solid (71 mg, 14.7%), LC/MS = 837 (M^++1). ^{1}H NMR (300 MHz, CD_3OD): δ 8.63 (s, 1H), 8.34 (d, 1H), 8.17 (s, 1H), 7.76 (s, 1H), 7.64 (d, 1H), 5.69 (b, 1H), 5.38 (b, 2H), 4.73-4.50 (m, 3H), 4.16 (s, 1H), 4.20-3.98 (m, 3H), 2.80-2.58 (m, 2H), 2.0-1.8 (m, 2H), 1.66 (m, 4H), 0.98 (s, 2H), 0.34 (m, 2H).

Example 23: Preparation of Compound 23



Step 1: Bis-phenol (7 g, 23.4 mmol) was dissolved in DMF (50 ml), cesium carbonate (15.25 g, 46.8 mmol) was added to the mixture, followed by bromoacetaldehyde dimethyl acetal (4.13 mL, 35.1 mmol). The mixture was then vigorously stirred at 65 °C and monitored by HPLC and LC/MS. Another 0.5eq of bromoacetaldehyde dimethyl acetal and 1eq of cesium carbonate were added. After 18 hrs LC/MS indicated no starting material remained, but lots of bis-alkylated by-product formed. The reaction was cooled to room temperature, and diluted with EtOAc. The mixture was washed with aqueous 3% LiCl solution, brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography with MeOH / EtOAc to give the desired product (1.72 g, 19%). LC/MS = 390 (M^++1).



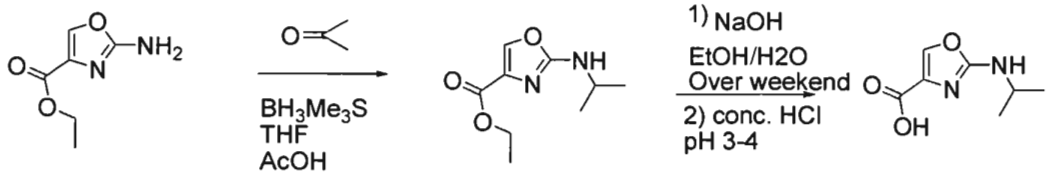
Step 2: To a mixture of tripeptide (1.46 g, 3.75 mmol) and cesium carbonate (1.58 g, 4.88 mmol) in NMP (18.5 ml) at room temperature was added quinoline (2.94 g, 4.12 mmol) in one portion. The mixture was stirred at 65 °C for 3 h. The reaction was cooled to room temperature, and EtOAc (100 ml) was added to the mixture. The mixture was washed with aqueous 3% LiCl (1 x 100 ml), brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography with EtOAc/Hexane to give the desired product as light brown solid (2.07 g, 64%). LC/MS = 837 (M^++18).

Step 3: To a solution of the acetal (1.24 g, 1.43 mmol) in glacial acetic acid (16 mL) was added 1.4 N HCl in H_2O (6 mL). The mixture was stirred at 60 °C for 1.5 h. Upon completion of the reaction, the mixture was concentrated to remove the solvents, coevaporated with toluene (x 2) to remove residual acetic acid. After the residue was then dissolved in EtOAc (100 mL) and sat. $NaHCO_3$ (100mL), the organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was further dried under high vacuum for 1 h to obtain the aldehyde (1.16g), and used as is for the next step.

Step 4: The crude aldehyde was dissolved in CH_2Cl_2 (16 ml), and then morpholine (164 µl, 1.89 mmol) and sodium triacetoxyborohydride (462 mg, 2.18 mmol) were added to the mixture at 0 °C. Glacial acetic acid (25 µl, 7.8 mmol) was then added dropwise to the mixture. The reaction was complete in 10 min at 0 °C. Sat. aqueous $NaHCO_3$ solution was added to quench the reaction. After stirring for another 20 min, the organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was clean enough (by LC/MS) to use as is. LC/MS = 890 (M^++1).

This crude product was dissolved in THF (60 ml), and then LiOH (1200 mg, 28.6 mmol) in H_2O (20 ml) was added, followed by MeOH (4 ml). The mixture was kept stirring at room temperature for 20 h. Upon completion of the reaction, TFA was added at 0 °C, to adjust the pH to 4. The mixture was extracted with EtOAc (2 x 200 ml). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. The crude product was purified by prep-HPLC to give Compound **23** as a yellow solid (1.086 g, 73%). LC/MS = 876 (M^++1). ^{1}H NMR (300 MHz, CD_3OD): δ 7.94 (d, 1H), 7.40 (s, 1H), 7.44 (d, 1H), 7.39 (s, 1H), 7.04-7.01 (m, 1H), 5.39 (m, 1H), 4.32-4.20 (m, 5H), 3.80-3.68 (m, 4H), 3.59 (bs, 3H), 3.40 (m, 2H), 3.35-3.24 (m, 4H), 3.93-3.92 (m, 2H), 2.40-2.19 (m, 2H), 1.65-1.47 (m, 2H), 1.33-1.25 (m, 3H), 1.16-1.11 (m, 1H), 1.05-1.01 (m, 1H), 0.96 (s, 3H), 0.95 (s, 3H), 0.86-0.79 (m, 3H), 0.65 (s, 9H), 0.57 (m, 2H).

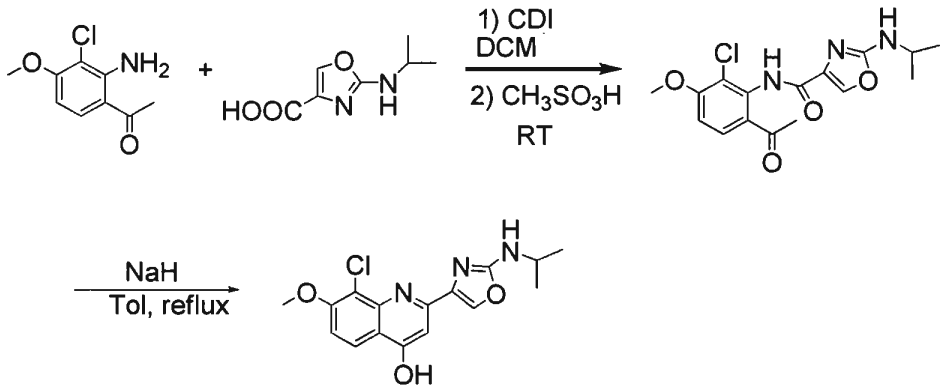
Example 24: Preparation of Compound 24



Step 1: The mixture of 2-amino-oxazole-4-carboxylic acid ethyl ester (500 mg, 3.2 mmol) and acetone (2.35 mL, 32 mmol) in THF (6 mL) was stirred at room temperature. Borane

($BH_3 \cdot SMe_2$) (10M in THF, 0.64 mL, 6.4 mmol) was added slowly via syringe to control the exotherm and bubbling. Next, AcOH (0.362 mL, 6.4 mmol) was added in the same manner. (Another 2eq of borane and AcOH were added 18h later) The mixture was stirred under a nitrogen atmosphere and monitored by LC/MS. After 3 days at room temperature, the reaction still had some SM left. It was concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (100 mL), washed with saturated NH_4Cl solution, 0.1 M NH_4OH and brine. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with EtOAc/Hexanes to give the desired product (0.40 g, 64%). LC/MS = 199 (M^++1).

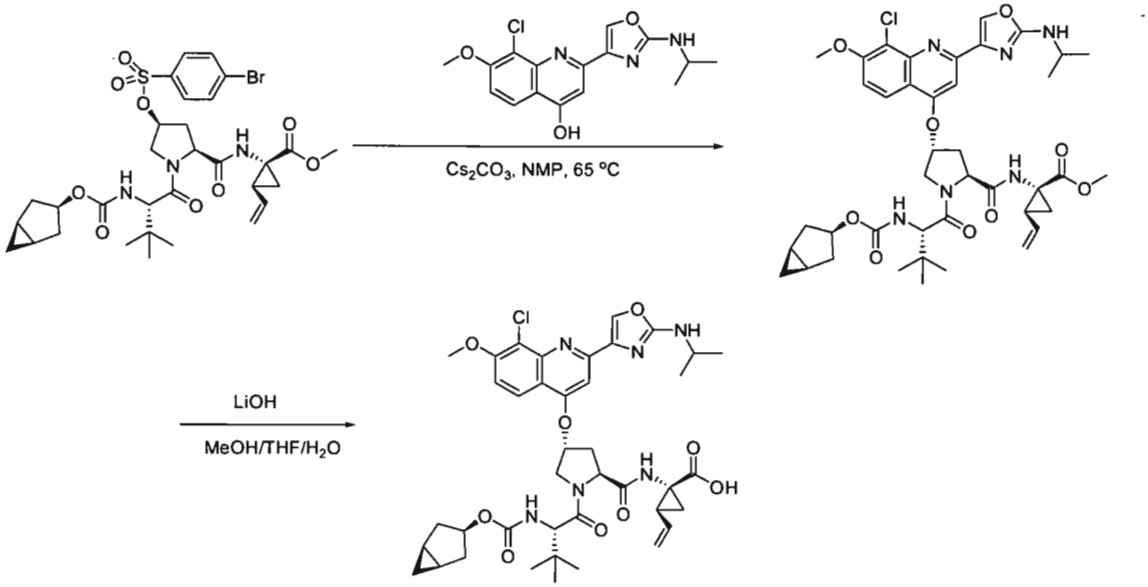
Step 2: To the mixture of ester obtained above (2.5, 10.86 mmol) in EtOH (42 mL) and water (28 mL) was added NaOH (3.1 g, 77.4 mmol). The mixture was stirred at room temperature for 16 h. It was monitored by TLC. After the mixture was done, it was cooled in an ice-bath and acidified by adding conc. HCl to adjust the pH to 3. The mixture was then concentrated *in vacuo* to remove ethanol. The remaining was extracted with CH_2Cl_2 (3 x 200mL). The organic phases were combined, dried ($MgSO_4$) and concentrated to give the desired product (1.86 g, 87%). LC/MS = 171 (M^++1).



Step 3: To acid (1.86 g, 10.94 mmol) in DCM (10 ml) was added CDI (1.774 g, 10.94 mmol). The mixture was then stirred at room temperature for 2 h. Aniline (1.446 g, 8.75 mmol) was added followed by CH_3SO_3H (2.13 mL, 32.82 mmol). The reaction was stirred for 18h at room temperature. Upon completion of the reaction, it was diluted with DCM

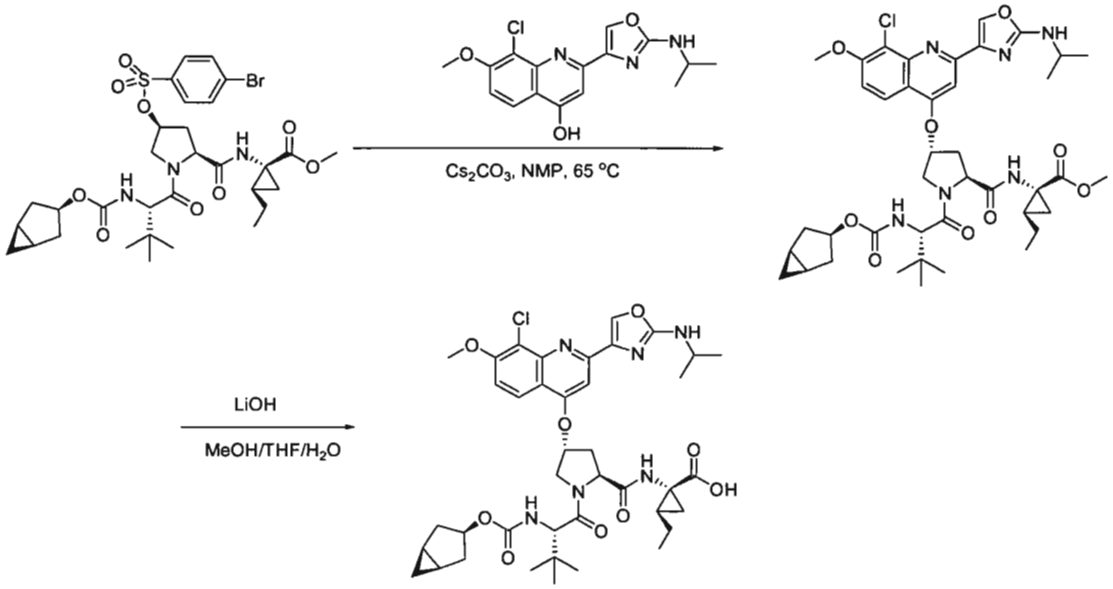
(100mL) and washed with 1N HCl (2x100mL). To this organic phase, was added K_2CO_3 (3.02 g, 21.88 mmol) and stirred for 2h at room temperature. Solids were removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluted with EtOAc/Hexane to give the desired product (863.4 mg, 22%). LC/MS = 382 (M^++1).

Step 4: The methyl ketone obtained above (863.4 mg, 2.45 mmol) was suspended in toluene (20 ml). NaH (147.3 mg, 3.68 mmol) was added to the vigorously stirred mixture while monitoring H_2 evolution. The reaction was refluxed (110°C) for 3 h. The mixture was not a clear solution. LC/MS showed still about 1/3 of starting material left. After cooling, about 80 mg of NaH was carefully added, followed by 20 mL of THF to help the solubility. The mixture was heated for another 2h and the reaction almost reached completion. After cooling to room temperature, it was quenched by the addition of conc. HCl to adjust the pH to about 2-3. The slurry was stirred for 1h at room temperature. 10 mL of CH_3CN was added, followed by 5 mL H_2O, and then 20 mL of ether. The mixture was stirred for another ½ h, and then the solids were collected by filtration and washed with ether and hexane. The wet cake was dried under high vacuum to a constant weight (390 mg of HCl salt, 840mg, 100%). LC/MS = 334 (M^++1).



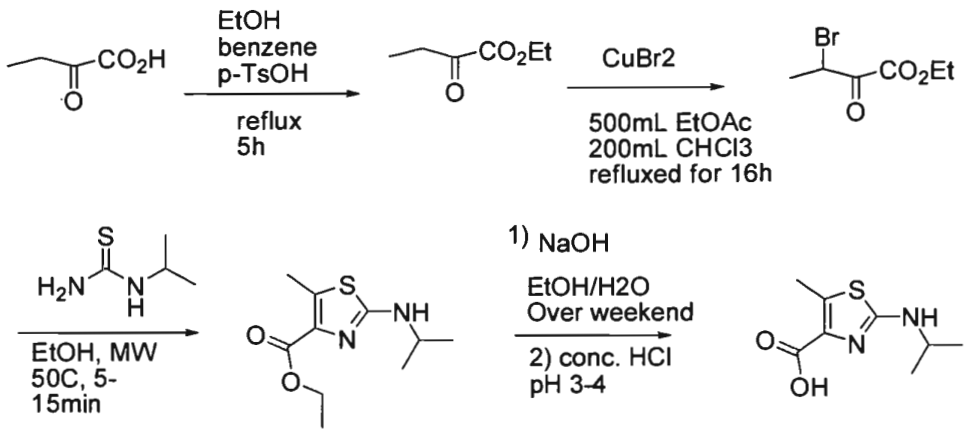
Step 5: Using the same procedure described before, Compound **24** was obtained after prep HPLC purification as a yellow solid (30mg). LC/MS = 794 (M^++1). ^{1}H NMR (300 MHz, CD_3OD): δ 8.74 (s, 1H),8.54 (s, 1H), 8.25 (d, 1H), 7.59 (m, 2H), 5.90-5.80 (m, 1H), 5.65 (bs, 1H), 5.31-5.09 (dd, 2H).4.73 (t, 1H), 4.54 (m, 1H), 4.14 (s, 3H), 4.11-3.99 (m, 5H), 2.81-2.60 (m, 2H), 2.2 (m, 1H), 2.00-1.60 (m, 4H), 1.50-1.40 (m, 2H), 1.35 (s, 3H), 1.33 (s, 3H), 1.20 (m, 2H), 1.02 (s, 9H), 0.34 (m, 2H).

Example 25: Preparation of Compound 25



Using the same procedure described before, Compound **25** was obtained after prep HPLC purification as a yellow solid. LC/MS = 796 (M^++1). ^{1}H NMR (300 MHz, CD_3OD): δ 8.64 (s, 1H),8.60 (s, 1H), 8.26 (d, 1H), 7.61 (m, 2H), 5.67 (bs, 1H), 4.73 (t, 1H), 4.53 (m, 1H), 4.15 (s, 3H), 4.12 (m, 5H), 2.81-2.60 (m, 2H), 2.2 (m, 1H), 2.00-1.40 (m, 6H), 1.36 (s, 3H), 1.34 (s, 3H), 1.23 (m, 2H), 1.02 (s, 9H), 0.34 (m, 2H).

Example 26: Preparation of Compound 26



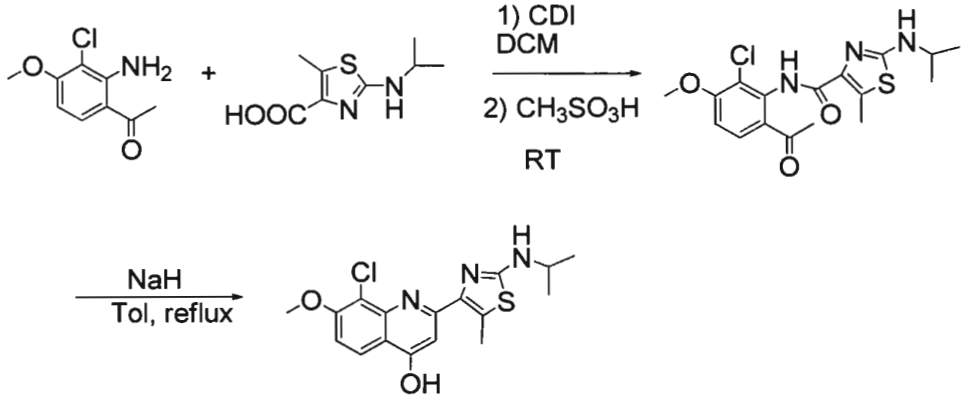
Step 1: The mixture of 2-oxo-butyric acid (15 g, 147 mmol), p-TsOH (300mg) in benzene (60 mL) and EtOH (125 mL) was stirred at 90°C (reflux) for 5 h. After the mixture was cooled to room temperature, it was concentrated *in vacuo* (water bath t < 20 °C). The resulting residue was dissolved in EtOAc (200 mL), washed with a saturated $NaHCO_3$ solution and brine. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* (water bath below 20 °C) to give the desired product (12.2 g, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.30 (q, 2H), 2.85 (q, 2H), 1.35 (t, 3H), 1.11 (t, 3H).

Step 2: To a suspension of $CuBr_2$ (32g, 147.1 mmol) in EtOAc (500 mL) was added the ester (6.2g, 47.7 mmol) in $CHCl_3$ (200 mL). The mixture was stirred at 90°C (reflux) for 16 h. It was monitored by TLC (EtOAc:Hexane = 1:4, R_f = 0.5, R_f = 0.4). After the mixture was cooled to room temperature, it was filtered through a bed of silica gel eluting with 200 mL of a 1:1 EtOAc:Hexane solution. The filtrate was concentrated *in vacuo* (water bath t < 20 °C) to give the desired product (10.75 g, 108%). No mass can be detected by LC/MS. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.17 (q, 1H), 4.38 (q, 2H), 1.81 (t, 3H), 1.38 (t, 3H).

Step 3: The mixture of the bromide (1.672g, 8mmol) and isopropyl-thiourea (0.944g, 8 mmol) in 12 mL of EtOH was microwaved at 50°C for 15 min. After the mixture was cooled to room temperature, it was concentrated *in vacuo*. The residue was purified by

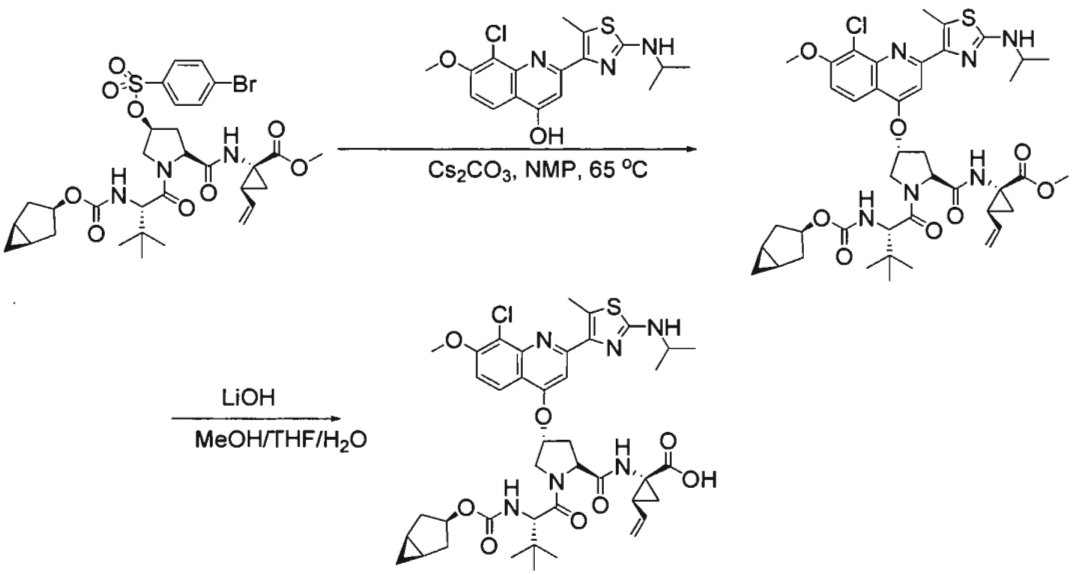
silica gel flash chromatography, eluting with EtOAc/Hexane to give the desired product. LC/MS = 229.9 (M^++1).

Step 4: To the mixture of the ester (1.7g, 7.45 mmol) in EtOH (12 mL) and water (8 mL) was added NaOH (1.8g, 44.7 mmol). The mixture was stirred at room temperature for 16 h. The reaction was monitored by TLC. After the reaction was done, it was cooled in an ice-bath and acidified with conc. HCl to adjust the pH to 3. The mixture was then concentrated *in vacuo* to remove ethanol. The remaining slurry was extracted with CH_2Cl_2 (3 x 200mL). The organic phases were combined, dried ($MgSO_4$) and concentrated to give the desired acid product (1.2 g, 80%).



Step 5: To the acid (1.2 g, 5.99 mmol) in DCM (10 ml) was added CDI (972 mg, 5.99 mmol. The mixture was then stirred at room temperature for 2 h. Aniline (792 mg, 4.89 mmol) was added followed by CH_3SO_3H (1.17 mL, 18 mmol). The reaction was stirred for 18h at room temperature. Upon completion of the reaction, it was diluted with DCM (100mL) and washed with 1N HCl (2x100mL). To the organic phase, was added K_2CO_3 (1.66g, 12 mmol) and this mixture was stirred for 2h at room temperature. Solids were removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel flash chromatography, eluting with EtOAc/Hexane to give the desired amide product (1.46 g, 70%). LC/MS = 382 (M^++1).

Step 6: The amide compound (1.46 g, 3.82 mmol) was suspended in toluene (30 ml). NaH (0.23 g, 5.73 mmol) was added to the vigorously stirred mixture while monitoring H_2 evolution. The mixture became a clear solution during heating to reflux. The reaction was complete after refluxing for 3 h. The reaction was cooled to room temperature, quenched with IPA (5mL), and then heptane (30mL) was added. The slurry was stirred for 1h at room temperature. The solids that formed were collected by filtration and washed with ether. The collected solids were dissolved in AcCN/H_2O (2:1) and then acidified with 3N HCl. The resulting slurry was stirred for 1h, and the solids were again collected by filtration. The wet cake was dried under high vacuum to a constant weight (390 mg of HCl salt, 1.07 mmol, 28%). LC/MS = 363 (M^++1).

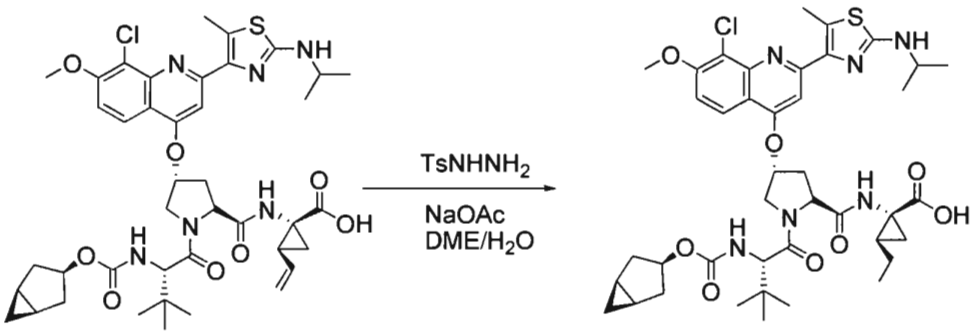


Step 7: To a mixture of quinoline (0.39 g, 1.07 mmol) and brosylate (692 mg, 0.974 mmol) in NMP (10 ml) was added cesium carbonate (696 mg, 2.14 mmol). The mixture was stirred at 65 °C for 2 h. The reaction was cooled to room temperature, and EtOAc (60 ml) and aqueous solution of 3% LiCl (60 ml) were added to the mixture. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was

purified by silica gel chromatography to give the desired methyl ester product as a yellow solid (0.59 g). LC/MS = 835).

Step 8: The methyl ester was dissolved in THF (20 ml), LiOH (0.6 g) in H_2O (10 ml) was added followed by addition of MeOH (1 ml). The mixture was kept stirring at room temperature for 20 h. Upon completion of the reaction, 40%TFA in H_2O was added to adjust pH to 7 at 0 °C. The mixture was extracted with EtOAc. The combined organic layer was concentrated *in vacuo* then purified by prep HPLC to give the compound **26** as a yellow solid (714 mg, 79%). LC/MS = 823 (M^++1). ^{1}H NMR (300 MHz, CD_3OD): δ 8.74 (s, 1H), 8.26 (d, 1H), 7.59 (d, 1H), 7.35 (s, 1H), 6.00-5.74 (m, 2H), 5.31-5.09 (dd, 2H).4.69 (t, 1H), 4.52 (dd, 1H), 4.21-3.96 (m, 10H), 2.81 (m, 5H), 2.58 (m, 1H), 2.20 (m, 1H), 1.94 (m, 1H), 1.85-1.60 (m, 4H), 1.45 (m, 1H), 1.38 (s, 3H), 1.35 (s, 3H), 1.20 (m, 2H), 1.01 (s, 9H), 0.33 (m, 2H).

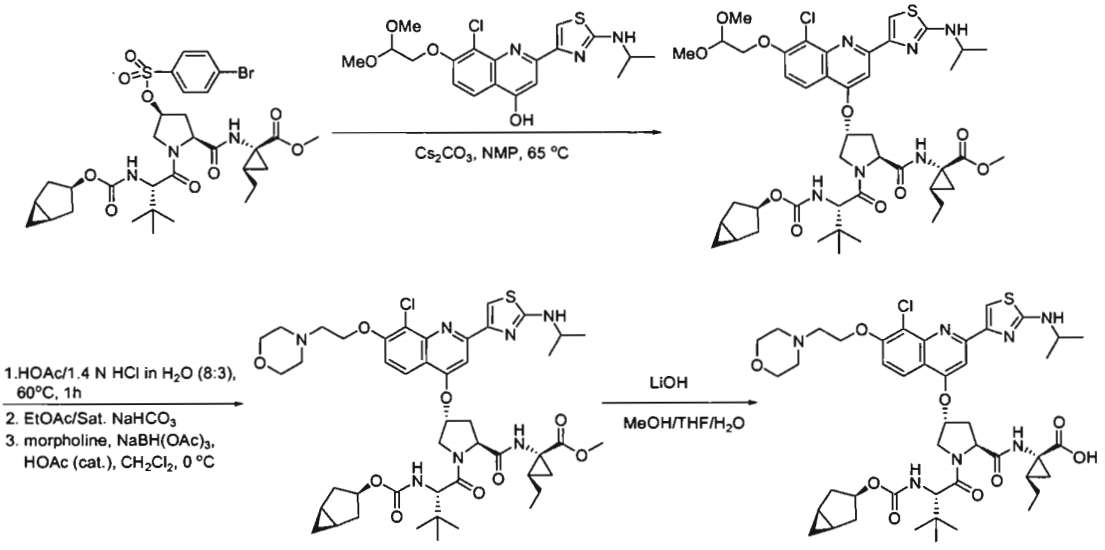
Example 27: Preparation of Compound 27



A mixture of compound **26** (320 mg, 0.388 mmol), p-$TsNHNH_2$ (542 mg, 2.91 mmol) and NaOAc (477 mg, 5,82 mmol) in a mixture of DME (10 mL) and H_2O (1 mL) was heated at 95°C for 2h. Upon completion of the reaction, it was cooled to room temperature, diluted with EtOAc (100mL) and the pH was adjusted to 3 with 1N HCl. After separation of the organic and aqueous layers, the aqueous layer was back extracted with EtOAc. The

organic layers were combined and concentrated. The crude product was purified by prep-HPLC to give compound **27** as a yellow solid (252 mg, 79%). LC/MS = 825 (M^++1). ^{1}H NMR (300 MHz, CD_3OD): δ 8.24 (d, 1H), 7.58 (d, 1H), 7.31 (s, 1H), 5.72 (m, 1H), 4.71 (t, 1H), 4.58 (dd, 1H), 4.43 (t, 1H), 4.14 (s, 3H), 4.05 (m, 1H), 3.93 (m, 1H), 2.81 (s, 3H), 2.59 (m, 1H),2.40 (dd, 2H), 1.94 (m, 1H), 1.80 (m, 1H), 1.64 (m, 3H), 1.52 (m, 1H), 1.38 (s, 3H), 1.36 (s, 3H), 1.27 (m, 2H), 1.01 (s, 9H), 0.33 (m, 2H).

Example 28: Preparation of Compound 28

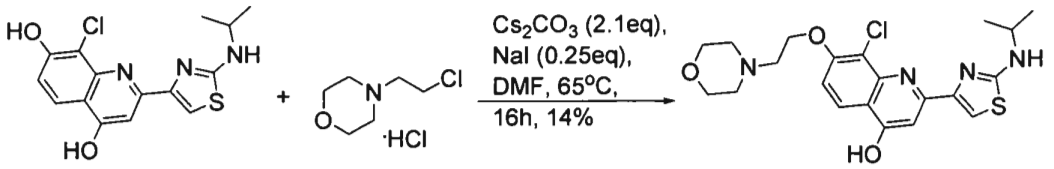


Step 1: To a mixture of brosylate intermediate **III** (15 g, 35 mmol) and **IV** (27.5 g, 38.5 mmol) in NMP (200 ml) was added cesium carbonate (25.1 g, 77 mmol). The mixture was stirred at 65 °C for 5 h. The reaction was cooled to room temperature and EtOAc (600 ml) and an aqueous solution of 3% LiCl (600 ml) were added to the mixture. The organic layer was washed with aqueous 3% LiCl (1 x 600 ml), brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give the desired methyl ester as a yellow solid (23.6 g, 75%). LC/MS = 900.13(M^++1).

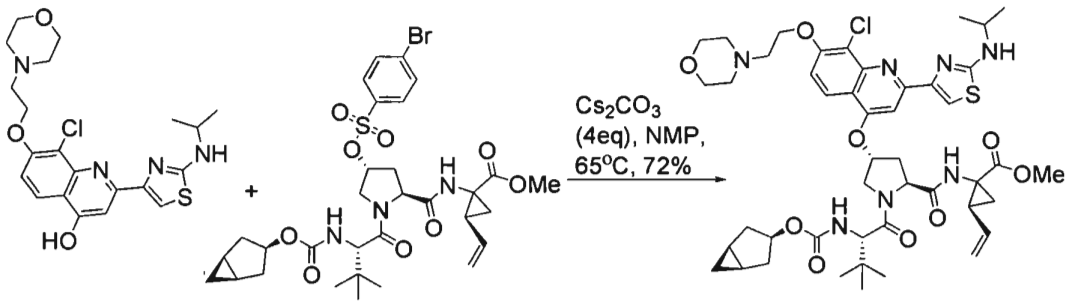
Step 2: Methyl ester (23.6 g, 26 mmol) was dissolved in glacial acetic acid (200 ml), 1.4 N HCl in H_2O (75 ml) was added to the solution. The mixture was stirred at 60 °C for 1 h. Upon completion of the reaction, the mixture was concentrated to remove the solvents, coevaporated with toluene (x 2) to remove residual acetic acid. The residue was then dissolved in EtOAc (500 ml) and sat. NaHCO3 aqueous solution (enough to neutralize the mixture) while monitoring CO_2 evolution. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was further dried under high vacuum for 1 h and used as is for the next step. The crude was dissolved in CH_2Cl_2 (360 ml), morpholine (3.4 g, 39 mmol) and sodium triacetoxyborohydride (7.2 g, 34 mmol) were added to the mixture at 0 °C. Then glacial acetic acid (0.47 g, 7.8 mmol) was added dropwise to the mixture. The reaction was complete in 10 min at 0 °C. Sat. $NaHCO_3$ aqueous solution was added to quench the reaction. After stirring for another 20 min, the organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give the desired amine product as a yellow solid (12 g, 50%). LC/MS = 924.63(M^++1).

Step 3: Amine (12 g, 13 mmol) was dissolved in THF (200 ml), LiOH (11g, 260 mmol) in H_2O (200 ml) was added, followed by MeOH (200 ml). The mixture was kept stirring at room temperature for 20 h. Upon completion of the reaction, 4 N HCl in H_2O was added to adjust pH to 7 at 0 °C. The mixture was extracted with EtOAc (2 x 400 ml). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give the Compound **28** as a yellow solid (11 g, 93%). LC/MS = 911.52(M^++1). ^{1}H NMR (300MHz, CD_3OD) δ 7.95 (d, 1H), 7.90 (s, 1H), 7.48 (s, 1H), 7.31 (d, 1H), 5.42 (s, 1H), 4.37 (dd, 1H), 4.20 (m, 2H), 3.83-3.56 (m, 7H), 3.50 (m, 2H), 3.39 (m, 2H), 2.45 (m, 1H), 2.27(m, 1H), 1.62 (m, 2H), 1.50 (m, 1H), 1.33 (m, 2H), 1.18 (m, 1H), 1.05 (m, 8H), 0.90 (m, 3H), 0.76 (m, 11H), 0.14-0.04 (m, 2H)

Example 29: Preparation of Compound 29

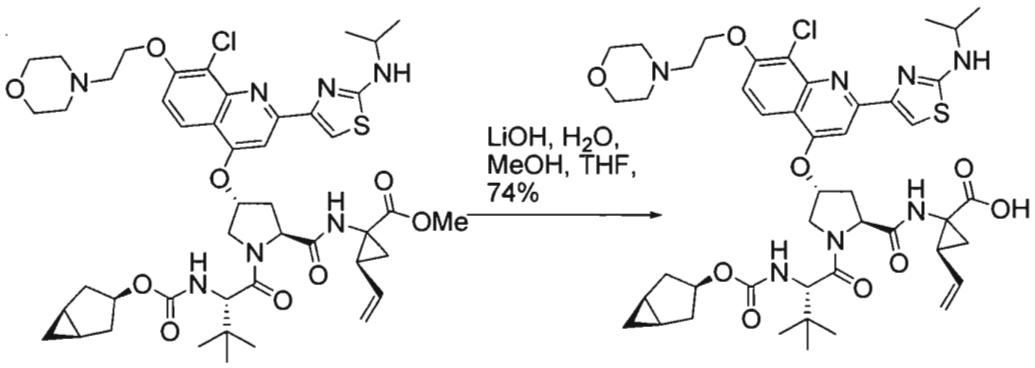


Step 1: An N_2 purged flask was charged with bisphenol (939mg, 2.79mmol), morpholine ethyl chloride (545mg, 2.93mmol), Cs_2CO_3 (1.9g, 5.87mmol), and NaI (84mg, 0.56mmol). To this mixture was then added DMF (20mL) and the heterogeneous mixture was heated in a preheated 65°C oil bath for 16h. The reaction was cooled to room temperature and aliquots were removed and filtered. The desired product was isolated from these aliquots by preparative reverse phase HPLC. This yielded the quinoline product as the TFA salt. Conversion to the HCl salt was effected by dissolving the TFA salt in a MeOH:4N HCl/dioxanes mixture and evaporating. This process was done three times to yield 200mg of product in a 14% yield. LC/MS = 449.32 (M^++1)



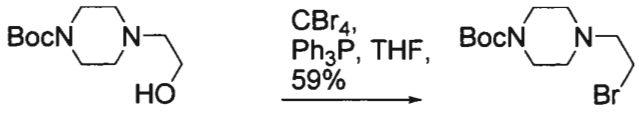
Step 2: An N_2 purged flask was charged with quinoline (200mg, 0.38mmol), brosylate (323mg, 0.456mmol), and Cs_2CO_3 (372mg, 0.76mmol). To this mixture was then added NMP (5mL) and the resulting heterogeneous mixture was heated in a preheated 65°C oil bath for 4.5h. No reaction as determined by LC/MS. Additional Cs_2CO_3 (124mg, 0.25mmol) was added. After 2h the brosylate was completely consumed, as determined by LC/MS, while quinoline remained. Additional brosylate (68mg, 0.095mmol) was added to the reaction and heating was continued overnight. The reaction was complete as determined by LC/MS and HPLC. The reaction was cooled to room temperature and

diluted with CH_2Cl_2. A small volume of 5% $LiCl_{(aq.)}$ was added to this and the layers were separated. The aqueous layer was back extracted with CH_2Cl_2 (1x) and the combined organic layers were clarified with MeOH and concentrated. The residue was re-dissolved in MeOH and 317mg of methyl ester (72% yield) was isolated as a yellow solid by reverse phase HPLC. LC/MS = 922.59 (M^++1).

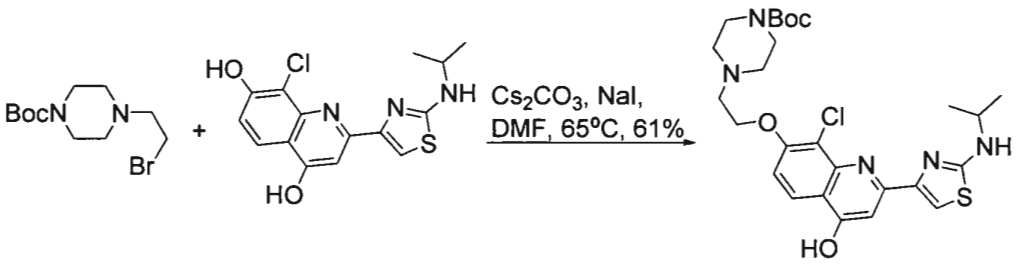


Step 3: Methyl ester (306mg, 0.266mmol) was dissolved in a mixture of THF (1.5mL) and MeOH (1mL), and the solution was cooled to 0°C. $LiOH{\cdot}H_2O$ (45mg, 1.06mmol) was dissolved in dH_2O (0.5mL) and this was slowly added to the solution of ester in THF/MeOH. Upon complete addition the ice bath was removed. After 2h the reaction was not complete. Additional $LiOH{\cdot}H_2O$ (23mg, 0.54mmol) was added. After another hour the reaction was still not complete, so additional $LiOH{\cdot}H_2O$ (23mg, 0.54mmol) was added. After another 3.5h the reaction appeared complete by HPLC. The reaction was cooled to 0°C and neutralized with 2N HCl. Compound **29** was directly isolated from the reaction mixture by reverse phase HPLC. 223mg (74% yield) of **29** was isolated as a yellow solid. LC/MS = 910.53 (M^++1). ^{1}H NMR (300MHz, CD_3OD) δ 8.33 (d, J = 9.3 Hz, 1H), 8.23 (s, 1H), 7.78 (s, 1H), 7.62 (d, J = 9.3 Hz, 1H), 5.86 (dd, J = 9.9, 16.5 Hz, 1H), 5.73 (s, 1H), 5.29 (d, J = 17.1 Hz, 1H), 5.11 (d, J = 10.2 Hz, 1H), 4.79 (s, 2H), 4.70 (t, J = 8.7 Hz, 1H), 4.56 (m, 2H), 4.20-3.92 (m, 8H), 3.83 (s, 3H), 3.59 (brds, 4H), 2.78 (dd, J = 7.2, 14.1 Hz, 1H), 2.61 (m, 1H), 2.21 (q, J = 8.9 Hz, 1H), 1.98 (m, 1H), 1.86 (m, 1H), 1.76-1.64 (m, 2H), 1.46 (m, 1H), 1.39 (d, J = 6.3 Hz, 6H), 1.19 (m, 2H), 1.04 (s, 12H), 0.38 (m, 2H).

Example 30: Preparation of Compound 30

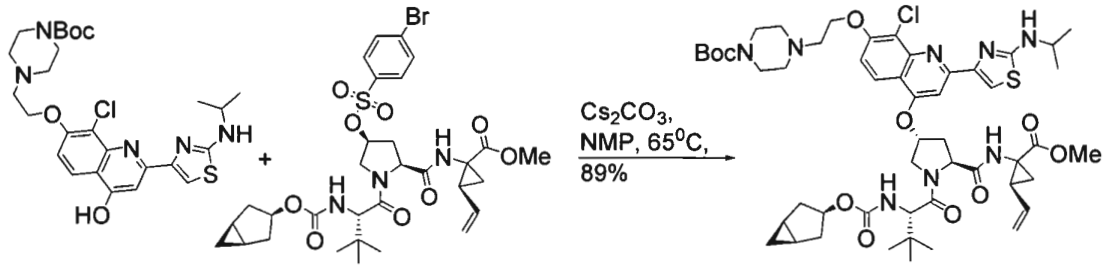


Step 1: Alcohol (3.42g, 0.015mmol) was dissolved in THF (55mL). To this solution was added CBr_4 (5.47g, 0.017mmol). Ph_3P (4.46g, 0.017mmol) was dissolved in THF (20mL) and slowly added to the reaction via an addition funnel. The reaction was stirred at room temperature for 16h. The reaction was complete as determined by TLC. The reaction was diluted with hexanes and the white precipitate that formed was removed by filtration. More solids crashed in the filtrate. The mixture was transferred to a separatory funnel and the organic layer was extracted with sat. $NaHCO_{3(aq.)}$ (2x), dH_2O (2x) and brine (1x). The organic layer was dried over Na_2SO_4 and a small amount of $MgSO_4$. The drying agents were removed by vacuum filtration and bromide (2.59g, 59% yield) was isolated from the filtrate by silica gel column chromatography, eluting with a mixture of EtOAc/hexanes. The bromide was isolated as a colorless oil that turns to a crystalline solid upon sitting. LC/MS = 293.02 (M^++1).

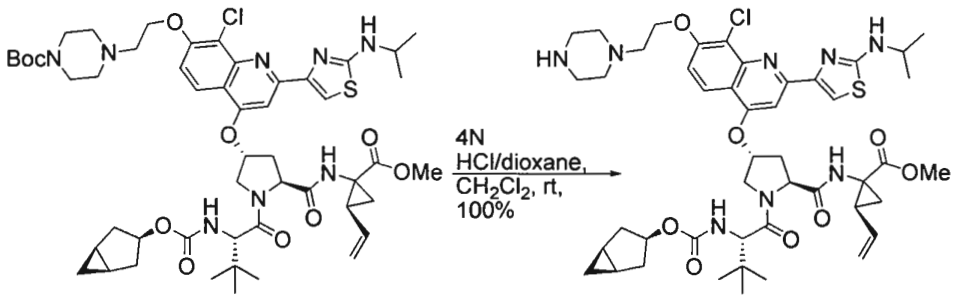


Step 2: An N_2 purged flask was charged with the bromide (738mg, 2.5mmol), bisphenol (1g, 2.4mmol), Cs_2CO_3 (1.21g, 3.7mmol) and NaI (72mg, 0.48mmol). To this mixture was added DMF (24mL) and the heterogeneous mixture was heated in a preheated 65°C oil bath. After 2h very little of the bromide remained. Additional bromide (141mg, 0.48mmol) was added to the reaction and heating continued for 16h. The reaction was complete, as determined by LC/MS, the next day. The reaction was cooled to room temperature and diluted with EtOAc. This mixture was extracted with 5% $LiCl_{(aq.)}$ basified

with a small amount of sat. $NaHCO_{3(aq.)}$ (2x) and brine (1x). The organic phase was then dried over Na_2SO_4 with a small amount of $MgSO_4$. After removal of the drying agents by vacuum filtration, the quinoline was isolated from the filtrate (800mg, 61%) as a yellow-brown solid. LC/MS = 548.26 (M^++1).

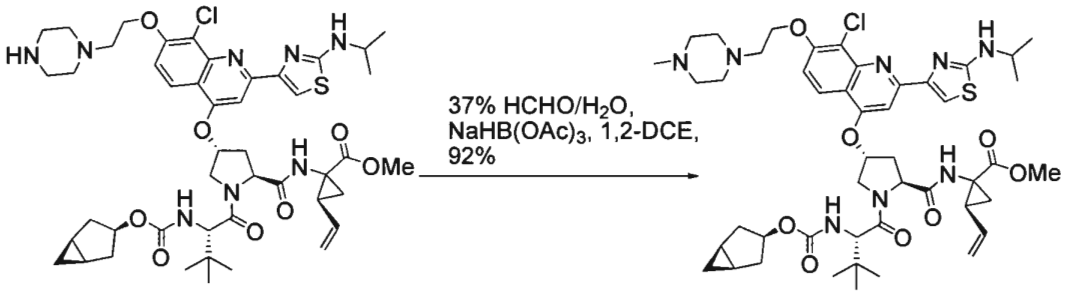


Step 3: An N_2 purged flask was charged with quinoline (800mg, 1.46mmol), brosylate (1.24g, 1.75mmol) and Cs_2CO_3 (570mg, 1.75mmol). To this mixture was then added NMP (14.6mL) and the resulting heterogeneous mixture was heated in a preheated 65°C oil bath. After 2h the reaction shows a lot of progress. Heating continued for another 9h and then the reaction was stirred at room temperature for 7h. The reaction was diluted with EtOAc and the resulting mixture was extracted with 5% $LiCl_{(aq.)}$ (2x), and brine (1x). The organic phase was then dried over Na_2SO_4 and a small amount of $MgSO_4$. The drying agents were removed by vacuum filtration. The methyl ester was isolated from the filtrate by silica gel column chromatography as a slightly yellow-brown solid (1.33g, 89%). LC/MS = 1021.75 (M^++1).

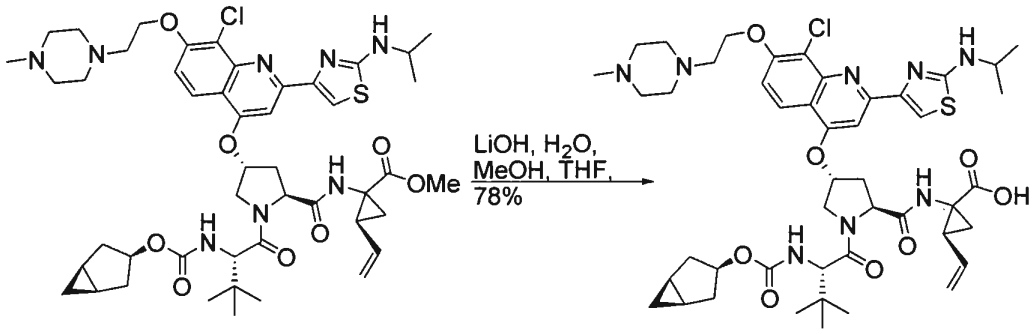


Step 4: The methyl ester (1.33g, 1.3mmol) was dissolved in CH_2Cl_2 (10mL). This solution was cooled to 0°C and 4N HCl in dioxanes (3.25mL, 13mmol) was added

dropwise. The cold bath was then removed. The reaction was complete after 2h, as determined by LC/MS. The reaction was concentrated, re-dissolved in CH_2Cl_2, and concentrated again. The residue was re-dissolved in CH_2Cl_2 again and then extracted with sat. $NaHCO_{3(aq.)}$ (1x). The organic phase was dried over Na_2SO_4 and a small amount of $MgSO_4$. The drying agents were removed by vacuum filtration and the filtrate was concentrated to yield the amine as slightly yellow foam (1.23g, 100%).
LC/MS = 921.53 (M^++1).

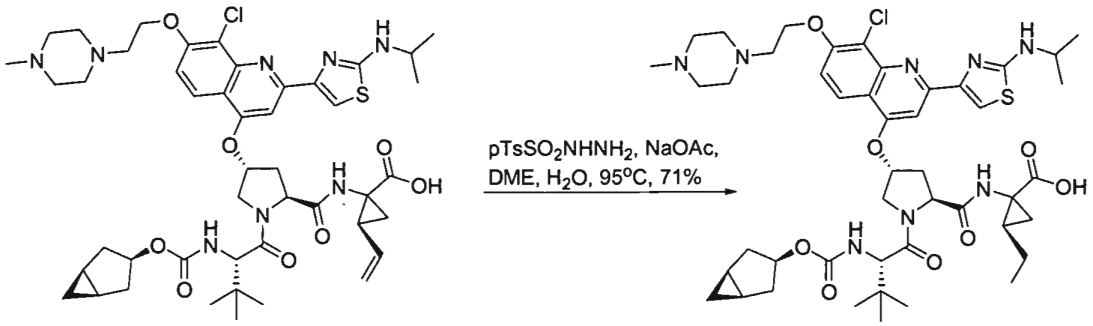


Step 5: The amine (608mg, 0.66mmol) was dissolved in 1,2-DCE (7mL). To this solution was added 37% $HCHO/H_2O$ (49μL, 0.66mmol). To this mixture was then added $NaHB(OAc)_3$ (560mg, 2.64mmol). The reaction was determined to be complete by LC/MS after 30min. The reaction was quenched by the addition of sat. $NaHCO_{3(aq.)}$. The reaction was then diluted with EtOAc and extracted with sat. $NaHCO_{3(aq.)}$ (3x) and brine (1x). The organic phase was then dried over Na_2SO_4 and a small amount of $MgSO_4$. The drying agents were removed by vacuum filtration and the filtrate was concentrated. The residue was re-dissolved in MeOH and this solution was concentrated. This MeOH dissolution and concentration was repeated 2 more times to yield the methyl amine (569mg, 92% yield) as a pink-orange foam. LC/MS = 935.59 (M^++1).



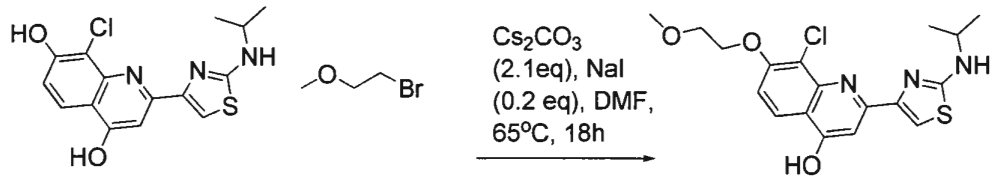
Step 6: The methyl ester (615mg, 0.658mmol) was dissolved in MeOH (2.2mL) and THF (3.3mL). This solution was cooled to 0°C and a solution of $LiOH \cdot H_2O$ (138mg, 3.29mmol) in dH_2O (0.5mL) was slowly added. The cold bath was then removed. After 3.5h reaction was complete, as determined by LC/MS and HPLC. The reaction was cooled to 0°C and quenched by the addition of 1N HCl. Compound **30** (590mg, 78% yield) was isolated from the quenched reaction, by reverse phase HPLC, as a yellow solid. LC/MS = 921.48 (M^++1). ^{1}H NMR (300MHz, CD_3OD) δ 8.30 (d, J = 10.2 Hz, 1H), 8.29 (s, 1H), 7.81(s, 1H), 7.62 (d, J = 10.2 Hz, 1H), 5.86 (dt, J = 9.9, 16.8 Hz, 1H), 5.76 (s, 1H), 5.28 (d, J = 17.1 Hz, 1H), 5.11 (d, J = 10.2 Hz, 1H), 4.72 (t, J = 8.4 Hz, 1H), 5.59 (d, J = 5.4 Hz, 3H), 4.47 (t, J = 6.3 Hz, 1H), 4.15 (s, 1H), 4.12-3.99 (m, 2H), 3.43 (s, 4H), 3.32-3.18 (m, 8H), 2.93 (s, 3H), 2.80 (dd, J = 6.6, 14.1 Hz, 1H), 2.61 (m, 1H), 2.22 (dd, J = 8.4, 9 Hz, 1H), 1.95 (m, 1H), 1.86-1.60 (m, 3H), 1.46 (dd, J = 5.4, 9.3 Hz, 1H), 1.38 (d, J = 6.6 Hz, 6H), 1.20 (m, 2H), 1.03 (s, 12H), 0.34 (m, 2H).

Example 31: Preparation of Compound 31



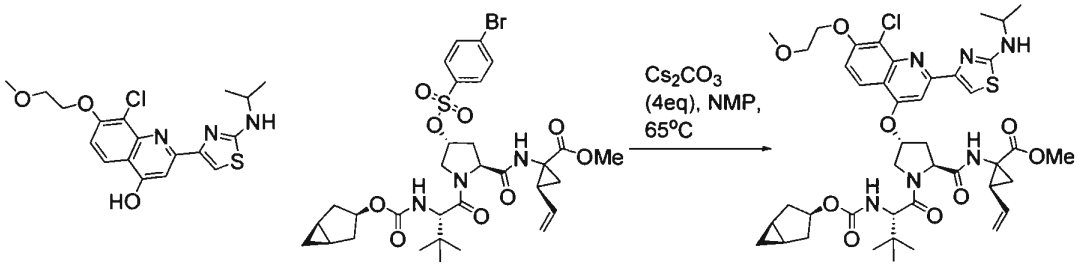
Compound **30** (97mg, 0.084mmol) was dissolved in DME (2mL). To this solution was added dH_2O (200uL), $pTolSO_2NHNH_2$ (117mg, 0.63mmol) and NaOAc (103mg, 1.26mmol). The reaction flask was then placed in a preheated 95°C oil bath for 2h. The reaction was determined to be complete by LC/MS. The reaction was cooled to room temperature and a small amount of MeOH was added to make the reaction mono-phasic. The reaction was then filtered and compound **31** (69mg, 71% yield) was isolated from the filtrate, by reverse phase HPLC, as a yellow solid. LC/MS = 923.52 (M^++1). ^{1}H NMR (300MHz, CD_3OD) δ 8.29 (d, J = 9 Hz, 1H), 8.28 (s, 1H), 7.80 (s, 1H), 7.60 (d, J = 9 Hz, 1H), 5.74 (s, 1H), 4.74-4.56 (m, 4H), 4.49 (t, J = 6.3 Hz, 1H), 4.15 (s, 1H), 4.18-3.99 (m, 2H), 3.53 (s, 6H), 3.47 (s, 6H), 2.96 (s, 3H), 2.78 (dd, J = 7.2, 14.1 Hz, 1H), 2.60 (m, 1H), 1.96 (m, 1H), 1.82 (m, 1H), 1.65 (m, 3H), 1.52 (t, J = 7.5 Hz, 1H), 1.43 (m, 2H), 1.39 (d, J = 6.3 Hz, 6H), 1.23 (q, J = 3.9 Hz, 2H), 1.20 (m, 1H), 1.02 (s, 14H), 0.37 (m, 2H).

Example 32: Preparation of Compound 32

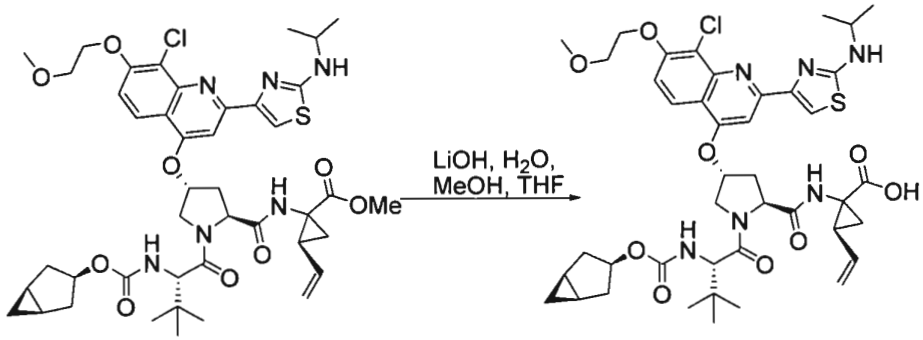


Step 1: A N_2 purged flask was charged with bisphenol (998mg, 2.97mmol), bromide (293μL, 3.11mmol), Cs_2CO_3 (2.03g, 6.24mmol), and NaI (89mg, 0.59mmol). To this mixture was then added DMF (33mL) and the heterogeneous mixture was heated in a

preheated 65°C oil bath for 7h and then cooled to room temperature and stirred overnight. The reaction mixture was taken up in 100 mL of EtOAc. The solids were filtered off and washed with 50 mL of EtOAc. The organics were combined and extracted with 3 X 100 mL of 5% LiCl aqueous, followed by brine. The organics were dried over Na_2SO_4, the solids were filtered off and the solvent removed under reduced pressure. The crude was taken up in 10 mL of methanol and purified by preparative reverse phase HPLC. This yielded quinoline as the TFA salt. Conversion to the HCl salt was effected by dissolving the TFA salt of quinoline in a MeOH:4N HCl/dioxanes mixture and evaporating. This process was done three times to afford 305mg of the quinoline in a 24% yield as a yellow solid. LC/MS = 394 (M^++1).

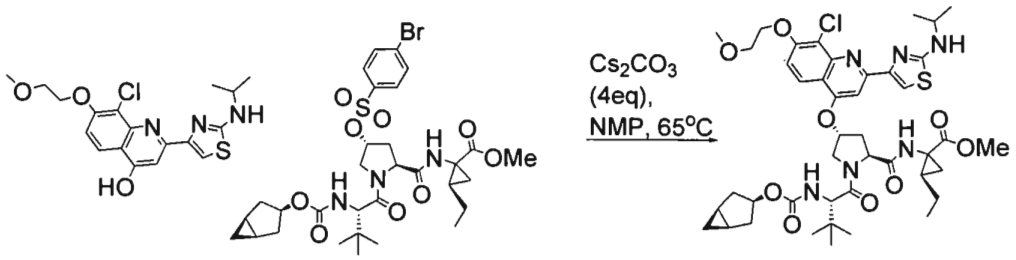


Step 2: A N_2 purged flask was charged with quinoline (305mg, 0.78mmol), brosylate (554mg, 0.78mmol), and Cs_2CO_3 (760mg, 2.34mmol). To this mixture was then added NMP (10mL) and the resulting heterogeneous mixture was heated in a preheated 65°C oil bath for 4.5h. The reaction was not proceeding, as determined by LC/MS. Additional Cs_2CO_3 (250mg, 0.78mmol) was added and the reaction was heated overnight. The reaction was complete as determined by LC/MS and HPLC. The reaction was cooled to room temperature and diluted with EtOAc. A small volume of 5% $LiCl_{(aq.)}$ was added to this and the layers were separated. The aqueous layer was back extracted with EtOAc (1x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was re-dissolved in DCM and 382mg of methyl ester (57% yield) was isolated as a yellow solid by silica gel chromatography. LC/MS = 868 (M^++1).

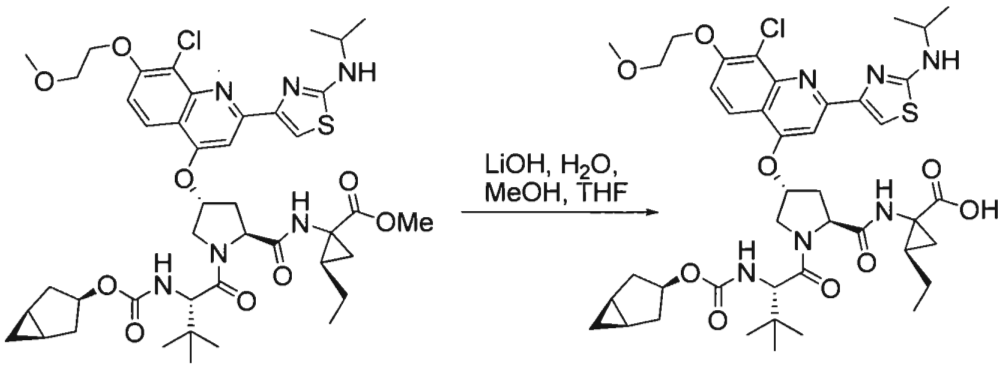


Step 3: The methyl ester (380mg, 0.44mmol) was dissolved in a mixture of THF (5mL) and MeOH (2.5mL) and cooled to 0°C. $LiOH{\cdot}H_2O$ (32mg, 1.32mmol) was dissolved in dH_2O (2.5mL) and this was slowly added to the solution of ester in THF/MeOH. Upon complete addition the ice bath was removed. After 2h the reaction was not complete. Additional $LiOH{\cdot}H_2O$ (32mg, 1.32mmol) was added. After another hour the reaction was still not complete, so additional $LiOH{\cdot}H_2O$ (32mg, 1.32mmol) was added. After another 3.5h the reaction appeared complete by HPLC. The reaction was cooled to 0°C and neutralized with 2N HCl. Compound **32** was directly isolated from the reaction mixture by reverse phase HPLC. 235mg (63% yield) of **32** was isolated as a yellow solid. LC/MS = 853 (M^++1). ^{1}H NMR (300MHz, CD_3OD) d 8.75 (s, 1H), 8.29 (s, 1H), 8.27 (d, J = 9.4Hz, 1H), 7.83 (s, 1H), 7.68 (d, J = 9.4 Hz, 1H), 5.86 (dd, J = 9.1, 16.5 Hz, 1H), 5.77 (s, 1H), 5.31 (d, J = 17.4 Hz, 1H), 5.13 (d, J = 11 Hz, 1H), 4.75 (t, J = 8.9 Hz, 1H), 4.62 (d, J = 12.2 Hz, 1H), 4.52 (s, 1H), 4.41 (m, 1H), 4.13-4.05 (m, 4H), 3.87 (s, 3H), 3.31 (s, 3H), 2.76 (m, 1H), 2.61 (m, 1H), 2.22 (q, J = 8.7 Hz, 1H), 1.92-1.59 (m, 7H), 1.48 (m, 1H), 1.39 (d, J = 6.4 Hz, 6H), 1.20 (m, 2H), 1.02 (s, 9H), 0.49-0.32 (m, 3H).

Example 33: Preparation of Compound 33



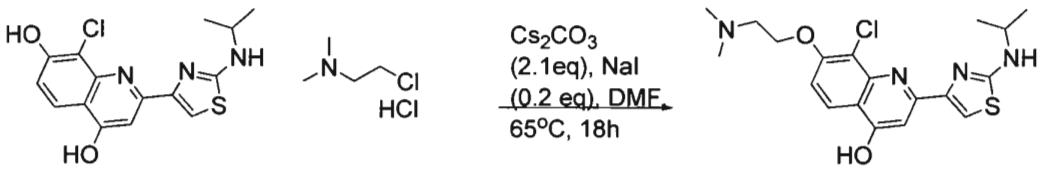
Step 1: A N_2 purged flask was charged with quinoline (810mg, 2.05mmol), intermediate **III** (1.46g, 2.05mmol), and Cs_2CO_3 (1.39g, 4.3mmol). To this mixture was then added NMP (10mL) and the resulting heterogeneous mixture was heated in a preheated 65°C oil bath for 16h. The reaction was complete as determined by LC/MS and HPLC. The reaction was cooled to room temperature and diluted with EtOAc. A small volume of 5% $LiCl_{(aq.)}$ was added to this and the layers were separated. The aqueous layer was back extracted with EtOAc (1x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was re-dissolved in DCM and 382mg of the methyl ester (63% yield) was isolated as a yellow solid by silica gel chromatography. LC/MS = 869 (M^++1)



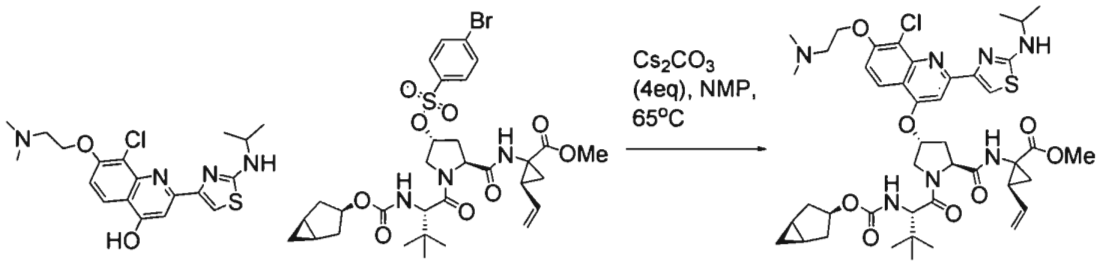
Step 2: The methyl ester (1.12g, 1.29mmol) was dissolved in a mixture of THF (5mL) and MeOH (2.5mL). LiOH (309mg, 12.9mmol) was dissolved in dH_2O (4mL) and this was slowly added to the solution of the ester in THF/MeOH, which had been cooled to 0°C. Upon complete addition the ice bath was removed. After 4h the reaction was 70% complete. The reaction was allowed to stir at room temperature overnight. Additional

$LiOH{\cdot}H_2O$ (32mg, 1.32mmol) was added. After another 3.5h the reaction appeared complete by HPLC. The reaction was cooled to 0°C and neutralized with 2N HCl. Compound **33** was directly isolated from reaction mixture by reverse phase HPLC. 913 mg (83% yield) of **33** was isolated as a yellow solid. LC/MS = 855 (M^++1). ^{1}H NMR (300MHz, CD_3OD) δ 8.64 (s, 1H), 8.30 (s, 1H), 8.26 (d, J = 9.5 Hz, 1H), 7.83 (s, 1H), 7.67 (d, J = 9.5 Hz, 1H), 5.76 (s, 1H), 4.75 (t, J = 8.3 Hz, 1H), 4.62 (t, J = 11.9 Hz, 1H), 4.51 (s, 2H), 4.40 (m, 1H), 4.13-4.05 (m, 4H), 3.87 (s, 3H), 3.31 (s, 3H), 2.78 (m, 1H), 2.60 (m, 1H), 1.94-1.59 (m, 9H), 1.48 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 1.21 (m, 2H), 1.01 (s, 9H), 0.36-0.32 (m, 3H).

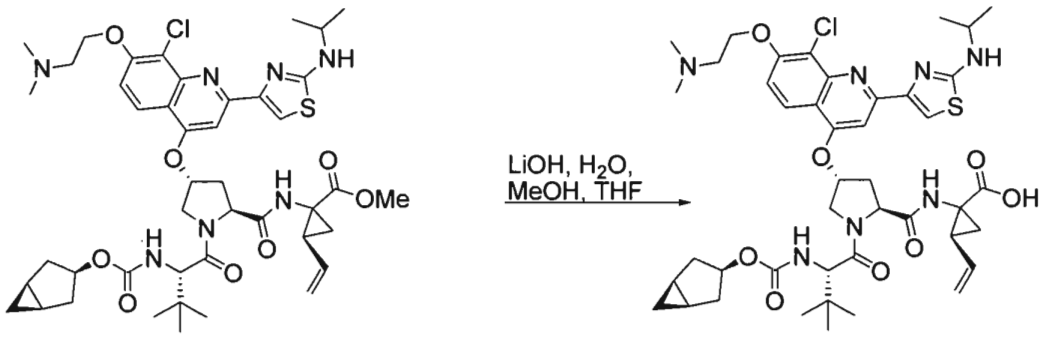
Example 34: Preparation of Compound 34



Step 1: A N_2 purged flask was charged with bisphenol (1.02g, 2.98mmol), chloride (471mg, 3.27mmol), Cs_2CO_3 (2.01g, 6.23mmol), and NaI (89mg, 0.59mmol). To this mixture was then added DMF (24mL) and the heterogeneous mixture was heated in a preheated 65°C oil bath for 7h. No reaction progress was detected by LC/MS. Heating was continued overnight. The next day, <20% conversion by LC/MS was observed. An additional 0.8 equivalents of NaI was added and the temperature was increased to 85 °C. The reaction mixture was heated again overnight. LC/MS indicated complete conversion. The reaction mixture was filtered through a loose pack of C18. Solvent was then removed under reduced pressure. The crude material was taken up in 10 mL of methanol. The quinoline was purified by preparative reverse phase HPLC. This yielded the quinoline as the TFA salt. Conversion to the HCl salt was effected by dissolving the TFA salt in a MeOH:4N HCl/dioxanes mixture and evaporating. This process was done three times to yield 327mg of quinoline HCl salt in a 25% yield. LC/MS = 408 (M^++1).



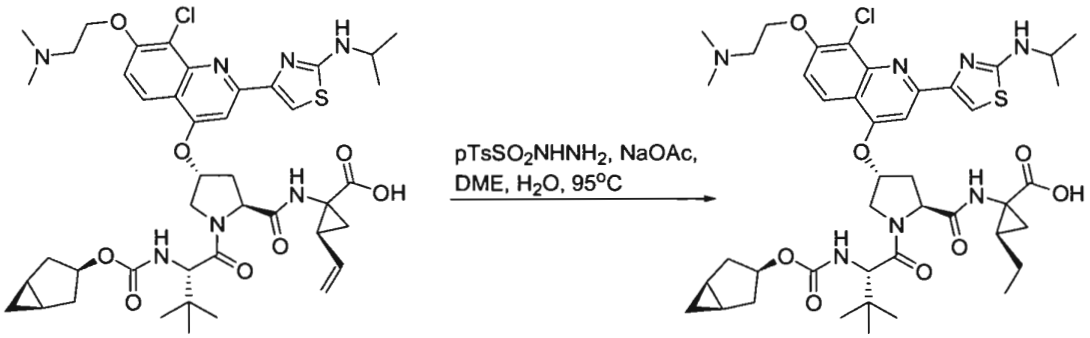
Step 2: A N_2 purged flask was charged with quinoline (180mg, 0.375mmol), brosylate (400mg, 0.563mmol), and Cs_2CO_3 (366mg, 1.13mmol). To this mixture was then added NMP (5.6mL) and the resulting heterogeneous mixture was heated in a preheated 65°C oil bath for 4.5h. There was no reaction progress, as determined by LC/MS. Additional Cs_2CO_3 (150mg, 0.45mmol) was added and the reaction was heated overnight. The reaction was complete as determined by LC/MS and HPLC. The reaction was cooled to room temperature and diluted with EtOAc. A small volume of 5% $LiCl_{(aq.)}$ was added to this and the layers were separated. The aqueous layer was back extracted with EtOAc (1x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was re-dissolved in DCM and 237mg of the methyl ester (42% yield) was isolated as a yellow solid by silica gel chromatography. LC/MS = 881 (M^++1).



Step 3: The methyl ester (237mg, 0.269mmol) was dissolved in a mixture of THF (1.5mL) and MeOH (1mL). $LiOH{\cdot}H_2O$ (30mg, 1.07mmol) was dissolved in dH_2O (0.5mL) and this was slowly added to the solution of ester in THF/MeOH, which had been cooled to 0°C. Upon complete addition the ice bath was removed. After 4h the reaction was 40%

complete. The reaction was allowed to stir at room temperature overnight. The reaction was cooled to 0°C and neutralized with 2N HCl. Compound **34** was directly isolated from the reaction mixture by reverse phase HPLC. 218mg (94% yield) of **34** was isolated as a yellow solid. LC/MS = 867 (M^++1).

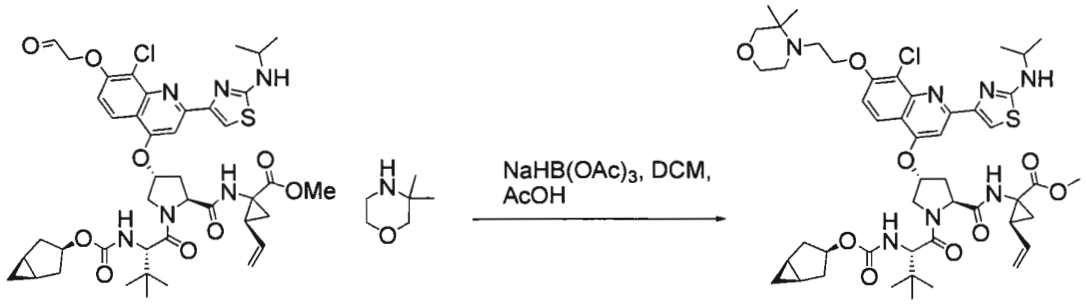
Example 35: Preparation of Compound 35



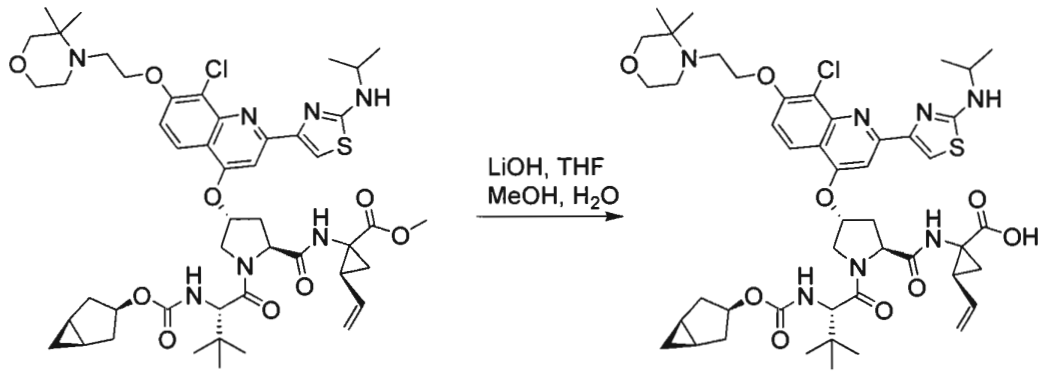
Compound **34** (145mg, 0.167mmol) was dissolved in DME (1.5mL). To this solution was added dH_2O (150uL), $pTolSO_2NHNH_2$ (187mg, 1.0mmol) and NaOAc (150mg, 1.84mmol). The reaction flask was then placed in a preheated 95°C oil bath for 2h. The reaction was determined to be complete by LC/MS. The reaction was cooled to room temperature and a small amount of MeOH was added to make the reaction mono-phasic. The reaction was then filtered and **35** (97mg, 63% yield) was isolated from the filtrate, by reverse phase HPLC, as a yellow solid.

LC/MS = 868 (M^++1).

Example 36: Preparation of Compound 36

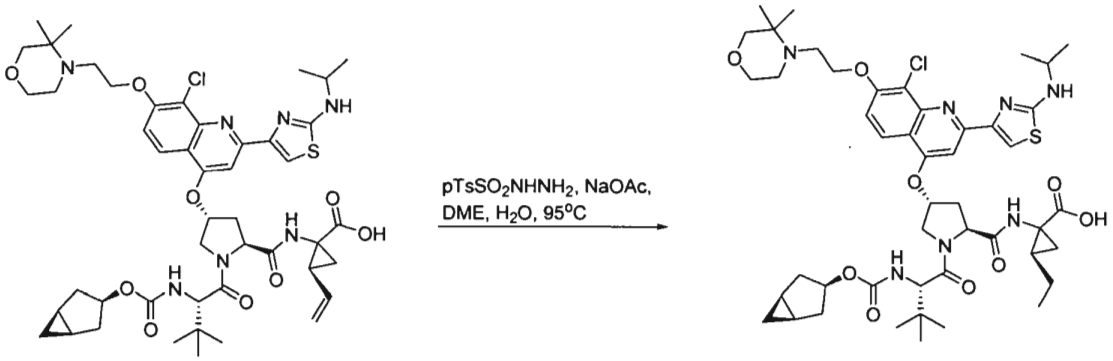


Step 1: Aldehyde (prepared in similar manner to example **28**) (1.17g, 1.38mmol) was dissolved in DCM (15mL). To this solution was added morpholine (239mgs, 2.07mmol). To this mixture was then added $NaHB(OAc)_3$ (380mg, 1.79mmol), followed immediately by AcOH (24μL, 0.414mmol). The reaction was determined to be complete by LC/MS after 10min. The reaction was quenched by the addition of half sat. $NaHCO_{3(aq.)}$. The reaction was then diluted with DCM and extracted with sat. $NaHCO_{3(aq.)}$ (3x) and brine (1x). The organic phase was then dried over Na_2SO_4. The drying agents were removed by vacuum filtration and the filtrate was concentrated. The residue was re-dissolved in MeOH and this solution was concentrated. This MeOH dissolution and concentration was repeated 2 more times. The crude material was taken up in minimal DCM and purified by silica gel chromatography to yield the methyl ester (908mg, 70% yield) as a yellow solid. LC/MS = 950 (M^++1).



Step 2: Methyl ester (772mg, 0.813mmol) was dissolved in a mixture of THF (7mL) and MeOH (5mL). $LiOH{\cdot}H_2O$ (171mg, 4.07mmol) was dissolved in dH_2O (3mL) and this was slowly added to the solution of ester in THF/MeOH, which had been cooled to 0°C. Upon complete addition the ice bath was removed. After 3h the reaction was complete. The reaction was cooled to 0°C and neutralized with 2N HCl. Compound **36** was extracted into EtOAc. The organics were then extracted with 1N HCl, brine, and then dried over Na_2SO_4. The solids were removed by filtration and the organics removed under reduced pressure. Compound **36** (701 mgs) was isolated as a yellow solid using prep-HPLC. LC/MS = 936 (M^++1).

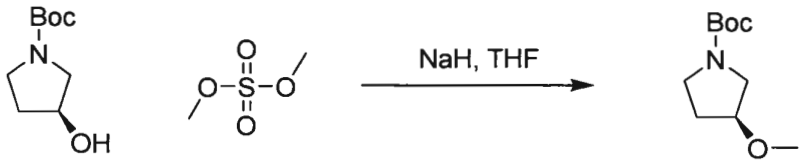
Example 37: Preparation of Compound 37



Compound **36** (701mg, 0.748mmol) was dissolved in DME (5mL). To this solution was added dH_2O (500uL), $pTolSO_2NHNH_2$ (697mg, 3.74mmol) and NaOAc (613mg, 7.48mmol). The reaction flask was then placed in a preheated 95°C oil bath for 2h. The reaction was determined to be complete by LC/MS. The reaction was cooled to room temperature and a small amount of MeOH was added to make the reaction mono-phasic. The reaction was then filtered and **37** (802mg, 92% yield) was isolated from the filtrate, by

reverse phase HPLC, as a yellow solid. LC/MS = 938 (M^++1). ^{1}H NMR (400MHz, CD_3OD) δ 8.26 (s, 1H), 7.98 (d, J = 9.4 Hz, 1H), 7.86 (s, 1H), 7.42 (s, 1H), 7.24 (d, J = 9.5 Hz, 1H), 5.36 (s, 1H), 4.51 (s, 6H), 4.38-4.19 (m, 5H), 3.82-3.45 (m, 5H), 2.53-2.32 (m, 3H), 1.84 (m, 1H), 1.66-1.28 (m, 5H), 1.18 (s, 7H), 1.03 (d, J = 6.5 Hz, 6H), 0.89 (m, 1H), 0.67 (s, 14H), 0.14-0.04 (m, 2H).

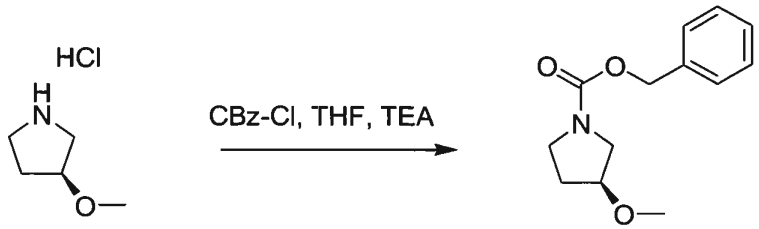
Example 38: Preparation of Compound 38



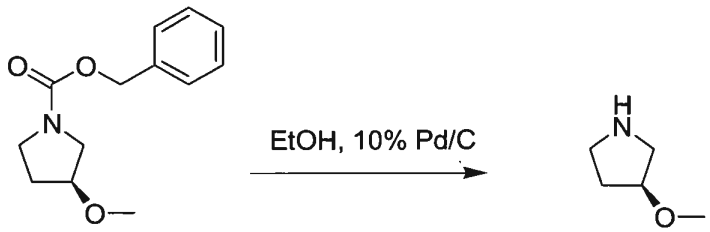
Step 1: An Ar purged flask was charged with 60% NaH (4.26g, 106mmol) and THF (60mL). The alcohol (5g, 26.67mmol) in solution with THF (40mL), was slowly added. The mixture was stirred at room temperature for 30min then dimethylsulfate (5.07mL, 53.3mmol) was added. The reaction was stirred at room temperature overnight. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (note: extreme outgassing). The mixture was stirred for 15min and then the organic layer was separated from the aqueous layer. The aqueous layer was extracted with EtOAc. The organics were combined and concentrated under reduced pressure. The residue was taken up in EtOAc and washed with ½ sat $NaHCO_{3(aq)}$ followed by brine. The organics were dryed over Na_2SO_4, filtered and solvent was removed under reduced pressure to afford the crude methyl ether (8.56g, 42.03mmol) as a colorless oil. LC/MS = 202 (M^+ + 1).



Step 2: An Ar purged flask was charged with the methyl ether (8.56g, 42.03mmol), followed by DCM (30mL). 4.0 N HCl in dioxane (30mL, 120mmol) was slowly added. The reaction was stirred at room temperature for 2h. The reaction was determined to be complete by LC/MS. The solvent was removed under reduced pressure to afford crude amine (7g, 50mmol) and used as is for the next step. LC/MS = 102 ($M^+ + 1$).

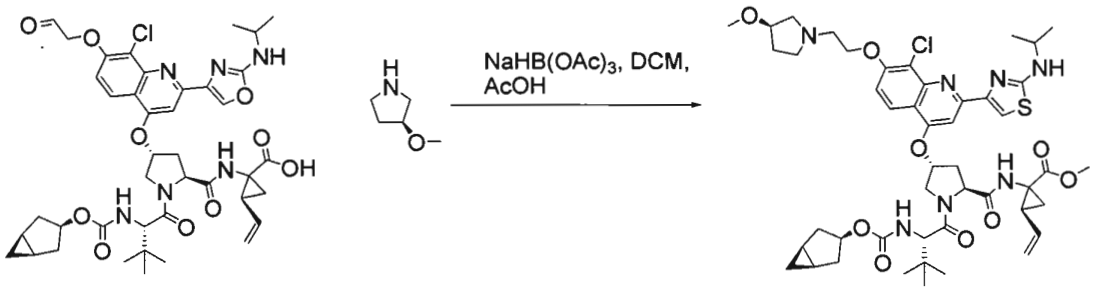


Step 3: An Ar purged flask was charged with amine (7g, 50mmol), THF (150mL), CBz-Cl (10.7mL, 76mmol) and cool to 0°C with an ice bath. Et_3N (21.1mL, 150mmol) was slowly added. The reaction was monitored by LCMS. The reaction is complete after 1h. The solvent was removed under reduced pressure. The residue was taken up in EtOAc and washed with 0.5N $HCl_{(aq)}$, brine, and dryed over Na_2SO_4. The solvent was removed under reduced pressure. The residue was dissolved in minimal DCM and purified by silica gel chromatography to afford the carbamate (4.52g, 72% overall yield) as a white solid. LC/MS = 236 ($M^+ + 1$).

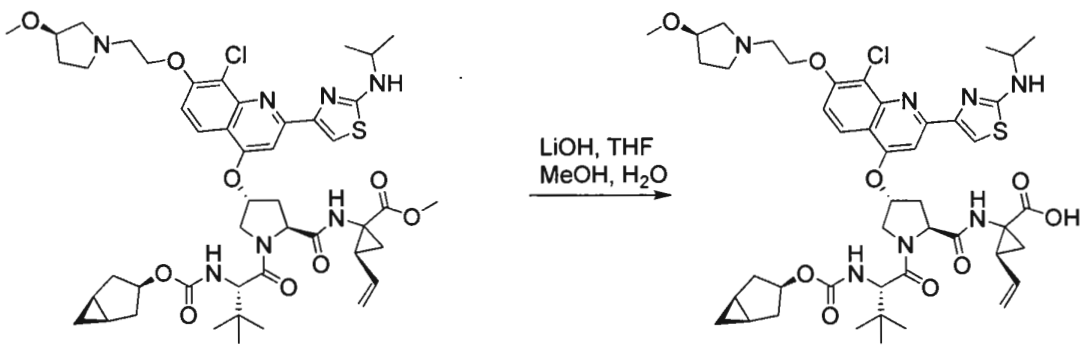


Step 4: An Ar purged flask was charged with carbamate (4.5g, 19.1mmol) and EtOH (50mL). The flask was evacuated and re-pressurized with Ar. This process was repeated three times. The reaction flask was then charged with 10% Pd/C, and the flask was evacuated. The flask was then refilled with an atmosphere of H_2. The reaction was stirred at room temperature under an H_2 atmosphere, monitoring the reaction progress by LC/MS.

The reaction was complete after 3h. The solids were removed by vacuum filtration using a PTFE filter. The filtrate was concentrated under reduced pressure. The residue was coevaporated with EtOAc 3 X 50mL to afford the crude amine (2.03g, 20.0mmol) as a colorless oil. LC/MS = 102 (M^+ + 1).

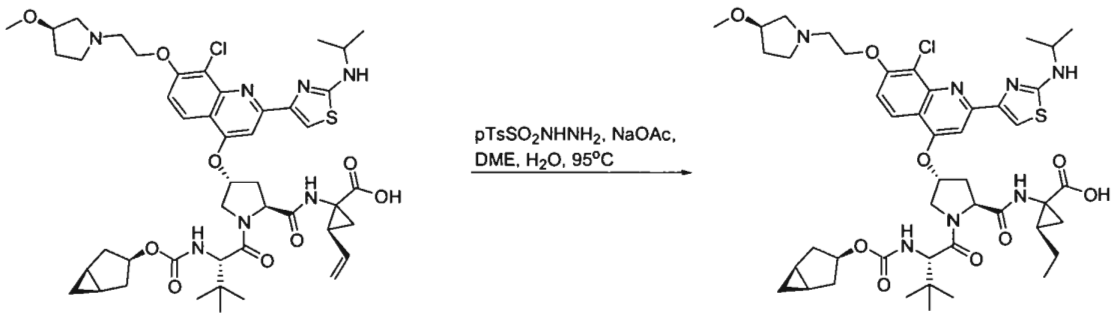


Step 5: The aldehyde (1.00g, 1.17mmol) was dissolved in DCM (15mL), and the amine (176mgs, 1.75mmol) was added. To this mixture was then added $NaHB(OAc)_3$ (322mg, 1.52mmol), followed immediately by AcOH (20μL, 0.3mmol). The reaction was determined to be complete by LC/MS after 10min. The reaction was quenched by the addition of ½ sat. $NaHCO_{3(aq.)}$. The reaction was then diluted with DCM and extracted with sat. $NaHCO_{3(aq.)}$ (3x) and brine (1x). The organic phase was then dried over Na_2SO_4. The drying agents were removed by vacuum filtration and the filtrate was concentrated. The residue was re-dissolved in MeOH and this solution was concentrated. This MeOH dissolution and concentration was repeated 2 more times to afford the crude methyl ester (968mg, 88% yield) as a yellow solid. LC/MS = 936 (M^++1).



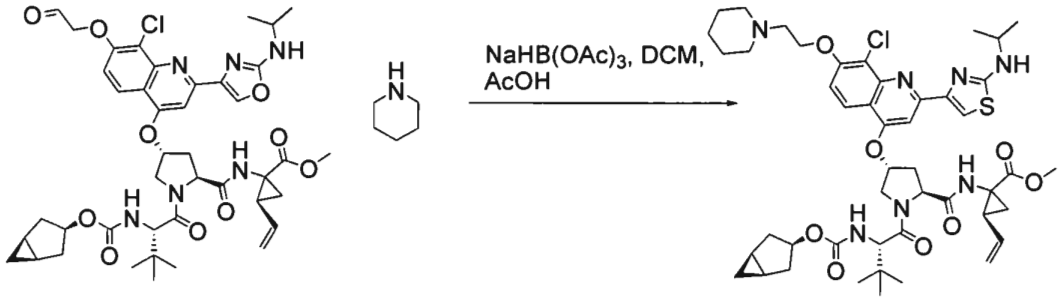
Step 6: The ester (968mg, 1.03mmol) was dissolved in a mixture of THF (10mL) and MeOH (6mL). LiOH (200mg, 4.67mmol) was dissolved in dH_2O (3mL) and this was slowly added to the solution of ester in THF/MeOH, which had been cooled to 0°C. Upon complete addition the ice bath was removed. After 3h the reaction was complete. The reaction was cooled to 0°C and neutralized with 2N HCl. Compound **38** was extracted into EtOAc, which was then extracted with 1N HCl, and brine. The organics were then dried over Na_2SO_4. The solids were removed by filtration and the volatile organics removed under reduced pressure. Compound **38** (900 mgs) was isolated as a yellow solid. LC/MS = 922 (M^++1).

Example 39: Preparation of Compound 39

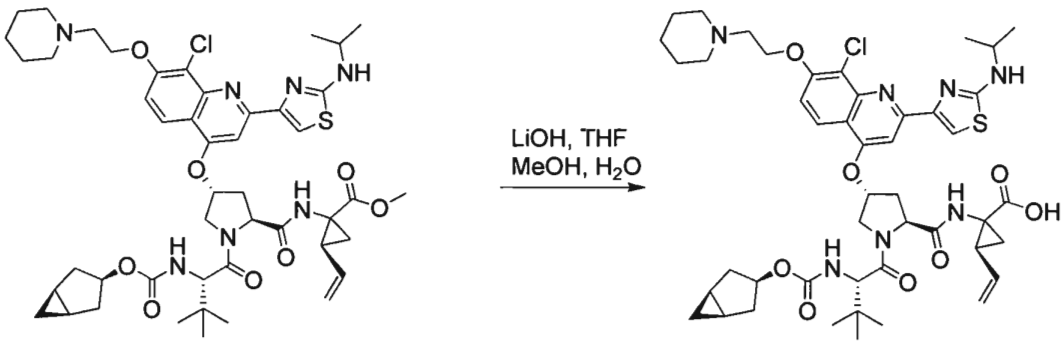


Compound **38** (900mg, 0.977mmol) was dissolved in DME (5mL). To this solution was added dH_2O (1mL), $pTolSO_2NHNH_2$ (920mg, 4.93mmol) and NaOAc (850mg, 10.36mmol). The reaction flask was then placed in a preheated 95°C oil bath for 2h. The reaction was determined to be complete by LC/MS. The reaction was cooled to room temperature and a small amount of MeOH was added to make the reaction mono-phasic. The reaction was then filtered and **39** (686mg, 76% yield) was isolated from the filtrate, by reverse phase HPLC, as a yellow solid. LC/MS = 924 (M^++1).

Example 40: Preparation of Compound 40



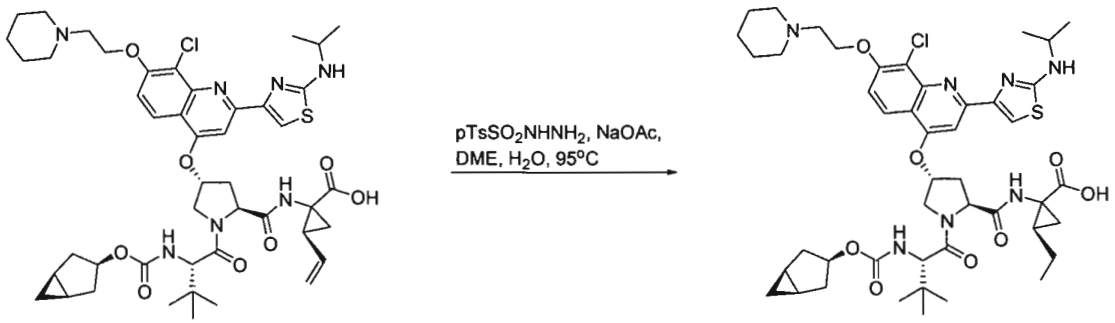
Step 1: The aldehyde (1.00g, 1.17mmol) was dissolved in DCM (15mL). To this solution was added piperidine (173μL, 1.75mmol). To this mixture was then added $NaHB(OAc)_3$ (322mg, 1.52mmol), followed immediately by AcOH (20μL, 0.3mmol). The reaction was determined to be complete by LC/MS after 10min. The reaction was quenched by the addition of ½ sat. $NaHCO_{3(aq.)}$. The reaction was then diluted with DCM and extracted with sat. $NaHCO_{3(aq.)}$ (3x) and brine (1x). The organic phase was then dried over Na_2SO_4. The drying agents were removed by vacuum filtration and the filtrate was concentrated. The residue was re-dissolved in MeOH and this solution was concentrated. This MeOH dissolution and concentration was repeated 2 more times to afford the crude ester (964mg, 90% yield) as a yellow solid. LC/MS = 920 (M^++1).



Step 2: Ester (964mg, 1.02mmol) was dissolved in a mixture of THF (10mL) and MeOH (6mL). LiOH (200mg, 4.67mmol) was dissolved in dH_2O (3mL) and this was slowly added to the solution of ester in THF/MeOH, which had been cooled to 0°C. Upon complete addition the ice bath was removed. After 3h the reaction was complete. The reaction was cooled to 0°C and neutralized with 2N HCl. Compound **40** was extracted into EtOAc, which was then extracted with 1N HCl, and then brine. The organics were then

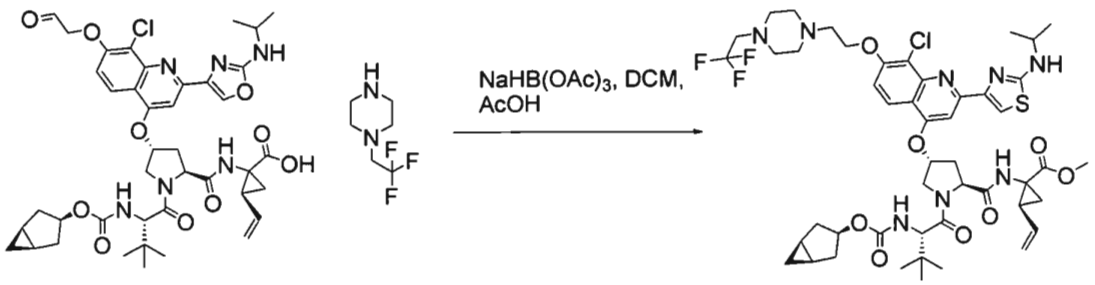
dried over Na_2SO_4. The solids were removed by filtration and the volatile organics removed under reduced pressure. Compound **40** (900 mg) was isolated as a yellow solid. LC/MS = 906 (M^++1).

Example 41: Preparation of Compound 41

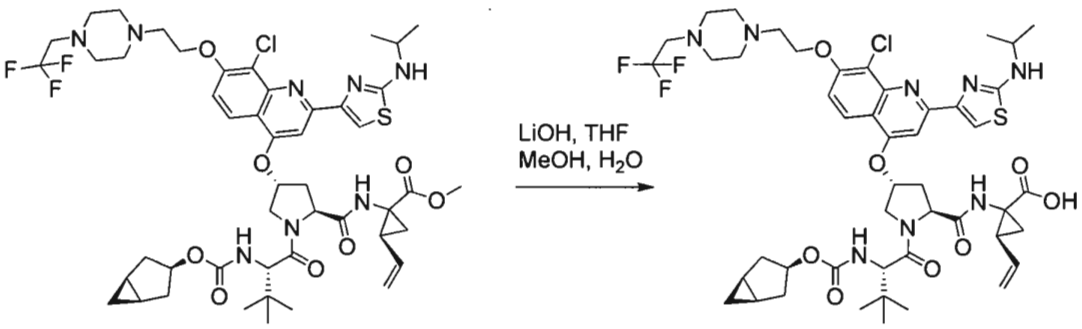


Compound **40** (900mg, 0.977mmol) was dissolved in DME (5mL). To this solution was added dH_2O (1mL), $pTolSO_2NHNH_2$ (920mg, 4.93mmol) and NaOAc (850mg, 10.36mmol). The reaction flask was then placed in a preheated 95°C oil bath for 2h. The reaction was determined to be complete by LC/MS. The reaction was cooled to room temperature and a small amount of MeOH was added to make the reaction mono-phasic. The reaction was then filtered and **41** (631mg, 69% yield) was isolated from the filtrate, by reverse phase HPLC, as a yellow solid. LC/MS = 908 (M^++1).

Example 42: Preparation of Compound 42



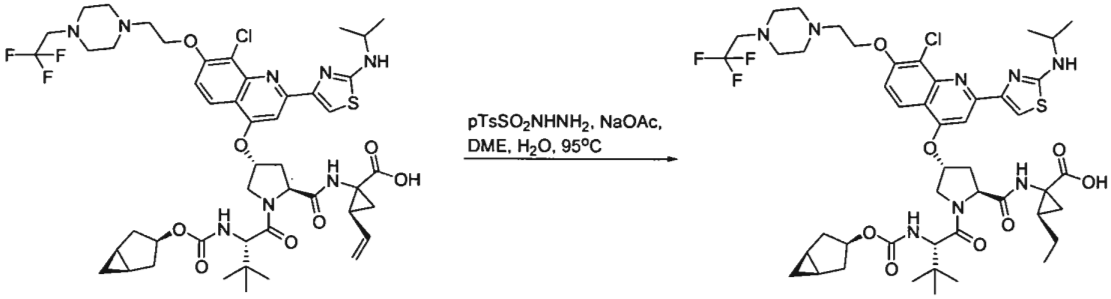
Step 1: The aldehyde (0.5g, 0.584mmol) was dissolved in DCM (8mL). To this solution was added the amine (181mg, 0.887mmol). To this mixture was then added $NaHB(OAc)_3$ (161mg, 0.76mmol), followed immediately by AcOH (10μL, 0.15mmol). The reaction was determined to be complete by LC/MS after 10min. The reaction was quenched by the addition of ½ sat. $NaHCO_{3(aq.)}$. The reaction was then diluted with DCM and extracted with sat. $NaHCO_{3(aq.)}$ (3x) and brine (1x). The organic phase was then dried over Na_2SO_4. The drying agent was removed by vacuum filtration and the filtrate was concentrated. The residue was redissolved in MeOH and this solution was concentrated. This MeOH dissolution and concentration was repeated 2 more times to afford the crude ester (503mg, 95% yield) as a yellow solid. LC/MS = 1003 (M^++1).



Step 2: The ester (503mg, 0.501mmol) was dissolved in a mixture of THF (5mL) and MeOH (3mL). LiOH (100mg, 2.34mmol) was dissolved in dH_2O (1.5mL) and this was slowly added to the solution of ester in THF/MeOH, which had been cooled to 0°C. Upon complete addition the ice bath was removed. After 3h the reaction was complete. The reaction was cooled to 0°C and neutralized with 2N HCl. Compound **42** was extracted into

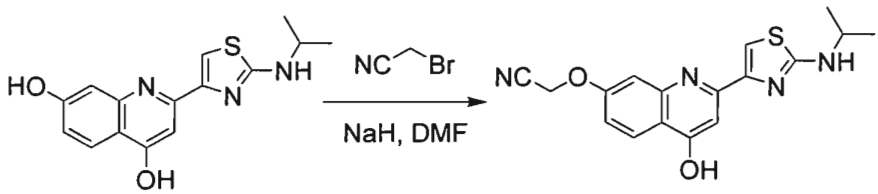
EtOAc, which was then extracted with 1N HCl, and then brine. The organics were then dried over Na_2SO_4. The solids were removed by filtration and the volatile organics were removed under reduced pressure. Compound **42** (450 mg) was isolated as a yellow solid. LC/MS = 989 (M^++1).

Example 43: Preparation of Compound 43



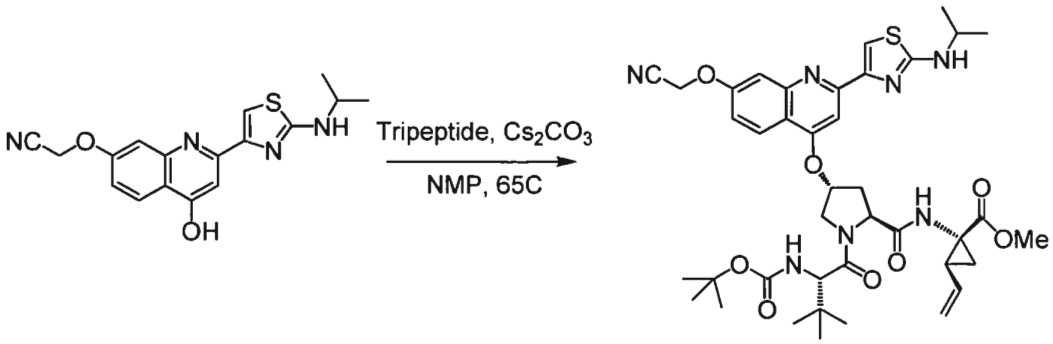
Compound **42** (450mg, 0.501mmol) was dissolved in DME (3mL). To this solution was added dH_2O (0.5mL), $pTolSO_2NHNH_2$ (425mg, 2.46mmol) and NaOAc (425mg, 5.17mmol). The reaction flask was then placed in a preheated 95 °C oil bath for 2h. The reaction was determined to be complete by LC/MS. The reaction was cooled to room temperature and a small amount of MeOH was added to make the reaction mono-phasic. The reaction was then filtered and **43** (334mg, 67% yield) was isolated from the filtrate, by reverse phase HPLC, as a yellow solid. LC/MS = 991 (M^++1).

Example 44: Preparation of Compound 44

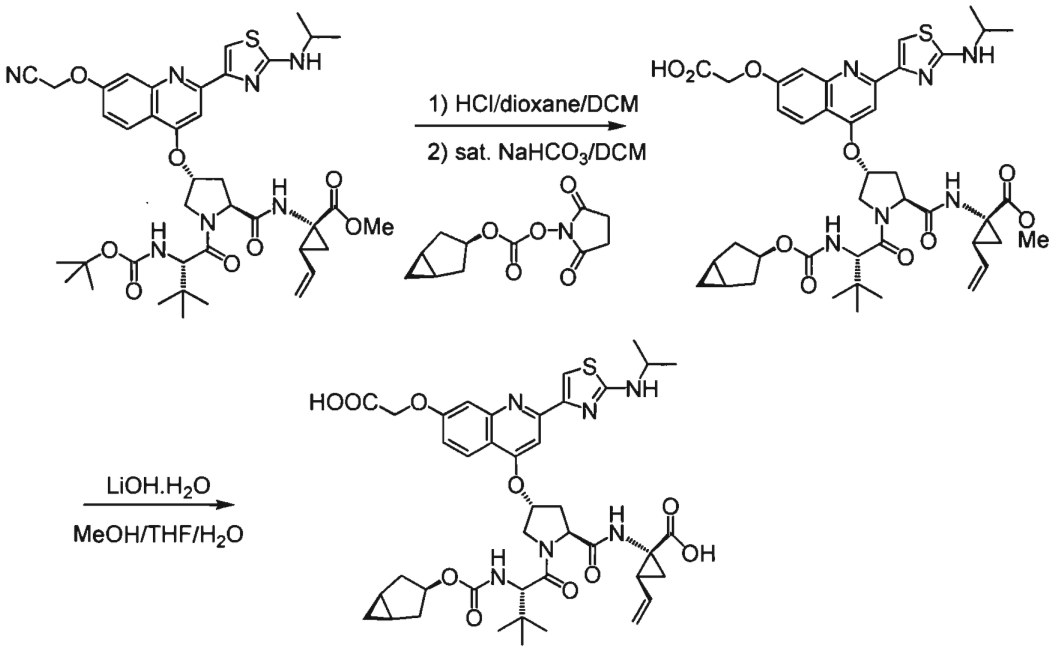


Step 1: 2-(2-isopropylamino-thiazol-4-yl)-quinoline-4,7-diol (2g, 6.6 mmol) was dissolved in DMF (20 mL) under N_2. This was followed with the addition of NaH (60%)

(0.56 g, 14.2 mmol) at 0 °C. The reaction was stirred at 0 °C for 30 minutes and then bromo-acetonitrile was added. The mixture was warmed up to room temperature, and it was stirred at room temperature overnight. The mixture was diluted with EtOAc, and washed with 1N HCl, while maintaining a pH = 4. The desired product crashed out. After filtration, yellow solids were obtained that were fairly pure. This material was used directly in the next step. LC/MS = 341.33 (M^++1).



Step 2: To a mixture of the quinoline obtained above (1.32 g, crude) and brosylate tripeptide (2.9 g, 4.3 mmol) in NMP (10 mL) was added cesium carbonate (2.5 g, 7.7 mmol). The mixture was stirred at 65 °C for 5 h. The reaction was cooled to room temperature, and then EtOAc (600 mL) and aqueous 3% LiCl solution were added to the mixture. The organic layer was separated and washed with aqueous 3% LiCl, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by silica gel chromatography to give the desired product as a yellow solid (1.18 g, 1.49 mmol). LC/MS = 790.38 (M^++1).

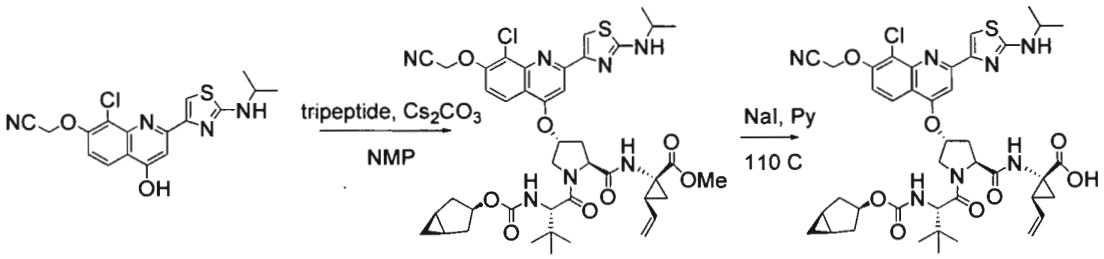


Step 3: To a solution of Boc tripeptide (1.18 g, 1.5 mmol) in DCM (10 mL) was added 4 N HCl in dioxane (30 mmol, 7.5 mL) at room temperature. The mixture was stirred at room temperature for 2 h. LC/MS showed two products were formed, one of them is the desired de-Boc intermediate, and another one is de-Boc intermediate with C-7 position nitrile hydrolyzed to the acid. The reaction solvent was removed under reduced pressure to give the crude material. To the crude material in DCM was added a sat. $NaHCO_3$ aqueous solution (15 mL) and the mixture was stirred at room temperature for 1h. Intermediate I (0.54 g, 2.25 mmol) was added in one portion, and the resulting reaction mixture was stirred at room temperature for another 30 minutes. LC/MS showed two products were formed in a 1:1 ratio; one peak is the desired product and another peak is the corresponding C-7 acid compound. The organic phase was partitioned and washed with brine, dryed over Na_2SO_4 and concentrated *in vacuo*. The crude material was obtained as a yellow solid and was used directly in the next step. LC/MS = 814.42 (M^++1).

Step 4: To the above crude material in dioxane was added a LiOH (0.19 g, 4.5 mmol) aqueous solution. The reaction was stirred at room temperature overnight. LC/MS

indicated that two major compounds were formed. The reaction solvent was removed *in vacuo* and the crude material was purified by preparative HPLC. Compound **44** (0.153 g, 0.183 mmol) was obtained as yellow solids. ^{1}H NMR (300MHz, CD_3OD) δ 8.30 (d, 1H), 8.18 (s, 1H), 7.73 (m, 2H), 7.41 (d, 1H), 5.92-5.77 (m, 2H), 5.28 (d, 1H), 5.11 (d, 1H), 4.96 (s, 2H), 4.73-4.55 (m, 3H), 4.19-4.06 (m, 3H), 2.78 (m, 1H), 2.58 (m, 1H), 2.21 (m, 1H), 1.96 (m, 2H), 1.74-1.63 (m, 3H), 1.46 (m, 3H), 1.33 (m, 6H), 1.22 (m, 2H), 1.04 (s, 9H), 0.49-0.37 (m, 2H). LC/MS = 819.44 (M^++1).

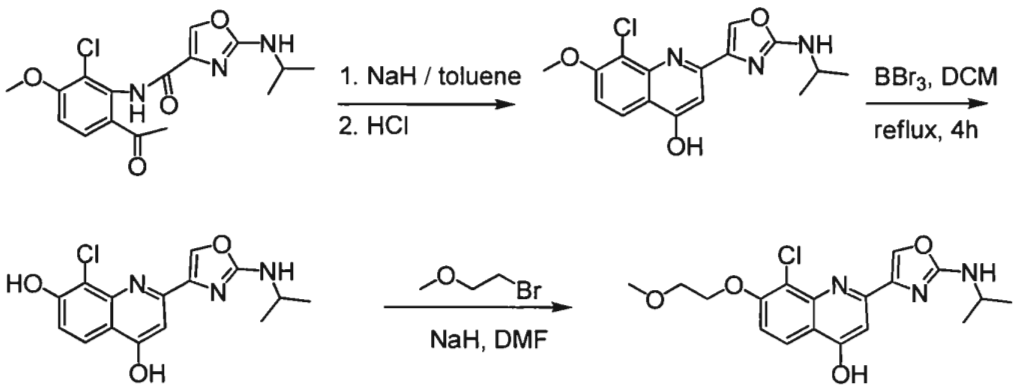
Example 45: Preparation of Compound 45



Step 1: To a mixture of quinoline (0.2 g, 0.53 mmol) and brosylate tripeptide (0.412 g, 0.59 mmol) in NMP (4 mL) was added cesium carbonate (0.345 g, 1.1 mmol). The mixture was stirred at 65 °C for 7 h. The reaction was cooled to room temperature, diluted with EtOAc and washed with an aqueous 3% LiCl solution, brine, and then dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by silica gel chromatography to give the desired product as a yellow solid (0.26 g, 0.31 mmol, 59 %). LC/MS = 848.44 (M^++1).

Step 2: A mixture of ester (0.26g, 0.31 mmol) and NaI (0.70g, 0.45 mmol) in pyridine (7 mL) was heated at 110 °C overnight under N_2. The reaction was monitored by LC-MS. LC-MS showed 95 % conversion. The solvent was removed under reduced pressure. The crude material was purified by preparative HPLC, to yield **45** (0.085 g, 0.1 mmol, 34 %) as yellow solid. LC/MS = 834.41 (M^++1).

Example 46: Preparation of Compound 46

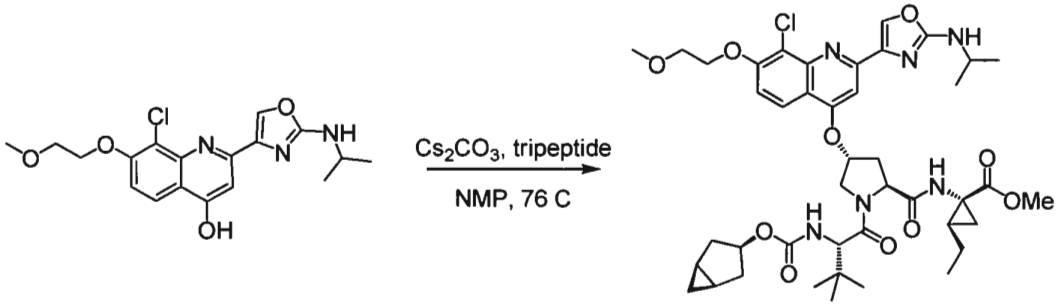


Step 1: To suspension of amide compound (1.2 g, 3.41 mmol) in toluene (28 mL) was added NaH (60%) (0.20 g, 5.12 mmol) at room temperature. The mixture was heated to reflux and stirred for 2.5 h. LC-MS indicated the reaction was complete. The reaction was cooled to 0 °C and AcOH (0.90 mL, 5.80 mmol) in 3 mL H_2O was added, and the mixture was stirred at 0 °C for 45 minutes. During the stirring a lot of yellow solids crashed out. After filtration, the filter cake was washed with H_2O, Et_2O and dried under high vacuum. The crude yellow solid (1.00 g, 3.00 mol, 88 %) was used directly in the next step. LC/MS = 334.34 (M^++1).

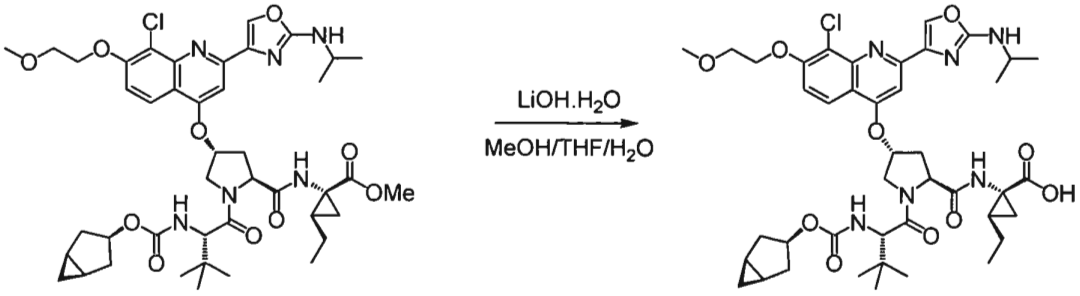
Step 2: To a suspension of the crude product obtained above, dissolved in DCM (50 mL), was added BBr_3 (1 N in DCM) (13.4 mL, 13.4 mmol). The mixture was heated to reflux and stirred for 4 h. The reaction was cooled to room temperature and poured into ice. 4N NaOH was used to adjust the pH to 14. The aqueous phase was extracted with DCM twice and the pH was adjusted to about 4 with 2 N HCl. Yellow solids crashed out and these were isolated by filtration. The filter cake was washed with H_2O, Et_2O, and dried under

high vacuum. A yellow solid was obtained (0.41 g, 1.28 mmol, 42 %) and used directly in the next reaction. LC/MS = 320.33 (M^++1).

Step 3: To a mixture of the bisphenol (0.41 g, 1.28 mmol) and 1-bromo-2-methoxy-ethane (0.18 g, 1.28 mmol) in DMF (3 mL) at room temperature was added NaH (60 %) (0.062g, 2.58 mmol) in one portion. The reaction was stirred overnight under N_2. The crude material was purified by prep-HPLC, and the title compound as the desired product (0.202 g, 0.53 mmol, 41 %) was obtained as a yellow solid. LC/MS = 378.34 (M^++1).

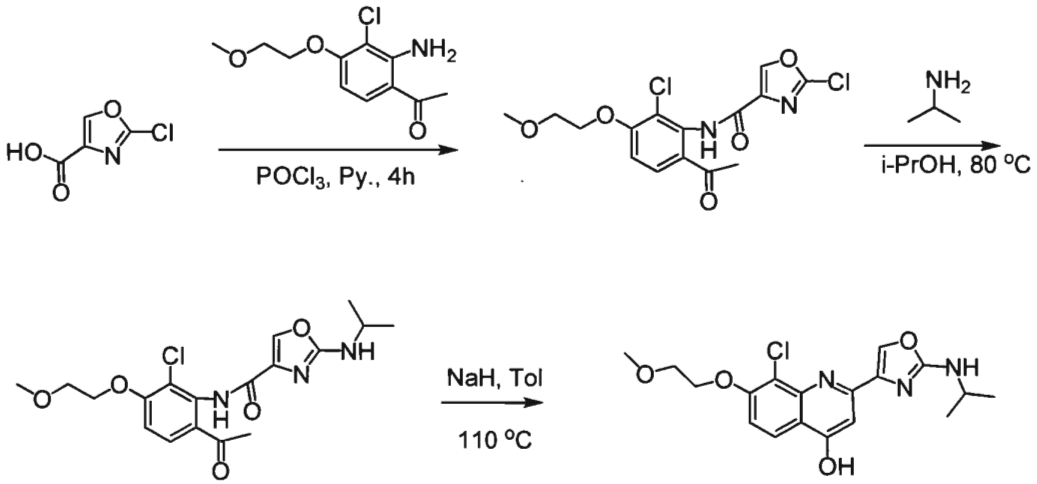


Step 4: A mixture of the quinoline (0.2 g, 0.53 mmol), Cs_2CO_3 (0.35 g, 1.05 mmol) and intermediate **III** (0.415 g, 0.58 mmol) in NMP (4 mL) was heated to 65 °C (Is it 65 or 76? See your graphic) and stirred for 6 h. 10 mL of EtOAc was added to dilute the reaction, and the mixture was washed with H_2O, 5% LiCl, and brine. After drying over Na_2SO_4 and concentration, the crude material was purified by silica gel chromatography to afford the methyl ester as a form (0.19 g, 0.22 mmol, 42 %). LC/MS = 854.08 (M^++1).



Step 5: To a solution of the methyl ester (0.19 g, 0.22 mmol) in MeOH (1 mL) and THF (1 mL) was added a LiOH (0.18 g, 4.2 mmol) aqueous solution. The mixture was stirred at room temperature overnight. The crude material was purified by preparative HPLC to afford **46** as a yellow solid compound (0.11 g, 0.13 mmol, 60 %). ^{1}H NMR (300MHz, CD_3O D): δ 8.64 (s, 1H), 8.26 (d, 1H), 7.69 (s, 1H), 7.64 (d, 1H), 5.69 (s, 1H), 4.72 (dd, 1H), 4.60-4.43 (m, 3H), 4.14-4.01 (m, 3H), 3.87 (s, 2H), 3.47 (s, 2H), 2.74 (m, 1H), 2.63 (m, 1H), 1.97-1.80 (m, 2H), 1.67 (m, 3H), 1.51 (m, 1H), 1.49-1.34 (m, 7H), 1.22 (m, 2H), 1.02 (s, 9H), 0.34 (m, 2H). LC/MS = 841.56 (M^++1).

Example 47: Preparation of Compound 47

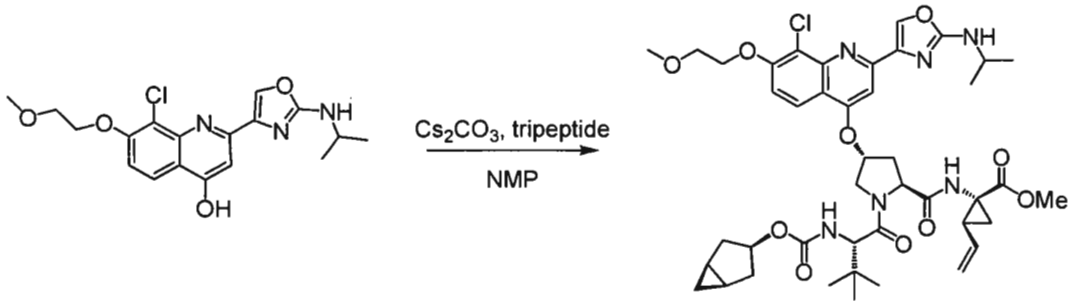


Step 1: The acid starting material (2.87 g, 19.5 mmol) and 1-[2-Amino-3-chloro-4-(2-methoxy-ethoxy)-phenyl]-ethanone (4.72 g, 19.5 mmol) were dissolved in pyridine (180 mL). The resulting solution was cooled to -30 °C, and then $POCl_3$ was added to the solution, dropwise. After the addition, the reaction was warmed up to -10 °C in 30 minutes and stirred at -10 °C for 4 h. 20 mL of H_2O was added to quench the reaction at 0 °C and the resulting mixture was stirred at 0 °C for 5 minutes. Solvent was removed under reduced pressure. To the residue was added EtOAc, and resulting solution was washed

with sat. $NaHCO_3$, H_2O and brine. After drying over Na_2SO_4 and being concentrated, the crude material was purified by silica gel chromatography to afford the desired product (4.2 g, 11.3 mmol, 58 %). LC/MS = 373.01 (M^++1).

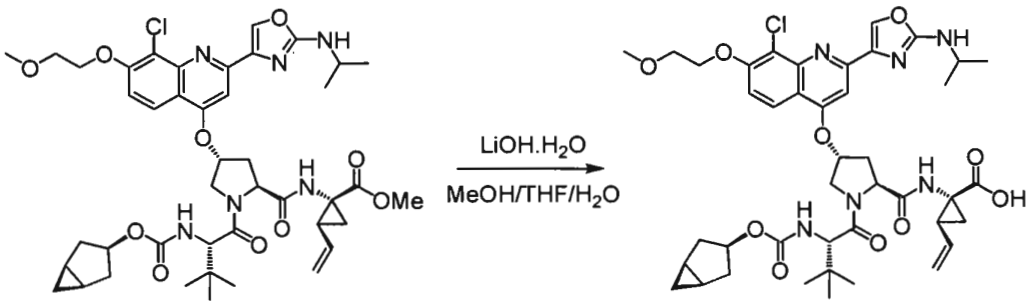
Step 2: The mixture of amide (2.0 g, 5.4 mmol) and isopropylamine (3.2 g, 54 mmol) in propan-2-ol (20mL) in a sealed tube was heated to 70 °C. After heating 3.5 h, the reaction was cooled to room temperature. And the solvent was removed under reduced pressure. The residue was dissolved in THF (15 mL) and 0.3 N HCl (40 mL) was added to this solution. This mixture was stirred at room temperature. For 24 h. The mixture was partitioned and organic phase was concentrated under reduced pressure. The residue was purified by silica gel chromatography, to afford the amine (0.84 g, 2.13 mmol, 40 %). LC/MS = 396.21 (M^++1).

Step 3: To a suspension of the amine (1.38 g, 3.49 mmol) in toluene (20 mL) was added NaH (60%) (0.20 g, 5.12 mmol) at room temperature. The mixture was heated to reflux 2.5 h. LC-MS indicated the reaction was complete. The reaction was cooled to 0 °C and AcOH (0.90 mL, 5.80 mmol) in 3 mL of H_2O was added to the reaction, and the mixture was stirred at 0 °C for 45 minutes. During this stirring, the quinoline product crashed out. After filtration, the filter cake was washed with H_2O, Et_2O and dried under high vacuum. A crude yellow solids (1.18 g, 3.13 mol, 90 %) with fair purity were obtained and used directly in the next reaction. LC/MS = 378.34 (M^++1).



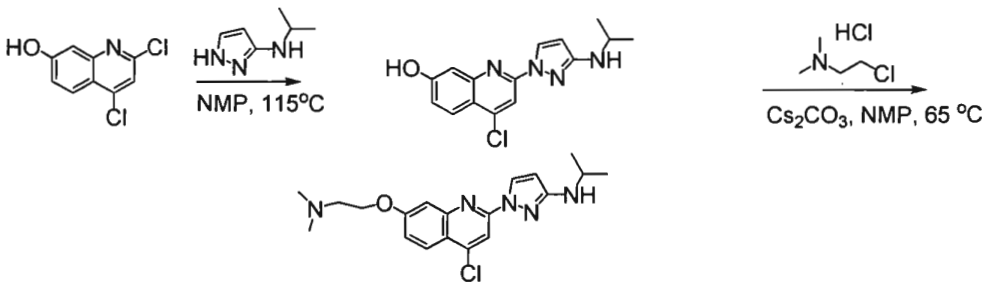
Step 4: A mixture of the quinoline (0.77 g, 2.03 mmol), Cs_2CO_3 (1.3 g, 4 mmol) and tripeptide methyl ester (1.6 g, 2.2 mmol) in NMP (10 mL) was heated to 65 °C and stirred

for 6 h. 25 mL of EtOAc was added to dilute the reaction, and the mixture was washed with H_2O, 5% LiCl, and brine. After drying the organics over Na_2SO_4 and concentration, the crude material was purified by silica gel chromatography to afford title compound as a solid (1.2 g, 1.4 mmol, 69 %). LC/MS = 851.84 (M^++1).



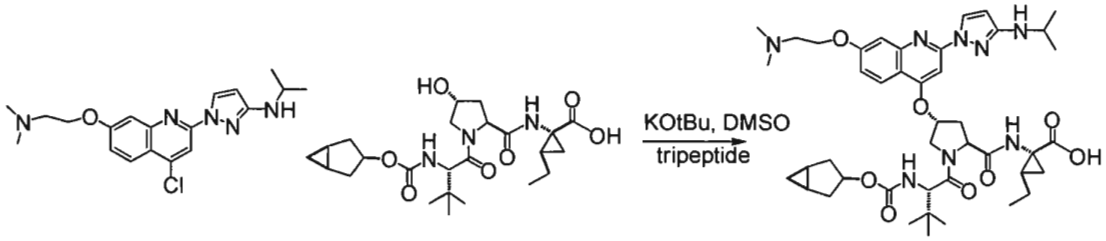
Step 5: To a solution of the methyl ester (0.5 g, 0.58 mmol) in MeOH (5 mL) and THF (5 mL) was added a LiOH (0.24 g, 5.8 mmol) aqueous solution (How much water?). The mixture was stirred at room temperature overnight. Crude material was purified by preparative HPLC to afford Compound **47** as a yellow solid (0.33 g, 0.4 mmol, 69 %). ^{1}H NMR (300MHz, CD_3OD): δ 8.58 (s, 1H), 8.26 (d, 1H), 7.66 (s, 1H), 7.62 (d, 1H), 5.89 (m, 1H), 5.67 (bs, 1H), 5.29 (dd, 1H), 5.11 (m, 1H), 4.72 (m, 1H), 4.54-4.49 (m, 4H), 4.15 (s, 1H), 4.10-4.00 (m, 2H), 3.87 (m, 2H), 3.47 (s, 3H), 2.75 (m, 1H), 2.61(m, 1H), 2.21 (m, 2H), 1.94 (m, 1H), 1.85 (m, 1H), 1.72-1.61 (m, 3H), 1.40-1.10 (m, 9H), 1.02 (s, 9H), 0.49-0.34 (m, 2H). LC/MS = 837.94 (M^++1).

Example 48: Preparation of Compound 48



Step 1: 2,4-dichloro-quinolin-7-ol (2.23 g, 10.4 mmol) and isopropyl-(1H-pyrazol-3-yl)-amine (1.44 g, 11.5 mmol) were dissolved in NMP (30 mL) at room temperature. The resulting mixture was heated to 115 °C and stirred for 12 h. The reaction was diluted with EtOAc and washed with 5% LiCl, and brine. After drying the organic fraction over Na_2SO_4 and concentration, the crude material was purified by silica gel chromatography to afford title compound (1.6 g, 5.28 mmol, 51 %). LC/MS = 303.30 (M^++1).

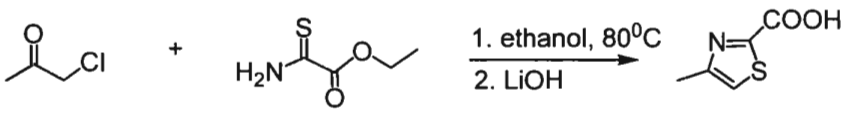
Step 2: Quinoline (0.81 g, 2.67 mmol) and (2-chloro-ethyl)-dimethyl-amine HCl salt (0.42 g, 2.94 mmol) were dissolved in DMF (10 mL). This was followed by the addition of Cs_2CO_3 (1.74 g, 5.34 mmol). The reaction was heated to 65 °C and stirred for 17 h. The reaction was diluted with EtOAc and washed with 5% LiCl, and brine. After drying the organic fraction over Na_2SO_4 and concentration, the crude material was purified by silica gel chromatography to afford the title compound (0.5 g, 1.34 mmol, 50 %). LC/MS = 374.24 (M^++1).



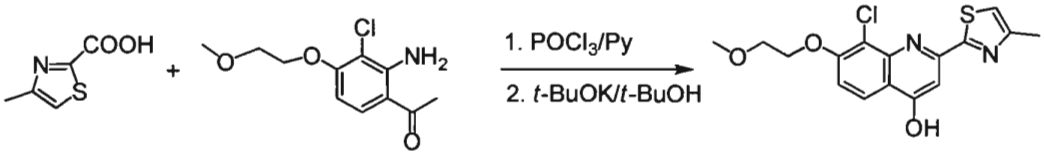
Step 3: Tripeptide acid (0.51 g, 1.06 mmol) was dissolved in DMSO (10 mL). To this solution was added KO^{t}Bu (0.6 g, 5.3 mmol). The mixture was stirred at room temperature. For 1.5 h. The chloroquinoline (0.44 g, 1.17 mmol) was then added to the reaction in one potion, and the resulting reaction was stirred at room temperature overnight. 0.5 mL AcOH was added into the reaction and the reaction mixture was purified by preparative HPLC to afford compound **48** (0.309 g, 0.37 mmol, 36 %). ^{1}H NMR (300MHz, $CDCl_3$) ^{1}H NMR (300MHz, CD_3O D): δ 8.64 (s, 1H), 8.16 (d, 1H), 7.68 (s, 1H), 7.34 (d, 1H), 7.28 (d, 1H), 6.28 (m, 1H), 5.62 (bs, 1H), 4.64 (dd, 2H), 4.55 (m, 2H), 4.19 (s, 1H), 4.15-3.97 (m, 2H), 3.69 (m, 2H), 3.30 (s, 2H), 3.02 (s, 6H), 2.90-2.53 (m, 3H), 2.02-1.80 (m, 3H), 1.71-1.98 (m,

3H), 1.51-1.34 (m, 3H), 1.29 (d, 6H), 1.23-1.06 (m, 3H), 1.02 (s, 9H), 0.49-0.34 (m, 2H). LC/MS = 817.71 (M^++1).

Example 49: Preparation of Compound 49

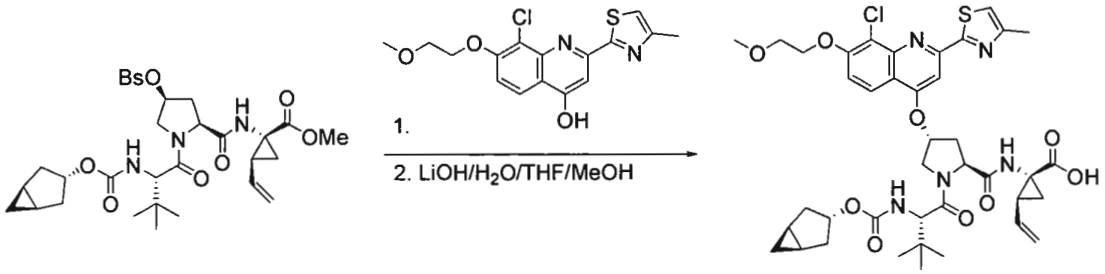


Step 1: A mixture of α-chloro acetone (10.4 g, 112.8 mmol) and amino-thioxo-acetic acid ethyl ester (5.0 g, 37.6 mmol) in ethanol (100 mL) was stirred at 80 °C for 6 h. After concentration, the residue was purified by silica gel column chromatography, affording the ester (3.2 g, 50%) as white solids. The ethyl ester product (1.5 g, 8.8 mmol) was then dissolved in a THF/MeOH /water (10 mL / 10 mL / 10 mL) mixture. Excess lithium hydroxide (3.0 g) was added and the reaction mixture was stirred at room temperature for 1 h. Ethyl acetate (100 mL) was added to the reaction mixture. The pH was adjusted to 4 by slowly adding 1N HCl to the mixture. After separation, the organic layer was dried over $MgSO_4$. After concentration, the desired product (0.8 g, 64%) was obtained as white solids. LC/MS = 143.7 (M^++1).



Step 2: To a mixture of the acid (0.36 g, 2.47 mmol) and the aniline (0.40 g, 1.65 mmol) in pyridine (15 mL) was slowly added $POCl_3$ (0.38 g, 2.47 mmol) at -40 °C. The mixture was then stirred at 0 °C for 4 h. Upon completion of the reaction, H_2O (5 mL) was added dropwise to the mixture. The mixture was then stirred at 0 °C for another 15 min. The mixture was concentrated *in vacuo*. The residue was diluted with EtOAc, and washed with sat. $NaHCO_3$ aqueous solution. The organic layer was dried (Na_2SO_4) and

concentrated *in vacuo*. The residue was purified by silica gel column chromatography, affording the amide (0.45 g, 74%) as solids. The amide (0.45 g, 1.22 mmol) was suspended in *t*-BuOH (10mL). *t*-BuOK (0.29 g, 2.57 mmol) was added to the vigorously stirred mixture. The mixture was heated to 75 °C for 4 h. The mixture was cooled to room temperature. 4 N HCl/dioxane (1 mL) was slowly added to acidify the mixture. After concentration, the crude was poured into 1N KH_2PO_4/H_2O (50 mL). The solids that formed were isolated by filtration and washed with water. After drying under high vacuum overnight, the quinoline (0.4 g, 93%) was obtained as solids. LC/MS = 350.8 (M^++1).

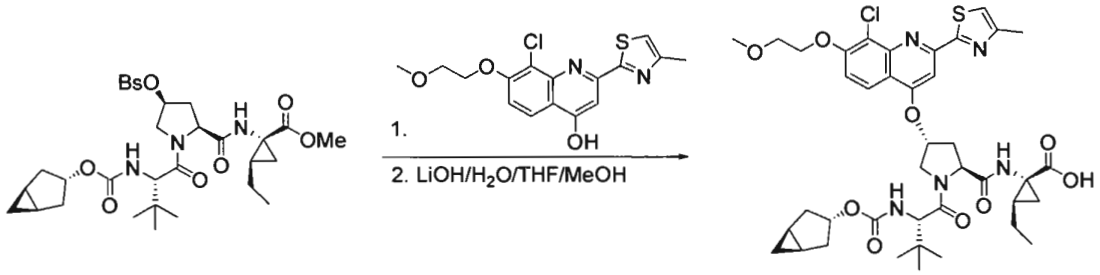


Step 3: To a mixture of tripeptide (0.20 g, 0.28 mmol) and quinoline (0.10 g, 0.28 mmol) in NMP (5 mL) was added cesium carbonate (0.18 g, 0.56 mmol). The mixture was stirred at 85 °C for 6 h. The reaction was cooled to room temperature, and EtOAc (50 mL) and an aqueous 3% LiCl (50 mL) solution were added to the mixture. The organic layer was washed with aqueous 3% LiCl (1 x 50 mL), brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give the desired methyl ester product as yellow solids (0.15 g, 65%).

Step 4: The methyl ester (0.15 g, 0.18 mmol) was dissolved in THF (2 mL), and a solution of LiOH (0.05g, 1.8 mmol) in H_2O (2 mL) was added, followed by the addition of MeOH (2 mL). The mixture was kept stirring at room temperature for 3 h. Upon completion of the reaction, 4 N HCl in H_2O was added at 0 °C to adjust the pH to 4. The mixture was extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo* to give compound **49** as yellow solids (0.14 g, 95%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.10 (d, J = 9.6 Hz, 1H), 7.70 (s,

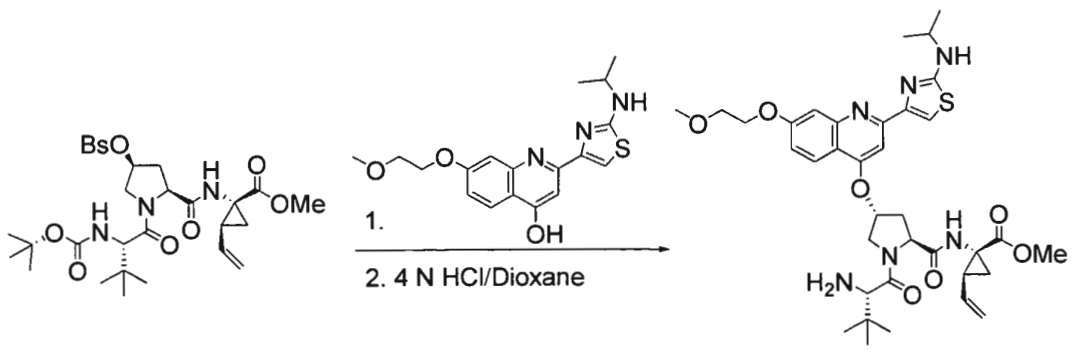
1H), 7.44 (d, J = 9.6 Hz, 1H), 7.36 (s, 1H), 5.82 (dd, 1H), 5.53 (brs, 1H), 5.30 (d, J = 17.1 Hz, 1H), 5.12(d, J = 10.2 Hz, 1H), 4.65 (m, 1H), 4.58 (m, 1H), 4.39 (m, 2H), 4.22 (s, 1H), 4.10 (m, 2H), 3.86 (m, 2H), 3.49 (m, 4H), 2.83 (m, 3H), 2.57 (m, 3H), 2.39 (m, 1H), 2.18 (m, 1H), 2.07 (m, 1H), 1.84 (m, 1H), 1.68 (m, 2H), 1.44 (m, 1H), 1.35 (m, 1H), 1.23 (m, 1H), 1.04 (s, 9H), 0.48 (m, 1H), 0.30 (m, 1H). LC/MS = 810.4 (M^++1).

Example 50: Preparation of Compound 50



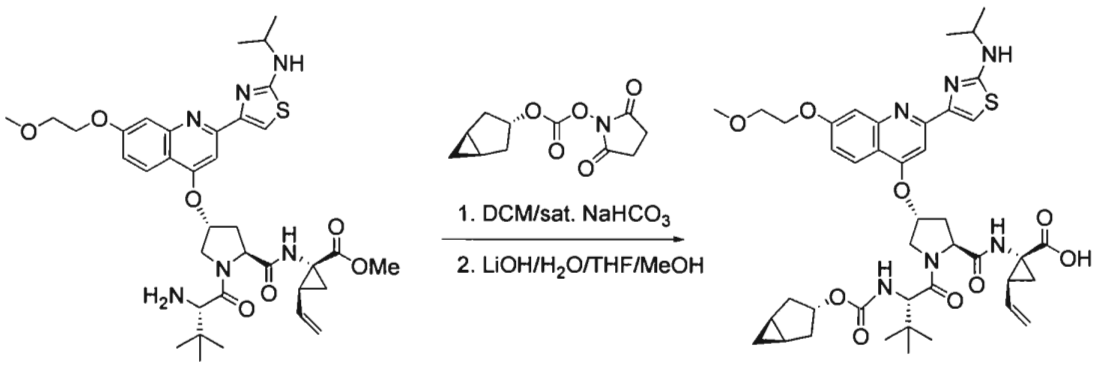
Compound **50** was obtained by following procedures similar to those for preparation of Compound **49**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.62 (s,1H), 8.08 (d, J = 8.7 Hz, 1H), 7.69 (s, 1H), 7.42 (d, J = 9.3 Hz, 1H), 7.34 (s, 1H), 5.51 (brs, 1H), 4.65-4.52 (m, 2H), 4.38 (m, 2H), 4.22 (s, 1H), 4.10 (m, 1H), 3.85 (m, 2H), 3.49 (s, 3H), 2.74 (m, 1H), 2.56 (s, 3H), 2.20 (m, 1H), 2.08 (m, 1H), 1.85 (m, 1H), 1.68 (m, 3H), 1.50-1.21 (m, 7H), 1.02 (m, 12H), 0.48 (m, 1H), 0.30 (m, 1H). LC/MS = 812.6 (M^++1).

Example 51: Preparation of Compound 51



Step 1: To a mixture of tripeptide (1.30 g, 1.92 mmol) and quinoline (0.55 g, 1.53 mmol) in NMP (15 mL) was added cesium carbonate (0.94 g, 2.88 mmol). The mixture was stirred at 85°C for 6 h. The reaction was cooled to room temperature, and EtOAc (50 mL) and an aqueous 3% LiCl (50 mL) solution were added to the mixture. The organic layer was washed with aqueous 3% LiCl (1 x 50 mL), brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give the desired methyl ester product as a yellow solid (0.85 g, 65%).

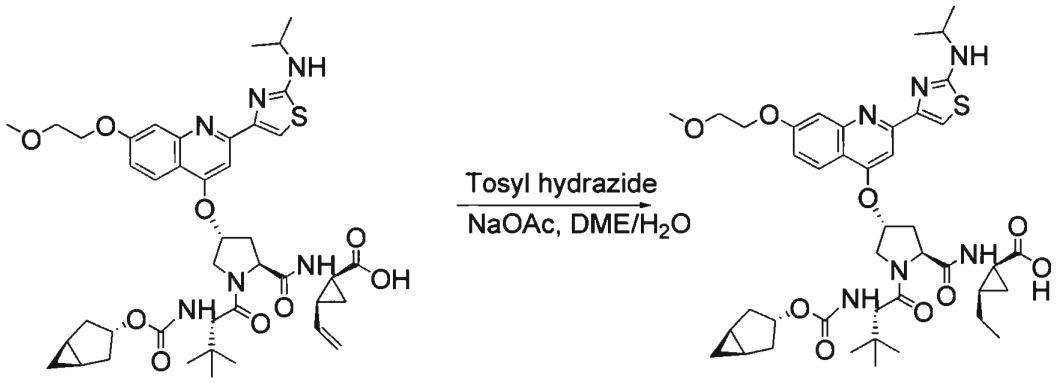
A solution of the above product in dichloromethane (10 mL) was treated with 4N HCl in dioxane (20 mL) for 2 h at room temperature and concentrated to dryness, affording the amine compound as the HCl salt. LC/MS = 708.9 (M^++1).



Step 2: To a biphasic solution of the amine (0.71 g, 1.0 mmol) in dichloromethane (40 mL) and 5% aqueous sodium bicarbonate (40 mL) was added a solution of intermediate I (0.36 g, 1.5 mmol) in dichloromethane in four portions. These additions continued until the starting material was completely consumed. The dichloromethane layer was taken and concentrated. The methyl ester product was then dissolved in a mixture of THF/MeOH /water (5 mL / 5 mL / 5 mL). Excess lithium hydroxide (240 mg) was added and the reaction was stirred at room temperature for 4 h. Ethyl acetate (40 mL) was added and the pH was adjusted to 4 by slowly adding 1 N HCl to the mixture. After separation, the organic layer was concentrated. The residue was purified by preparative HPLC using water / acetonitrile (0.05% TFA) as eluents, which afforded Compound **51** (750mg, 91%)

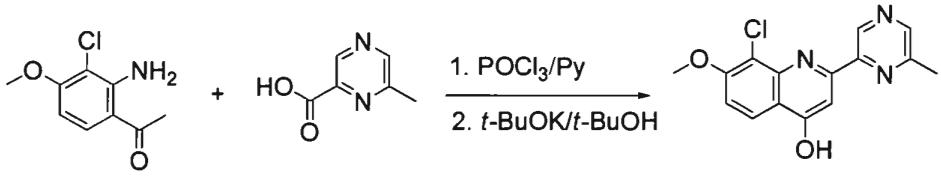
as a yellow solid. ^{1}H NMR (300 MHz, CD_3OD): δ 8.76 (s,1H), 8.25 (d, J = 9.6 Hz, 1H), 8.18 (s, 1H), 7.75 (m, 2H), 7.36 (d, J = 9.3 Hz, 1H), 5.91-5.82 (m, 1H), 5.77 (brs, 1H), 5.31 (d, J = 15.9 Hz, 1H), 5.12 (d, J = 10.2 Hz, 1H), 4.74 (m, 1H), 4.62 (m, 1H), 4.52 (m, 1H), 4.36 (m, 2H), 4.25-4.05 (m, 3H), 3.87 (m, 2H), 3.46 (s, 3H), 2.82 (m, 1H), 2.61 (m, 1H), 2.22 (m, 2H), 1.99-1.62 (m, 5H), 1.35 (d, J = 6.3 Hz, 6H), 1.49-1.21 (m, 4H), 1.02 (m, 9H), 0.48 (m, 1H), 0.34 (m, 1H). LC/MS = 819.5 (M^++1).

Example 52: Preparation of Compound 52

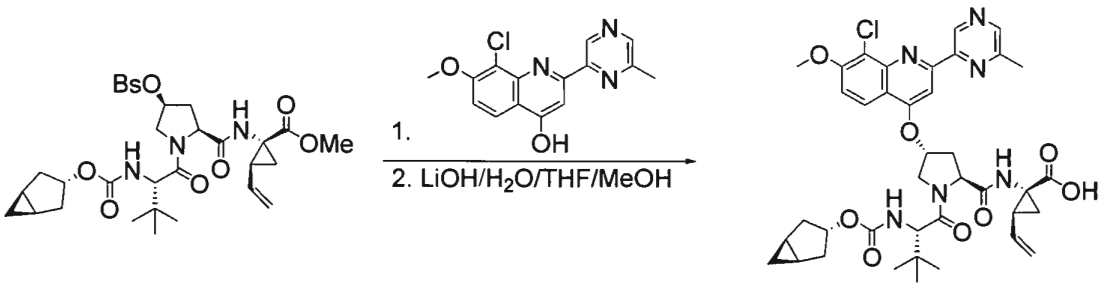


To a mixture of **51** (0.60 g, 0.73 mmol) and sodium acetate (0.83 g, 10.2 mmol) in DME/H_2O (9 mL/ 1 mL) was added *p*-toluenesulfonhydrazide (0.96 g, 5.1 mmol). The mixture was stirred at 95°C for 3 h. The reaction was cooled to room temperature, and EtOAc (50 ml) was added to the mixture. The organic layer was washed with aqueous 0.05 N HCl (1 x 50 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by preparative HPLC using water / acetonitrile (0.05% TFA) as eluents, which afforded Compound **52** (450mg, 75%) as a yellow solid. ^{1}H NMR (300 MHz, CD_3OD): δ 8.65 (s,1H), 8.27 (d, J = 9.0 Hz, 1H), 8.18 (s, 1H), 7.76 (m, 2H), 7.38 (d, J = 9.0 Hz, 1H), 5.77 (brs, 1H), 4.74 (t, 1H), 4.62 (d, 1H), 4.52 (t, 1H), 4.37 (m, 2H), 4.18- 4.04 (m, 3H), 3.86 (m, 2H), 3.46 (s, 3H), 2.76 (m, 1H), 2.58 (m, 1H), 2.20 (q, 1H), 1.97-1.85 (m, 2H), 1.70-1.65 (m, 3H), 1.54 (m, 1H), 1.46-1.41 (m, 2H), 1.35 (m, 6H), 1.22 (m, 2H), 1.02 (m, 12H), 0.48 (m, 1H), 0.30 (m, 1H). LC/MS = 821.6 (M^++1).

Example 53: Preparation of Compound 53



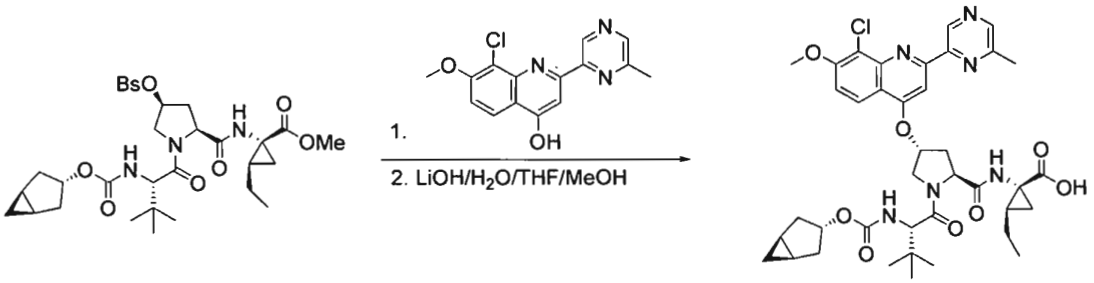
Step 1: To a mixture of aniline (1.21 g, 6.06 mmol) and acid (0.84 g, 6.09 mmol) in pyridine (55 mL) was slowly added $POCl_3$ (1.02 g, 6.68 mmol) at -40°C. The mixture was then stirred at 0°C for 4 h. Upon completion of the reaction, H_2O (5 mL) was added dropwise to the mixture. The mixture was then stirred at 0°C for another 15 min. The mixture was concentrated *in vacuo*. The residue was diluted with EtOAc, and washed with a sat. $NaHCO_3$ aqueous solution. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate / hexanes), affording the amide (1.77 g, 92%) as a solid. The amide (1.70 g, 5.3 mmol) was suspended in *t*-BuOH (40mL). *t*-BuOK (1.30 g, 11.2 mmol) was added to the vigorously stirred mixture. The mixture was heated to 75°C for 5 h. The mixture was cooled to room temperature. 4 N HCl/Dioxane (5 mL) was slowly added to acidify the mixture. After concentration, the crude was poured into 1N KH_2PO_4/H_2O (100 mL). The solid formed isolated by filtration and washed with water. After drying under high vacuum overnight, quinoline (1.5 g, 94%) was obtained as a solid. LC/MS = 302.4 (M^++1).



Step 2: Compound **53** was obtained by the procedures similar to those for preparation of Compound **50** except using quinoline obtained from above. ^1H NMR (300 MHz, DMSO):

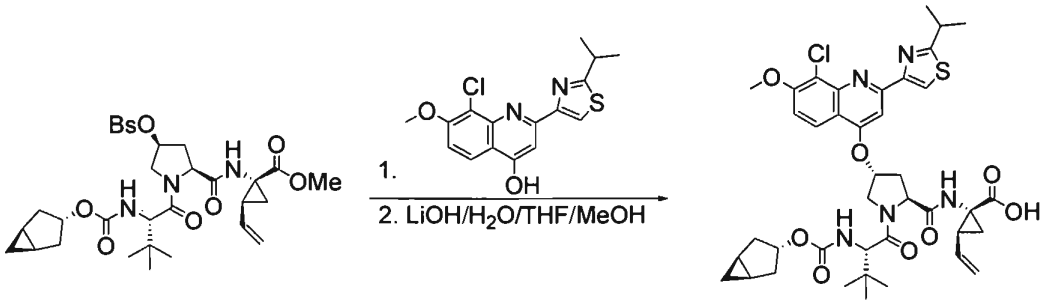
δ 12.43 (brs, 1H), 9.59 (s, 1H), 8.69 (s, 1H), 8.57 (m,1H), 8.13 (d, J = 8.7 Hz, 1H), 7.83 (s, 1H), 7.51 (d, J = 8.7 Hz, 1H), 7.06 (d, J = 8.7 Hz, 1H), 5.68 (m, 1H), 5.60 (brs, 1H), 5.21 (d, J = 18.0 Hz, 1H), 5.07(d, J = 9.9 Hz, 1H), 4.67 (m, 1H), 4.45 (m, 1H), 4.32 (m, 1H), 4.04 (m, 4H), 2.66 (s, 3H), 2.28 (m, 2H), 2.03-1.80 (m, 4H), 1.35-1.19 (m, 4H), 0.95 (s, 9H), 0.44 (m, 1H), 0.33 (m, 1H). LC/MS = 761.5 (M^++1).

Example 54: Preparation of Compound 54



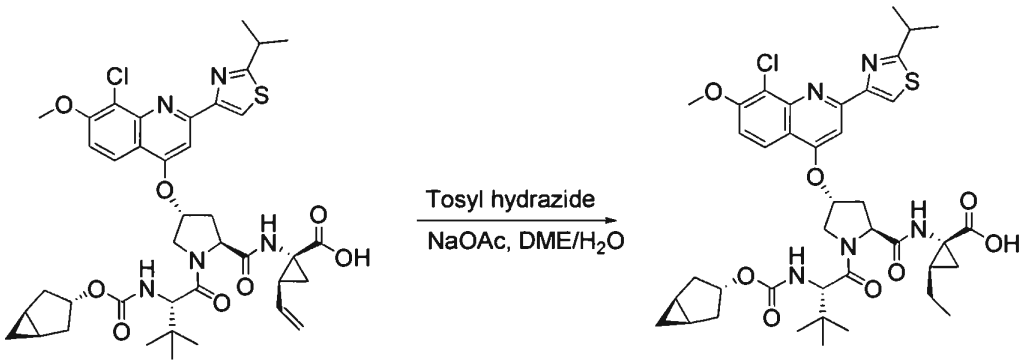
Compound **54** was obtained by the procedures similar to those for preparation of compound **50**.Compound **52**. ^{1}H NMR (300 MHz, DMSO): δ 9.59 (s, 1H), 8.69 (s, 1H), 8.41 (m,1H), 8.14 (d, J = 9.3 Hz, 1H), 7.84 (s, 1H), 7.51 (d, J = 8.7 Hz, 1H), 7.04 (d, J = 8.7 Hz, 1H), 5.60 (brs, 1H), 4.68 (m, 1H), 4.45 (m, 1H), 4.29 (m, 1H), 4.04 (m, 5H), 2.67 (m, 4H), 2.28 (m, 2H), 2.03-1.80 (m, 4H), 1.58-1.42 (m, 4H), 0.94 (m, 12H), 0.44 (m, 1H), 0.35 (m, 1H). LC/MS = 763.3 (M^++1).

Example 55: Preparation of Compound 55



Compound **55** was obtained by the procedures similar to those for preparation of Compound **50** except using the P2 quinoline as shown. ^{1}H NMR (300 MHz, CD_3OD): δ 9.01 (s, 1H), 8.76 (s, 1H), 8.37 (d, J = 9.0 Hz, 1H), 7.99 (s, 1H), 7.70 (d, J = 9.9 Hz , 1H), 5.89 (m, 1H), 5.83 (brs, 1H), 5.31 (d, J = 15.3 Hz, 1H), 5.13 (d, J = 9.6 Hz, 1H), 4.75 (m, 1H), 4.65 (m, 1H), 4.41 (m, 1H), 4.19-4.07 (m, 5H), 3.56 (m, 1H), 2.82 (m, 1H), 2.63 (m, 1H), 2.22 (m, 1H), 1.91 (m, 1H), 1.75-1.63 (m, 2H), 1.56 (d, J = 7.2 Hz, 6H), 1.49-1.20 (m, 5H), 0.98 (s, 9H), 0.48 (q, 1H), 0.34 (m, 1H). LC/MS = 794.5 (M^++1).

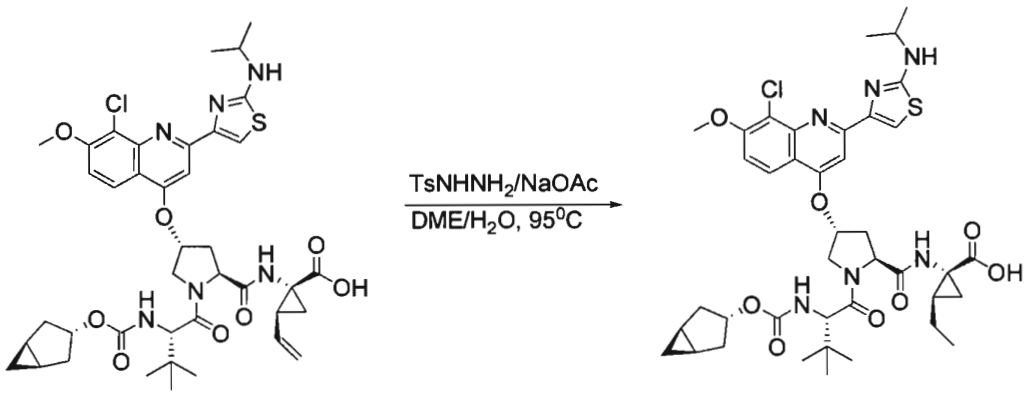
Example 56: Preparation of Compound 56



Compound **56** was obtained by the procedures similar to those for preparation of Compound **52** except using **55** as reactant. ^{1}H NMR (300 MHz, CD_3OD): δ 8.92 (s, 1H), 8.65 (s, 1H), 8.30 (d, J = 9.6 Hz, 1H), 7.92 (s, 1H), 7.63 (d, J = 9.3 Hz , 1H), 5.77 (brs, 1H), 4.75 (m, 1H), 4.62 (m, 1H), 4.45 (m, 1H), 4.16 (m, 5H), 3.55 (m, 1H), 2.79 (m, 1H),

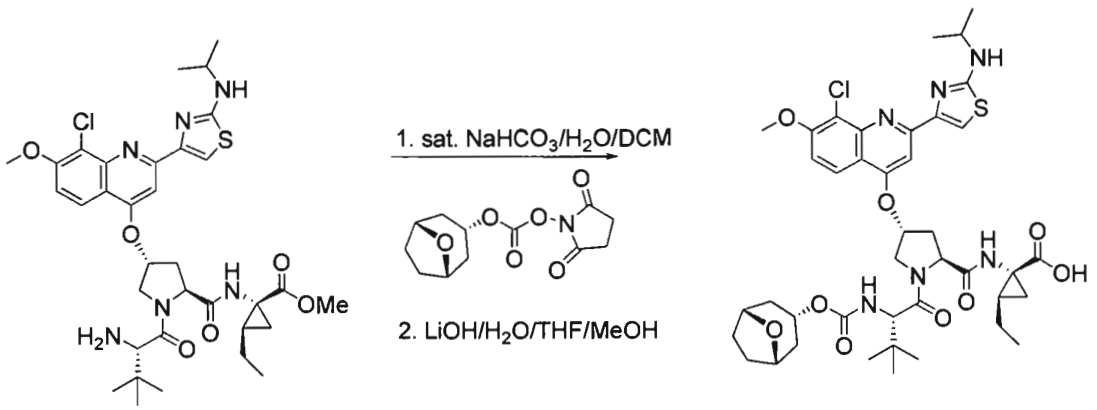
2.61 (m, 1H), 2.20 (m, 1H), 1.97 (m, 1H), 1.89 (m, 1H), 1.80 (m, 3H), 1.56 (d, J = 6.9 Hz, 6H), 1.59-1.22 (m, 6H), 1.05 (m, 12H), 0.48 (q, 1H), 0.30 (m, 1H). LC/MS = 796.4 (M^++1).

Example 57: Preparation of Compound 57



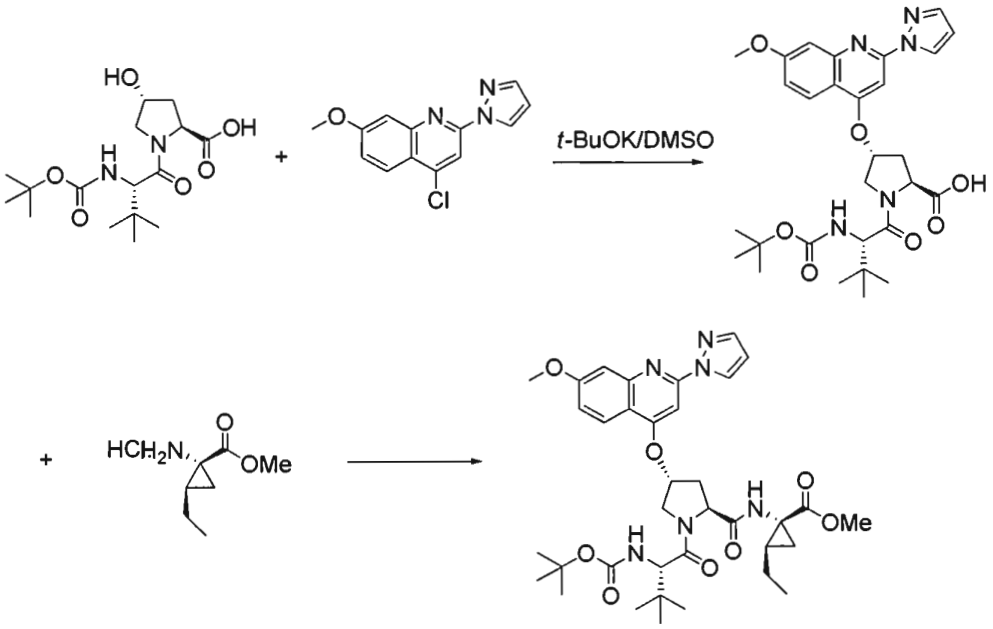
Compound **57** was obtained by the procedures similar to those for preparation of Compound **52**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.33 (m, 1H), 7.83 (s, 1H), 7.65 (d, J = 9.6 Hz, 1H), 5.77 (brs, 1H), 4.77 (m, 1H), 4.62 (m, 1H), 4.42 (m, 1H), 4.17 (s, 3H), 4.17-4.05 (m, 3H), 2.79 (m, 1H), 2.61 (m, 1H), 2.20 (m, 1H), 1.98 (m, 1H), 1.79 (m, 1H), 1.70-1.49 (m, 4H), 1.45-1.21 (m, 5H), 1.38 (d, J = 6.6 Hz, 6H), 1.05 (m, 12H), 0.48 (m, 1H), 0.30 (m, 1H). LC/MS = 811.4 (M^++1).

Example 58: Preparation of Compound 58



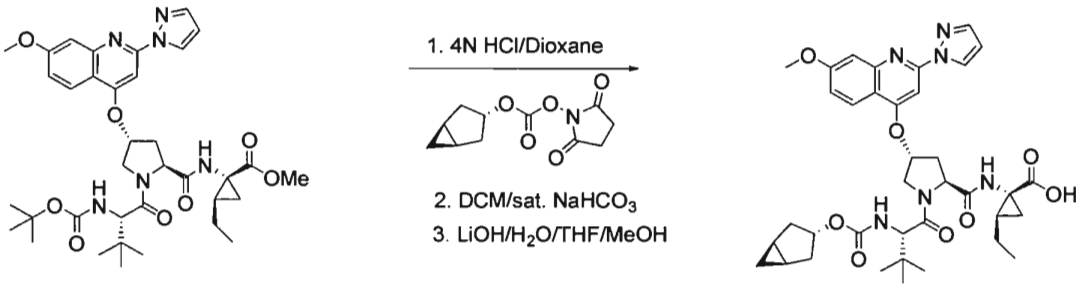
To a biphasic solution of the amine (0.15 g, 0.19 mmol) in dichloromethane (10 mL) and 5% aqueous sodium bicarbonate (10 mL) was added a solution of carbonate (0.08 g, 0.29 mmol) in dichloromethane in four portions, until the starting material amine was completely consumed. The dichloromethane layer was taken and concentrated. The methyl ester product was then dissolved in a mixture of THF/MeOH /water (2 mL / 2 mL / 2 mL). Excess lithium hydroxide (46 mg) was added and the reaction was stirred at room temperature for 4 h. Ethyl acetate (40 mL) was added and the pH was adjusted to 4 by slowly adding 1 N HCl/H_2O to the mixture. After separation, the organic layer was concentrated. The residue was purified by preparative HPLC using water / acetonitrile (0.05% TFA) as eluents, which afforded Compound **58** (140mg, 88%) as a yellow solid. ^1H NMR (300 MHz, CD_3OD): δ 8.66 (m, 1H), 8.32 (m, 2H), 7.82 (s, 1H), 7.63 (d, J = 9.3 Hz, 1H), 5.76 (brs, 1H), 4.77 (m, 1H), 4.66 (m, 1H), 4.28-4.03 (m, 8H), 2.84 (m, 1H), 2.65 (m, 1H), 2.08 (m, 2H), 1.86-1.63 (m, 6H), 1.79 (m, 1H), 1.70-1.49 (m, 3H), 1.55-1.36 (m, 2H), 1.39 (d, J = 6.9 Hz, 6H), 1.28 (m, 2H) 1.04 (m, 12H), LC/MS = 841.4 (M^++1).

Example 59: Preparation of Compound 59



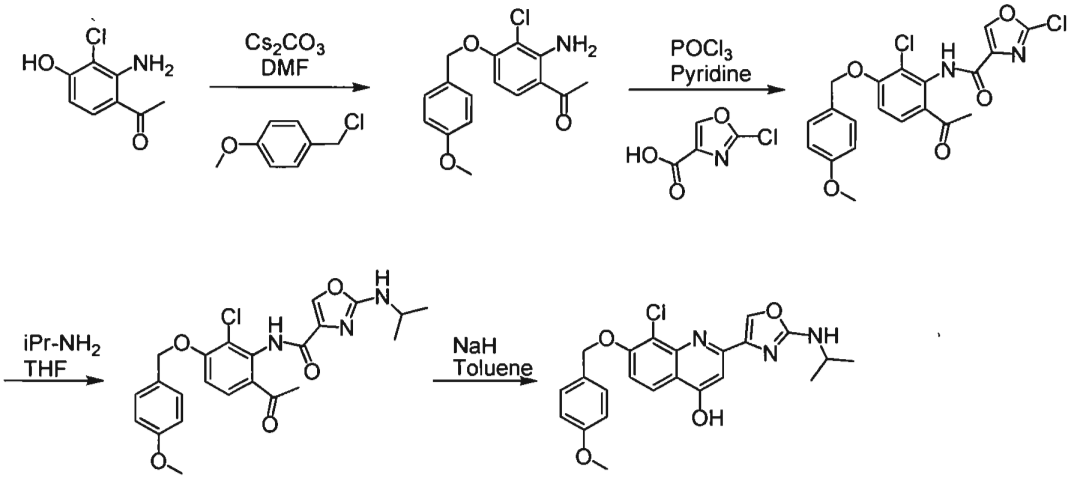
To a solution of alcohol (0.40 g, 1.1 mmol) in DMSO (5 mL) was slowly added potassium *tert*-butoxide (0.38 g, 3.3 mmol). This was followed by the addition of the chloro-quinoline (0.32 g, 1.2 mmol). The reaction mixture was stirred at room temperature overnight. Ethyl acetate (50 mL) was added to the mixture and the pH was adjusted to 2 by adding 1N HCl. After separation, the organic layer was dried over Na_2SO_4. After concentration, the crude product was dried under high vacuum overnight and used for the next step directly.

To a solution of the acid (0.60 g, crude, 1.1 mmol), (1R,2S)-1-amino-2-ethyl-cyclopropanecarboxylic acid methyl ester hydrochloride (0.22 g, 1.2 mmol) and NMM (0.56 g, 5.5mmol) was added HATU (0.63 g, 1.65 mmol) at 0°C. The reaction was stirred for 30 min. Ethyl acetate (50 mL) and 3% aqueous LiCl (50 mL) were added to the mixture while stirring. The organic layer was taken and washed with 3% aqueous LiCl (50 mL), and then with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate / hexanes), affording the coupled tripeptide product (0.28 g, 37%) as white solids. LC/MS = 692.8 (M^++1).



Compound **59** was obtained by following procedures similar to those described above. ^{1}H NMR (300 MHz, CD_3OD): δ 8.81 (s, 1H), 8.05 (d, J = 9.3 Hz, 1H), 7.91 (s, 1H), 7.49 (s, 1H), 7.35 (m, 1H), 7.12 (d, J = 9.0 Hz , 1H), 6.67 (s, 1H), 5.53 (brs, 1H), 4.65 (m, 2H), 4.55 (d, J = 12.3 Hz, 1H), 4.22- 4.16 (m, 3H), 3.95 (s, 3H), 2.75 (m, 1H), 2.56 (m, 1H), 2.20 (m, 1H), 2.10-1.85 (m, 3H), 1.71-1.64 (m, 3H), 1.52-1.38 (m, 3H), 1.29-1.20 (m, 2H), 1.02 (m, 12H), 0.48 (m, 1H), 0.36 (m, 1H). LC/MS = 703.4 (M^++1).

Example 60: Preparation of Compound 60



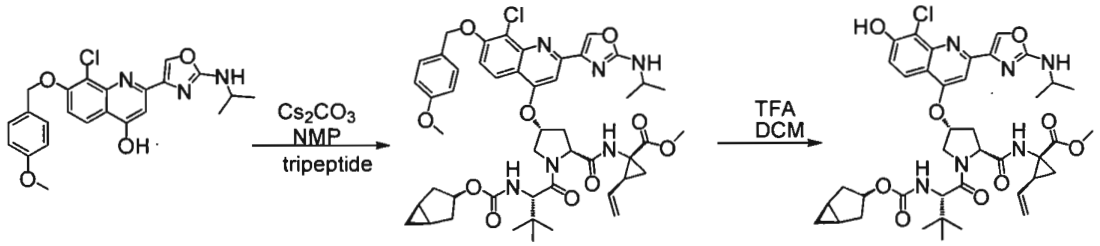
Step 1: The aniline (38.3 g, 206 mmol) and 1-chloromethyl-4-methoxy-benzene (29.4 mL, 216 mmol) were dissolved in anhydrous DMF (412 mL) and treated with Cs_2CO_3 (77.2 g, 326 mmol), then stirred for 90 min. at 50°C. The reaction mixture was concentrated, and then partitioned between H_2O and EtOAc to get a homogeneous solution. EtOAc was then evaporated. The solid crashed was filtered, and then washed with H_2O, MeOH, 30% DCM/Hexane, and 50% EtOAc/Hexane. The solid was dried under high vacuum to provide the PMB protected product (52.2 g, 83 %) LC/MS = 306 (M^++1).

Step 2: The aniline (52.2g, 171 mmol) and the acid (29.0 g, 196 mmol) were dissolved in anhydrous Pyridine (853 mL) and treated with $POCl_3$ (18.8 mL, 205 mmol) at -8 °C. After

60 min. stirring, the reaction mixture was concentrated and partitioned with EtOAc and 1N HCl, then extracted with EtOAc and DCM. After removal of solvent, the crude product was purified by column chromatography (30–80% EtOAc/Hexane) on silica to provide the amide (44.6 g, 60 %), m/z 436. (M+H).

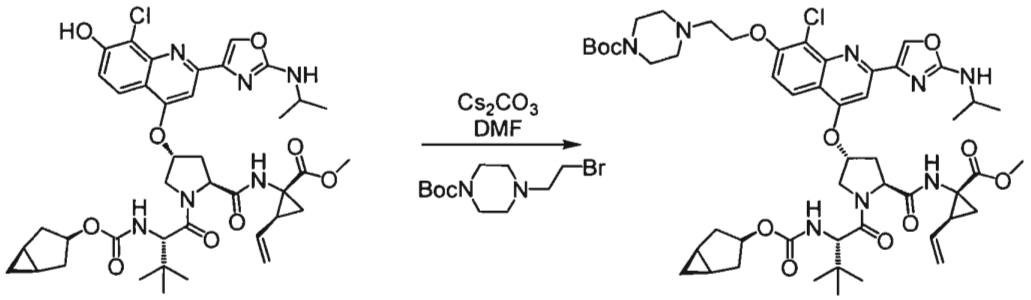
Step 3: Amide (9.04g, 20.8 mmol) and isopropyl amine (17.7 mL, 208 mmol) in THF (177 mL) were stirred for 4 hours at 65 °C. The mixture was concentrated and partitioned between EtOAc and 1N HCl, and then extracted with EtOAc and DCM. After removal of solvent, the crude product was purified by silica gel column chromatography (50–80% EtOAc/Hexane) to provide the amine (6.06 g, 64 %). LC/MS = 457.8 (M^++1).

Step 4: Amine (18.4 g, 40.3 mmol) was suspended in toluene (300 mL), and then NaH (2.42 g, 60.4 mmol) was added. The mixture was stirred for 80 min. at 125 °C. After cooling to room temperature, AcOH (3.76 mL, 66.4 mmol) in H_2O (300 mL) was added. The solid formed was filtered and washed with H_2O and toluene, and then dried under high vacuum overnight to give the quinoline (15.0 g, 84 %). LC/MS = 440 (M^++1).

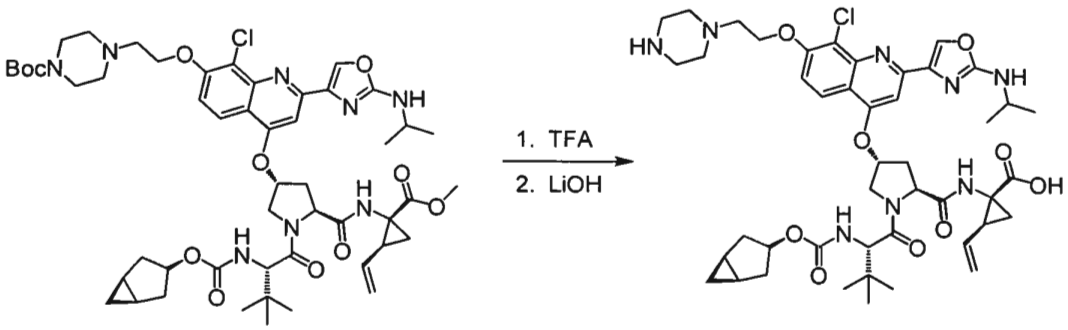


Step 5: The quinoline (1.00 g, 2.27 mmol), tripeptide brosylate (1.78 g, 2.50 mmol) and Cs_2CO_3 (1.85 g, 5.68 mmol) in NMP were stirred for three and half hours at 65 °C. The reaction mixture was partitioned between EtOAc and brine, and then extracted with EtOAc. After evaporation of the volatile organics, the crude product was purified by silica gel column chromatography (50–100% EtOAc/Hexane) to provide the ester (1.64 g, 79 %). LC/MS = 914 (M^++1).

Step 6: To the ester (6.29 g, 6.89 mmol) in DCM (100 mL) was added TFA (10 mL). After stirring for 100 min. at room temperature, 100 mL of toluene was added, and then the mixture was concentrated. The crude was partitioned between sat. $NaHCO_3$ and DCM, and then extracted with DCM. After removal of the volatile organics, the crude product was purified by silica gel column chromatography (65–100% EtOAc/Hexane) to provide the phenol (4.50 g, 82 %). LC/MS = 793.7 (M^++1).

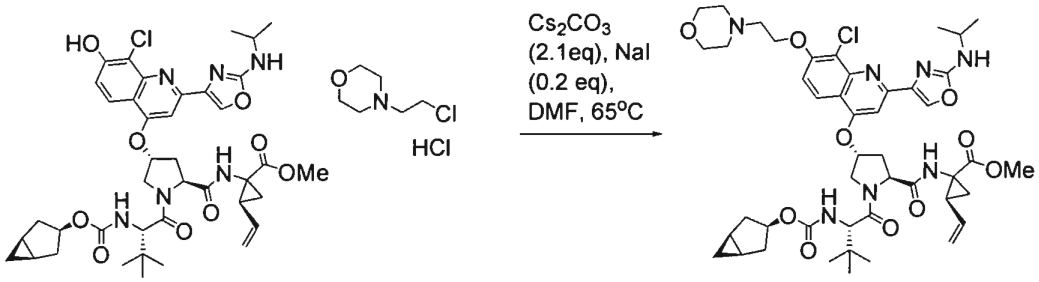


Step 7: The phenol (520 mg, 0.655 mmol) and bromide (231 mg, 0.787 mmol) were dissolved in anhydrous DMF (5 mL) and treated with Cs_2CO_3 (534 mg, 1.64 mmol). The reaction was then stirred for 45 min. at 50 °C. The reaction mixture was partitioned between H_2O and EtOAc, and extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. After removal of the volatile organics, the crude product was purified by silica gel column chromatography (80–100% EtOAc/Hexane) to provide the ester (600 mg, 91 %). LC/MS = 1005.7 (M^++1).



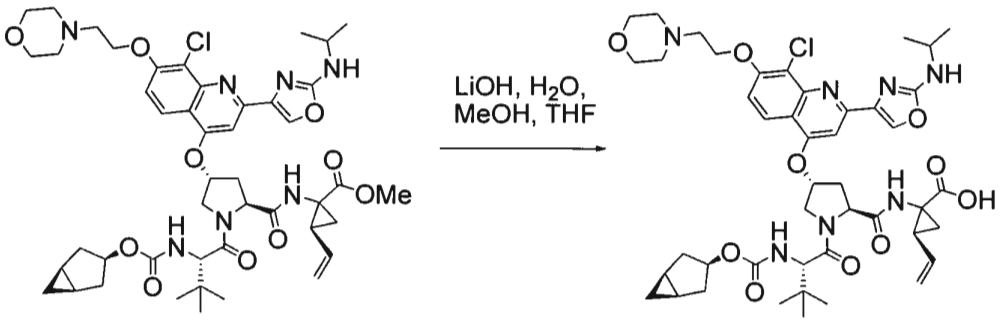
Step 8: The ester (600 mg, 0.597 mmol) was dissolved in anhydrous DCM (6 mL), and then treated with 4 N HCl/dioxane (3 mL, 12.0 mmol). After stirring for 2 hours at room temperature, toluene (6 mL) was added, and the reaction was concentrated. The resulting solid was dissolved in THF (5.37 mL) after drying under high vacuum for 30 min. To the mixture were added MeOH (1.79 mL) and 2N LiOH (3.58 mL). After stirring for 65 min. at 40 °C, the reaction mixture was cooled to room temperature. The reaction mixture was neutralized with 2 N HCl (3.8 mL) and concentrated. The crude material was purified by preparative HPLC to provide Compound **60** (301 mg, 50 %): ^{1}H NMR (CD_3OD, 300 MHz): δ 8.63 (s, 1H), 8.47 (s, 1H), 8.16 (d, 1H), 7.53 (s, 1H), 7.48 (d, 1H), 5.80-5.71 (m, 1H), 5.56 (bs, 1H), 5.18 (d, 1H), 5.10 (d, 1H), 4.61 (t, 1H), 4.49-4.41 (m, 3H), 4.06-3.89 (m, 3H), 3.29-3.18 (m, 8H), 3.14 (t, 2H), 3.07 (t, 2H), 2.67-2.62 (m, 1H), 2.54-2.51 (m, 1H), 2.14-2.08 (m, 1H), 1.89-1.84 (m, 1H), 1.76-1.71 (m, 1H), 1.63-1.53 (m, 2H), 1.38-1.31 (m, 2H), 1.27-1.24 (d, 6H), 1.13-1.08 (m, 2H), 0.93 (s, 9H), 0.29-0.23 (m, 2H); LC/MS = 891 (M^++1).

Example 61: Preparation of Compound 61



Step 1: An N_2 purged flask was charged with phenol (604mg, 0.761mmol), the chloride (170mg, 0.913mmol), Cs_2CO_3 (620mg, 1.90mmol), and NaI (60mg, 0.45mmol). To this mixture was then added DMF (7mL) and the heterogeneous mixture was heated in a preheated 65°C oil bath. After 30 min, the reaction was <40% complete by LC/MS. After 6 h, the reaction was complete. The reaction mixture was diluted with EtOAc and washed with 3 X 100mL 5% LiCl, 100mL ½ sat $NaHCO_{3(aq)}$, and brine. The organics were dried

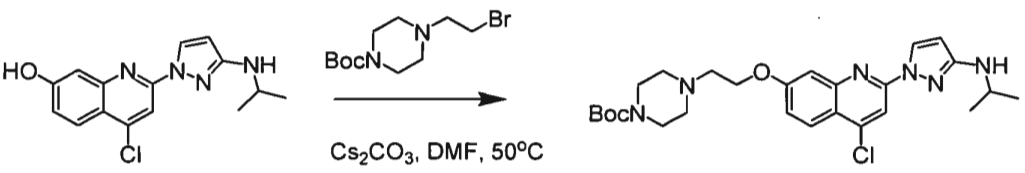
over Na_2SO_4, solids were removed by filtration and the filtrate was concentrated. The crude methyl ester was used as is for the next step. LC/MS = 907 (M^++1).



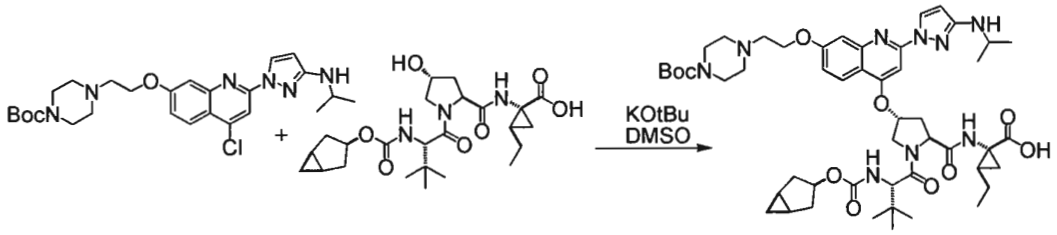
Step 2: The ester (620mg, 0.69mmol) was dissolved in a mixture of THF (6mL) and MeOH (2mL). LiOH·$H_2$0 (143mg, 3.41mmol) was dissolved in dH_2O (2mL) and this was slowly added to the solution of ester in THF/MeOH, which had been cooled to 0 °C. Upon complete addition the ice bath was removed. After 3 h the reaction was complete. The reaction was cooled to 0 °C and neutralized with 2 N HCl. Compound **61** was directly isolated from the reaction mixture by reverse phase HPLC to afford 472mg (78% yield) as off-white solids.

LC/MS = 892 (M^++1). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.31 (s, 1H), 8.02 (s, 1H), 7.89 (d, J = 9.2 Hz, 1H), 7.18-7.14 (m, 2H), 5.53 (dd, J = 9.0, 15.8 Hz, 1H), 5.20 (s, 1H), 4.93 (d, J = 17.4 Hz, 1H), 4.74 (d, J = 10.2 Hz, 1H), 4.33 (m, 4H), 4.11 (d, J = 12.7 Hz, 1H), 3.84-3.22 (m, 12H), 2.93 (brs, 8H), 2.29 (q, J = 4.5 Hz, 1H), 1.87 (m, 1H), 1.66 (m, 1H), 1.55 (m, 1H), 1.35 (m, 1H), 1.14 (m, 1H), 0.97 (d, J = 6.45 Hz, 6H), 0.87 (m, 1H), 0.67 (s, 9H), 0.13-0.01 (m, 2H).

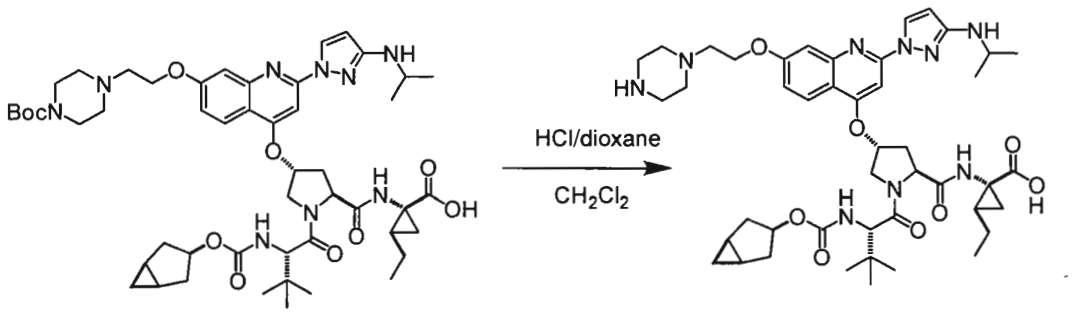
Example 62: Preparation of Compound 62



Step 1: To a solution of phenol (1.10 g, 4.64 mmol) in DMF (21 mL) was added bromide (1.40 g, 4.77 mmol, 1.2 equiv.) and cesium carbonate (3.80 g, 11.6 mmol, 2.5 equiv.). The resulting mixture was placed in a preheated bath (50 °C, external temperature, oil bath), and stirred vigorously for 55 min. Upon cooling to room temperature, the reaction mixture was diluted with EtOAc and washed with water (1x). The water layer was back extracted with EtOAc (1x). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography (50% to 75% EtOAc/hexanes) to provide the quinoline (1.71g, 50%); LC/MS found 515.28 (M^++H, $C_{26}H_{36}ClN_6O_3$ requires 515.25).

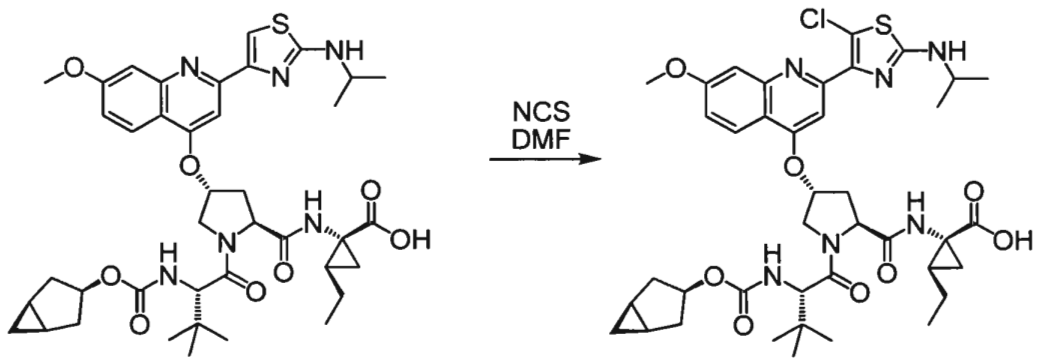


Step 2: To a solution of tripeptide acid (303 mg, 0.634 mmol) in DMSO (3.3 mL) was added potassium *tert*-butoxide (365 mg, 3.17 mmol, 5 equiv.). The resulting slurry was stirred at room temperature for 2 h. A solution of quinoline (359 mg, 0.697 mmol, 1.1 equiv.) in DMSO (3 mL) was added dropwise to the reaction mixture. The resulting slurry was stirred at room temperature for 16.5 h. The reaction was quenched with acetic acid (0.3 mL) and purified by reverse phase HPLC (30 to 90 % MeCN/H_2O-1% TFA) to provide acid (100mg, 16%); LC/MS found 958.27 (M^++H, $C_{50}H_{72}N_9O_{10}$ requires 958.54).



Step 3: To a solution of acid (100mg, 0.104 mmol) in CH_2Cl_2 (0.2mL) was added a solution of 4 N HCl in dioxane (1.0 mL). The resulting mixture was stirred at room temperature for 1.25 hour, concentrated and purified by reverse phase HPLC (30 to 90 % MeCN/H_2O-1% TFA) to provide Compound **62** (10mg, 11%): ^1H NMR (d_3-MeOD, 400 MHz): δ 8.48 (s, 1H), 7.98 (d, 1H), 7.43 (s, 1H), 7.21 (s, 1H), 7.05 (dd, 1H), 7.03 (d, 1H), 6.10 (d, 1H), 5.49 (s, 1H), 4.52-4.56 (m, 2H), 4.41 (d, 1H), 4.23 (t, 2H), 4.10 (s, 1H), 3.97 (m, 2H), 3.85 (t, 1H), 3.18 (q, 4H), 2.93 (t, 2H), 2.85 (m, 4H), 2.61 (m, 1H), 2.46 (m, 1H), 2.03 (m, 1H), 1.89 (m, 1H), 1.80 (m, 2H), 1.55 (t, 4H), 1.41 (m, 2H), 1.35 (d, 2H), 1.19 (d, 8H), 0.92 (s, 9H); LCMS found 858.30 (M^++H, $C_{45}H_{64}N_9O_8$ requires 858.49).

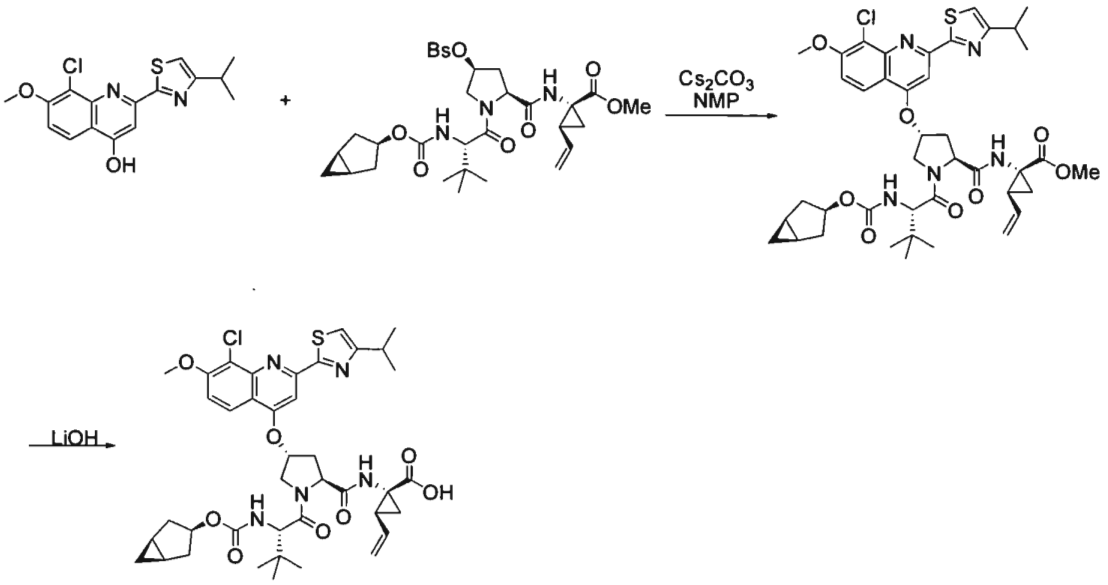
Example 63: Preparation of Compound 63



A solution of 89.5 mg (0.115 mmol) of acid and 15.5 mg (0.116 mmol) of N-chlorosuccinmide in 2 mL of DMF was stirred at 0 °C for 20 h and an additional 5 mg of N-chlorosuccinmide was added to the reaction. The resulting solution was stirred at 0 °C

for 42 h. After the solution was filtered, the product was purified by repeated preparative HPLC and the purified product was freeze-dried to obtain 78.4 mg of the Compound **63**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.63 (s,1H), 8.30 (d, 1H, J = 9.0 Hz), 7.87 (s, 1H), 7.74 (s, 1H), 7.38 (d, 1H, J = 9.0 Hz), 5.76 (s,1H), 4.62-4.74 (m, 2H), 4.55 (appt t, 1H, J = 6.8 Hz), 4.13-4.24 (m, 2H), 4.05-4.13 (m, 1H), 4.06 (s, 3H), 2.75-2.85 (m, 1H), 2.55-2.67 (m, 1H), 1.82-2.05 (m, 2H), 1.60-1.72 (m, 3H), 1.37-1.58 (m, 3H), 1.32 (d, 6H, J = 6.6 Hz), 1.14-1.27 (m, 3H), 0.95-1.06 (m, 12H), 0.35-0.44 (m, 2H); LC/MS = 811 (M^++1).

Example 64: Preparation of Compound 64

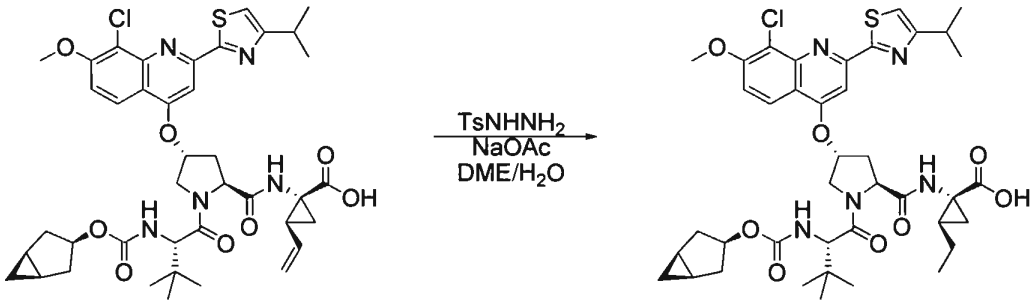


Step 1: A mixture of 1.0 g (1.41 mmol) of the tripeptide, 448.9 mg (1.34 mmol) of quinoline, and 920 mg (2.82 mmol) of cesium carbonate in N-methylpyrrolidine was stirred in a 65 °C bath for 6 h. After the mixture was diluted with ethyl acetate (20 mL) and 5% aqueous LiCl solution (20 mL), the resulting mixture was stirred at room temperature for 30 min and the two phases were separated. The aqueous fraction was extracted with ethyl acetate (20 mL). The organic fractions were washed with water, combined, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography using a hexane and ethyl acetate mixture as eluent, to give 864 mg (76%) of tripeptide with some impurities. LC/MS = 808 (M^++1).

Step 2: A mixture of 864 mg (1.07 mmol) of methyl ester and 128.5 mg (5.37 mmol) of LiOH in THF (5 mL), methanol (5 mL), and water (5 mL) was stirred at room temperature for 14.5 h. The reaction was concentrated to a half volume using a rotary evaporator. After the concentrated solution was acidified by adding 0.83 mL (10.77 mmol) of trifluoroacetic acid, the mixture was diluted with water (5 mL) and methanol (5 mL) and stirred in a 0 °C bath for 1 h. The solids were filtered, washed with water, and dried under vacuum. The solids were dissolved in a dioxane-acetonitrile-water mixture by heating and

then freeze-dried to obtain 818 mg of compound **64**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.09 (d, 1H, J = 9.3 Hz), 7.72 (s, 1H), 7.40 (d, 1H, J = 9.3 Hz), 7.34 (s, 1H), 5.77-5.92 (m,1H), 5.56 (s, 1H), 5.28 (d, 1H, J = 18.0 Hz), 5.10 (d, 1H, J = 10.2 Hz), 4.56-4.70 (m, 2H), 4.52 (m, 1H), 4.24 (br s, 1H), 4.00-4.16 (m, 2H), 4.06 (s, 3H), 3.23 (hept, 1H, J = 6.6 Hz), 2.72-2.82 (m, 1H), 2.45-2.58 (m, 1H), 2.07-2.26 (m, 1H), 1.92-2.06 (m, 1H), 1.76-1.92 (m, 1H), 1.62-1.76 (m, 2H), 1.26-1.50 (m, 1H), 1.41 (d, 6H, J = 6.6 Hz), 1.12-1.26 (m, 2H), 1.02 (m, 9H), 0.27-0.42 (m, 2H); LC/MS = 794 (M^++1).

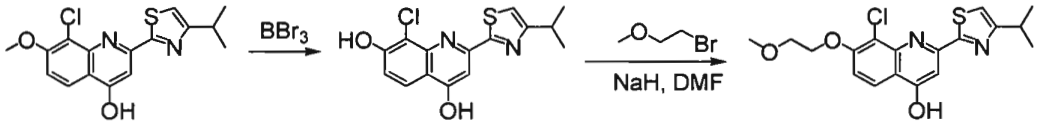
Example 65: Preparation of Compound 65



A mixture of 520.9 mg (0.573 mmol) of compound **64**, 810 mg (4.35 mmol) of tosylhydrazide, and 707 mg (8.62 mmol) of sodium acetate in dimethoxyethane (10 mL) and water (1 mL) was stirred in a 95 °C bath for 1 h. The reaction mixture was diluted with water and a small amount of an aq. $NaHCO_3$ solution. This mixture was then extracted with ethyl acetate (x 2). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was triturated with 50% aq. Methanol at 0 °C for 1 h and the solids that formed were isolated by filtration. The solids were dissolved in a mixture of dioxane, acetonitrile, and water, acidified by adding 2-3 drops of trifluoroacetic acid, and freeze-dried to obtain 447 mg of compound **65**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.07 (d, 1H, J = 9.0 Hz), 7.70 (s, 1H), 7.39 (d, 1H, J = 9.0 Hz), 7.34 (s, 1H), 5.54 (s,1H), 4.56-4.69 (m, 2H), 4.51 (m, 1H), 4.23 (br s, 1H), 4.00-4.14 (m, 2H), 4.05 (s, 3H), 3.22 (hept, 1H, J = 6.9 Hz), 2.68-2.80 (m, 1H), 2.40-2.58 (m, 1H), 1.93-2.06 (m, 1H), 1.78-1.93 (m, 1H),

1.58-1.72 (m, 3H), 1.37-1.58 (m, 1H), 1.41 (d, 6H, J = 6.9 Hz), 1.27-1.37 (m, 1H), 1.10-1.27 (m, 3H), 0.94-1.10 (m, 12H), 0.27-0.42 (m, 2H); LC/MS = 796 (M^++1).

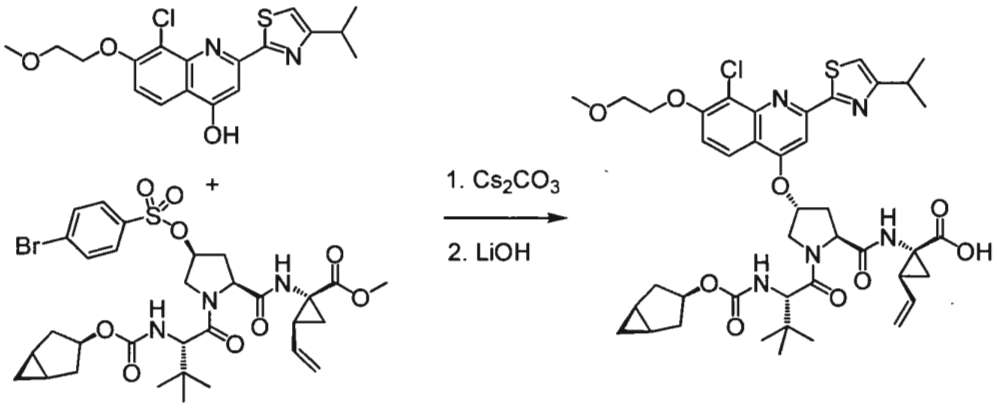
Example 66: Preparation of Compound 66



Step 1: A solution of 2.721 g (8.13 mmol) of methyl ether in 100 mL of CH_2Cl_2 was stirred at room temperature. 42 mL (42 mmol) of BBr_3 in CH_2Cl_2 was then added. The resulting mixture was refluxed in a 50 °C bath for 5 h and then an additional 8.4 mL (8.4 mmol) of BBr_3 in CH_2Cl_2 was added. After 2 h of reflux, an additional 8.4 mL (8.4 mmol) of BBr_3 in CH_2Cl_2 was added and the resulting mixture was refluxed for 18 h. The resulting mixture was poured into 300 g of ice and the mixture was basified by adding ~ 18 g (~450 mmol) of NaOH. After the two phases were separated, the aqueous fraction was extracted with water (100 mL). The two aqueous fractions were washed with CH_2Cl_2, combined, and brought to pH ~6 using conc. HCl. The resulting mixture was stirred in an ice bath for 1 h and filtered. The solids were washed with water and dried. The solids were triturated in 100 mL water at room temperature for 1 h and the solids that formed were filtered and washed with water before drying under vacuum to obtain 2.566 g (98%) of bisphenol.

Step 2: A mixture of 2.454 g (7.65 mmol) of bisphenol and 671 mg (16.78 mmol) of 60% NaH was placed in a 250 mL round bottom flask and 40 mL of DMF was added at 0 °C. After the mixture was stirred at 0 °C for 30 min, 0.80 mL (8.51 mmol) of 2-bromoethyl methyl ether was added. The resulting mixture was stirred at 4 °C for 48 h and diluted with ethyl acetate (120 mL) and 5% aqueous LiCl solution (120 mL). After the mixture was adjusted to pH 4-6 with 1 N HCl and diluted with additional ethyl acetate (~1 L), the

mixture was stirred at room temperature for 1 h. The upper organic fraction was separated from the lower aqueous fraction, which contained solids. The solids in the aqueous fraction were dissolved with ethyl acetate (1 L) and the organic fraction was separated. The two organic fractions were washed with water (1 L), combined, dried ($MgSO_4$) and concentrated. The residue was triturated with 200 mL of CH_2Cl_2 and the insoluble material was filtered. The filtrate was concentrated and purified by silica gel chromatography using with a mixture of hexane, ethyl acetate, and methanol as eluent, to obtain 732 mg of the quinoline. LC/MS = 379 (M^++1).

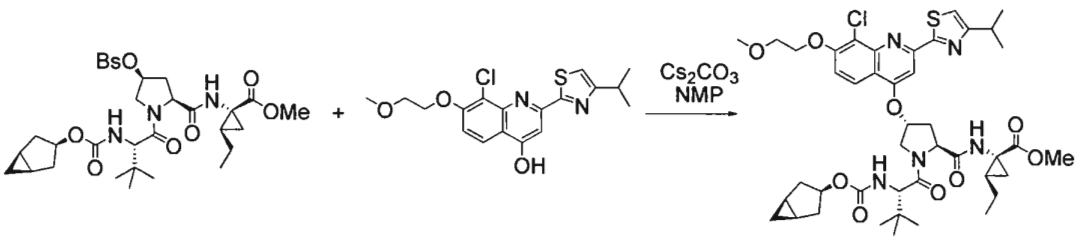


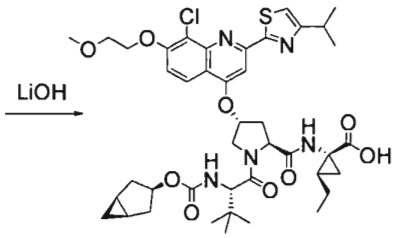
Step 3: A mixture of 595 mg (0.837 mmol) of tripeptide, 300 mg (0.791 mmol) of quinoline, and 546 mg (1.68 mmol) of cesium carbonate in 4.2 mL of N-methylpyrrolidine was stirred in a 65 °C bath for 16.5 h. After the mixture was diluted with ethyl acetate (20 mL) and a 5% aqueous LiCl solution (20 mL), the resulting mixture was stirred at room temperature for 30 min and the two phases were separated. The aqueous fraction was extracted with ethyl acetate (20 mL). The organic fractions were washed with water (x 2), combined, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography using with a mixture of hexane and ethyl acetate as eluent, to give 410 mg (61%) of the methyl ester with some impurities. LC/MS = 852 (M^++1).

Step 4: A mixture of 410 mg (0.48 mmol) of ester and 115 mg (4.81 mmol) of LiOH in THF (2 mL), methanol (2 mL), and water (2 mL) was stirred at room temperature for 4 h

and then concentrated. The residue was dissolved in DMF and acidified by adding 0.45 mL (5.84 mmol) of trifluoroacetic acid. The mixture was diluted with ethyl acetate (200 mL), washed with water (x 2), dried ($MgSO_4$), and concentrated. The residue was dissolved in dioxane and freeze-dried to get 372 mg of compound **66**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.73 (s, 1H), 8.08 (d, 1H, J = 8.6 Hz), 7.73 (s, 1H), 7.41 (d, 1H, J = 9.0 Hz), 7.34 (s, 1H), 5.76-5.94 (m, 1H), 5.56 (s,1H), 5.28 (d, 1H, J = 16.8 Hz), 5.10 (d, 1H, J = 10.8 Hz), 4.57-4.70 (m, 2H), 4.52 (m, 1H), 4.38 (br m, 2H), 4.23 (br, 1H), 4.05-4.16 (m, 1H), 3.86 (br m, 2H), 3.49 (s, 3H), 3.23 (hept, 1H, J = 6.6 Hz), 2.70-2.82 (m, 1H), 2.46-2.58 (m, 1H), 2.12-2.26 (m, 1H), 1.83-2.07 (m, 2H), 1.62-1.75 (m, 2H), 1.37-1.48 (m, 2H), 1.41 (d, 6H, J = 6.6 Hz), 1.26-1.37 (m, 1H), 1.19 (br, 1H), 1.02 (s, 9H), 0.27-0.42 (m, 2H); LC/MS = 838 (M^++1).

Example 67: Preparation of Compound 67



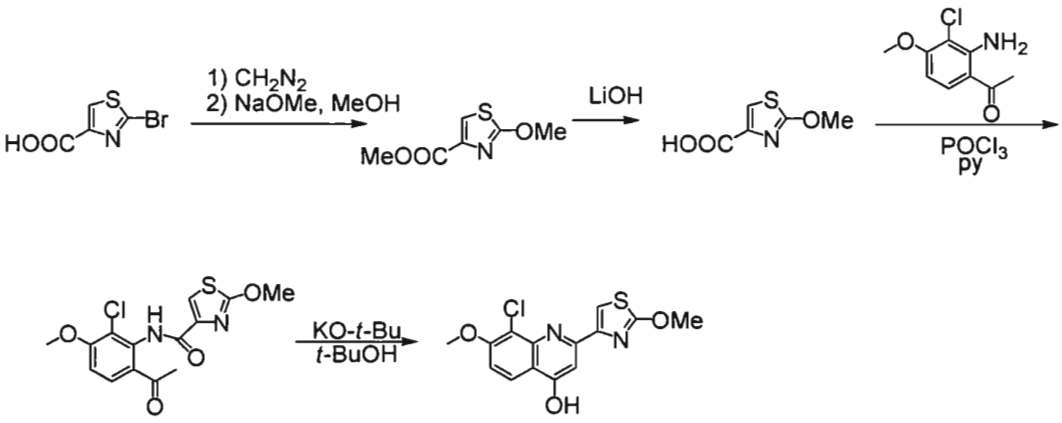


Step 1: A mixture of 628 mg (0.881 mmol) of intermediate III, 317 mg (0.837 mmol) of quinoline, and 632 mg (1.94 mmol) of cesium carbonate in 4.4 mL of N-methylpyrrolidine was stirred in a 65 °C bath for 16 h. After the mixture was diluted with ethyl acetate (20 mL) and a 5% aqueous LiCl solution (20 mL), the resulting mixture was stirred at room temperature for 30 min and the two phases were separated. The aqueous fraction was extracted with ethyl acetate (20 mL). The organic fractions were washed with water (x 2),

combined, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography using with a mixture of hexane and ethyl acetate as eluent, to give 504 mg (71%) of ester. LC/MS = 854 (M^++1).

Step 2: A mixture of 504 mg (0.59 mmol) of ester and 71 mg (2.96 mmol) of LiOH in THF (2 mL), methanol (2 mL), and water (2 mL) was stirred at room temperature for 15 h. An additional 71 mg (2.96 mmol) of LiOH was added and the mixture was stirred at room temperature for 6 h. After the solution was concentrated, the residue was dissolved in ethyl acetate and acidified by adding trifluoroacetic acid. The solution was washed with water (x 2), dried ($MgSO_4$), and concentrated. The residue was triturated in 50% aq. Methanol (5 mL) at 0 °C for 2 h and filtered. After the solids were washed with water, they were dried under vacuum to obtain 535 mg (95%) of compound **67.** ^{1}H NMR (300 MHz, CD_3OD): δ 8.09 (d, 1H, J = 8.7 Hz), 7.74 (s, 1H), 7.42 (d, 1H, J = 8.7 Hz), 7.37 (s, 1H), 5.57 (s,1H), 4.48-4.70 (m, 3H), 4.39 (m, 2H), 4.22 (m, 1H), 4.04-4.16 (m, 1H), 3.86 (m, 2H), 3.49 (s, 3H), 3.23 (hept, 1H, J = 6.9 Hz), 2.69-2.82 (m, 1H), 2.46-2.60 (m, 1H), 1.76-2.08 (m, 2H), 1.27-1.76 (m, 6H), 1.41 (d, 6H, J = 6.9 Hz), 1.22 (m, 3H), 1.01 (s, 9H), 0.90-1.10 (m, 3H), 0.28-0.42 (m, 2H); LC/MS = 840 (M^++1).

Example 68: Preparation of Compound 68



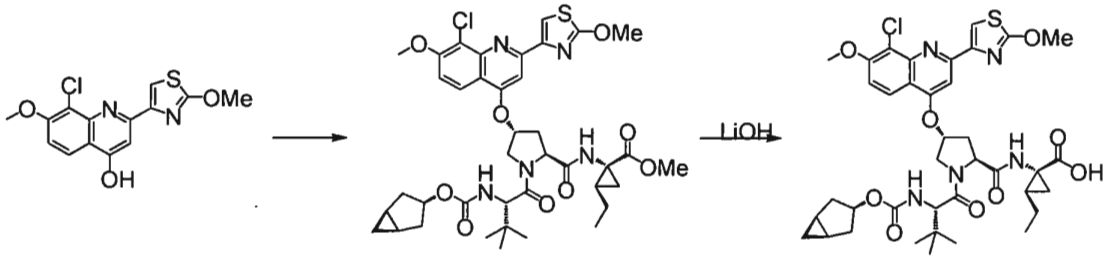
Step 1: A slurry of 2.000 g (9.62 mmol) of acid in methanol (20 mL) and toluene (20 mL) was stirred at 0 °C as 8 mL (16 mmol) of 2.0 M $TMSCHN_2$ in ether was added dropwise. After 30 min at 0 °C and 10 min at room temperature, the solution was concentrated at using a rotary evaporator with the bath temp <30 °C, and the residue was further dried under vacuum. To the residue in methanol (15 mL) was added 3.75 mL (16.4 mmol) of 25% sodium methoxide in methanol and the resulting solution was refluxed in a 70 °C bath for 1 h. After the solution was concentrated, the residue was adsorbed on silica gel and purified by chromatography to obtain 997 mg of ester. LC/MS = 174 (M^++1).

Step 2: A solution of 992 mg of ester and 274 mg (11.44 mmol) of LiOH in THF (9 mL), methanol (3 mL) and water (3 mL) was stirred at room temperature for 30 min. The mixture was concentrated to ~ 1/3 volume, diluted with water (25 mL) and then extracted with ethyl acetate (25 mL). The organic washing was extracted with water (1 x 25 mL). The aqueous fractions were combined and acidified with 1 N HCl (15 mL) and the product was extracted with ethyl acetate (3 x 30 mL). The combined extracts were dried ($MgSO_4$) and concentrated to afford 835 mg (92%) of acid. LC/MS = 160 (M^++1).

Step 3: A solution of 824 mg of acid and 274 mg (5.18 mmol) of LiOH in pyridine (50 mL) was stirred at -30 min. The resulting mixture was stirred in a freezer for 2.5 h and then quenched with 2.5 mL of water and concentrated. The residue was dissolved in ethyl acetate and a saturated aq. $NaHCO_3$ solution. The aqueous fraction was extracted with water (1 x 1). The aqueous fractions were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography to obtain 495 mg (28%) of acid. LC/MS = 341 (M^++1).

Step 4: A mixture of 495 mg (1.45 mmol) of amide and 350 mg (3.12 mmol) of potassium *tert*-butoxide in *tert*-BuOH (7.3 mL) was stirred at 75 °C for 7.5 h. The mixture was concentrated after 1.5 mL (6 mmol) of 4 N HCl in dioxane was added. The residue was triturated with 1 N NaH_2PO_4 (25 mL) at room temperature for 1 h and filtered. The

solids were washed with water and then ether, and dried in vacuum to obtain 423 mg of quinoline. LC/MS = 323 (M^++1).



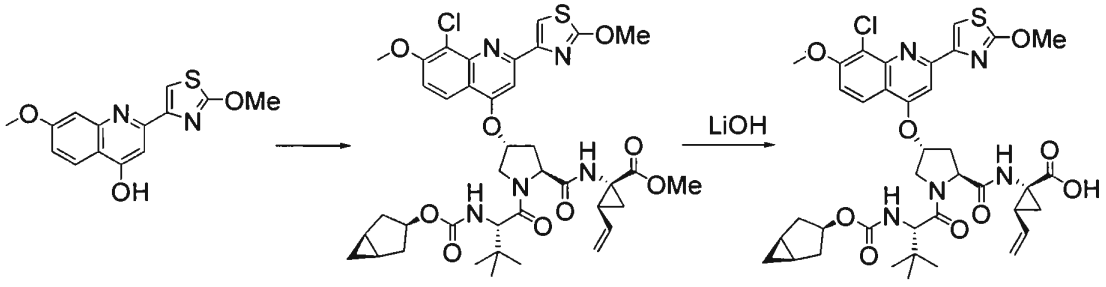
Step 5: A mixture of 302 mg (0.424 mmol) of tripeptide, 130 mg (0.402 mmol) of quinoline, and 304 mg (0.932 mmol) of cesium carbonate in 3 mL of N-methylpyrrolidine was stirred in a 65 °C bath for 16 h. After the mixture was diluted with ethyl acetate (15 mL) and a 5% aqueous LiCl solution (15 mL), the resulting mixture was stirred at room temperature for 30 min and the two phases were separated after further dilution with water and ethyl acetate. The organic fraction was washed with water (x 1), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography using with a mixture of hexane and ethyl acetate as eluent, to give 199 mg (62%) of ester with some impurities. LC/MS = 798 (M^++1).

Step 5: A mixture of 302 mg (0.424 mmol) of intermediate III, 130 mg (0.402 mmol) of quinoline, and 304 mg (0.932 mmol) of cesium carbonate in 3 mL of N-methylpyrrolidine was stirred at 65 °C bath for 16 h. After the mixture was diluted with ethyl acetate (15 mL) and 5% aqueous LiCl solution (15 mL), the resulting mixture was stirred at room temperature for 30 min and the two phases were separated after further dilution with water and ethyl acetate. The organic fraction was washed with water (x 1), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography using combi-flash with hexane-ethyl acetate to give 199 mg (62%) of ester with some impurities. LC/MS = 798 (M^++1).

A mixture of 199 mg (0.25 mmol) of ester and 59 mg (2.48 mmol) of LiOH in THF (4 mL), methanol (2 mL), and water (2 mL) was stirred at room temperature for 20 h and

concentrated. The residue was dissolved in ethyl acetate and water, and acidified by adding 0.3 mL (4.04 mmol) of trifluoroacetic acid. After the two phases were separated, the aqueous fraction was extracted with ethyl acetate. After the combined organic fractions were dried ($MgSO_4$) and concentrated, the residue was purified by preparative HPLC to obtain 132 mg of compound **68**. ^1H NMR (300 MHz, CD_3OD): δ 8.48 (s, 1H), 8.08 (d, 1H, J = 9.6 Hz), 7.86 (s, 1H), 7.63 (d, 1H, J = 9.6 Hz), 5.76 (br,1H), 4.76 (m, 1H), 4.60 (m, 1H), 4.45 (t, 1H), 4.31 (s, 3H), 4.17 (s, 3H), 4.15 (m, 1H), 4.03-4.12 (m, 1H), 2.74-2.85 (m, 1H), 2.55-2.67 (m, 1H), 1.86-2.02 (m, 1H), 1.74-1.86 (m, 1H), 1.28-1.74 (m, 6H), 1.12-1.28 (m, 3H), 1.02 (m, 9H), 0.96-1.12 (m, 3H), 0.30-0.44 (m, 2H); LC/MS = 784 (M^++1).

Example 69: Preparation of Compound 69

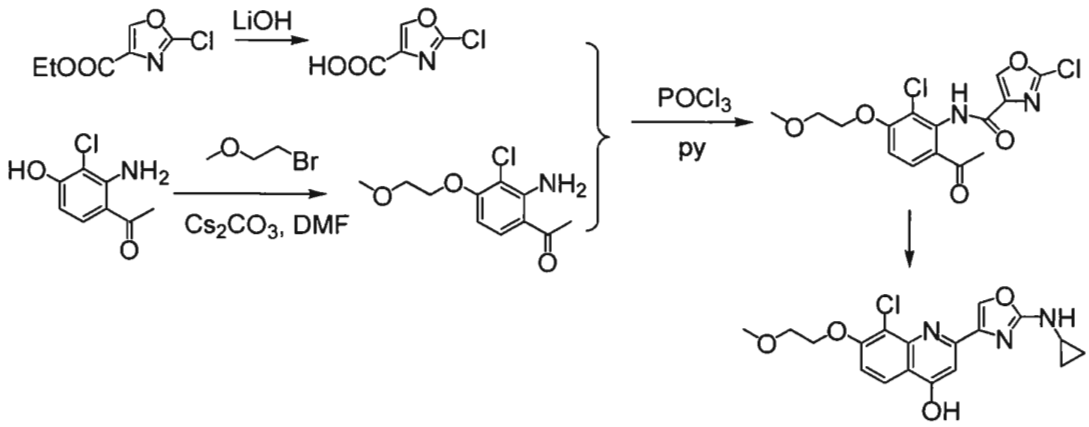


A mixture of 101 mg (0.142 mmol) of the tripeptide, 44 mg (0.136 mmol) of quinoline, and 104 mg (0.320 mmol) of cesium carbonate in 1 mL of N-methylpyrrolidine was stirred in a 65 °C bath for 16 h. After the mixture was diluted with ethyl acetate (5 mL) and a 5% aqueous LiCl solution (5 mL), the resulting mixture was stirred at room temperature for 30

min. The two phases were separated after further dilution with water and ethyl acetate. The organic fraction was washed with water (x 1), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography using with a mixture of hexane and ethyl acetate as eluent, to give 71 mg of the ester with some impurities. LC/MS = 796 (M^++1).

A mixture of 71 mg (0.090 mmol) of ester and 21 mg (0.881 mmol) of LiOH in THF (2 mL), methanol (1 mL), and water (1 mL) was stirred at room temperature for 5 h and then concentrated. The residue was dissolved in ethyl acetate and water, and acidified by adding 0.1 mL of trifluoroacetic acid. After the two phases were separated, the aqueous fraction was extracted with ethyl acetate. After the combined organic fractions were dried ($MgSO_4$) and concentrated, the residue was purified by preparative HPLC to obtain 54 mg of compound **69**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.75 (s, 1H), 8.48 (s, 1H), 8.31 (d, 1H, J = 9.6 Hz), 7.86 (s, 1H), 7.63 (d, 1H, J = 9.0 Hz), 5.86 (m, 1H), 5.77 (br,1H), 5.29 (d, 1H, J = 17.1 Hz), 5.12 (d, 1H, J = 10.8 Hz), 4.73 (m, 1H), 4.60 (m, 1H),), 4.45 (m, 1H), 4.31 (s, 3H), 4.17 (s, 3H), 4.15 (m, 1H), 4.05-4.13 (m, 1H), 2.74-2.92 (m, 1H), 2.54-2.66 (m, 1H), 2.14-2.27 (m, 1H), 1.87-2.02 (m, 2H), 1.76-1.87 (m, 1H), 1.69-1.76 (m, 1H), 1.63 (m, 1H), 1.42-1.50 (m, 1H), 1.28-1.42 (m, 1H), 1.19 (br, 1H), 1.03 (m, 9H), 0.30-0.44 (m, 2H); LC/MS = 782 (M^++1).

Example 70: Preparation of Compound 70



Step 1: A solution of 7.413 g (42.22 mmol) of ester in THF (45 mL) was stirred in a 0 °C bath as 1 N LiOH (45 mL) was added over 30 min. After addition, the solution was stirred at 0 °C for 2 h and acidified by adding 13 mL (52 mmol) of 4 N HCl. The resulting mixture was concentrated to a half volume under reduced pressure. After the concentrated mixture was diluted with water, the product was extracted with ethyl acetate (100 mL x 2). The extracts were combined, washed with brine (50 mL x 1), dried ($MgSO_4$), and concentrated to afford 5.972 (96%) of acid.

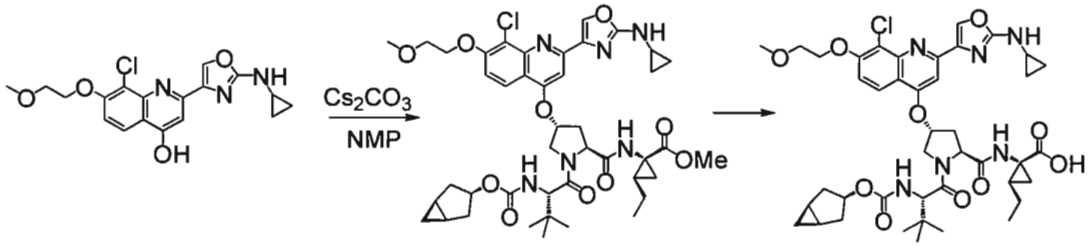
Step 2: A mixture of 3.345 g (18.02 mmol) of crude phenol and 7.055 g (21.65 mmol) of cesium carbonate in DMF (30 mL) was stirred at room temperature as 1.9 mL (20.22 mmol) of 2-bromoethyl methyl ether was added. The mixture was stirred at 65 °C for 5 h and diluted with ethyl acetate (500 mL) and 5% aq. LiCl (250 mL). After the two layers were separated, the aqueous fraction was extracted with ethyl acetate (300 mL) and the organic fractions were washed with water (300 mL), the organics were combined, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography using a mixture of hexane and ethyl acetate as eluent, to give 3.611 g (82%) of aniline. LC/MS = 244 (M^++1).

Step 3: A mixture of 778 mg (5.28 mmol) of acid and 1.157 g (4.75 mmol) of aniline in DMF (30 mL) was stirred in a -25 °C bath as 1.9 mL (5.90 mmol) of $POCl_3$ was added. The mixture was stirred in a -5 ~ -15 °C for 3 h and then 2.5 mL) and 5% aq. LiCl (250 mL). After 5 min, the mixture was concentrated. The residue was purified by silica gel chromatography using with a mixture of hexane, and ethyl acetate as eluent, to give 1.131 g (64%) of amide. LC/MS = 373 (M^++1).

Step 4: A mixture of 1.031 g (2.76 mmol) of amide in THF (9.5 mL) and cyclopropylamine (1.9 mL, 27.42 mmol) was placed in a pressure tube, stirred in a 65 °C bath for 5 h, and concentrated. After the residue was combined with water and the mixture was stirred at room temperature for 24 h and then diluted with a saturated aq.

NaHCO3 solution (50 mL). The product was then extracted with ethyl acetate (100 mL x 2). The organic extracts were combined, washed with water (100 mL), dried ($MgSO_4$) and concentrated, the product was purified by silica gel chromatography using with a mixture of hexane and ethyl acetate as eluent, to give 769 mg (71%) of amine. LC/MS = 394 (M^++1).

Step 5: A suspension of 767 mg (1.95 mmol) of amine and 119 mg (2.98 mmol) of NaH (60% dispersion in mineral oil) in toluene (11.5 mL) was refluxed at 110 °C bath for 3 h before an additional 41 mg (1.03 mmol) of 60% NaH was added. After 2 h of reflux, an additional 80 mg (2.0 mmol) of 60% NaH was added and the mixture was refluxed for 1 h and then cooled to room temperature. To the suspension was added a solution of 0.38 mL (6.64 mmol) of acetic acid in 2.3 mL water and the resulting mixture was stirred in a 0 °C bath for 30 min and filtered. The collected solids were washed with water and dried under vacuum to get 612 mg (84%) of quinoline. LC/MS = 376 (M^++1).

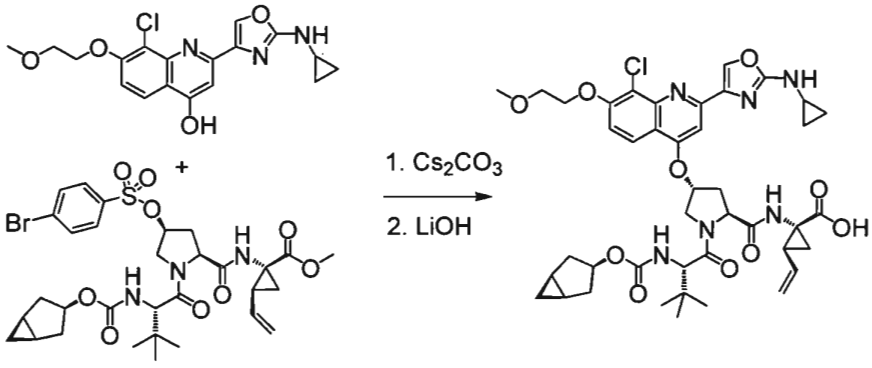


Step 6: A mixture of 663 mg (0.930 mmol) of tripeptide **III**, 332 mg (0.883 mmol) of quinoline, and 674 mg (2.07 mmol) of cesium carbonate in 6.6 mL of N-methylpyrrolidine was stirred in a 65 °C bath for 16 h. After the mixture was diluted with ethyl acetate (15 mL) and a 5% aqueous LiCl solution (26 mL), the resulting mixture was stirred at room temperature for 30 min, additional 5% aqueous LiCl solution and ethyl acetate were added and the two phases were separated. The aqueous fraction was extracted with ethyl acetate (x 1) and two organic fractions were washed with water (x 1), combined, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography using a mixture

of hexane and ethyl acetate as eluent, to give 359 mg of ester compound. LC/MS = 851 (M^++1).

Step 7: A mixture of 359 mg (0.423 mmol) of ester and 200 mg (8.35 mmol) of LiOH in THF (5 mL), methanol (5 mL), and water (5 mL) was stirred at room temperature for 16 h. After the solution was acidified by adding trifluoroacetic acid, the mixture was concentrated. The residue was dissolved in ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography, using a mixture of hexane and ethyl acetate as eluent, and the collected product was freeze-dried with trifluoroacetic acid to give 261 mg of compound **70**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.66 (s, 1H), 8.27 (d, 1H, J = 9.7 Hz), 7.70 (s, 1H), 7.64 (d, 1H, J = 9.7 Hz), 5.68 (s,1H), 4.35-4.78 (m, 4H), 4.02-4.20 (m, 2H), 3.87 (br, 2H), 3.47 (s, 3H), 2.4-2.9 (m, 2H), 1.89-2.04 (m, 1H), 1.77-1.89 (m, 1H), 1.28-1.77 (m, 4H), 1.23 (m, 3H), 0.94-1.11 (m, 12H), 0.85-0.94 (m, 2H), 0.70 (br, 2H), 0.28-0.44 (m, 2H); LC/MS = 837 (M^++1).

Example 71: Preparation of Compound 71

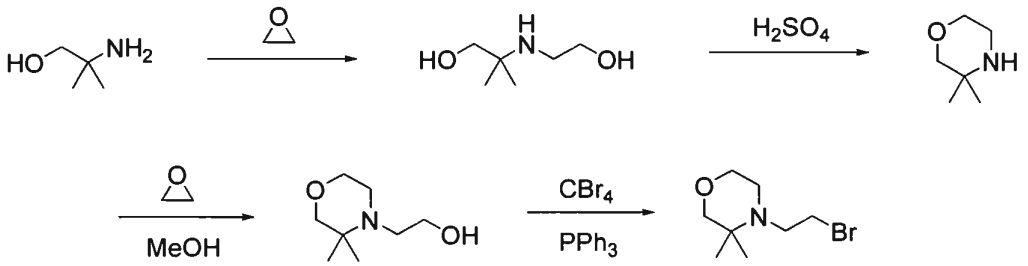


A mixture of 557 mg (0.784 mmol) of tripeptide, 279 mg (0.741 mmol) of the quinoline, and 563 mg (1.73 mmol) of cesium carbonate in 5.6 mL of N-methylpyrrolidine was stirred in a 65 °C bath for 16 h. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate (5 mL) and a 5% aqueous LiCl solution (20 mL). The resulting mixture was stirred at room temperature for 30 min and the two phases were separated

after further dilution with a 5% aqueous LiCl solution (30 mL) and ethyl acetate (50 mL). The aqueous fraction was extracted with ethyl acetate (x 1) and two organic fractions were washed with water (x 1), combined, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography, using a mixture of hexane and ethyl acetate as eluent, to give 288 mg (46%) of ester. LC/MS = 849 (M^++1).

A mixture of 288 mg (0.339 mmol) of the ester and 41 mg (1.71 mmol) of LiOH in THF (4 mL), methanol (4 mL), and water (4 mL) was stirred at room temperature for 16 h. After the solution was acidified by adding trifluoroacetic acid, the mixture was concentrated. The residue was dissolved in ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography, using a mixture of hexane and ethyl acetate as eluent, and the collected product was freeze-dried with trifluoroacetic acid to give 238 mg of compound **71**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.58 (s, 1H), 8.24 (d, 1H, J = 8.7 Hz), 7.64 (s, 1H), 7.60 (d, 1H, J = 8.7 Hz), 5.77-5.96 (m, 1H), 5.66 (s,1H), 5.29 (d, 1H, J = 17.4 Hz), 5.11 (d, 1H, J = 9.9 Hz), 4.71 (m, 1H), 4.42-4.62 (m, 3H), 4.04-4.20 (m, 2H), 3.87 (br, 2H), 3.47 (s, 3H), 2.54-2.88 (m, 2H), 2.10-2.30 (m, 1H), 1.55-2.06 (m, 5H), 1.27-1.50 (m, 3H), 1.21 (m, 3H), 1.03 (m, 9H), 0.80-0.93 (m, 2H), 0.69 (br, 2H), 0.30-0.44 (m, 2H); LC/MS = 835 (M^++1).

Example 72: Preparation of Compound 72



Step 1: 2-(2-Hydroxy-ethylamino)-2-methyl-propan-1-ol was prepared from 2-amino-2-methyl-propan-1-ol following a modified procedure from Cottle *et al. J. Chem. Soc.* **1946**, 289. To a solution of 2-amino-2-methyl-propan-1-ol (250 mL, 2.61 mol, 1.76 equiv.) in

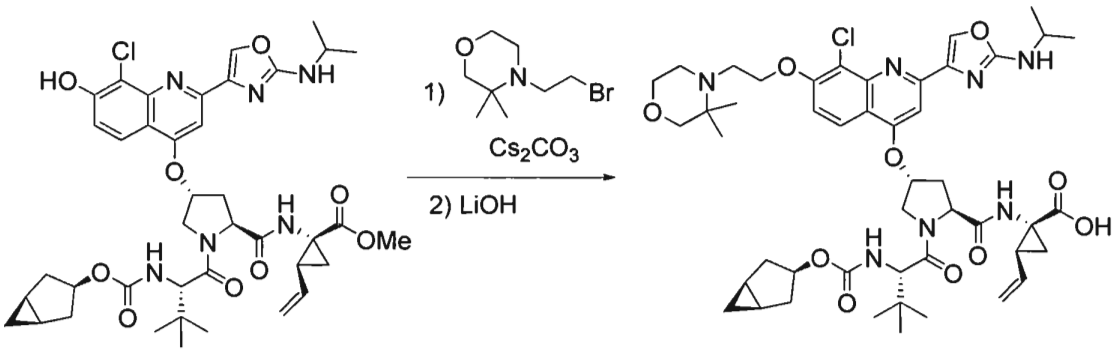
H_2O (400 mL) at -5 °C (external temperature, NaCl/ice bath) was added ethylene oxide (65.25 g, 1.48 mol, condensed at -78 °C). The solution was stirred over 16 hours, during which time the temperature warmed to room temperature. The H_2O was removed *in vacuo* and the remaining 2-amino-2-methyl-propan-1-ol was distilled. The crude residue was dissolved in boiling EtOAc and precipitated with the addition of hexanes to provide 2-(2-Hydroxy-ethylamino)-2-methyl-propan-1-ol (145.5 g, 74%) as colorless crystals. LC/MS found 134.03 (M^++H, $C_6H_{16}NO_2$ requires 134.12).

Step 2: 3,3-Dimethylmorpholine was prepared from 2-(2-Hydroxy-ethylamino)-2-methyl-propan-1-ol following a modified procedure from Cottle *et al. J. Chem. Soc.* **1946**, 289. To H_2SO_4 (110 mL, 2.06 mol, 1.85 equiv.) at 3 °C (internal temperature, ice bath) was slowly added 2-(2-Hydroxy-ethylamino)-2-methyl-propan-1-ol (145.5g, 1.09 mol) in portions. The internal temperature of the reaction rose to 70 °C. The resulting solution was heated to 185 °C (internal temperature, oil bath) for 2 hours, during which time the solution turns brown. Upon cooling to room temperature, H_2O (250 mL) was added followed by the slow addition of solid NaOH until the pH of the solution was basic. The solution was diluted with EtOAc (500 mL) and the biphasic mixture was stirred vigorously for 15 hours. The solution was then filtered through celite and washed with H_2O and EtOAc. The organic layer was separated and washed with brine. The aqueous layers were twice back-extracted with EtOAc. The resulting organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo* (pressure > 80 torr). The crude product was distilled (76 °C, 98 torr) to provide 3,3-dimethylmorpholine (46.0 g, 36%) as a colorless oil. LC/MS found 116.04 (M^++H, $C_6H_{14}NO$ requires 116.11).

Step 3: In a pressure vessel containing 3,3-dimethylmorpholine (12.15 g, 106 mmol) in MeOH (17 mL) at -78 °C (external temperature, acetone/CO_2(s)) was added ethylene oxide (6.2 mL, 125 mmol, 1.2 equiv., condensed at -78 °C). The solution was sealed and stirred over 20 hours, during which time the temperature warmed to room temperature. The reaction mixture was concentrated *in vacuo* and the crude product was distilled (75 °C, 0.5 torr) to provide 2-(3,3-dimethyl-morpholin-4-yl)-ethanol (14 g, 82%) as a colorless

oil contaminated with ~15% of 3,3-dimethyl-morpholine. LC/MS found 160.10 (M^++H, $C_8H_{18}NO_2$ requires 160.13).

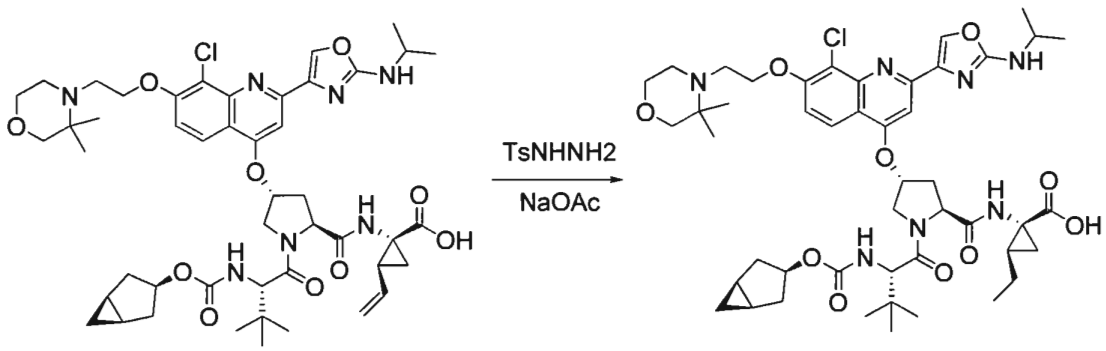
Step 4: To a solution of 2-(3,3-dimethyl-morpholin-4-yl)-ethanol (7.2 g, 45 mmol) and CBr_4 (16.4 g, 49 mmol, 1.1 equiv.) in THF (150 mL) was added dropwise a solution of PPh_3 (12.9 g, 49 mmol, 1.1 equiv.) in THF (75 mL). The resulting slurry was stirred at room temperature for 19 hours, at which time the slurry was diluted with hexanes and filtered. The filtrate was concentrated *in vacuo* and the resulting oil was diluted with CH_2Cl_2. The solution was then washed twice with $NaHCO_3$ (aqueous, saturated) and brine. The aqueous layers were back-extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was distilled (65 °C, 0.5 torr) to provide 4-(2-Bromo-ethyl)-3,3-dimethyl-morpholine (5.4 g, 54%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.69 (t, 2H), 3.28 (s, 2H), 3.28 (t, 2H), 2.70 (t, 2H), 2.58 (t, 2H), 0.99 (s, 6H); LC/MS found 222.02 (M^++H, $C_8H_{17}BrNO$ requires 222.05).



Step 5: To a solution of tripeptide intermediate (504 mg, 0.63 mmol) in DMF (6 mL) was added 4-(2-Bromo-ethyl)-3,3-dimethyl-morpholine (165 mg, 0.74 mmol, 1.2 equiv) and Cs_2CO_3 (520 mg, 1.59 mmol, 2.5 equiv.). The slurry was heated to 50 °C (external temperature, oil bath) for 45 min. Additional 4-(2-Bromo-ethyl)-3,3-dimethyl-morpholine (410 mg, 1.84 mmol, 3 equiv.) was added in portions until the reaction was judged complete by HPLC. The reaction mixture was cooled to room temperature, diluted with

EtOAc, and washed with brine. The aqueous layer was back-extracted with EtOAc and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was dissolved in a mixture of THF (4 mL) and MeOH (1.2 mL), to which was added LiOH (1N (aqueous), 3.2 mL, 5 equiv.). The slurry was stirred at room temperature for 12 hours, at which time HCl (1N, 3.2 mL) was added and the solution was concentrated *in vacuo*. The crude product was purified by reverse phase HPLC (30 to 95 % MeCN/H_2O/0.1% TFA) to provide compound **72** (498 mg, 85%) as a yellow powder. ^1H NMR (d_3-MeOD, 400 MHz, 4:1 mixture of rotomers) Major rotomer): δ 8.70 (s, 1H), 8.43 (s, 1H), 8.26 (d, 1H), 7.50 (s, 1H), 7.52 (d, 1H), 5.86 (dt, 1H), 5.59 (s, 1H), 5.28 (dd, 1H), 5.10 (dd, 1H), 4.69 (m, 3H), 4.48 (d, 1H), 3.95-4.21 (m, 4H), 3.75 (m, 3H), 2.67 (m, 3H), 2.17 (m, 1H), 2.04 (m, 1H), 1.94 (m, 1H), 1.84 (m, 1H), 1.65-1.73 (m, 2H), 1.53 (s, 6H), 1.43-1.53 (m, 2H), 1.40 (m, 1H) 1.35 (s, 3H), 1.33 (s, 3H), 1.21-1.27 (m, 2H), 1.06 (m, 2H), 1.04 (s, 9H), 0.39 (m, 2H); LC/MS found 920.15 (M^++H, $C_{47}H_{63}ClN_7O_{10}$ requires 920.43).

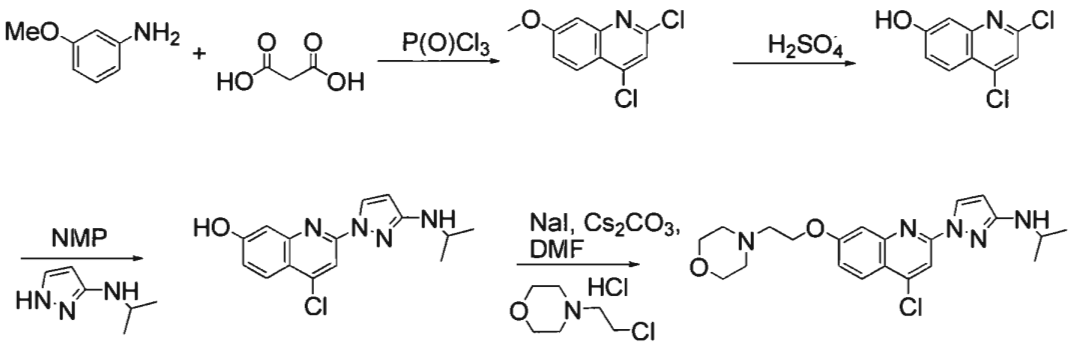
Example 73: Preparation of Compound 73



To a solution of compound **72** (164 mg, 0.18 mmol) in DME (3.6 mL) and H_2O (0.4 mL) was added *p*-toluenesulfonyl hydrazide (251 mg, 1.35 mmol, 7.5 equiv.) and NaOAc (221 mg, 2.69 mmol, 15 equiv.). The reaction mixture was heated to 95 °C (external temperature, oil bath) for 1.25 hours. The solution was cooled to room temperature and diluted with MeOH and filtered. The filtrate was purified by reverse phase HPLC (20 to

65 % MeCN/H_2O/0.1% TFA) to provide compound **73** (35 mg, 21%) as a yellow powder. ^1H NMR (d_3-MeOD, 400 MHz, 4:1 mixture of rotomers) Major rotomer: δ 8.59 rotomer (s, 1H), 8.43 (s, 1H), 8.25 (d, 1H), 7.53 (s, 1H), 7.50 (d, 1H), 5.59 (s, 1H), 4.66 (m, 3H), 4.47 (d, 1H), 3.95-4.21 (m, 4H), 3.75 (m, 4H), 2.67 (m, 4H), 2.22 (m, 2H), 2.01 (m, 1H), 1.91 (m, 1H), 1.65-1.73 (m, 4H), 1.53 (s, 6H), 1.43-1.53 (m, 4H), 1.35 (s, 3H), 1.33 (s, 3H), 1.21-1.27 (m, 3H), 1.04 (s, 9H), 0.39 (m, 2H); LC/MS found 922.15 (M^++H, $C_{47}H_{65}ClN_7O_{10}$ requires 922.45).

Example 74: Preparation of Compound 74

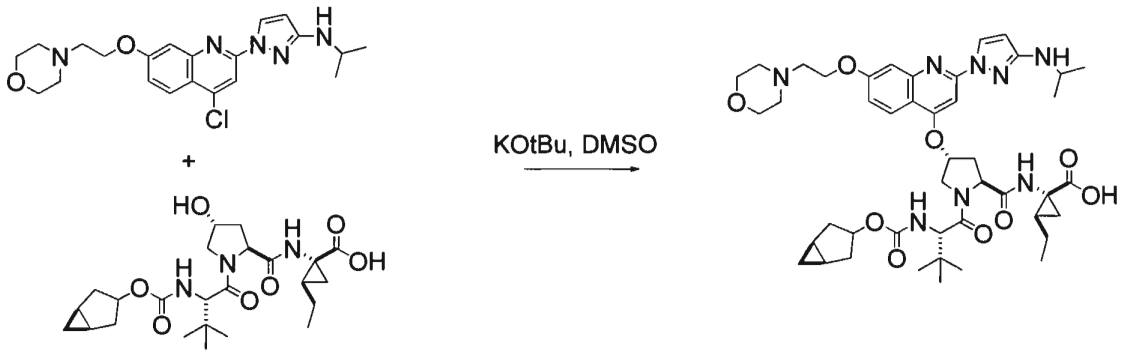


Step 1: To a three neck flask fitted with an overhead stirrer and reflux condenser was added malonic acid (25.4 g, 244 mmol) and m-anisidine (27 mL, 244 mmol). Phosphorous oxychloride (33.5 mL, 366 mmol) was then added in portions. After gas evolution ceased, the slurry was slowly heated to 95°C and stirred for 30 min. The resultant foam was then cooled to room temperature and phosphorous oxychloride (100 mL, 732 mmol) was added. The mixture was heated to 120°C and stirred for 3 h. After being cooled in an ice-bath, ice-water was slowly added to quench the remaining phosphorous oxychloride, followed by 5N NaOH, until the solution reached pH =8. The mixture was then diluted with ethyl acetate and the organic layer was collected. The organic phase then washed with water and brine. After drying over sodium sulfate and being concentrated, the crude residue was purified by column chromatography on silica (CH_2Cl_2) to provide the dichloride.

Step 2: The dichloride was dissolved in sulfuric acid (150 mL) and heated in a 160°C oil bath for 2 h. After cooling to room temperature the mixture was poured into ice-cold water. The suspension was diluted with ethyl acetate then the organic phase was washed with water and saturated aqueous $NaHCO_3$. The organic phase was then dried over sodium sulfate and concentrated to afford phenol (18.4 g, 35% over two steps).

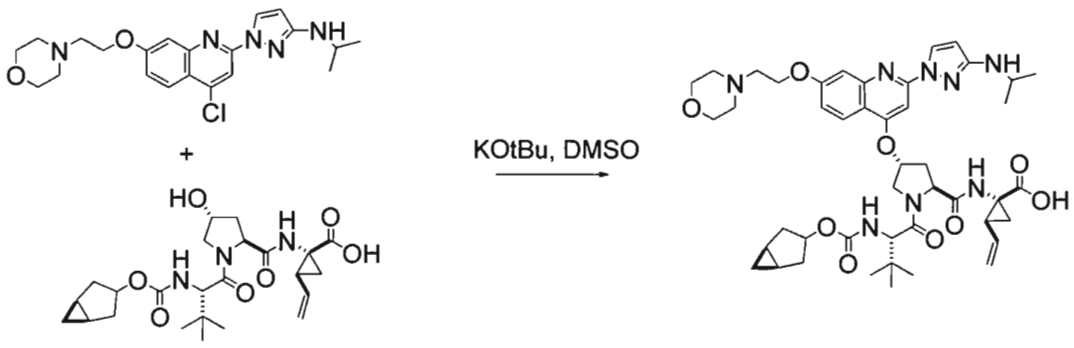
Step 3: To phenol (2.13 g, 9.95 mmol) in 1-methyl2-pyrollidinone (5 mL) was added pyrazole (1.37 g, 10.9 mmol) and the mixture was heated to 115°C overnight. After cooling to room temperature the reaction mixture was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was then dried over sodium sulfate and concentrated to afford desired product (2.92 g, 97%).

Step 4: A solution of phenol obtained above (2.92 g, 9.68 mmol), 4-(2-chloroethyl) morpholine hydrochloride (2.16 g, 11.6 mmol), Cs_2CO_3 (6.94 g, 21.3 mmol) and NaI (200 mg, 1.33 mmol) was heated to 65°C overnight. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and then washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was then dried over sodium sulfate, concentrated, and purified by HPLC to afford quinoline intermediate (1.54 g, 38%).



Step 5: Tripeptide (500 mg, 1.04 mmol) was dissolved in anhydrous DMSO (10 mL) and then treated with solid KOtBu (350 mg, 3.12 mmol). After stirring for 1 h at room temperature, the quinoline intermediate (380 mg, 1.97 mmol) was added and the reaction was stirred overnight. The reaction was then quenched with acetic acid (700 μL) and purified by HPLC to afford compound **74** (161 mg, 18%). ^{1}H NMR (CD_3OD, 300 MHz) δ 8.57 (s, 1H), 8.11 (d, 1H), 7.53 (s, 1H), 7.31 (s, 1H), 7.18 (dd, 1H), 6.17 (d, 1H), 5.56 (m, 1H),, 4.71 (t, 1H), 4.64 (t, 1H), 4.59-4.55 (m, 2H), 4.50 (d, 1H), 4.17 (s, 1H), 4.10-3.78 (m, 6H), 3.75-3.71 (m, 2H), 3.64-3.28 (m, 4H), 2.72-2.53 (m, 2H), 2.05-1.88 (m, 2H), 1.73-1.61 (m, 3H), 1.50 (dd,1H), 2.53 (dd, 1H), 1.38-1.02 (m, 5H), 1.29 (s, 3H), 1.37 (s, 3H), 1.02 (s, 9H), 0.40-0.37 (m, 2H); LRMS calcd for $C_{45}H_{63}N_8O_9$ $[M+H]^+$: 859.5, found 859.2.

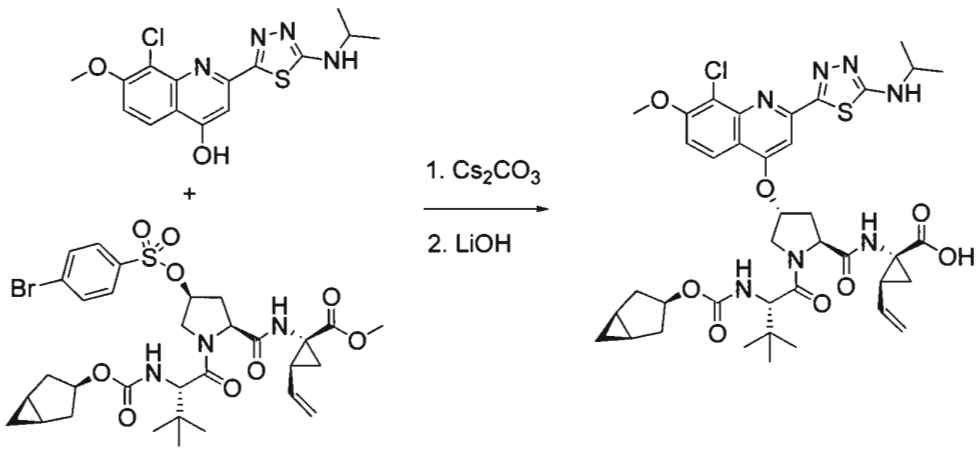
Example 75: Preparation of Compound 75



Tripeptide (450 mg, 0.94 mmol) was dissolved in anhydrous DMSO (10 mL) and treated with solid KOtBu (582 mg, 5.18 mmol). After 1 h at room temperature, quinoline (437 mg, 1.04 mmol) was added and the reaction was stirred overnight. The reaction was quenched with acetic acid (400 μL) then purified by HPLC to afford Compound **75** (632 mg, 80%). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.68 (s, 1H), 8.58 (d, 1H), 8.12 (d, 1H), 7.56 (d, 1H), 7.31 (s, 1H), 7.19 (dd, 1H), 6.19 (d, 1H), 5.86-5.79 (m, 1H), 5.57 (m, 1H), 5.26 (dd, 1H), 5.09 (dd, 1H), 4.70 (t, 1H), 4.64 (t, 1H), 4.59-4.56 (m, 2H), 4.51 (d, 1H), 4.21 (s, 1H), 4.13-3.84 (m, 6H), 3.75-3.73 (m, 2H), 3.30-3.65 (m, 4H), 2.74-2.68 (m, 1H), 2.58-

2.51 (m, 1H), 2.22-2.16 (m, 1H), 2.05-1.98 (m, 1H), 1.94-1.89 (m, 1H), 1.73-1.64 (m, 2H), 1.52 (d, 1H), 1.44 (dd, 1H), 1.29 (s, 3H), 1.27 (s, 3H), 1.26-1.18 (m, 2H), 1.03 (s, 9H), 0.40-0.37 (m, 2H); LRMS calcd for $C_{45}H_{61}N_8O_9$ $[M+H]^+$: 857.5, found 857.2.

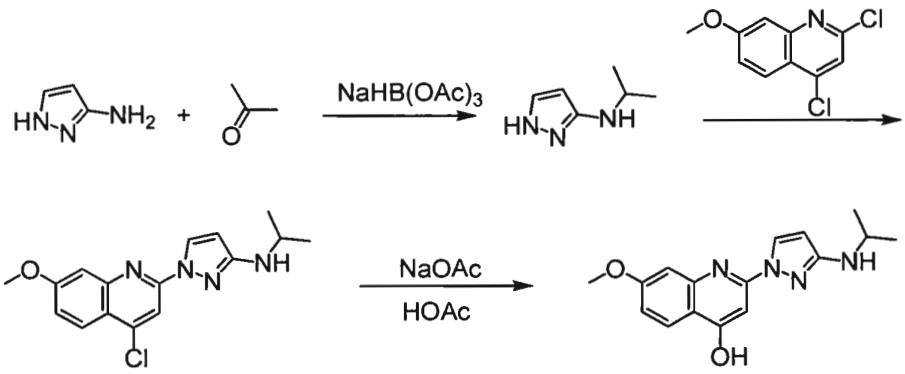
Example 76: Preparation of Compound 76



A mixture of 1-{[1-[2-(bicyclo[3.1.0]hex-3-yloxycarbonylamino)-3,3-dimethyl-butyryl]-4-(4-bromo-benzenesulfonyloxy)-pyrrolidine-2-carbonyl]-amino}-2-vinyl-cyclopropanecarboxylic acid methyl ester (100 mg, 0.14 mmol), 2-(5-isopropylamino-[1,3,4]thiadiazol-2-yl)-7-methoxy-quinolin-4-ol (62 mg, 0.18 mmol) and cesium carbonate (60 mg, 0.18 mmol) in NMP (1 mL) was stirred at 65 °C for 3 h. The mixture was neutralized with TFA (0.16 mL), and purified by HPLC to obtain the ester. This was dissolved in methanol (10 mL), THF (15 mL) and aqueous lithium hydroxide (120 mg / 3 mL). The mixture was stirred at 45 °C for 1 h, concentrated to remove the volatile solvents, neutralized with 1 N HCl, and extracted with ethyl acetate. The organic extract

was concentrated and purified by HPLC, affording compound **76** (5.5 mg, 5%). LC/MS = 810.5 (M^++1).

Example 77: Preparation of Compound 77

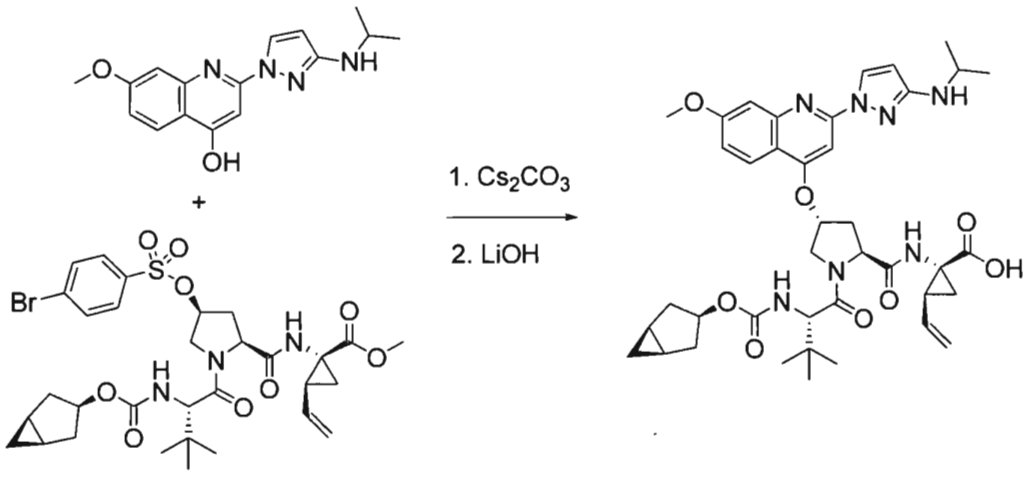


Step 1: To a mixture of 1*H*-pyrazol-3-ylamine (8.3 g, 100 mmol), acetone (7.4 mL, 100 mmol) and acetic acid (12 mL, 200 mmol) in THF (280 mL) was added, in portions, sodium triacetoxyborohydride (27 g, 120 mmol) while cooling with an ice-water bath. The mixture was stirred at room temperature for 1h and then at 50 °C for 3h. After cooling to room temperature, 10 N NaOH (40 mL) was added dropwise, and stirred gently for 1 h. The clear solution was isolated with decantation. The gummy residue was washed with THF (2 x 50 mL). All the THF solutions were combined and concentrated. The residue was purified by silica gel column chromatography (EtOAc), affording

isopropyl-(1*H*-pyrazol-3-yl)-amine (8.5 g, 68%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d,1H), 5.62 (d, 1H), 3.58 (m, 1H), 1.22 (d, 6H).

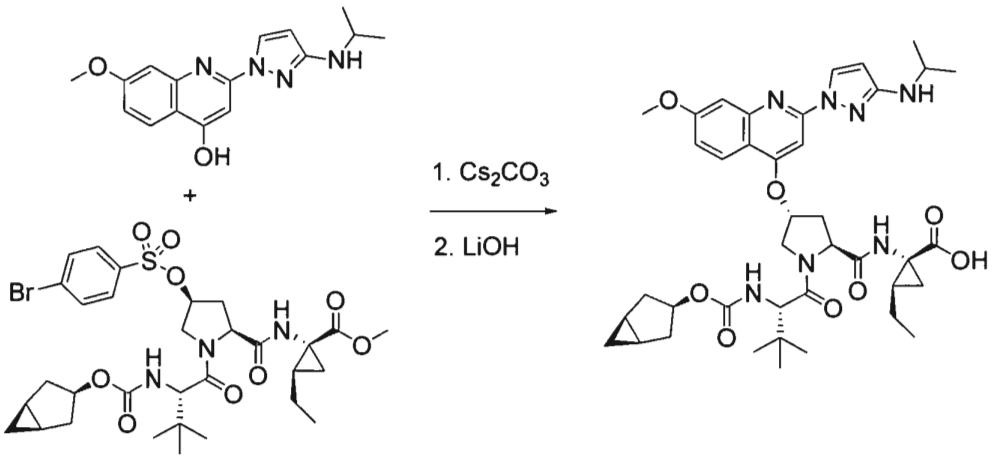
Step 2: A mixture of 2,4-dichloro-7-methoxy-quinoline (1.34 g, 5.88 mmol) and isopropyl-(1*H*-pyrazol-3-yl)-amine (1.10 g, 8.80 mmol) was heated at 115 °C for 3 h while stirring in a sealed tube. After ~20 min. of heating, the pressure built up in the tube was released by using a needle. The mixture was then dissolved in dichloromethane and loaded onto a silica gel column. Elution with dichloromethane and methanol afforded [1-(4-chloro-7-methoxy-quinolin-2-yl)-1*H*-pyrazol-3-yl]-isopropyl-amine (1.53 g, 82%). LC/MS = 317.2 (M^++1).

Step 3: A mixture of [1-(4-chloro-7-methoxy-quinolin-2-yl)-1*H*-pyrazol-3-yl]-isopropyl-amine (0.52 g, 1.6 mmol) and sodium acetate monohydrate (1.0 g) in acetic acid (5 mL) was stirred at 130 °C for 2 d. The mixture was concentrated and then partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate / hexanes), affording [1-(4-hydroxy-7-methoxy-quinolin-2-yl)-1*H*-pyrazol-3-yl]-isopropyl-amine (0.09 g, 19%). LC/MS = 299.1 (M^++1).



Step 4: A mixture of the tripeptide (420 mg, 0.59 mmol), [1-(4-hydroxy-7-methoxy-quinolin-2-yl)-1*H*-pyrazol-3-yl]-isopropyl-amine (174 mg, 0.58 mmol) and cesium carbonate (0.22 mg, 0.68 mmol) in NMP (2 mL) was stirred at 65 °C for 16 h. To this mixture, a solution of LiOH hydrate (400 mg) in water (3 mL) was added. While stirring at 40 °C, methanol was added until the mixture became nearly homogeneous, which was then stirred for 2 h. After removal of the volatile solvents, the mixture was partitioned between ethyl acetate and a 3% LiCl aqueous solution. The aqueous solution was neutralized with 1N HCl before the organic layer was taken out. The aqueous layer was extracted with ethyl acetate. The ethyl acetate layers were combined and concentrated. The residue was purified by HPLC, affording compound **77** (260 mg, 51%) as a TFA salt. ^{1}H NMR (300 MHz, CD_3OD): δ 8.60 (d, J = 3.0 Hz,1H), 8.07 (d, J = 9.0 Hz, 1H), 7.62 (s, 1H), 7.29 (s, 1H), 7.17 (d, J = 9.3 Hz, 1H), 6.26 (d, J = 2.7 Hz, 1H), 5.85 (m, 1H), 5.63 (brs, 1H), 5.28 (d, J = 16.2 Hz, 1H), 5.11 (d, J = 10.5 Hz, 1H), 4.69 (t, 1H), 4.56 (m, 1H), 4.16 (m, 1H), 3.99 (s, 3H), 2.74 (m, 1H), 2.55 (m, 1H), 2.21 (q, 1H), 1.98 (m, 1H), 1.84 (m, 1H), 1.70 (m, 2H), 1.44 (m, 2H), 1.31 (d, 6H), 1.21 (m, 2H), 1.04 (s, 9H), 0.98 (m, 2H), 0.34 (m, 2H). LC/MS = 758.5 (M^++1).

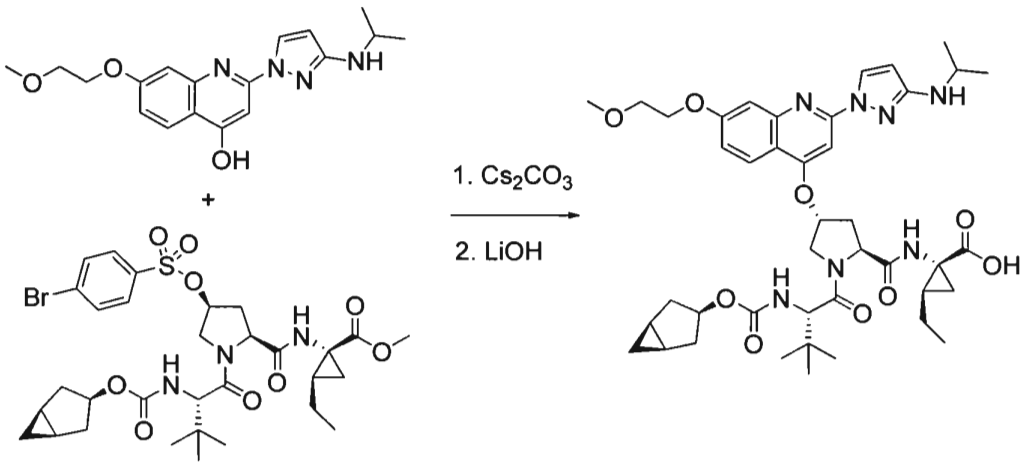
Example 78: Preparation of Compound 78



Following procedures similar to those for preparation of **77** except using intermediate III, Compound, compound **78** was obtained. ^{1}H NMR (300 MHz, CD_3OD): δ 8.65 (s, 1H,

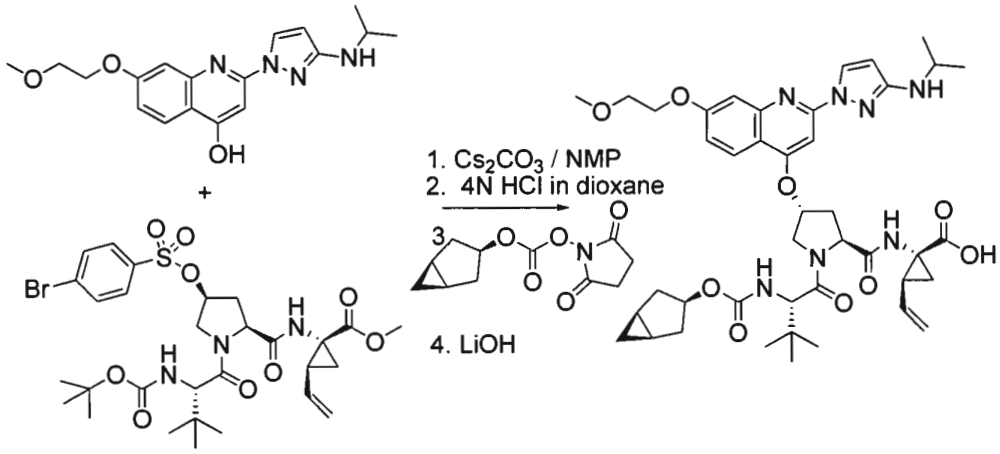
exchangeable), 8.61 (d, J = 2.7 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H), 7.62 (s, 1H), 7.30 (s, 1H), 7.17 (d, J = 9.6 Hz, 1H), 6.25 (d, J = 2.7 Hz, 1H), 5.63 (brs, 1H), 4.69 (t, 1H), 4.55 (m, 2H), 4.18 (m, 1H), 4.05 (m, 2H), 4.00 (s, 3H), 2.74 (m, 1H), 2.55 (m, 1H), 1.95 (m, 1H), 1.82 (m, 1H), 1.65 (m, 2H), 1.41 (m, 4H), 1.30 (d, 6H), 1.22 (m, 4H),1.02 (s, 9H), 0.98 (m, 2H), 0.35 (m, 2H). LC/MS = 760.5 (M^++1).

Example 79: Preparation of Compound 79



Compound **79** was obtained by following procedures described before. ^{1}H NMR (300 MHz, CD_3OD): δ 8.68 (s, 1H, exchangeable), 8.62 (d, J = 3.0 Hz, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.62 (s, 1H), 7.29 (s, 1H), 7.19 (d, J = 8.7 Hz, 1H), 6.26 (d, J = 2.7 Hz, 1H), 5.62 (brs, 1H), 4.69 (t, 1H), 4.54 (m, 2H), 4.30 (m, 2H), 4.17 (s, 1H), 4.03 (m, 2H), 3.84 (m, 2H), 3.46 (s, 3H), 2.74 (m, 1H), 2.55 (m, 1H), 1.96 (m, 1H), 1.84 (m, 1H), 1.68 (m, 3H), 1.52 (t, 1H), 1.42 (m, 2H), 1.30 (d, 6H), 1.22 (m, 4H), 1.02 (s, 9H), 0.98 (m, 2H), 0.35 (m, 2H). LC/MS = 804.7 (M^++1).

Example 80: Preparation of Compound 80



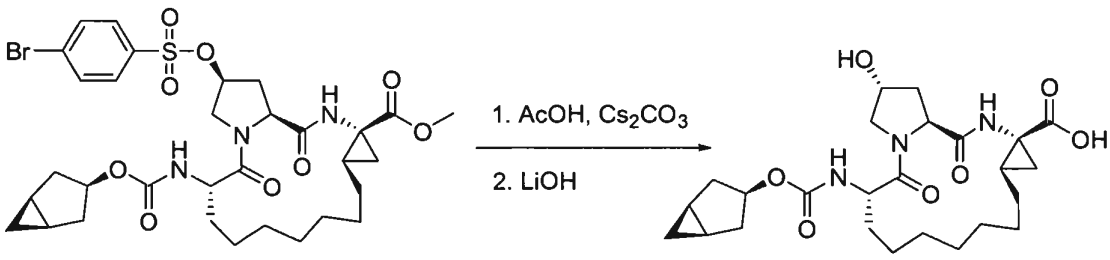
Step 1: A mixture of the tripeptide (830 mg, 1.2 mmol), 2-(3-isopropylamino-pyrazol-1-yl)-7-(2-methoxy-ethoxy)-quinolin-4-ol (410 mg, 1.2 mmol) and cesium carbonate (440 mg, 1.35 mmol) in NMP (4 mL) was stirred at 65 °C for 16 h. The mixture was partitioned between ethyl acetate (30 mL) and 3% LiCl (30 mL). The aqueous layer was extracted with ethyl acetate (2 x 30 mL). The ethyl acetate extracts were combined and concentrated.

Step 2: The crude coupled product thus formed was dissolved in dichloromethane (20 mL) and 4N HCl in dioxane (20 mL) was added. The mixture was stirred for 1 h at room temperature and concentrated to dryness. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate. To this biphasic solution, a solution of intermediate I (344 mg, 1.4 mmol) in ethyl acetate (3 mL) was added dropwise, while gently stirring. The ethyl acetate layer was taken and concentrated.

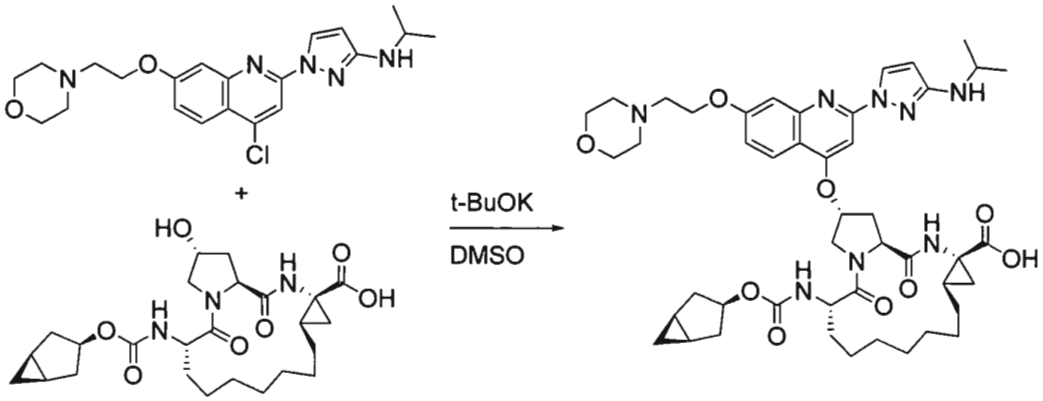
Step 3: The resulting residue was then re-dissolved in THF (20 mL), MeOH (20mL), and water (10 mL) containing LiOH monohydrate (1.0 g), and stirred at 45 °C for 1 h. After removal of volatile solvents, the solution was neutralized with 1 N HCl to pH ~5 and extracted with ethyl acetate (50 mL). The organic extract was concentrated and purified by HPLC affording compound **80** (632 mg as a TFA salt, 57%) as a pale yellow solid, after lyophilization of the desired fractions. ^{1}H NMR (300 MHz, CD_3OD): δ 8.75 (s, 1H,

exchangeable), 8.57 (d, J = 2.7 Hz, 1H), 8.05 (d, J = 9.3 Hz, 1H), 7.55 (s, 1H), 7.25 (s, 1H), 7.16 (d, J = 9.0 Hz, 1H), 6.24 (d, J = 2.7 Hz, 1H), 5.86 (m, 1H), 5.58 (brs, 1H), 5.28 (d, J = 15.9 Hz, 1H), 5.11 (d, J = 10.5 Hz, 1H), 4.71 (t, 1H), 4.54 (m, 2H), 4.28 (m, 2H), 4.18 (s, 1H), 4.03 (m, 2H), 3.83 (m, 2H), 3.46 (s, 3H), 2.74 (m, 1H), 2.55 (m, 1H), 2.20 (m, 1H), 1.96 (m, 1H), 1.84 (m, 1H), 1.68 (m, 2H), 1.42 (m, 2H), 1.30 (d, 6H), 1.22 (m, 1H), 1.02 (s, 9H), 0.98 (m, 2H), 0.36 (m, 2H). LC/MS = 802.7 (M^++1).

Example 81: Preparation of Compound 81

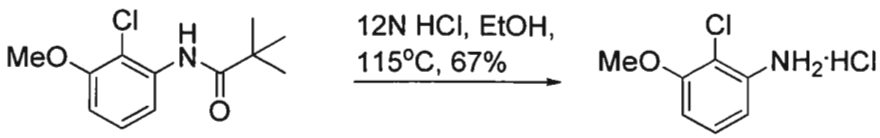


Step 1: To a mixture of brosylate methyl ester (1.41 g, 1.95 mmol) and cesium carbonate (1.90 g, 5.82 mmol) in NMP (6.5 mL) was added acetic acid (0.35 mL, 5.82 mmol). The resulting mixture was stirred at room temperature for 30 min. and then 65 °C for 16 h. The mixture was partitioned between ethyl acetate (40 mL) and 3% aqueous LiCl (40 mL). The ethyl acetate layer was concentrated to dryness, and re-dissolved in methanol (20 mL) and THF (20 mL). Aqueous lithium hydroxide (1.0 g / 10 mL) was added and stirred at room temperature for 16 h. An additional lithium hydroxide solution (0.5 g / 5 mL) was added and stirred at 45 °C for 2 h. After removal of the volatile solvents, ethyl acetate (40 mL) was added. The aqueous layer was neutralized with 6 N HCl to pH ~2. The ethyl acetate layer was then washed with brine, and concentrated to dryness, affording alcohol (920 mg, 96%) as a colorless solid. LC/MS = 490.3 (M^--1).



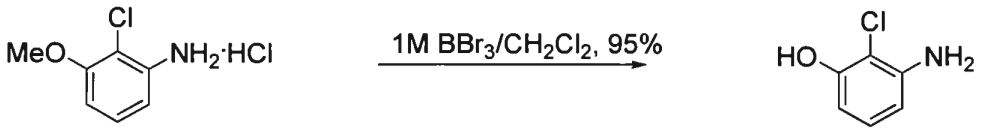
Step 2: To a solution of alcohol (420 mg, 0.85 mmol) in DMSO (10 mL) was added 1.0 M potassium t-butoxide in THF and stirred at room temperature for 30 min. A solution of {1-[4-chloro-7-(2-morpholin-4-yl-ethoxy)-quinolin-2-yl]-1H-pyrazol-3-yl}-isopropyl-amine (440 mg, 1.06 mmol) in THF (2 mL) was added. The mixture was then stirred for 16 h at room temperature, neutralized with acetic acid, and concentrated to remove the volatile solvent. The residue was subjected to HPLC, affording compound **81** (340 mg as the TFA salt, 35%) as a yellowish solid upon lyophilization. ^{1}H NMR (300 MHz, CD_3OD): δ 8.62 (d, J = 2.7 Hz,1H), 8.17 (d, J = 9.3 Hz, 1H), 7.62 (s, 1H), 7.33 (s, 1H), 7.23 (d, J = 9.3 Hz, 1H), 6.25 (d, J = 2.4 Hz, 1H), 5.62 (brs, 1H), 4.75 (m, 2H), 4.67 (s, 1H), 4.59 (m, 2H), 4.33 (d, J = 6.6 Hz, 1H), 3.8-4.1 (m, 6H), 3.75 (m, 2H), 3.49 (brs, 4H) 2.68 (m, 2H), 1.1-2.1 (m, 28H, including doublet of J = 6.3 Hz at 1.30 ppm for isopropyl Me), 0.39 (m, 2H). LC/MS = 871.6 (M^++1).

Example 82: Preparation of Compound 82

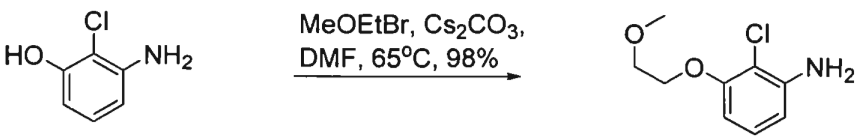


Step 1: The amide (18.8 g, 0.078 mmol) was dissolved in EtOH (75 mL). To this solution was added 12 N $HCl_{(aq.)}$. The reaction mixture was then placed in a preheated 115 °C bath

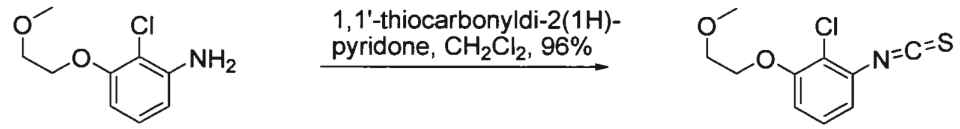
and stirred for 5 h. The reaction was cooled to room temperature and then further cooled with an ice bath. The small white needles that formed were isolated by vacuum filtration, washed with Et_2O, and placed under high vacuum for 16 h. The yield of the hydrochloride salt was 10.1 g (67%). LC/MS = 158.3 (M^++1).



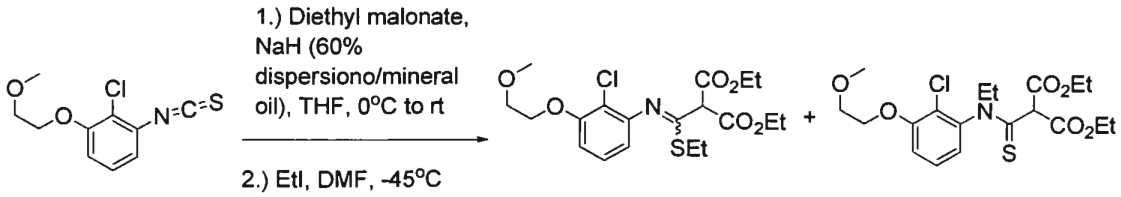
Step 2: The amine (10.1 g, 0.052 mol) was dissolved in a 1 M solution of BBr_3 in CH_2Cl_2 (163 mL, 0.163 mol). This resulted in copious smoking and out-gassing. The reaction was placed in a preheated 40 °C bath. The reactions N_2 line was replaced with a drying tube filled with $CaSO_4$. The reaction was heated for 8 h and then stirred at room temperature overnight. The next day the reaction was complete as determined by LC/MS. The reaction was placed in an ice bath and MeOH was added very slowly, resulting in copious HBr gas formation. The reaction eventually turned very thick, as a white suspension forms. Additional MeOH was added to this suspension until everything went into solution. This was then concentrated to a white syrup. This was dissolved in dH_2O and this solution was extracted with EtOAc (2x). These washes were set aside as they contained pure phenol. The aqueous layer was then brought to pH = 7 with solid $NaHCO_3$ and extracted with additional EtOAc (2x). These organic washes were combined, extracted with brine and dried over Na_2SO_4. The drying agent was removed by vacuum filtration and the filtrate was concentrated. The phenol was isolated from this residue by silica gel column chromatography, eluting with a mixture of EtOAc and hexanes. This material was combined with the original EtOAc extracts containing pure phenol, to yield 7.07 g (95%) of a slightly off-white solid. LC/MS = 144.3 (M^++1).



Step 3: To a flask charged with the phenol (3.5 g, 0.024 mol) and Cs_2CO_3 (9.4 g, 0.029 mol) was added DMF (120 mL) and then MeOEtBr (2.52 mL, 0.027 mol). This mixture was then placed in a preheated 65 °C bath. The reaction was stirred for 4.25 h additional MeOEtBr (200 μL, 0.0021 mol) was added. After an additional hour of stirring the reaction was cooled to room temperature The reaction was partitioned between EtOAc and 5% $LiCl_{(aq.)}$. The solids that formed were dissolved by adding dH_2O to the mixture. The layers were separated and the organic layer was washed with additional 5% $LiCl_{(aq.)}$ (2x) and brine (1x). The organic layer was then dried over Na_2SO_4. The drying agent was removed by vacuum filtration and the filtrate was concentrated. The phenolic ether was isolated from the residue by silica gel column chromatography, eluting with a mixture of EtOAc and hexanes, as a colorless liquid (4.7 g, 98%). LC/MS = 202.2 (M^++1).

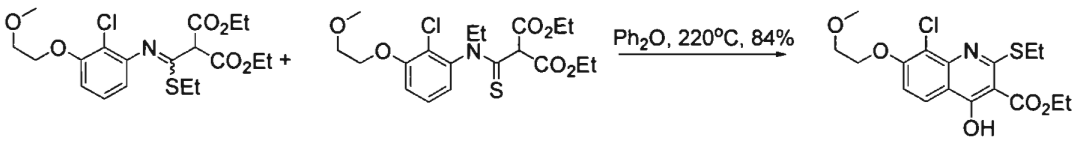


Step 4: The aniline (4.7 g, 0.023 mol) was dissolved in CH_2Cl_2 (125 mL). To this solution was added 1,1'-thiocarbonyldi-2(1H)-pyridone (5.58 g, 0.023 mol) in one portion. The reaction was allowed to stir at room temperature for 2 h. The reaction was then concentrated, resulting in white solids crashing out of solution. Everything was re-dissolved in CH_2Cl_2 and the isothiocyanate was isolated by silica gel column chromatography, eluting with a mixture of EtOAc and hexanes, as a white solid (5.36 g, 96%). ^{1}H NMR (400MHz, $(CD_3)_2SO$): δ 7.35 (t, J = 8 Hz, 1H), 7.19 (dd, J = 8.8, 4.6 Hz, 1H), 7.14 (dd, J = 8, 1.6 Hz, 1H), 4.22 (m, 2H), 3.69 (m, 2H), 3.32 (s, 3H).



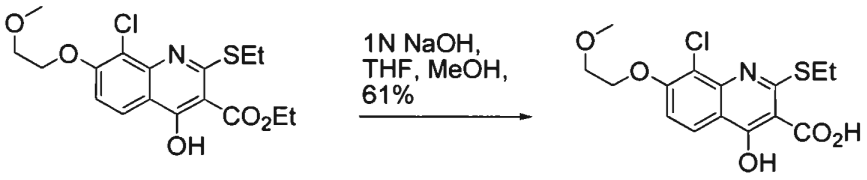
Step 5: To a slurry of NaH, 60% dispersion in mineral oil, (1.06 g, 0.026 mol) in THF (120 mL), that was cooled in an ice bath, diethyl malonate (3.34 mL, 0.022 mol) was added in a dropwise fashion. The ice bath was then removed and the reaction was stirred at room temperature for 1.5 h. The reaction was then cooled in an ice bath and a solution of the isothiocyanate (5.36 g, 0.022 mol) in THF (80 mL) was added in a slow, continuous stream. The flask in which the solution of the isothiocyanate and THF was made in was rinsed with more THF (20 mL) and this was also added to the reaction. The cold bath was then removed and the reaction was stirred for 3 h. The reaction was then concentrated and the resulting yellow foam was placed under high vacuum overnight.

A solution of the above synthesized product in DMF (100 mL) was cooled to -45 °C. Ethyl iodide (2.13 mL, 0.026 mol) was slowly added to the reaction in a drop-wise fashion. The reaction was stirred for 2 h in a -45°C bath and then left to warm and stir overnight. The reaction was diluted with dH_2O, resulting in it turning opaque with a white precipitate. The quenched reaction was then extracted with a 1:1 mixture of Et_2O and hexanes, followed by Et_2O, and then EtOAc. The EtOAc extracts were combined and back-extracted with a 5% aqueous solution of LiCl (2x). The organics were combined and extracted with brine and then dried over Na_2SO_4. The drying agent was then removed by vacuum filtration and the filtrate was concentrated. A mixture of S-alkylated and N-alkylated compounds were isolated from this residue by silica gel column chromatography, eluting with a mixture of EtOAc and hexanes, as a waxy crystalline solid (9.11 g, 96%). LC/MS (R_T = 3.95) = 432.2 (M^++1); LC/MS (R_T = 4.02) = 432.0 (M^++1).

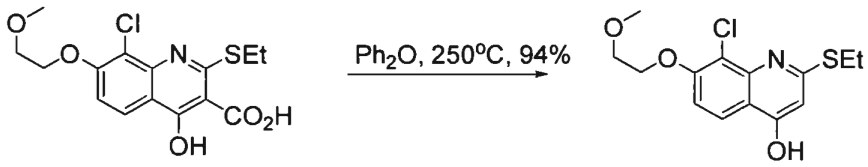


Step 6: A mixture of S-alkylated and N-alkylated compounds (9.1 g, 0.021 mol) was dissolved in Ph_2O (80 mL). This solution was placed in a preheated 320 °C sand bath. After 17 minutes with an internal temperature of 220°C the reaction was determined to be complete by TLC analysis. The reaction was cooled to room temperature and the quinoline was isolated by loading the reaction directly onto a silica gel column. The Ph_2O was eluted

off using an eluent of 100% hexanes. The quinoline was then eluted off the column by ramping the percentage of EtOAc in the eluent to 35%. The quinoline was isolated as a white, crystalline solid (6.8 g, 84%). LC/MS = 386.2 (M^++1).

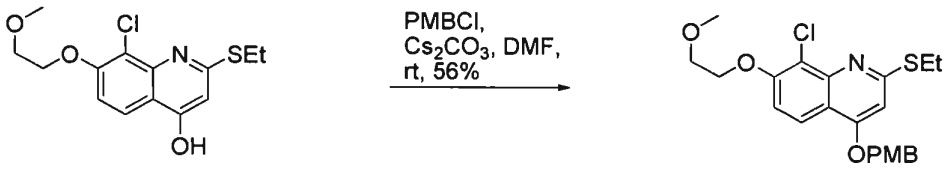


Step 7: The quinoline (6.8 g, 0.0176 mol) was mixed with THF (40 mL). MeOH was then added (40 mL) and then 1N $NaOH_{(aq.)}$ (88 mL, 0.088 mol) was added in one portion. Everything goes into solution and the reaction heats up. The reaction was then placed in a preheated 85°C bath and stirred for 19.5 h and checked by LC/MS. The reaction was not complete so additional NaOH (1.2 g in 20 mL of dH_2O) was added and the reaction was kept stirring. After an additional 4 h, the reflux condenser was removed and the reaction was concentrated by evaporating some of the organic solvents in the reaction. The reflux condenser was then put back on the reaction flask and heating continued for another 10 h. The reaction was allowed to cool to room temperature and stir overnight. At this point the reaction was complete, as determined by LC/MS. The reaction was placed in an ice bath and brought to pH = 4 with 4 N HCl. This caused the quenched reaction to turn thick with precipitate. This was extracted with CH_2Cl_2. The organic phases were concentrated and the residue was suspended in MeOH. The white solids were isolated by vacuum filtration, to yield the carboxylic acid as a shiny white solid (3.84 g, 61%). LC/MS = 358.1 (M^++1).

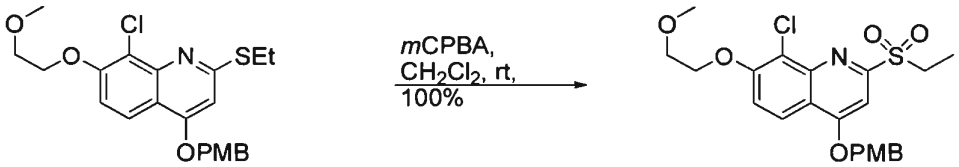


Step 8: The carboxylic acid (3.84 g, 0.0107 mol) was suspended in Ph_2O (32 mL). This mixture was placed in a pre-heated 310°C sand bath. When the internal temperature reached 150 °C the carboxylic acid went into solution. The reaction was kept at an internal

temperature of 250 °C for 15 minutes and then cooled to room temperature Solids crashed out of solution upon cooling. These solids were isolated by vacuum filtration, washing the filter cake with hexanes, to yield the de-carboxylated quinoline as a pale yellow solid (3.19 g, 94%). LC/MS = 314.2 (M^++1).

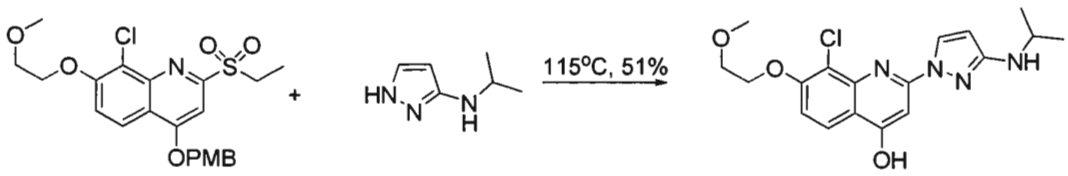


Step 9: The de-carboxylated quinoline (2.59 g, 0.0083 mol) was dissolved in DMF (28 mL). To this solution was added Cs_2CO_3 (8.1 g, 0.0249 mol), followed 3 minutes later with PMBCl (1.69 mL, 0.01245 mol). The reaction was stirred for 16 h at room temperature The reaction was determined to be complete by LC/MS. The reaction was quenched by the addition of 5% $LiCl_{(aq.)}$ and EtOAc. The aqueous layer was diluted with dH_2O and the layers were separated. The organic layer was extracted with dH_2O (1x), 5% $LiCl_{(aq.)}$ (3x) and brine (1x). The organic phase was then dried over a mixture of Na_2SO_4 and $MgSO_4$. The drying agents were removed by vacuum filtration and the filtrate was concentrated. The PMB protected quinoline was isolated from the residue by silica gel column chromatography, eluting with a mixture of EtOAc and hexanes (2.04 g, 56%). LC/MS = 434.1 (M^++1).

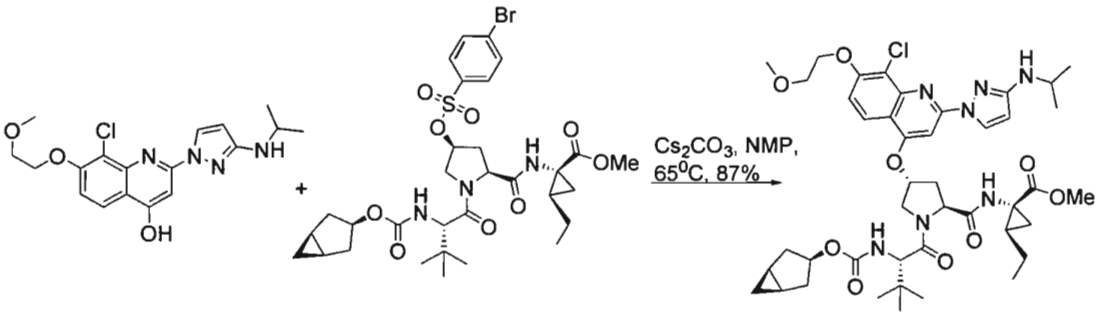


Step 10: The PMB protected quinoline (2.0 g, 0.00461 mol) was dissolved in CH_2Cl_2 (46 mL). To this solution was added *m*CPBA (4.59 g, 0.00922 mol) in one portion. Reaction monitored by LC/MS. Additional *m*CPBA (700 mg) was added to the reaction after 30 minutes and after 3 h (180 mg). The reaction progress was monitored by LC/MS. After 3.5 h the reaction was diluted with CH_2Cl_2 and sat. $NaHSO_{3(aq.)}$ was added to the reaction. All

solids dissolved into these two layers. The layers were separated and the organic layer was washed with sat. $NaHSO_{3(aq.)}$ (1x) and 2 N NaOH (2x). The organic phase was dried over Na_2SO_4. The drying agent was removed by vacuum filtration and the filtrate was concentrated to yield the sulfone (2.19 g, 100%) as a crystalline white solid. LC/MS = 466.1 (M^++1), 488.2 ((M^++23).

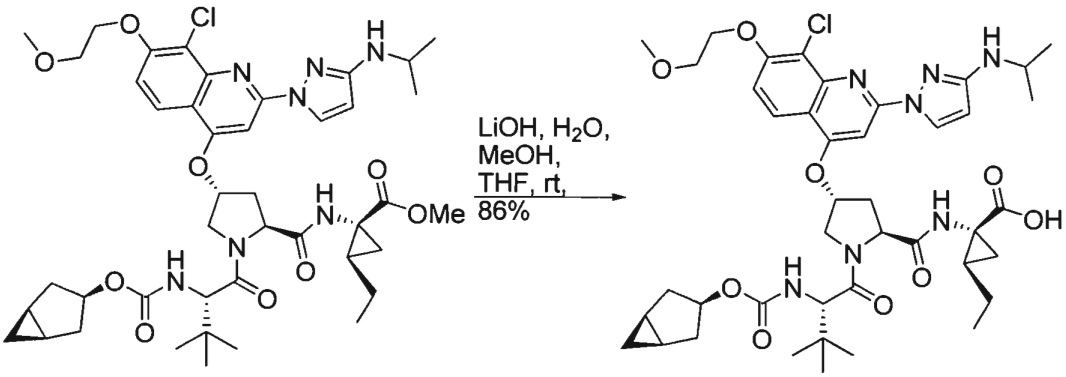


Step 11: To a flask containing the sulfone (600 mg, 0.00129 mol) was added the *i*Pr-aminopyrazole (1.6 g, 0.01288 mol). The reaction flask was placed in a pre-heated oil bath at 115°C. The reaction was stirred for 24 h and then cooled to room temperature The reaction was partitioned between dH_2O and EtOAc. The organic phase was extracted with dH_2O (1x), brine (1x) and then dried over Na_2SO_4. The drying agent was removed by vacuum filtration and the quinoline product was semi-purified by first removing gross impurities by silica gel chromatography, eluting with EtOAc and hexanes, and then flushing the column with a mixture of MeOH and CH_2Cl_2 to recover the still impure product. The purification was finished by reverse phase HPLC to yield the product quinoline (250 mg, 51%) as a yellow solid. LC/MS = 377.1 (M^++1).



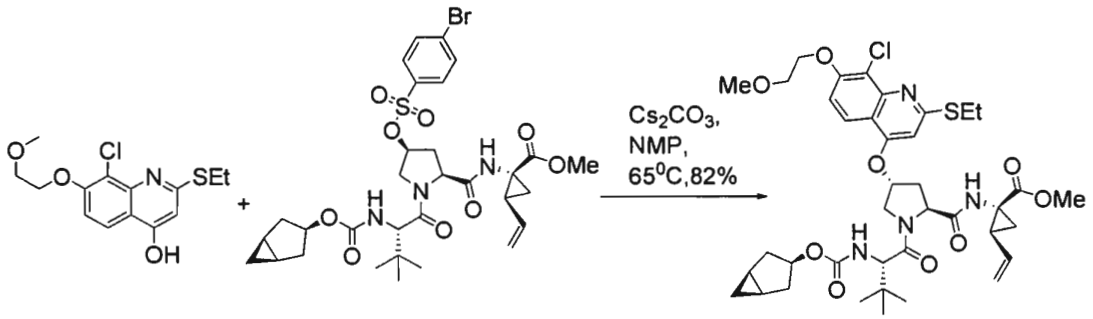
Step 12: A round bottom flask was charged with the quinoline (236 mg, 0.626 mmol), intermediate III (446 mg, 0.626 mmol), and Cs_2CO_3 (358 mg, 1.10 mmol). NMP (3.2 mL) was added and the reaction flask was placed in a 65 °C oil bath. The progress of the reaction was monitored by LC/MS. After 5.5 h there was no more reaction progress. The

reaction was cooled to room temperature and partitioned between EtOAc and dH_2O. The layers were separated and the organic phase was then extracted with dH_2O (1x), 5% $LiCl_{(aq.)}$ (3x) and brine (1x). The organic phase was then dried over a mixture of Na_2SO_4 and $MgSO_4$. The drying agents were removed by vacuum filtration and the filtrate was concentrated. The coupled product was isolated by silica gel column chromatography, eluting with a mixture of EtOAc and hexanes, as a white solid (465 mg, 87%). LC/MS = 852.1 (M^++1).

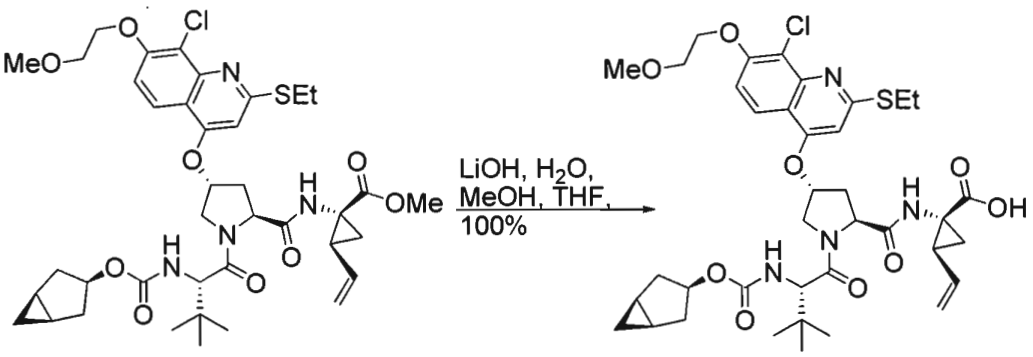


Step 13: The methyl ester (465 mg, 0.542 mmol) was dissolved in THF (2.7 mL) and MeOH (1.8 mL). In a separate flask a solution of LiOH (114 mg, 2.71 mmol) in dH_2O (900 □L) was prepared and added to the first flask at room temperature The reaction flask was then placed in a 32 °C oil bath. The reaction progress was monitored by LC/MS. After 6 h the reaction was cooled to room temperature The reaction was neutralized with 2 N HCl and clarified with MeOH. The mixture was stored in a freezer overnight. **Compound 82** was isolated from the mixture by reverse phase HPLC and then freeze drying to yield a yellow powder (434 mg, 86%). LC/MS = 839.0 (M^++1). ^1H NMR (400MHz, CD_3CN): δ 8.65 (d, J = 2.8 Hz, 1H), 8.61 (s, 1H), 8.01 (d, J = 9.2 Hz, 1H), 7.31 (d, J = 9.2 Hz, 1H), 7.31 (s, 1H), 6.21 (d, J = 2.8 Hz, 1H), 5.50 (s, 1H), 4.67 (t, J = 8 Hz, 1H), 4.58 (t, J = 6.8 Hz, 1H), 4.49 (d, J = 11.6 Hz, 1H), 4.37 (t, J = 4.4 Hz, 2H), 4.20 (s, 1H), 4.05 (d, J = 9.2 Hz, 1H), 3.86 (m, 1H), 3.85 (t, J = 4.4 Hz, 1H), 3.48 (s, 3H), 2.70 (dd, J = 13.6, 8 Hz, 1H), 2.56 (m, 1H), 2.00 (m, 1H), 1.88(m, 1H), 1.67 (m, 3H), 1.51 (quint, J = 8 Hz, 1H), 1.39 (m, 2H), 1.32 (d, J = 6.8 Hz, 6H), 1.22 (dd, J = 9.2, 4.4 Hz, 2H), 1.18 (m, 1H), 1.01 (m, 12H), 0.38 (m, 1H), 0.33 (m, 1H).

Example 83: Preparation of Compound 83



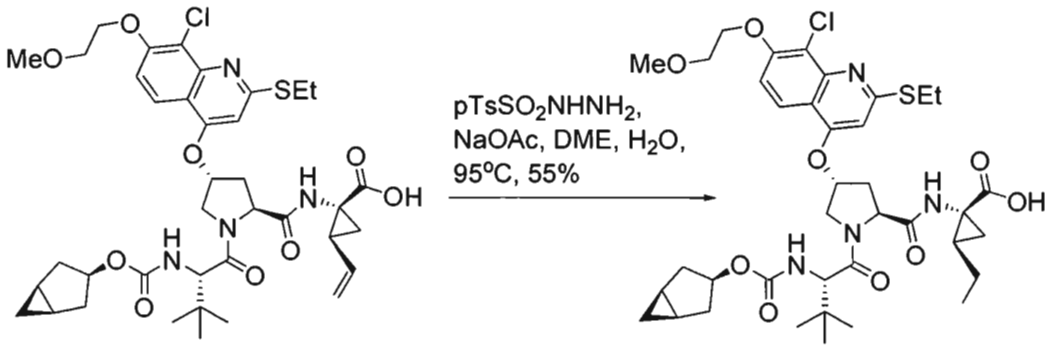
Step 1: A round bottom flask was charged with the quinoline (288 mg, 0.918 mmol), intermediate III (654 mg, 0.917 mmol), and Cs_2CO_3 (523 mg, 1.61 mmol). This mixture was then suspended in NMP. The reaction was then placed in a 65 °C bath and stirred for 7.5 h. The reaction was cooled to room temperature and partitioned between dH_2O and EtOAc. The organic layer was then extracted with dH_2O (1x), 5% $LiCl_{(aq.)}$ (3x) and brine (1x). The organic phase was then dried over a mixture of Na_2SO_4 and $MgSO_4$. The drying agents were removed by vacuum filtration and the filtrate was concentrated. The coupled product was isolated from the residue by silica gel column chromatography, eluting with a mixture of EtOAc and hexanes, as a white solid (590 mg, 82%). LC/MS = 787.7 (M^++1).



Step 2: The methyl ester (590 mg, 0.749 mmol) was dissolved in THF (3.75 mL) and MeOH (2.5 mL). This solution was cooled in an ice bath and then a solution of LiOH (157

mg, 3.74 mmol) in dH_2O (3.75 mL) was added drop-wise. The ice bath was then removed and the reaction was stirred at room temperature for 4 h. The reaction was cooled again in an ice bath and the pH of the reaction was brought to 1-2 using 1N HCl. The solution turned opaque with fine white solids. The reaction was extracted with EtOAc (2x) and the combined organic layers were extracted with brine and dried over Na_2SO_4. The drying agent was removed by vacuum filtration and the filtrate was concentrated to yield **compound 83** as a white foam (598 mg). 106mg of crude **compound 83** was purified by reverse phase HPLC and then freeze dried to yield a white powder (88 mg). LC/MS = 773.5 (M^++1). ^{1}H NMR (400MHz, CD_3CN): δ 7.51 (d, J = 9.2 Hz, 1H), 7.16 (s, 1H), 6.82 (d, J = 9.2 Hz, 1H), 6.26 (s, 1H), 5.95 (d, J = 8.4 Hz, 1H), 5.33 (dt, J = 19.6, 9.6 Hz, 1H), 4.91 (s, 1H), 4.89 (d, J = 11.2 Hz, 1H), 4.71 (d, J = 11.2 Hz, 1H), 4.31 (t, J = 6.4 Hz, 1H), 4.08 (t, J = 8.8 Hz, 1H), 3.99 (d, J = 12 Hz, 1H), 3.93 (d, J = 3.2 Hz, 2H), 3.86 (m, 1H), 3.55 (d, J = 10.4 Hz, 1H), 3.39 (t, J = 10.4 Hz, 2H), 3.02 (s, 3H), 2.98 (quart., J = 7.2 Hz, 2H), 2.16 (dd, J = 14.4, 7.2 Hz, 1H), 1.94 (m, 1H), 1.77, (quart., J = 8.8 Hz, 1H), 1.61 (m, 1H), 1.56 (quint., J = 2.4 Hz, 1H), 1.48 (m, 1H), 1.32 (dd, J = 7.6, 5.6 Hz, 1H), 1.24 (d, J = 14.4 Hz, 1H), 1.06 (t, J = 7.6 Hz, 3H), 0.97 (m, 2H), 0.80 (m, 2H), 0.58 (s, 9H), -0.02 (m, 2H).

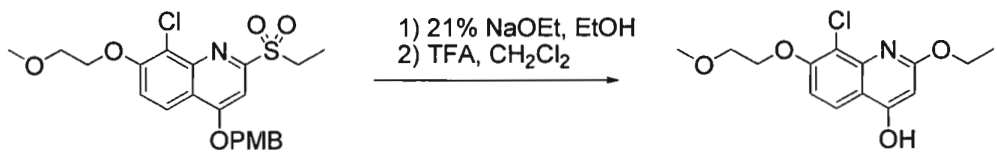
Example 84: Preparation of Compound 84



Compound 83 (490 mg, 0.634 mmol) was dissolved in DME (6.34 mL). To this solution was added dH_2O (634 μL), pTolSO$_2$NHNH$_2$ (884 mg, 4.75mmol), and then NaOAc (780 mg, 9.51 mmol). The reaction was then placed in a 95°C bath and stirred for 1.75 h. The

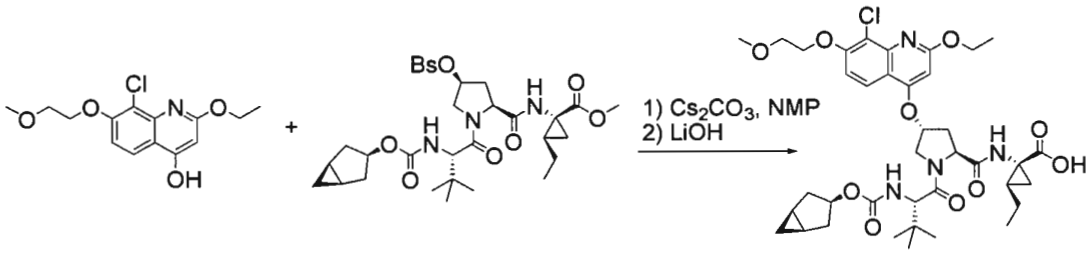
reaction was cooled to room temperature and **compound 84** was purified by reverse phase HPLC and then freeze dried to yield an off-white powder (270 mg, 55%). LC/MS = 775.7 (M^++1). ^{1}H NMR (400MHz, CD_3COD): δ 7.99 (d, J = 9.2 Hz, 1H), 7.33 (d, J = 9.2 Hz, 1H), 6.82 (s, 1H), 5.51 (s, 1H), 4.64 (t, J = 8.4 Hz, 1H), 4.52 (t, J = 7.2 Hz, 1H), 4.48 (d, J = 13.6 Hz, 1H), 4.38 (d, J = 3.2 Hz, 2H), 4.16 (s, 1H), 4.00 (dd, J = 14, 4.4 Hz, 1H), 3.84 (t, J = 4.4 Hz, 2H), 3.47 (s, 3H), 3.44 (dd, J = 6.8, 2 Hz, 2H), 2.69 (dd, J = 14.4, 8 Hz, 1H), 2.49 (ddd, J = 14.4, 9.6, 4.4 Hz, 1H), 1.98 (m, 1H), 1.85 (m, 1H), 1.65 (dt, J = 14.8, 7.6 Hz, 3H), 1.50 (t, J = 7.6 Hz, 4H), 1.40 (dd, J = 8, 4.8 Hz, 1H), 1.34 (d, J = 14.4 Hz, 1H), 1.20 (m, 3H), 1.00 (s, 12H), 0.36 (m, 1H), 0.32 (quint., J = 4 Hz, 1H).

Example 85: Preparation of Compound 85



Step 1: To a solution of the quinoline (450 mg, 0.965mmol) in THF (5.0 mL) was added slowly 21% NaOEt in ethanol (1.10 mL, 2.89mmol). After the solution was stirred at room temperature for 10 min, 2N HCl (10 mL) was added. The resulting mixture was stirred for 5 min, diluted with EtOAc (10 mL) and stirred for 5 min. After two layers were separated, the aqueous layer was extracted with EtOAc (10 mL). Combined organic fractions were dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography using a mixture of hexanes and ethyl acetate as the eluent to afford 385 mg (96%) of the PMB protected ethoxy quinoline. LC/MS = 418 (M^+ + 1).

Step 2: A solution of the PMB protected quinoline 385 mg (0.923mmol) in dichloromethane (5.0 mL) and TFA (5.0 mL) was stirred at room temperature for 10 min. The color goes from colorless to purple as the reaction proceeds. The solution was concentrated under reduced pressure, adjusted the pH to 8 using 5% sodium bicarbonate, then extracted with EtOAc (20 mL x 2). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography using a mixture of hexanes and ethyl acetate as the eluent to afford 254 mg (92%) of the hydroxyl quinoline. LC/MS = 298 ($M^+ + 1$).

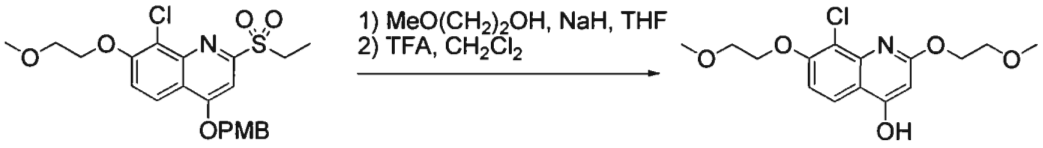


Step 3: A mixture of intermediate III (800 mg, 1.12 mmol), quinoline (332mg, 1.12 mmol) and cesium carbonate (802 mg, 2.46 mmol) in NMP (5mL) was stirred as 65 °C for 16 h. The mixture was then diluted with EtOAc (20 mL) and 5% LiCl (20mL) and stirred at room temperature for 30 min. The two layers were separated and the aqueous was extracted with EtOAc (20 mL). The combined organic fractions were washed with 5% LiCl (3 x 20 mL), water, and then brine. The organic fraction was dried (Na_2SO_4) and concentrated. The crude material was purified by silica gel chromatography using a mixture of hexanes and ethyl acetate as the eluent to afford 685 mg (79%) of the ester. LC/MS = 773 ($M^+ + 1$).

Step 4: To a mixture of ester (685 mg, 0.88 mmol) in THF (3mL) and methanol (5 mL), was added a solution of LiOH monohydrate (210 mg, 5.0 mmol) in water (3 mL). The mixture was stirred at 35 °C for 3h. The solution was concentrated under reduced pressure and the pH was adjusted to 2 with 10% HCl. Methanol (5mL) was added to the mixture and was purified by reverse phase preparative HPLC using a mixture of acetonitrile 0.1%

TFA and water 0.1% TFA as the eluent to afford 323 mg (48%) of **compound 85.** ^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 7.85 (d, J = 9.2 Hz, 1H), 7.15 (d, J = 9.2 Hz, 1H), 6.37 (s, 1H), 5.34 (br, 1H), 4.53 – 4.35 (br, 5H), 4.24 (br, 2H), 4.08 (s, 1H), 3.99-3.87 (br, 1H), 3.74-3.72 (m, 2H), 3.36 (s, 3H), 2.60 (m, 1H), 2.40 (m, 1H), 1.93 (m, 1H), 1.82 (m, 2H), 1.58-1.52 (br, 4H), 1.43-1.36 (br, 4H), 1.31-1.21 (br, 2H), 1.13-1.03 (br, 3H), 0.91 (s, 9H), 0.84 (s, 1H), 0.21-0.02 (br, 2H). LC/MS = 760 (M^+ + 1).

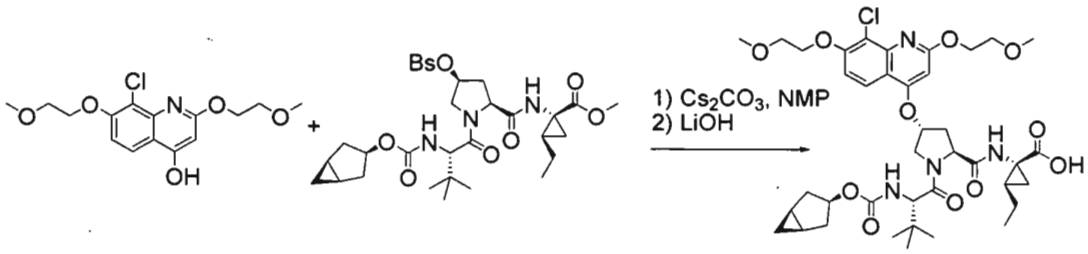
Example 86: Preparation of Compound 86



Step 1: To a mixture of NaH (214mg, 5.35 mmol) in THF (3.5 mL) was added 2-methoxyethyl alcohol (253 μL, 3.21mmol) dropwise. After the mixture was stirred at room temperature for 15 min, a solution of the quinoline (534 mg, 1.07mmol) in THF (1.5 mL) was added, and the resulting solution was stirred for 10 min. The reaction was quenched by addition of 2N HCl (10 mL) and the resulting mixture was stirred for 5 min. After the mixture was diluted with EtOAc (20 mL) and stirred for 5 min, two layers were separated and the aqueous fraction was extracted with EtOAc (20 mL). The combined organic fractions were dried (Na_2SO_4) and concentrate. The residue was purified by silica gel chromatography using a mixture of hexanes and ethyl acetate as the eluent to afford 504 mg (98%) of the PMB protected bis-methoxyethoxy quinoline. LC/MS = 448 (M^+ + 1).

Step 2: A solution of the PMB protected quinoline 504 mg (1.12 mmol) in dichloromethane (5.0 mL), and TFA (5.0 mL) was stirred at room temperature for 10 min. The color goes from colorless to purple as the reaction proceeds. The solution was concentrated under reduced pressure, adjusted the pH to 8 using 5% sodium bicarbonate, then extracted with EtOAc (2 x 10 mL). The combined organic fractions were dried

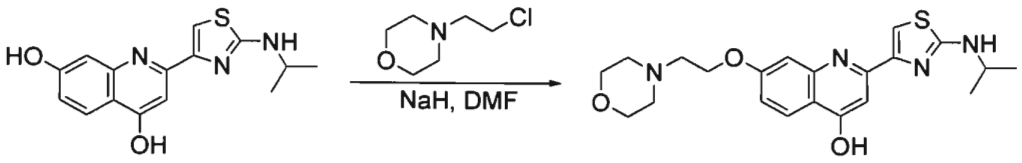
(Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography using a mixture of hexanes and ethyl acetate as the eluent to afford 367 mg (100%) of the hydroxyl quinoline. LC/MS = 328 ($M^+ + 1$).



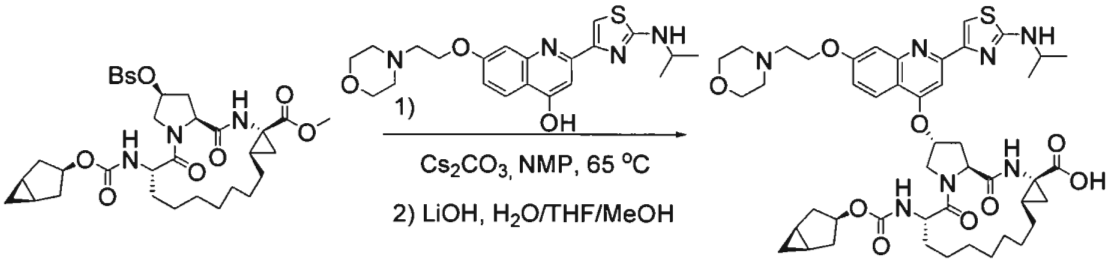
Step 3: A mixture of intermediate III (800 mg, 1.12 mmol), quinoline (367mg, 1.12 mmol) and cesium carbonate (802 mg, 2.46 mmol) in NMP (5mL) was stirred as 65 °C for 16 h. The mixture was then diluted with EtOAc (20 mL) and 5% LiCl (20mL) and stirred at room temperature for 30 min. The two layers were separated and the aqueous fraction was extracted with EtOAc (20 mL). After the combined organic fractions were washed with LiCl (3 x 20 mL), water, and then brine, it was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography using a mixture of hexanes and ethyl acetate as the eluent to afford 829 mg (92%) of the ester. LC/MS = 803 ($M^+ + 1$).

Step 4: To a mixture of ester (829 mg, 1.02 mmol) in THF (3 mL) and methanol (5 mL), was added a solution of LiOH monohydrate (210 mg, 5.0 mmol) in water (3 mL). The mixture was stirred at 35 °C for 3 h. The solution was concentrated under reduced pressure and the pH was adjusted to 2 with 10% HCl. Methanol (5 mL) was added to the mixture and was purified by reverse phase preparative HPLC using a mixture of acetonitrile 0.1% TFA and water 0.1% TFA as the eluent to afford 528 mg (66%) of **compound 86.** ^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 7.81 (d, J = 8.99 Hz, 1H), 7.10 (d, J = 9.2 Hz, 1H), 6.35 (s, 1H), 5.28 (br, 1H), 4.59 – 4.36 (br, 5H), 4.22 (br, 2H), 4.08 (s, 1H), 3.89-3.85 (br, 1H), 3.75-3.70 (m, 2H), 3.36 (s, 3H), 3.34 (s, 3H), 2.58 (m, 1H), 2.38 (m, 1H), 1.93 (m, 1H), 1.82 (m, H), 1.58-1.50 (br, 4H), 1.42-1.23 (br, 4H), 1.1-1.05 (br, 3H), 0.88 (s, 9H), 0.82 (s, 1H), 0.19-0.2 (br, 2H). LC/MS = 790 ($M^+ + 1$).

Example 87: Preparation of Compound 87

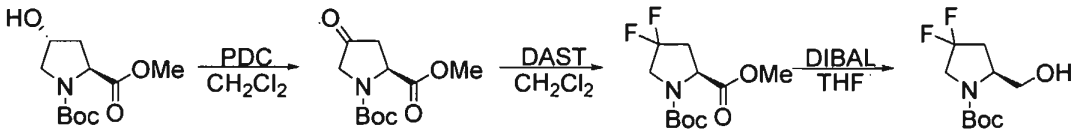


Step 1: The dihydroxyquinoline (2 g, 6.6 mmol) was dissolved in DMF (50 ml) at 0 °C and NaH (792mg, 19.8 mmol) was added in portions. It was stirred at 0 °C for 30 min, followed by addition of 4-(2-chloroethyl)-morpholine hydrochloric acid (1.36g, 7.3 mmol). The mixture was stirred at 60 °C for 5 h then room temperature overnight. The mixture was diluted with EtOAc and aqueous 3% LiCl solution. The two layers were separated and the aqueous fraction was extracted with EtOAc again. The combined organic fractions were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel with MeOH/EtOAc to yield 1.46g (43%) of the desired product. LC/MS = 415 (M^++1).



Step 2: Compound 87 (570mg as TFA salt, 74%) was obtained by the procedures similar to those for preparation of **compound 82** using macrocyclic tripeptide (1.2g mg, 1.7 mmol, with >30% impurities) and quinoline (500mg, 0.965, with 20% impurities). ^1H NMR (300 MHz, CD_3OD): δ 8.64 (s, 1H), 8.33 (d, 1H), 8.22 (s, 1H), 7.83 (s, 1H), 7.78 (d, 1H), 7.41 (dd, 1H), 5.7 (b, 1H), 4.78-4.62 (m, 5H), 4.30 (d, 1H), 4.29 – 4.07 (m, 7H), 3.79 (t, 2H), 3.54 (brs, 4H), 2.80-2.60 (m, 2H), 1.10-2.04 (m, 34H), 0.97-0.92 (m, 1H), 0.32-0.42 (m, 2H). LC/MS = 888.7 (M^++1).

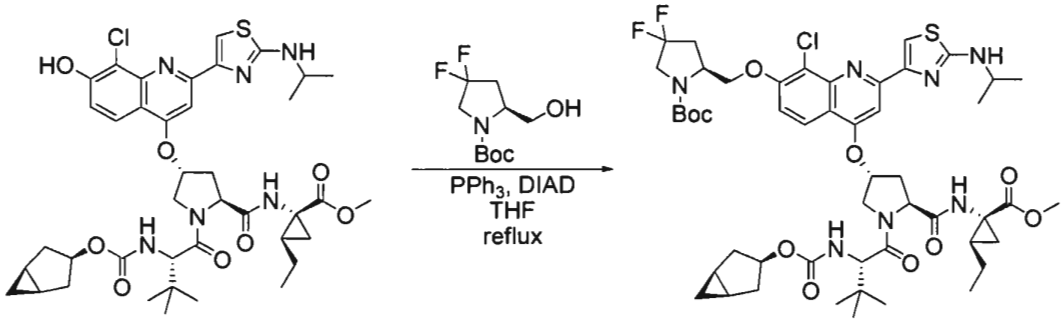
Example 88: Preparation of Compound 88



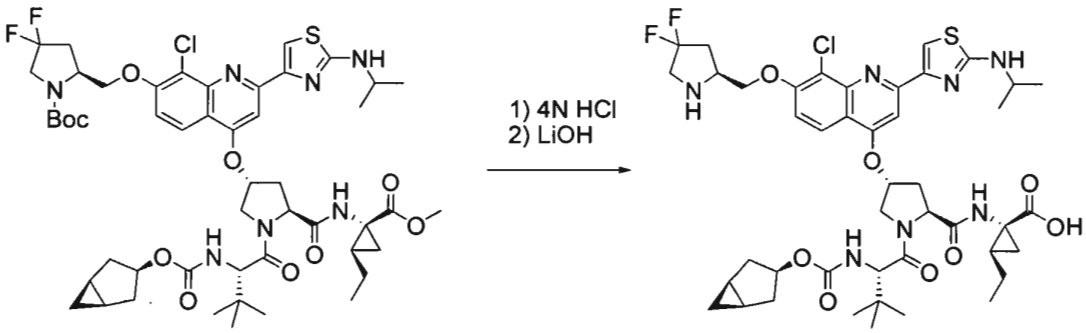
Step 1: A mixture of the protected hydroxyproline (10 g, 40.8 mmol), PDC (23.0 g, 61.2 mmol) and 10 g of 4A molecular sieves in dichloromethane (150 mL) was stirred at room temperature for 4 days. It was filtered through a pile of Celite, washed pad with more dichloromethane. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel with EtOAc/Hexane to afford 7.86g (79%) desired ketone. LC/MS = 144 (M^++1-Boc).

Step 2: A mixture of the ketone (4.3 g, 17.7 mmol) in dichloromethane (80 mL) was stirred at -78 °C under N_2 as DAST (5.8 mL, 44.25 mmol) was added slowly. The mixture was allowed to warm to room temperature and stirred for 24 h. The reaction mixture was quenched with ice-water. After the two layers were separated, the aqueous fraction was extracted with dichloromethane (300 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel with EtOAc/hexane to obtain 4.37g (93%) of the difluoro compound. LC/MS = 166 (M^++1-Boc).

Step 3: A mixture of difluoro-ester (4.37 g, 16.5 mmol) in THF (50 mL) was stirred at -78 °C under N_2 as 1 M DIBAL in THF (36.3 mL, 36.3 mmol) was added dropwise over 30 min period. The mixture was allowed to warm to room temperature and stirred for 48 h. The mixture was diluted with EtOAc (100 mL) and sat. sodium potassium tartrate (100 mL), and the resulting mixture was vigorously stirred for 30 min until two phases were apparent. After the two layers were separated, the aqueous fraction was extracted with EtOAc (2 x 100 mL) and the combined organic fractions were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel with EtOAc/hexane, gave 1.56g (40%) of the alcohol. LC/MS = 138 (M^++1-Boc).



Step 4: A mixture of the tripeptide (500 mg, 0.616 mmol) and the alcohol (175 mg, 0.739 mmol) in the previous step, PPh_3 (261 mg, 0.986 mmol), and DIAD (0.191 mL, 0.986 mmol) in THF (10 mL) was refluxed for 3 h. After the mixture was cooled to room temperature and concentrated, the residue was purified by flash chromatography on silica gel with EtOAc/Hexane to afford 628 mg (99%) of the desired product. LC/MS = 1031.3 (M^++1).

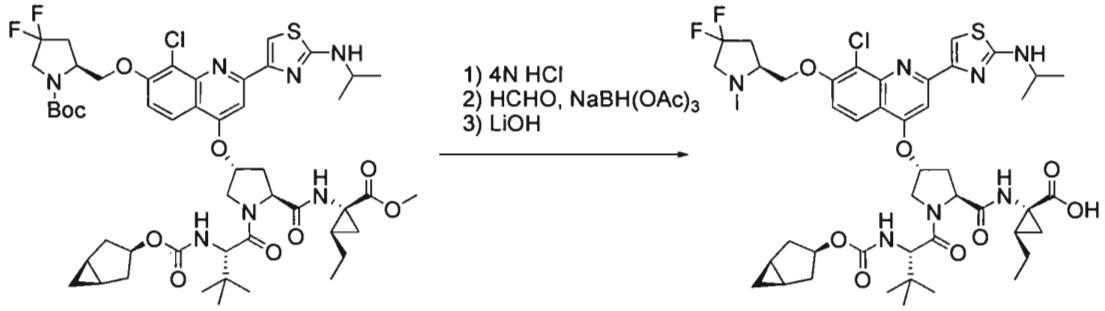


Step 5: The above Boc-protected compound was dissolved in 4N HCl in dioxane (10mL) and stirred at room temperature for 2 h. The mixture was concentrated *in vacuo* to give the crude product. LC/MS = 930.2 (M^++1).

Step 6: The above compound was dissolved in THF (3 mL), MeOH (3 mL), and water (10 mL) with LiOH (462 mg, 11.56 mmol) and stirred at room temperature for 24 h. The solution was acidified with TFA and then concentrated *in vacuo*. The residue was purified

by prep-HPLC to afford 500.8mg (76% for two steps) of **compound 88** as bis-TFA salt. ^{1}H NMR (300 MHz, CD_3OD): δ 8.64 (s,1H), 8.33 (d, 1H), 8.22 (s, 1H), 7.78 (s, 1H), 7.60 (d, 1H), 5.72 (b, 1H), 4.90-4.55 (m, 5H), 4.22-4.13 (m, 2H), 4.00-3.88 (m, 2H), 3.00-2.60 (m, 3H), 2.00-1.80 (m, 2H), 1.70-1.65 (m, 2H), 1.57-1.40 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 1.22 (m, 2H), 1.03- 0.92 (m, 10H), 0.35 (m, 2H). LC/MS = 916.2 (M^++1).

Example 89: Preparation of Compound 89



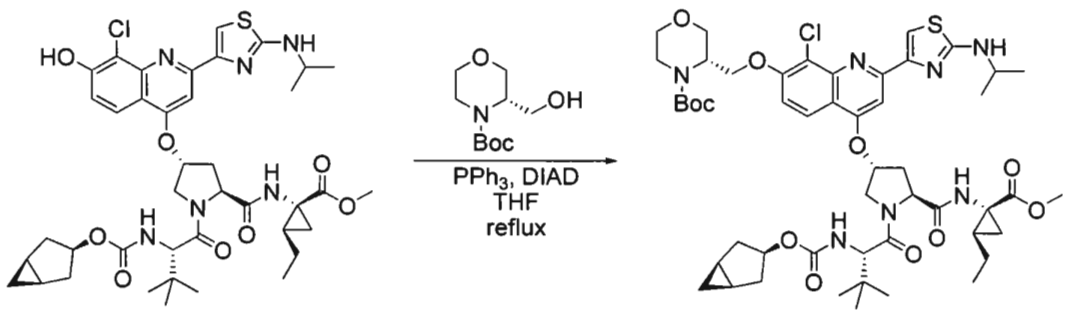
Step 1: The Boc deprotection was performed by the procedure in example **88**, Step 5.

Step 2: To a solution of the above de-Boc compound in 1,2-dichloroethane (6 mL) were added $NaBH(OAc)_3$ (520 mg, 2.45 mmol) and formaldehyde (37% in water, 0.1 mL, 1.23 mmol) at room temperature. After 1 hr, the mixture was concentrated, diluted with EtOAc (100mL), washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated *in* vacuo to give the crude methylated compound. LC/MS = 944.2 (M^++1).

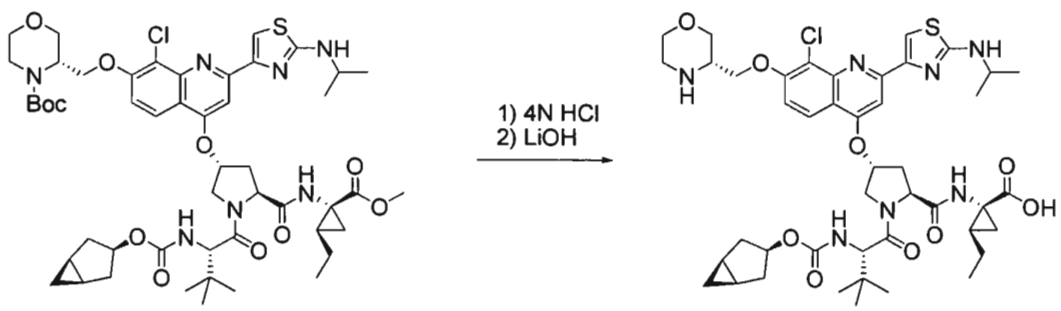
Step 3: The above methylated compound was dissolved in THF (3 mL), MeOH (3 mL), and water (10 mL) with LiOH (500 mg) and stirred at room temperature for 24 h. The solution was acidified with TFA and then concentrated *in vacuo.* The crude product was purified by prep-HPLC to afford 510 mg (69% for 3 steps) of **compound 89** as bis-TFA salt. ^{1}H NMR (300 MHz, CD_3OD): δ 8.64 (s,1H), 8.31 (d, 1H), 8.23 (s, 1H), 7.73 (s, 1H), 7.62 (d, 1H), 5.72 (b, 1H), 4.90-4.50 (m, 5H), 4.30-3.68 (m, 7H), 3.20 (s, 3H), 3.05-2.60

(m, 3H), 2.00-1.80 (m, 2H), 1.70-1.63 (m, 2H), 1.54-1.40 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 1.22 (m, 2H), 1.03- 0.92 (m, 10H), 0.34 (m, 2H). LC/MS = 930.2 (M^++1).

Example 90: Preparation of Compound 90



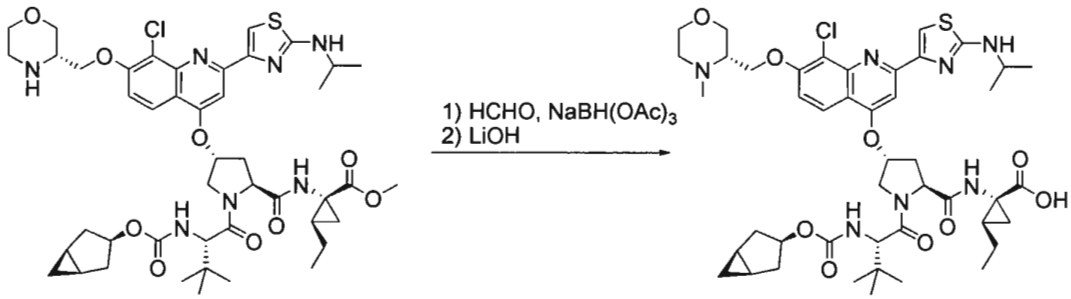
Step 1: A mixture of the reactant (1.17 g, 1.44 mmol) and 3-hydroxymethyl-morpholine-4-carboxylic acid tert-butyl ester (376 mg, 1.73 mmol), PPh_3 (604 mg, 2.30 mmol) and DIAD (0.445 mL, 2.30 mmol) in THF (15 mL) was refluxed for 3 h. LC/MS showed some product formed along with other by products and lots of starting material. Another half portions of reagents were added and refluxed overnight. The mixture was cooled to room temperature, diluted with EtOAc (100 mL), washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated *in vacuo.* The residue was purified by flash chromatography on silica gel with EtOAc/Hexane followed by prep-HPLC to afford 142 mg (10%) of the desired product. LC/MS = 1010.3 (M^++1).



Step 2: Above Boc-protected compound (55 mg, 0.054 mmol) was dissolved in 4N HCl in dioxane (3 mL) and stirred at room temperature for 1 h. The mixture was diluted with EtOAc (20 mL), washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude deprotected product. LC/MS = 910.3 (M^++1).

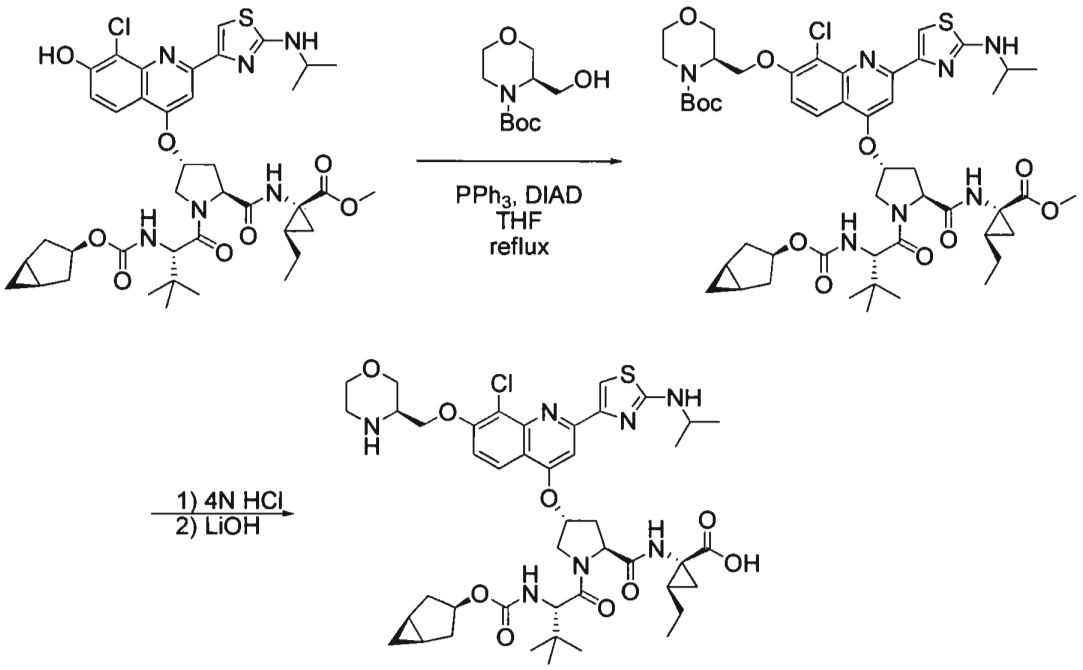
Step 3: Above compound and LiOH (50 mg) were dissolved in THF (5mL), MeOH (0.5 mL), and water (2 mL) and stirred at room temperature for 24 h. The solution was acidified with TFA and then concentrated *in vacuo* to give the crude product, which was purified by prep-HPLC to afford 17 mg (28% for two steps) of **compound 90**. ^{1}H NMR (300 MHz, CD_3OD): δ 8.64 (s,1H), 8.31 (d, 1H), 8.25 (s, 1H), 7.80 (s, 1H), 7.68-7.55 (m, 4H), 5.72 (b, 1H), 4.79-4.47 (m, 5H), 4.25-3.84 (m, 10H), 3.50-3.39 (m, 2H), 2.86-2.60 (m, 2H), 2.00-1.80 (m, 2H), 1.70-1.62 (m, 2H), 1.54-1.40 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 1.34-1.20 (m, 4H), 1.03- 0.92 (m, 10H), 0.35 (m, 2H). LC/MS = 896.2 (M^++1).

Example 91: Preparation of Compound 91



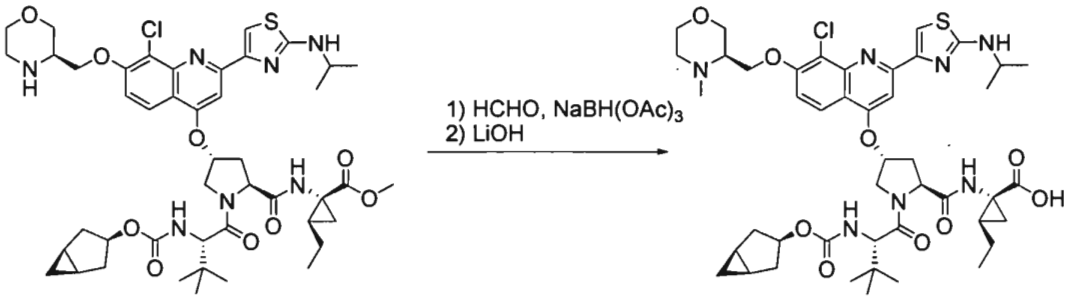
Compound 91 was obtained by the procedures described in **Example 89.** After purified by prep-HPLC, 25.5 mg (27%) of Compound **91** was obtained as bis-TFA salt. ^{1}H NMR (300 MHz, CD_3OD): δ 8.64 (s, 1H), 8.29 (d, 1H), 8.23 (s, 1H), 7.78 (s, 1H), 7.73 (m, 1H), 5.72 (b, 1H), 4.79-4.47 (m, 5H), 4.30-3.95 (m, 10H), 3.61-3.43 (m, 2H), 3.17 (s, 3H), 2.86-2.50 (m, 2H), 2.00-1.80 (m, 2H), 1.70-1.61 (m, 2H), 1.57-1.40 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 1.34-1.20 (m, 4H), 1.05- 0.90 (m, 10H), 0.35 (m, 2H). LC/MS = 910.3 (M^++1).

Example 92: Preparation of Compound 92



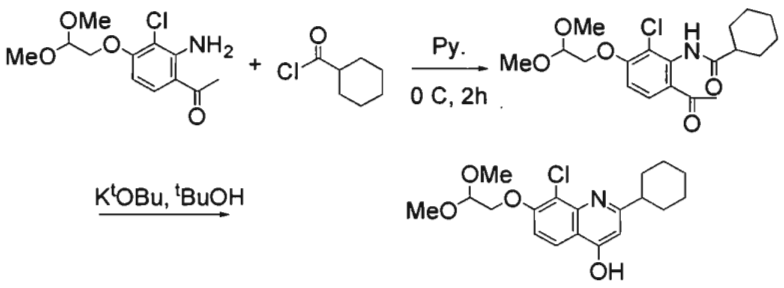
Compound 92 was obtained by the procedures described in **example 90.** After purified by prep-HPLC, 17.4 mg of **compound 92** was obtained as bis-TFA salt. ^{1}H NMR (300 MHz, CD_3OD): δ 8.64 (s, 1H), 8.29 (d, 1H), 8.22 (s, 1H), 7.78 (s, 1H), 7.61 (d, 1H), 5.71 (b, 1H), 4.73-4.49 (m, 5H), 4.25-3.84 (m, 10H), 3.50-3.39 (m, 2H), 2.86-2.60 (m, 2H), 2.00-1.80 (m, 2H), 1.70-1.62 (m, 2H), 1.54-1.40 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 1.30-1.20 (m, 4H), 1.05- 0.91 (m, 10H), 0.33 (m, 2H). LC/MS = 896.2 (M^++1).

Example 93: Preparation of Compound 93



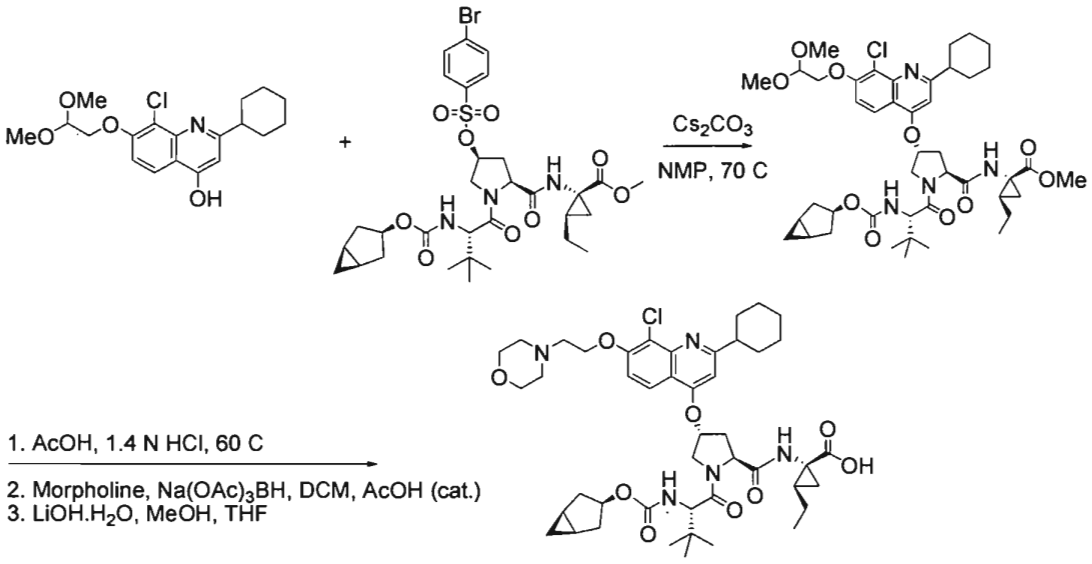
Compound 93 was obtained by the procedures described in **example 89.** After purified by prep-HPLC, 16.0 mg of **compound 93** was obtained as bis-TFA salt. ^{1}H NMR (300 MHz, CD_3OD): δ 8.63 (s, 1H), 8.31 (d, 1H), 8.24 (s, 1H), 7.80 (s, 1H), 7.64 (s, 1H), 5.72 (b, 1H), 4.75-4.47 (m, 5H), 4.20-3.92 (m, 10H), 3.61-3.40 (m, 2H), 3.18 (s, 3H), 2.80-2.55 (m, 2H), 2.00-1.80 (m, 2H), 1.70-1.62 (m, 2H), 1.50-1.40 (m, 2H), 1.40 (s, 3H), 1.38 (s, 3H), 1.20-1.10 (m, 4H), 1.05- 0.97 (m, 10H), 0.35 (m, 2H). LC/MS = 910.3 (M^++1).

Example 94: Preparation of Compound 94



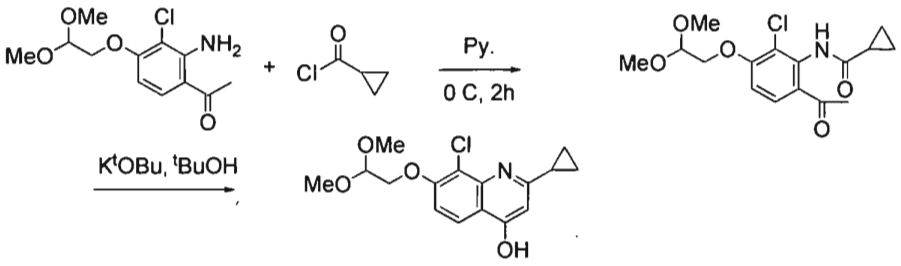
Step 1: To a solution of 1-[2-Amino-3-chloro-4-(2,2-dimethoxy-ethoxy)-phenyl]-ethanone (2 g, 7.3 mmol) in pyridine (20 mL) was slowly added cyclohexanecarbonyl chloride (1.12 g, 7.7 mmol) at 0 °C. After the mixture was stirred at room temperature for 2 h, H_2O (10 mL) was added to the mixture. The product was extracted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel chromatography to obtain 1.9 g, (65%) of the amide as white solids. LC/MS = 383.8 (M^++1).

Step 2: The amide (1.9 g, 5.0 mmol) and *t*-BuOK (0.62 g, 0.55 mmol) were dissolved in *t*-BuOH (20 mL) at room temperature and stirred under reflux for 2 h. Upon completion of the reaction, 3N HCl was added to the reaction to adjust pH around 3, which resulted the precipitation of the product. The solids were filtered, washed with ether, and dried under high vacuum to afford the quinoline as white solids (1.6 g, 100%). LC/MS = 366.1 (M^++1).

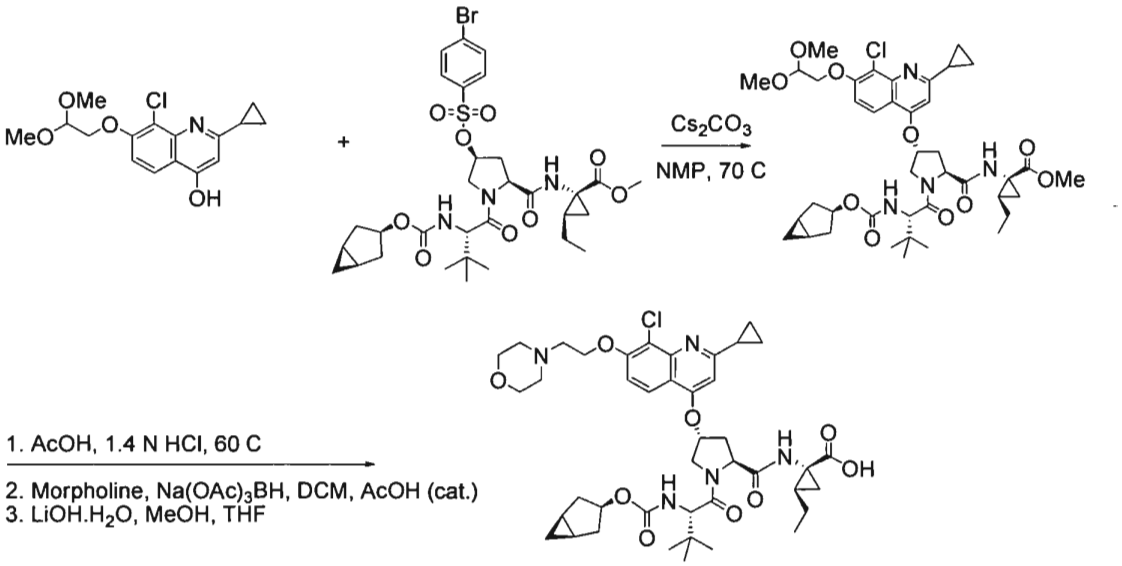


Step 3: Compound 94 (170 mg) was synthesized using the same procedure described before to prepare **compound 82**. LC/MS = 852.9 (M^++1). ^{1}H NMR (300 MHz, CD_3OD): d 8.06 (d, 1H), 7.32 (d, 1H), 7.04 (s, 1H), 5.45 (b, 2H), 4.34 (dd, 1H), 4.25 (d, 1H), 4.15 (dd, 1H).3.79-2.98(m, 11H), 2.42 (m, 1H), 2.25 (m, 1H), 1.75-1.61 (m, 3H), 1.54-1.45 (m, 3H), 1.35-1.00 (m, 10H), 0.91-0.84 (m, 2H), 0.73-0.61 (m, 12H), 0.14-0.03 (m, 2H).

Example 95: Preparation of Compound 95



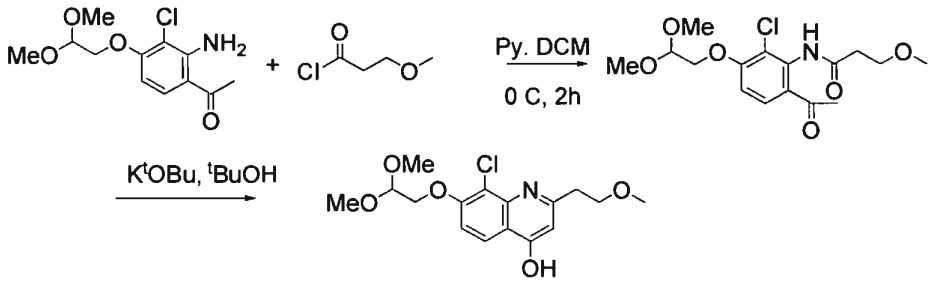
Step 1 and step 2: The quinoline was synthesized using the procedure described before in **example 94**. LC/MS = 324.2 (M^++1).



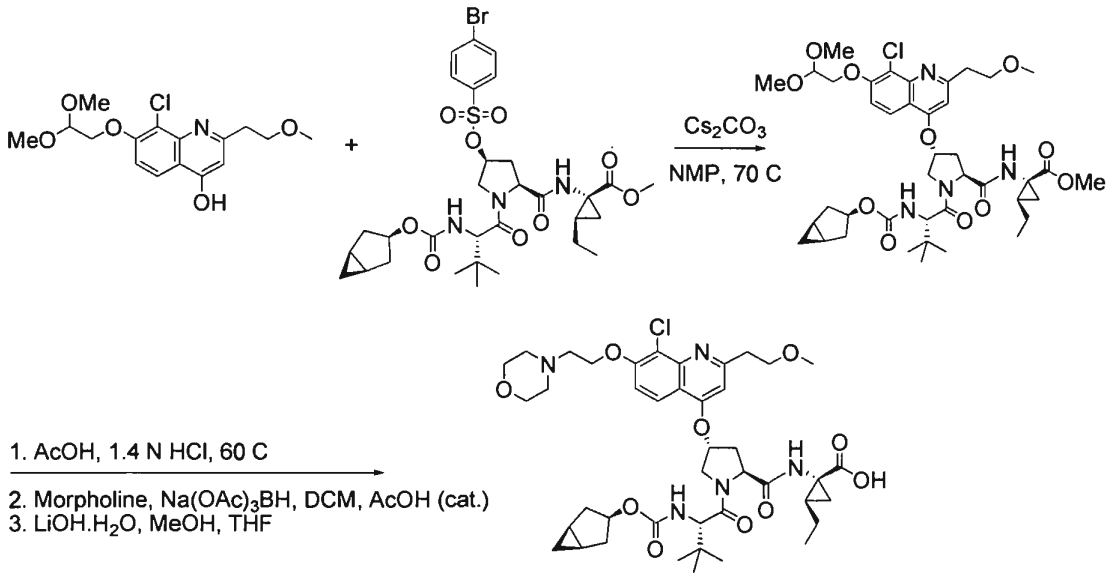
Step 3: Compound 95 (550 mg) was synthesized using the same procedure described before to prepare **compound 82**. LC/MS = 810.5 (M^++1). ^{1}H NMR (300 MHz, CD_3OD): d 8.33 (d, 1H), 7.60 (d, 1H), 6.77 (s, 1H),5.69 (bs, 1H), 4.78 (b, 2H), 4.66 (dd, 1H), 4.51 (m, 1H), 4.13-3.31(m, 11H), 2.96-2.68 (m, 2H),

2.57-2.49 (m, 1H), 2.01-1.81 (m, 2H), 1.69-1.35 (m, 10H), 1.24-1.10 (m, 2H), 1.05-0.94 (m, 12H), 0.36-0.33 (m, 2H).

Example 96: Preparation of Compound 96

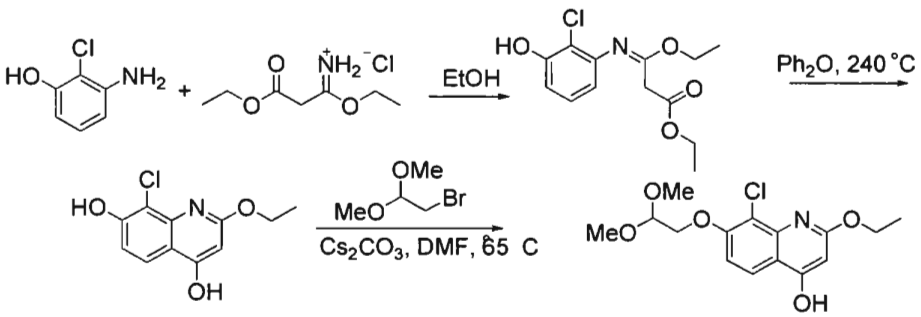


Step 1 and step 2: The quinoline was synthesized using the procedure described before in **example 94**. LC/MS = 342.7 (M^++1).



Step 3: Compound 96 (260 mg) was synthesized using the same procedure described before to prepare **compound 82**. LC/MS = 829.4 (M^++1).

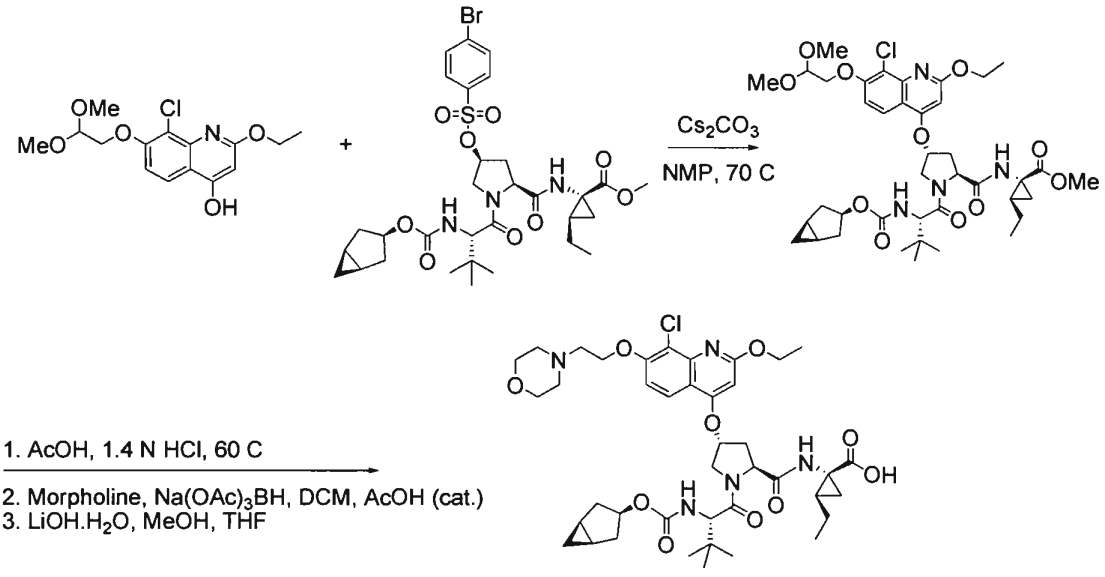
Example 97: Preparation of Compound 97



Step 1: The imidate salt (2.99 g, 16 mmol) and the aniline (2 g, 14.5 mmol) were dissolved in ethanol (7 mL) under N_2 atmosphere. The reaction mixture was stirred at 30 °C overnight. After the mixture was filtered, the filtrate was concentrated. The residue was purified by silica gel chromatography to obtain the condensation product in form of colorless oil (3.6 g, 87%). LC/MS = 285.9 (M^++1).

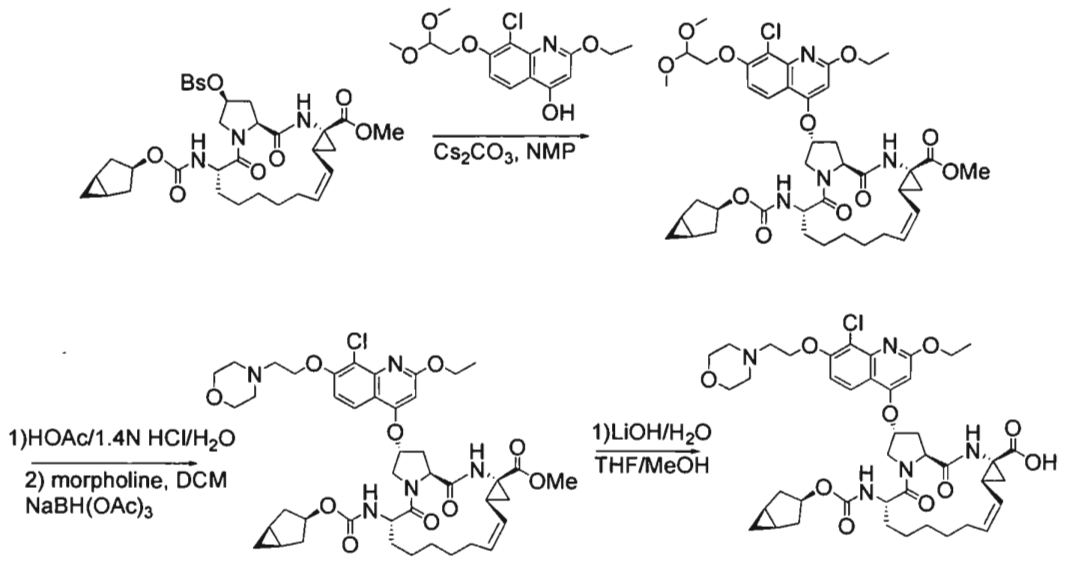
Step 2: A solution of the condensation product (3.6 g, 87%) in diphenyl ether (36 mL) was placed in a hot sand bath (300 °C) and the mixture was allowed to stir for 12 minutes while the solution temperature was kept around 240-250 °C. The mixture was cooled to room temperature and desired product was precipitated in brown solids. The solids were filtered, washed with hexane, and dried under high vacuum to afford the quinoline (2.33 g, 9.7 mmol, 77%). LC/MS = 240.0 (M^++1).

Step 3: To a solution of the quinoline (2.33 g, 9.7 mmol) in DMF (30 mL) were added cesium carbonate (12.64 g, 39 mmol) and 2-Bromo-1,1-dimethoxy-ethane (2.6 g, 15 mmol). The resulting mixture was stirred at 65 °C for 10 h. After the mixture was filtered, the filtrate was diluted with EtOAc and H_2O, and 3N HCl was added to adjust pH to 3. Organic fraction separated was washed with 5% LiCl and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford 8-Chloro-7-(2,2-dimethoxy-ethoxy)-2-ethoxy-quinolin-4-ol as white solids (1.27 g, 3.87 mmol, 40 %). LC/MS = 328.1 (M^++1).



Step 4: **Compound 97** (754 mg) was synthesized using the same procedure described before to prepare **compound 82**. LC/MS = 814.6 (M^++1). ^1H NMR (300 MHz, CD_3OD): d 7.61 (d, 1H), 6.82 (d, 1H), 6.01 (s, 1H),5.01 (s, 1H), 4.41-4.30 (m, 1H), 4.29-4.19 (m, 3H), 4.15-4.01 (m, 2H), 3.95-2.95(m, 12H), 2.30 (m, 1H), 2.10 (m, 1H), 2.84-0.59 (m, 19H), 0.2-0.04 (m, 2H).

Example 98: Preparation of Compound 98



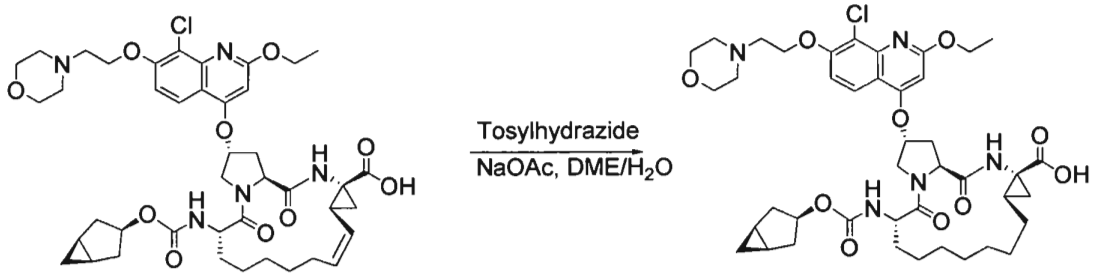
Step 1: To a mixture of the brosylate (1.1 g, 1.52 mmol) and cesium carbonate (0.99 g, 3.04 mmol) in NMP (10 mL) was added the quinoline (0.40g, 1.22 mmol) at room temperature in one portion. The mixture was stirred at 85 °C for 3 h, cooled to room temperature, and diluted with EtOAc (100 mL). The mixture was washed with aqueous 3% LiCl (1 x 100 mL), brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography with EtOAc/Hexane to give the desired product as light brown solid (0.70 g, 71%). LC/MS = 813 (M^++1).

Step 2: To a solution of the ester (0.70g, 0.86 mmol) in HOAc (10 mL) was added 1.4 N aq. HCl (5 mL) and the resulting solution was stirred at 60 °C for 1.5 h. Upon completion of the reaction, the mixture was concentrated to remove the solvents. After the residue was dissolved in EtOAc (100 mL) and washed with sat. $NaHCO_3$, the organic layer was dried (Na_2SO_4) and concentrated to afford the crude aldehyde. To a solution of the crude aldehyde in CH_2Cl_2 (20 mL) were added morpholine (112 μL, 1.29 mmol) and sodium triacetoxyborohydride (237 mg, 1.12 mmol) at 0 °C. Glacial acetic acid (25 μL, 7.8 mmol) was then added dropwise to the mixture. The reaction was completed in 10 min at 0 °C. Sat. $NaHCO_3$ solution was added to quench the reaction. After stirring the mixture

for 20 min, the separated organic layer was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was clean enough (by LC/MS) to use as is. LC/MS = 838 (M^++1).

Step 3: To a solution of this crude product in THF (6 mL), a solution of LiOH (384 mg, 16 mmol) in H_2O (6 mL) was added, followed by MeOH (6 mL). The mixture was stirred at room temperature for 20 h. Upon completion of the reaction, TFA was added at 0 °C to adjust the pH to 4 and the product was extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The product was purified by prep-HPLC to give **Compound 98** as white solids (0.51 g, 53%). LC/MS = 824 (M^++1). ^{1}H NMR (400 MHz, CD_3OD): δ 8.05 (d, J = 8.8 Hz 1H), 7.21 (d, J = 9.2 Hz,1H), 6.38 (s, 1H), 5.61 (m, 1H), 5.39 (m, 2H), 4.87 (m, 1H), 4.63-4.54 (m, 5H), 4.26 (m, 1H), 4.07 (m, 2H), 4.01 (m, 1H), 3.87 (m, 1H), 3.76 (m, 3H),3.48 (m, 2H), 2.63-2.54(m, 1H), 2.54-2.47 (m, 2H), 2.33-2.67 (m, 1H), 2.04-1.89 (m, 3H), 1.87 (m, 1H), 1.75 (m, 2H), 1.67-1.59 (m, 3H), 1.55 (m, 2H), 1.46-1.37(m, 8H), 1.29-1.14(m, 4H), 0.39 (m, 2H).

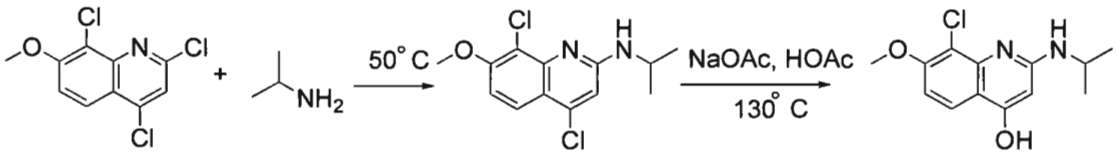
Example 99: Preparation of Compound 99



Compound 98 (0.20g, 0.24mmol) and *p*-toluenesulfonyl hydrazide (0.31 g, 1.68 mmol) were dissolved in ethylene glycol dimethyl ether (2 mL) and sodium acetate (0.28 g, 3.36 mmol) and H_2O (0.2 mL) were added. The suspension was then heated at 95 °C with stirring for 3 h. The mixture was cooled to room temperature, diluted with DMF (4 mL),

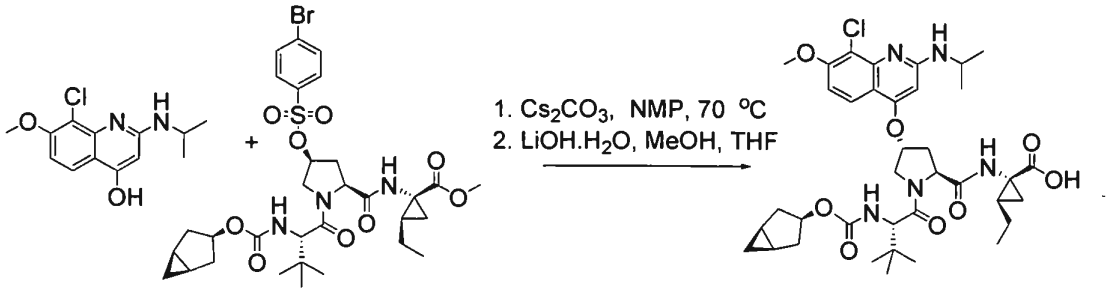
and purified by prep-HPLC to give **compound 99** as white solids (0.12 g, 60%). LC/MS = 826 (M^++1). ^{1}H NMR (400 MHz, CD_3OD): δ 8.03 (d, J = 9.2 Hz, 1H), 7.23 (d, J = 9.2), 3.42 (m, 2H), 2.59(m, 2H), 2.04-1.89 (m, 3H), 1.87 (m, 1H), Hz,1H), 6.41 (s, 1H), 5.38 (bs, 1H), 4.75-4.69 (m, 2H), 4.61-4.54 (m, 6H), 4.49 (m, 1H), 4.32 (m, 1H), 4.08-3.98 (m, 5H), 3.75 (m, 5H 1.75 (m, 2H), 1.67-1.59 (m, 3H), 1.55 (m, 2H), 1.46-1.37(m, 8H), 1.29-1.14(m, 4H), 0.37 (m, 2H).

Example 100: Preparation of Compound 100



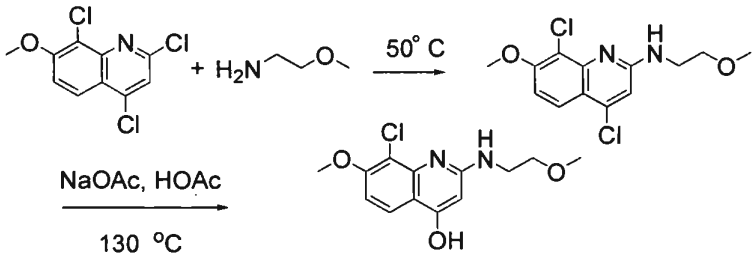
Step 1: 2,4,8-Trichloro-7-methoxyquinoline (0.32 g, 1.19 mmol) was dissolved in isopropylamine (4 mL) in a sealed tube and stirred at 50 °C for 10 h. The reaction mixture was diluted with EtOAc, washed with H_2O, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford the dichloroquinoline (0.231 g, 0.81 mmol, 68%). LC/MS = 285.1 (M^++1).

Step 2: A mixture of the dichloroquinoline (0.145 g, 0.51 mmol) and sodium acetate (0.625 g, 7.6 mmol) in HOAc (2 mL) was placed in a sealed tube and stirred at 130 °C for 17 h. After the mixture was cooled to room temperature, the solidified mixture was dissolved by additional EtOAc, and washed with H_2O and sat. $NaHCO_3$ (3 x). Along the wash with sat. $NaHCO_3$, the desired product was crashed out and filtered. The filter cake was treated with toluene and concentrated (3 x) to afford 8-Chloro-2-isopropylamino-7-methoxy-quinolin-4-ol (0.09 g, 67%). LC/MS = 267.1 (M^++1).

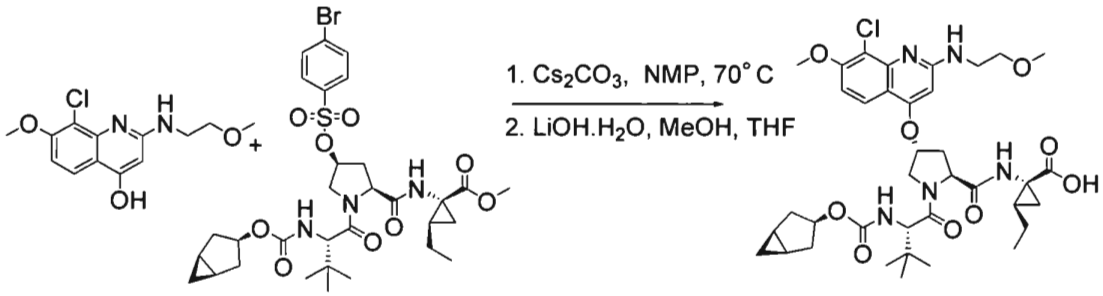


Step 3: Compound 100 (110 mg) was synthesized using the same procedure described before to prepare **compound 82**. LC/MS = 728.4 (M^++1). ^{1}H NMR (300 MHz, CD_3OD): d 8.02 (d, 1H), 7.26 (d, 1H), 6.45 (bs, 1H), 5.61 (bs, 1H), 5.06 (bs, 1H), 4.68 (dd, 1H), 4.56-4.45 (m, 2H), 4.25-3.97(m, 6H), 3.32 (s, 1H), 2.76-2.68 (m, 2H), 2.56-2.49 (m, 1H), 2.14 (m,1H), 1.99-1.78 (m, 2H), 1.68-1.64 (m, 3H), 1.53-1.16 (m,6H), 1.05-0.94 (m, 14H), 0.37-0.30 (m, 2H).

Example 101: Preparation of Compound 101

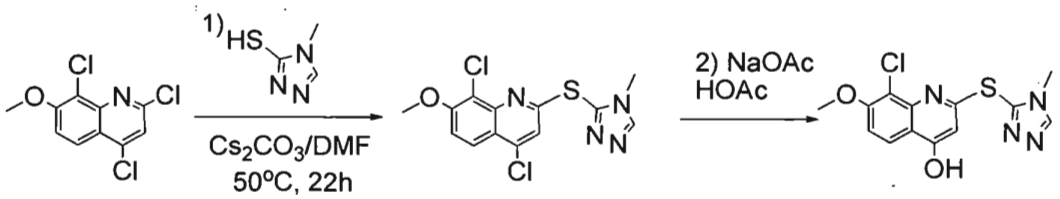


Step 1 and step 2: The quinoline was synthesized using the similar procedure described before in **example 100**. LC/MS = 283.1 (M^++1).



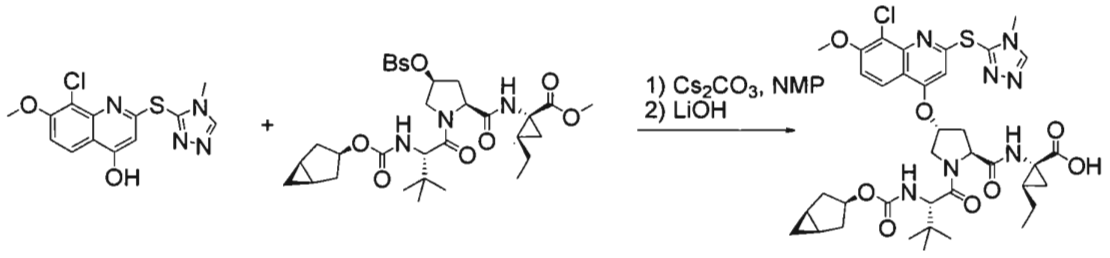
Step 3: Compound 101 (82 mg) was synthesized using the same procedure described before to prepare **compound 82**. LC/MS = 744.4 (M^++1). ^{1}H NMR (300 MHz, CD_3OD): d 8.02 (d, 1H), 7.306 (d, 1H), 6.51-6.37 (m, 1H), 5.58-5.45 (m, 1H), 4.68 (dd, 1H), 4.56-4.44 (m, 2H), 4.15-3.96(m, 5H), 3.79 (m, 4H), 3.55-3.47 (m, 2H), 3.31 (m, 1H), 2.72-2.49 (m, 2H), 2.14 (m,1H), 1.99-1.78 (m, 2H), 1.68-1.64 (m, 3H), 1.53-1.22 (m,6H), 1.20-0.94 (m, 14H), 0.37-0.30 (m, 2H).

Example 102: Preparation of Compound 102



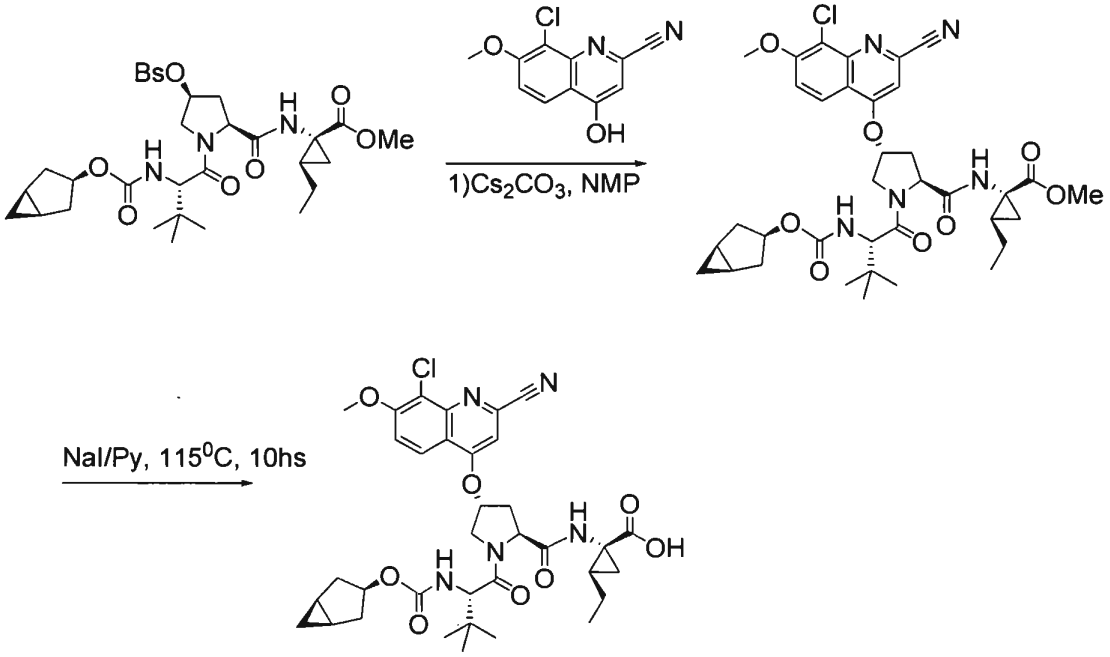
Step 1: A mixture of 2,4,8-Trichloro-7-methoxy-quinoline (100 mg, 0.38 mmol), 4-methyl-4H-1,2,4-triazole-3-thiol (44 mg, 0.38 mmol), and cesium carbonate (185 mg, 0.57 mmol) in DMF (2 mL) was stirred at 50 °C for 22 h. LC/MS showed some product formed along with other by-products. The mixture was cooled to room temperature, diluted with EtOAc (100mL), and washed with 3% LiCl and brine. The organic layer and insoluble material were combined and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford 89 mg (67%) of the monosubstituted product. LC/MS = 341.2 (M^++1).

Step 2: A mixture of the above dichloroquinoline (48 mg, 0.14 mmol) and NaOAc (173 mg, 2.11 mmol) in HOAc (2 mL) was stirred at 130 °C for 36 h in a sealed tube. After cooling to room temperature, the mixture was diluted with EtOAc (20mL), and washed with sat. $NaHCO_3$ and brine. The organic layer and insoluble material were combined and concentrated *in vacuo* to give the white solid compound which was clean desired hydroxyquinoline product, used as is for the next step. LC/MS = 323.11 (M^++1).



Step 3: A mixture of intermediate III (130 mg, 0.182 mmol), the hydroxyquinoline and cesium carbonate (137 mg, 0.42 mmol) in NMP (2 mL) was stirred at 65 °C for 5 h. After cooling to room temperature, the mixture was diluted with THF (5 mL) and MeOH (1 mL) and lithium hydroxide (100mg) in water (3 mL) was added to the mixture. The mixture was stirred for 16 hrs at room temperature, and neutralized with TFA. After removal of volatile solvents, the residue was purified by prep-HPLC to afford 53 mg (42% for two steps) of **compound 102** as TFA salt. ^{1}H NMR (300 MHz, CD_3OD): δ 8.85 (s,1H), 8.11 (d, 1H), 7.44 (d, 1H), 6.22 (s, 1H), 5.81 (b, 1H), 4.50 (m, 1H), 4.3-4.0 (m, 4H), 4.06 (s, 3H), 3.72 (s, 3H), 2.47 (m, 2H), 2.04 (m, 2H), 1.75-1.1.79 (m, 10H), 1.03- 0.92 (m, 14H), 0.44 (m, 2H). LC/MS = 784.1 (M^++1).

Example 103: Preparation of Compound 103



Step 1: To a mixture of intermediate III (0.15 g, 0.21 mmol) and cesium carbonate (0.14 g, 0.42 mmol) in NMP (5 mL) was added the quinoline (0.05 g, 0.21 mmol) at room temperature in one portion. The mixture was stirred at 85 °C for 3 h, cooled to room temperature, and diluted with EtOAc (30 mL). The mixture was washed with aqueous 3% LiCl (1 x 20 mL), brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel chromatography with EtOAc/Hexane to give the desired product as light brown solid (0.09 g, 60%). LC/MS = 710 (M^++1).

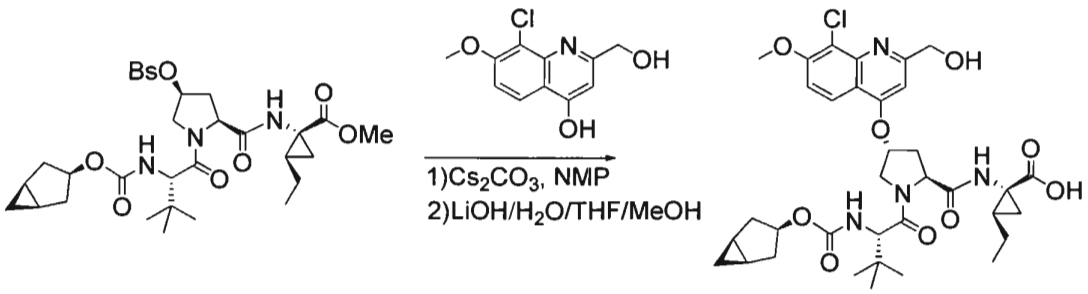
Step 2: The ester (0.06 g, 0.085 mmol) and sodium iodide (0.25 g, 1.67 mmol) were dissolved in pyridine (3 mL) and heated to 115 °C for 7 h. The reaction mixture was cooled to room temperature and concentrated to remove most of pyridine. The residue was dissolved in DMF (2 mL) and purified by prep-HPLC to give **compound 103** as solids (0.02 g, 35%). LC/MS = 696 (M^++1). ^{1}H NMR (300MHz, CD_3OD): d 8.15 (d, J = 9.0 Hz, 1H), 7.57 (d, J = 9.3Hz, 1H), 7.40 (s, 1H), 5.49 (s, 1H), 4.69 (m, 1H), 4.51-4.41 (m, 2H), 4.16 (m, 1H), 4.08(s, 3H), 4.01 (m, 1H), 2.69 (m, 1H), 2.49 (m, 1H), 2.00(m, 1H), 1.91

(m, 1H), 1.69 (m, 2H), 1.50 (m, 1H), 1.43-1.36 (m, 3H),1.25-1.13 (m, 3H), 1.04-0.95 (m, 12H), 0.35-0.27 (m, 2H).

Example 104: Preparation of Compound 104

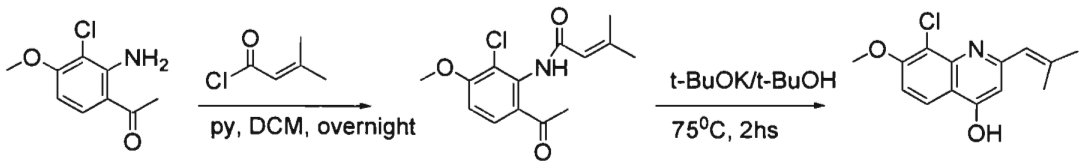


Step 1: The methyl ester quinoline (0.20 g, 0.75 mmol) was dissolved in THF (5 mL) and cooled to 0 °C as 1 M DIBAL in hexane (2.3 mL, 2.30 mmol) was added. After the mixture was stirred at room temperature for 1 h, H_2O (2 mL) was slowly added to the mixture. The pH of the mixture was adjusted to 2 by adding 1 N HCl. Solids formed were filtered and dried *in vacuo* overnight to afford the alcohol (180 mg, 93%). LC/MS = 240 (M^++1).



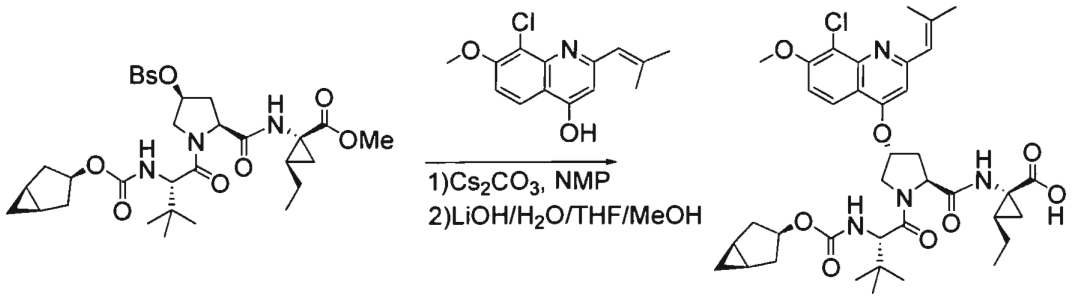
Step 2: Compound 104 (0.31 g, 56%) was synthesized using the procedure described before to prepare **compound 82**. LC/MS = 701 (M^++1). ^{1}H NMR (300MHz, CD_3OD) d 8.41 (d, J = 9.9 Hz, 1H), 7.74 (d, J = 9.3Hz, 1H), 7.54 (s, 1H), 5.75 (s, 1H), 5.16 (s, 2H), 4.73 (m, 1H), 4.61 (m, 1H), 4.49 (m, 1H), 4.33 (m, 1H), 4.19(s, 3H), 4.09 (m, 1H), 2.85 (m, 1H), 2.60 (m, 1H), 2.20 (m, 1H), 1.94(m, 1H), 1.91 (m, 1H), 1.69 (m, 2H), 1.50 (m, 1H), 1.43-1.36 (m, 3H),1.25-1.13 (m, 3H), 1.04-0.95 (m, 12H), 0.38-0.31 (m, 2H).

Example 105: Preparation of Compound 105



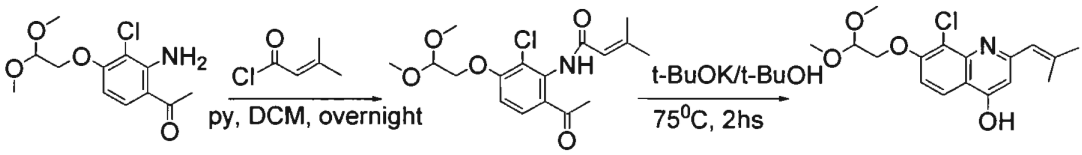
Step 1: A solution of the aniline (0.30 g, 1.5 mmol) and pyridine (0.24 g, 3.0 mmol) in dichloromethane (10 mL) was stirred at 0 °C while 3,3-dimethylacryloyl chloride (0.24 g, 2.0 mmol) was added over 15 min, and the reaction mixture was stirred at room temperature overnight. After the mixture was concentrated, the residue was dissolved in EtOAc (50 mL) and washed by sat. $NaHCO_3$, 1 N HCl, and brine. The organic fraction was dried (Na_2SO_4), concentrated, and purified by silica gel chromatography with EtOAc/Hexane to give the desired amide as light brown solids (0.35 g, 80.3%). LC/MS = 282 (M^++1).

Step 2: A solution of the amide (0.32 g, 1.1 mmol) in *t*-BuOH (10 mL) was stirred vigorously as *t*-BuOK (0.27 g, 2.4 mmol) was added. The reaction was heated at 75 °C for 3 h and cooled to room temperature. After the mixture was acidified with 4 N HCl (1 mL) and concentrated, the residue was dissolved in EtOAc (30), and washed with H_2O (10 mL) and brine (10 mL). The organic fraction was dried (Na_2SO_4), concentrated, and purified by silica gel chromatography with EtOAc/Hexane to give the desired quinoline as light brown solids (0.11 g, 37%). LC/MS = 264 (M^++1).



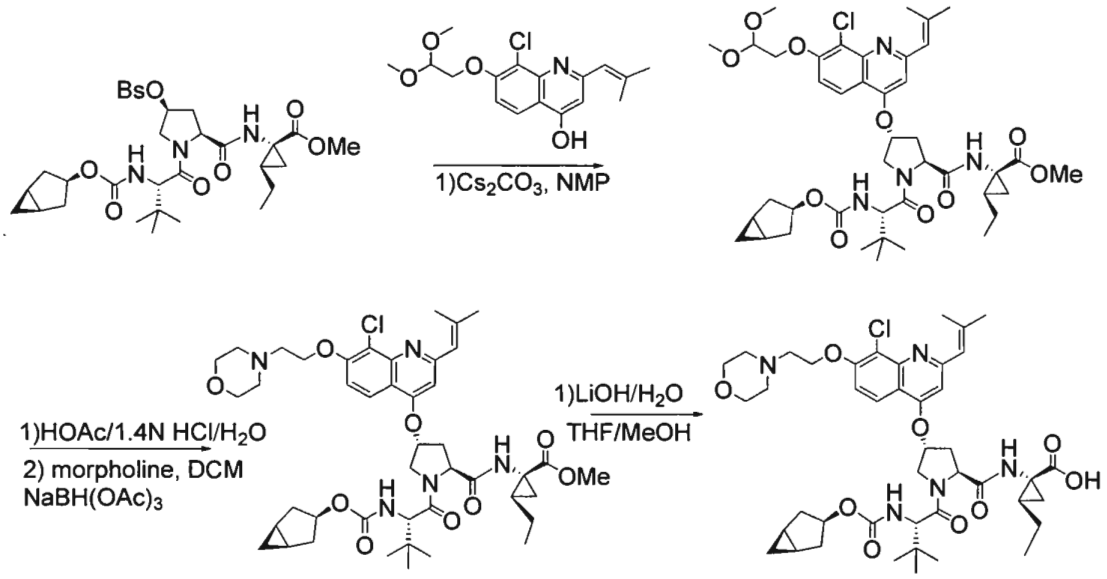
Step 3: Compound 105 (0.10g, 66%) was synthesized using the procedure described before to prepare **compound 82**. LC/MS = 725 (M^++1). ^{1}H NMR (400MHz, CD_3OD) d 8.35 (s, J = 9.6 Hz, 1H), 8.30 (s, 1H), 7.67 (d, J = 9.6 Hz, 1H), 7.33 (s, 1H), 6.79 (s, 1H), 5.73 (s, 1H), 4.76 (t, J = 8.8 Hz, 1H), 4.64 (d, J = 12.4 Hz, 1H), 4.30 (t, J = 10.8 Hz, 1H), 4.16 (s, 1H), 4.08-4.01 (m, 2H), 2.80 (m, 1H), 2.60 (m, 1H), 2.22(d, J = 12.8 Hz, 6H), 1.92 (m, 1H), 1.48 (m, 1H), 1.74-1.40 (m, 6H), 1.27-1.13 (m, 4H), 1.04-0.96 (m, 12H), 0.36-0.32 (m, 2H).

Example 106: Preparation of Compound 106



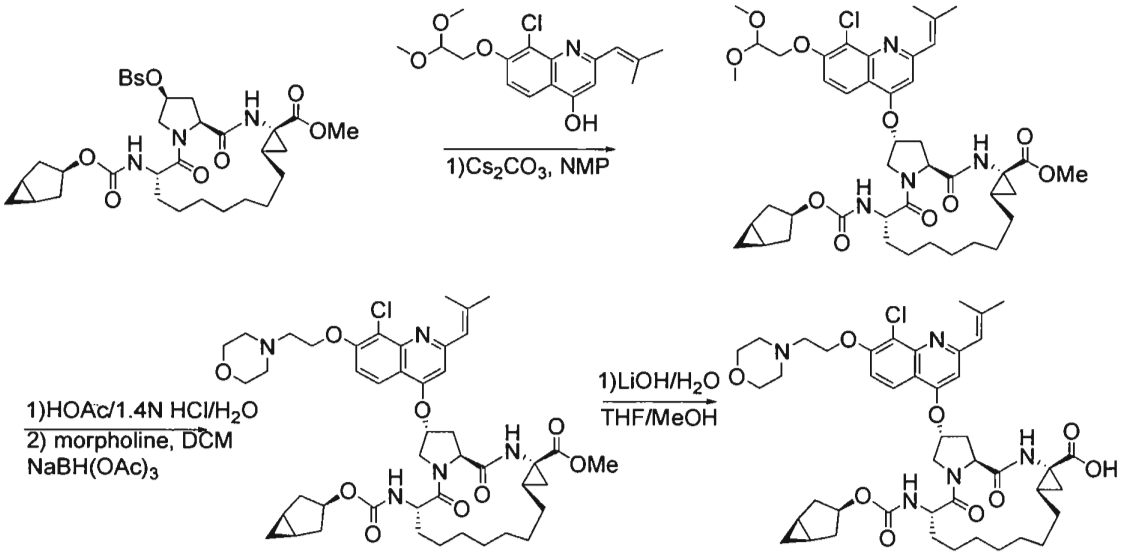
Step 1: A solution of the aniline (8.0 g, 29.3 mmol) and pyridine (4.6 g, 58.6 mmol)) in dichloromethane (100 mL) was stirred at 0 °C while 3,3-dimethylacryloyl chloride (4.2 g, 35.2 mmol) was added over 15 min. The reaction mixture was stirred at room temperature overnight. After the mixture was concentrated, the residue was dissolved in EtOAc (200 mL) and washed by sat. $NaHCO_3$, 1 N HCl, and brine. The organic fraction was dried (Na_2SO_4), concentrated, and purified by silica gel chromatography with EtOAc/Hexane to give the desired amide as light brown solids (6.0 g, 57.6%). LC/MS = 355 (M^++1).

Step 2: A solution of the amide (6.0 g, 16.9 mmol) in t-BuOH (120 mL) was stirred vigorously as *t*-BuOK (3.9 g, 35.4 mmol) was added. The mixture was heated at 75 °C for 3 h and cooled to room temperature. After the mixture was acidified with 4 N HCl (10 mL) and concentrated, the residue was dissolved in EtOAc (200 mL) , and washed with H_2O (50 mL) and brine (100 mL). The organic fraction was dried (Na_2SO_4), concentrated, and purified by silica gel chromatography with EtOAc/Hexane to give the desired quinoline as light brown solid (1.62 g, 28%). LC/MS = 338 (M^++1).



Step 3: Compound 106 (0.51g, 75%) was synthesized using the procedure described before to prepare **compound 98**. LC/MS = 824 (M^++1). ^{1}H NMR (300MHz, CD_3OD) d 8.30 (s, J = 9.3 Hz, 1H), 8.30 (s, 1H), 7.57 (d, J = 9.3Hz, 1H), 7.18 (s, 1H), 6.69 (s, 1H), 5.62 (s, 1H), 4.74-4.67 (m, 3H), 4.58-4.52 (m, 2H), 4.16 (m, 1H), 4.08-3.99(m, 6H), 3.79 (m, 2H), 3.57 (m, 4H), 2.80 (m, 1H), 2.60 (m, 1H), 2.29(s, 3H), 2.14 (s, 3H), 2.02 (m, 1H), 1.91 (m, 1H), 1.69 (m, 3H), 1.50 (m, 1H), 1.43-1.36 (m, 2H),1.24-1.13 (m, 3H), 1.04-0.96 (m, 12H), 0.36-0.32 (m, 2H).

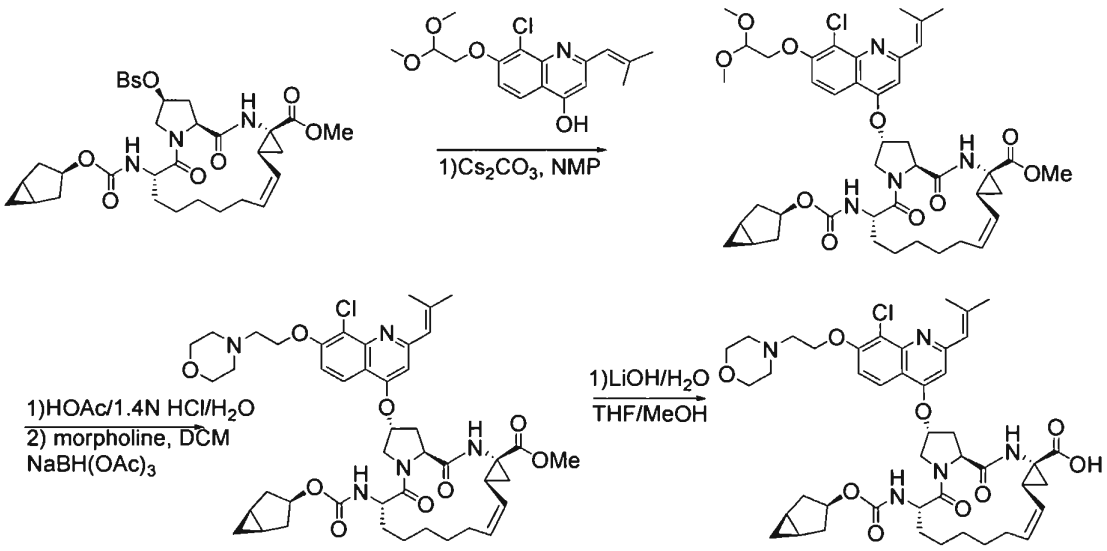
Example 107: Preparation of Compound 107



Compound 107 (0.14g, 70%) was synthesized using the procedure described before to prepare **compound 98**. LC/MS = 836 (M^++1). ^{1}H NMR (400 MHz, CD_3OD): δ 8.41 (d, J = 9.2 Hz, 1H), 7.68 (d, J = 9.2 Hz,1H), 7.34 (s, 1H), 6.78(s, 1H), 5.74 (bs, 1H), 4.81-4.72 (m, 5H), 4.48 (m, 1H), 4.24(m, 1H), 4.06-3.99(m, 4H), 4.08-3.98 (m, 5H), 3.82 (m, 2H), 3.57 (m, 4H), 2.74- 2.67(m, 2H), 2.24 (d, J = 21.2 Hz, 6H), 2.04-1.89 (m, 2H), 1.87 (m, 1H), 1.75 (m, 2H),

1.67-1.59 (m, 3H), 1.55 (m, 2H), 1.46-1.37(m, 4H), 1.29-1.14(m, 4H), 0.37 (m, 2H).

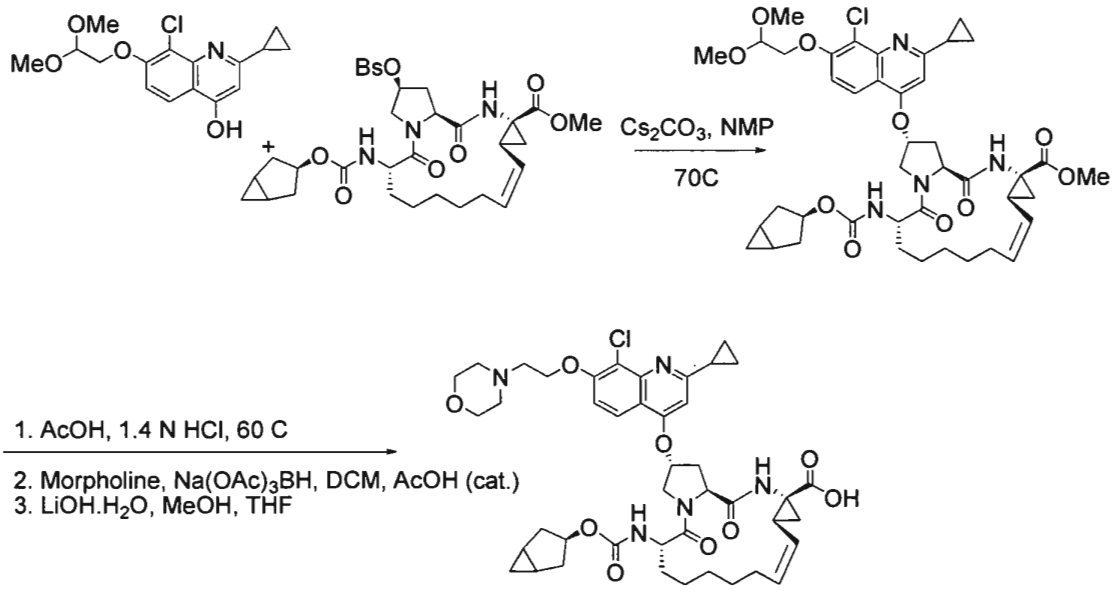
Example 108: Preparation of Compound 108



Compound 108 (0.17g, 60%) was synthesized using the procedure described before to prepare **compound 98**. LC/MS = 834 (M^++1). ^{1}H NMR (400 MHz, CD_3OD): δ 8.43 (d, J = 9.2 Hz, 1H), 7.66 (d, J = 9.6 Hz,1H), 7.35 (s, 1H), 6.78(s, 1H), 5.77 (bs, 1H),5.62 (m, 1H), 5.38 (m, 1H), 4.81 (m, 4H), 4.72 (t, J = 8.0

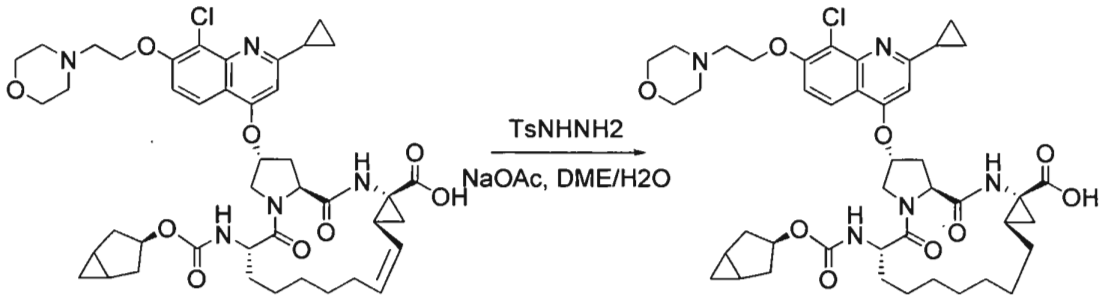
Hz, 1H), 4.39 (t, J = 6.8 Hz, 1H), 4.13 (m, 1H), 4.05-3.99(m, 4H), 3.82 (m, 2H), 3.56 (m, 3H), 2.74- 2.67(m, 2H), 2.22 (d, J = 16.0 Hz, 6H), 1.93-1.88 (m, 2H), 1.78-1.74 (m, 2H), 1.67-1.59 (m, 3H), 1.55 (m, 2H), 1.46-1.37(m, 4H), 1.29-1.14(m, 4H), 0.35 (m, 2H).

Example 109: Preparation of Compound 109



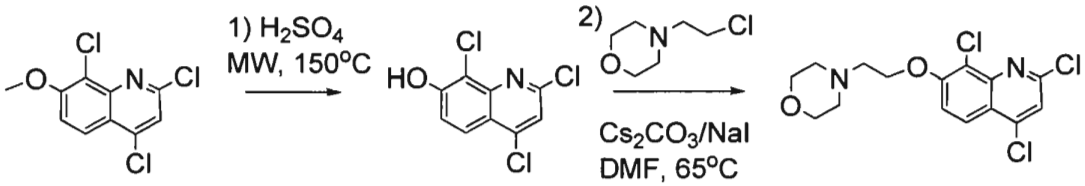
Compound 109 was synthesized using the procedure described before to prepare **compound 98**. LC/MS = 820.55 (M^++1). ^{1}H NMR (300 MHz, CD_3OD): d 8.00 (d, 1H), 7.23 (d, 1H), 6.46 (s, 1H), 5.37 (b, 1H), 5.29 (m, 1H), 5.04 (dd, 1H), 4.42-4.31 (m, 5H), 4.19(dd, 1H), 3.84 (m, 1H), 3.71-3.65 (m, 5H), 3.47 (m, 1H), 3.24 (m, 4H), 2.98 (m,3H), 2.37 (m, 2H), 2.27-2.15 (m, 2H), 1.96 (m, 1H), 1.67-1.44 (m,2H), 1.34-1.07 (m, 10H), 0.93-0.82 (m, 2H), 0.05-0.00 (m, 1H).

Example 110: Preparation of Compound 110



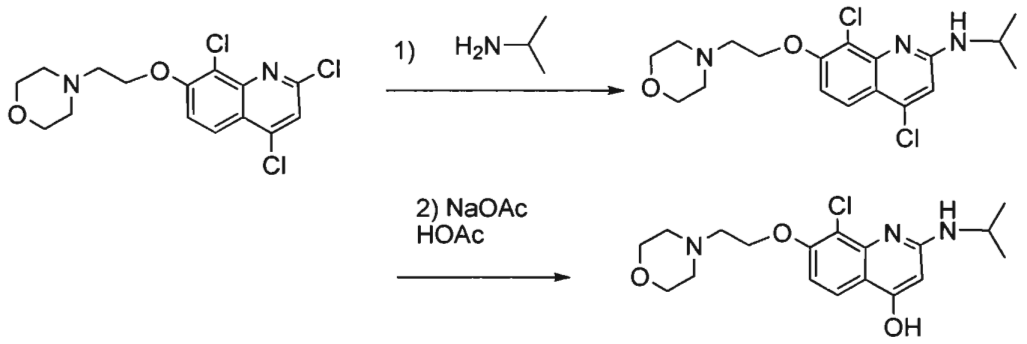
Compound 110 was synthesized using the procedure described before to prepare **compound 99**. LC/MS = 822.38(M^++1). ^{1}H NMR (300 MHz, CD_3OD): d 8.23 (d, 1H), 7.49 (d, 1H), 6.68 (s, 1H), 5.59 (s, 1H), 4.68-4.61 (m, 3H), 4.52 (dd, 1H), 4.45(dd, 1H), 4.17 (m, 1H), 3.95-3.80 (m, 4H), 3.71 (m, 2H), 3.48 (b, 3H), 3.22 (m,1H), 2.69-2.52 (m, 3H), 1.91-1.84 (m, 1H), 1.79-1.64 (m,3H), 1.59-1.08 (m, 20H), 0.31-0.24 (m, 1H).

Example 111: Preparation of Compound 111



Step 1: A mixture of 2,4,8-trichloro-7-methoxy-quinoline (2.48 mg, 9.45 mmol) and H_2SO_4 (20 mL) was sealed in a microwave tube and heated at 150°C for 1 hr in the microwave reactor. After cooling to room temperature, the mixture was slowly poured into ice-water mixture with vigorous stirring. The brown solid was filtered, washed with cold water, and dried to afford 1.54 g (66%) of the desired product. LC/MS = 350.24 (M^++3).

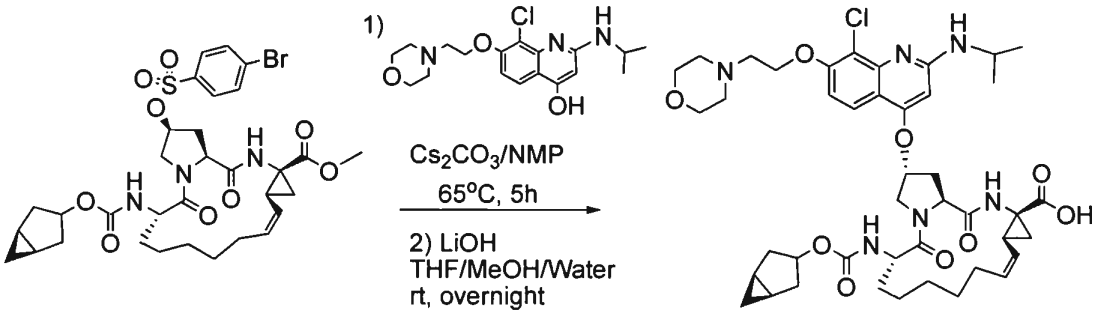
Step 2: To a solution of 2,4,8-trichloroquinolin-7-ol (1.74 g, 7.0 mmol) in DMF (70 mL) were added Cs_2CO_3 (10.26 g, 31.5 mmol) and NaI (210 mg, 1.4 mmol). The mixture was heated to 65 °C for 4 h. After cooling to room temperature, the mixture was diluted with EtOAc and aqueous 3% LiCl solution. After the two layers were separated, the organic fraction was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using EtOAc/hexane then MeOH/EtOAc as eluents to obtain 1.9 g (75%) of the desired product. LC/MS = 363.0 (M^++3).



Step 3: A mixture of 2,4,8-trichloro-7-(2-morpholin-4-yl-ethoxy)-quinoline (900 mg, 2.49 mmol) and isopropylamine (30mL) was sealed in a sealed tube and heated to 50 °C for 10 h. After the mixture was concentrated, the residue was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford 930 mg (97%) of the desired product. LC/MS = 384.0 (M^++1).

Step 4: A solution of the above 4,8-Dichloroquinoline (930 mg, 2.42 mmol) and sodium acetate (3.0 g, 36.3 mmol) in acetic acid (12 mL) was heated to 130°C for 18 h. After the

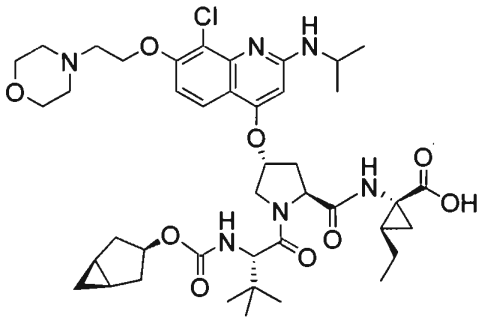
mixture was concentrated *in vacuo*, the residue was purified by prep-HPLC to give 882 mg (76%) of the desired hydroxyquinoline product. LC/MS = 366.0 (M^++1).

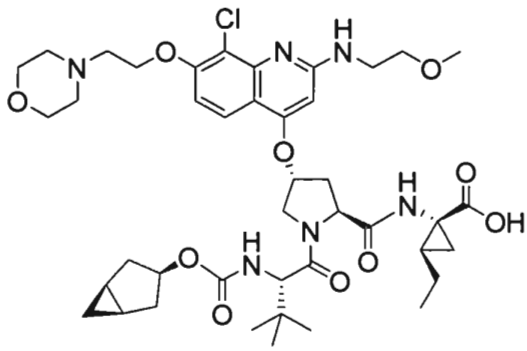


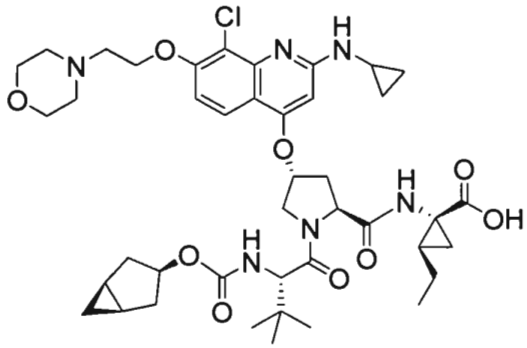
Step 5: Compound 111 (400 mg) was synthesized using the procedure described before to prepare **compound 98**. LC/MS = 837.4 (M^++1). ^{1}H NMR (400 MHz, CD_3OD): δ 8.63 (s,1H), 8.38 (d, 1H), 8.24 (s, 1H), 7.80 (d, 1H), 6.94 (s, 1H), 6.16 (b, 1H), 5.29 (m, 2H), 5.03 (t, 1H), 4.37 (m, 4H), 4.23 (m, 1H), 3.90 (m, 2H), 3.70 (m, 4H), 3.45 (t, 2H), 3.21 (b, 3H), 2.98 (s, 1H), 2.40 (m, 1H), 2.20 (m, 2H), 1.98 (q, 1H), 1.63-1.28 (m, 6H), 1.20-1.07 (m, 10H), 1.04- 0.84 (m, 2H), 0.39 (m, 2H).

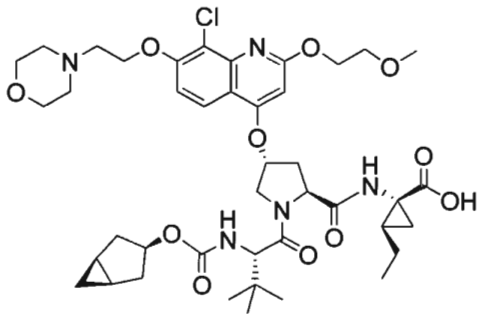
Example 112:

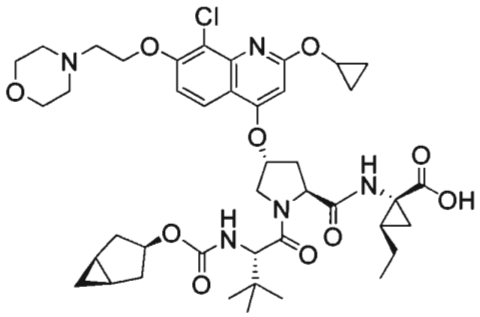
Using procedures similar to those described herein, the following compounds of formula (I) can also be prepared.



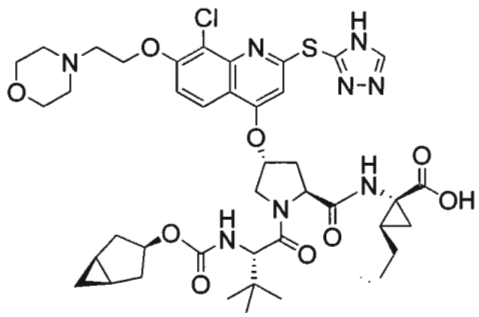


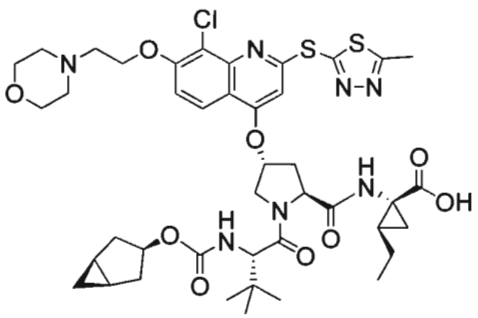


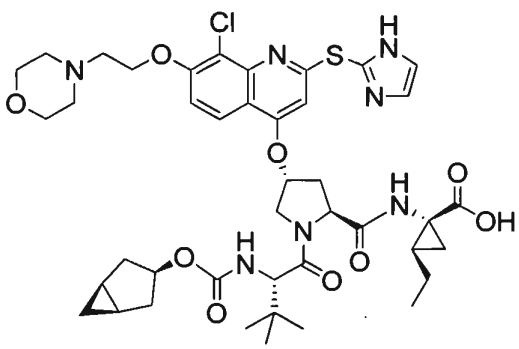


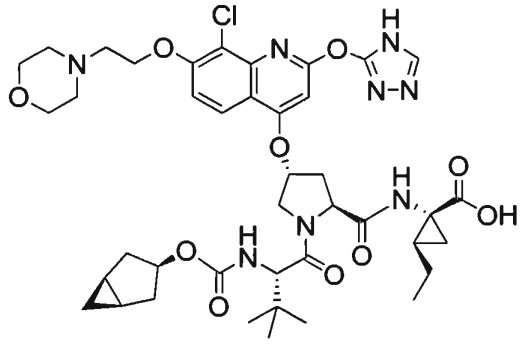


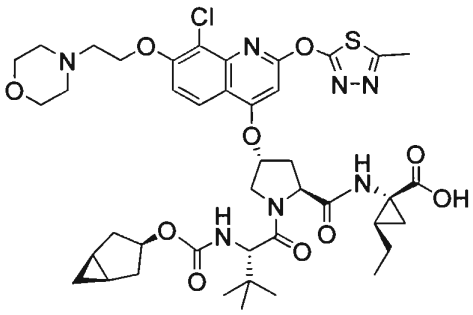
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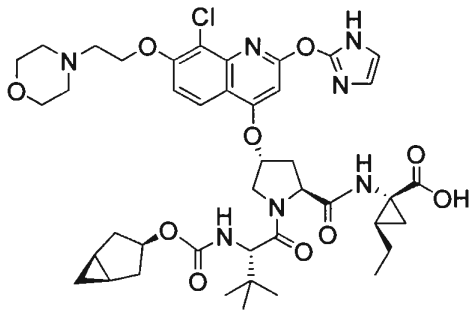






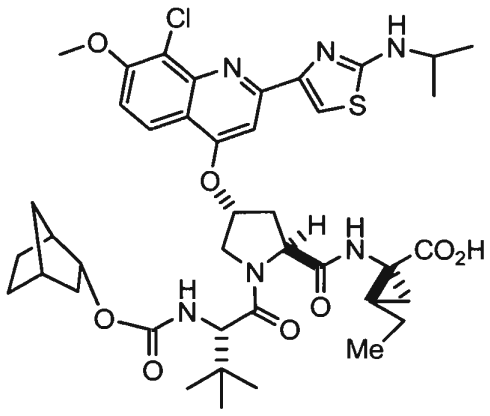


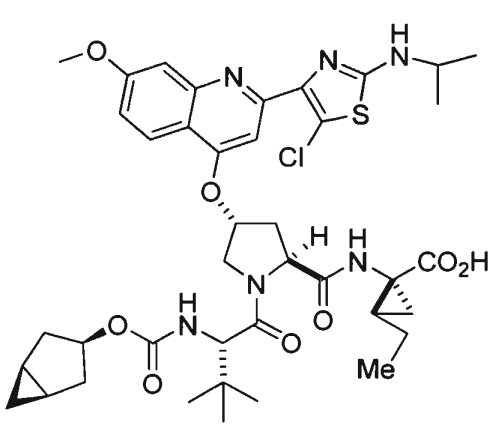


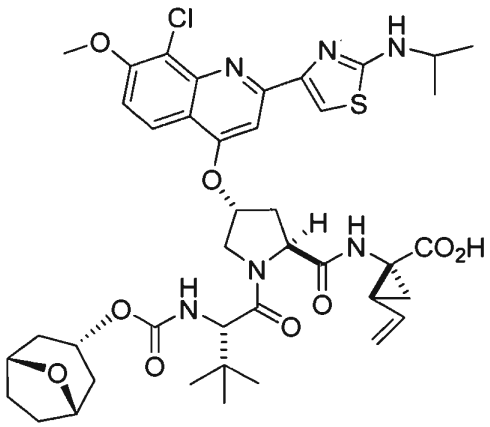


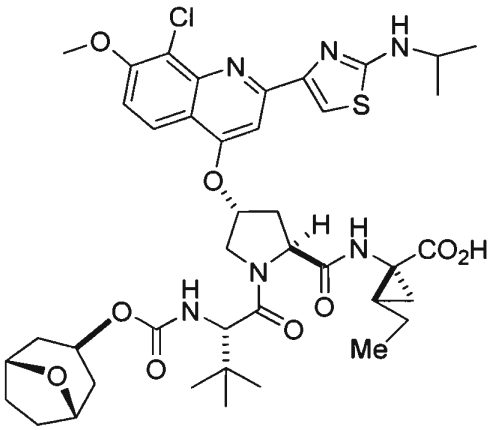
Example 113:

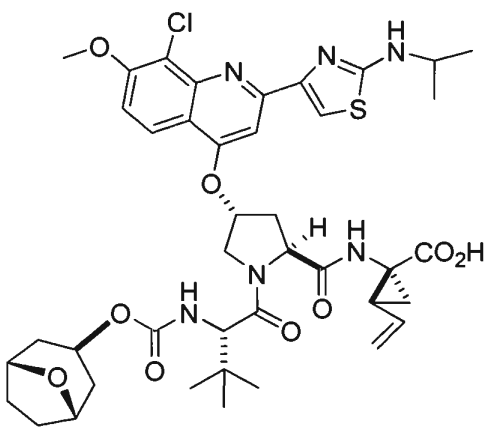
Using procedures similar to those described herein, the following compounds of formula (I) can also be prepared.

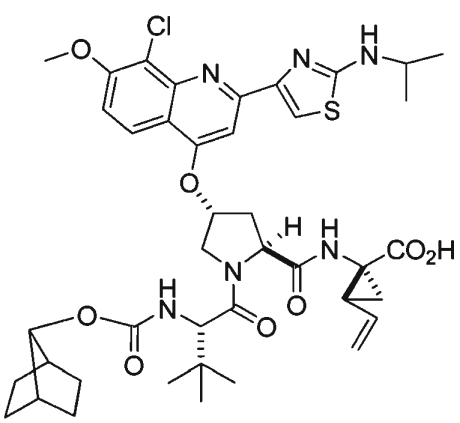


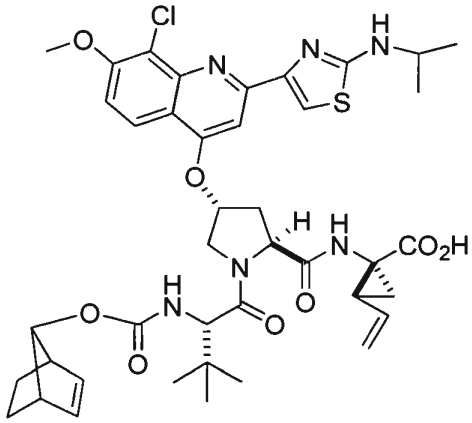


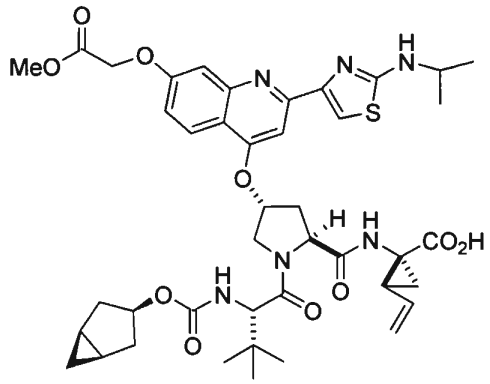






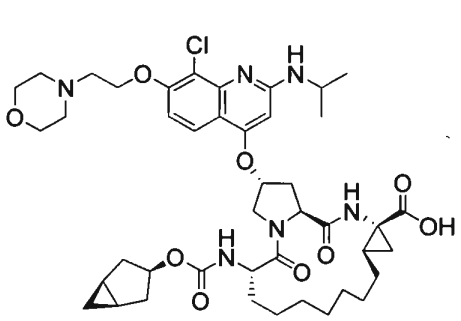


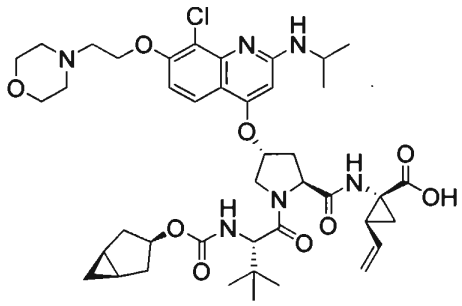


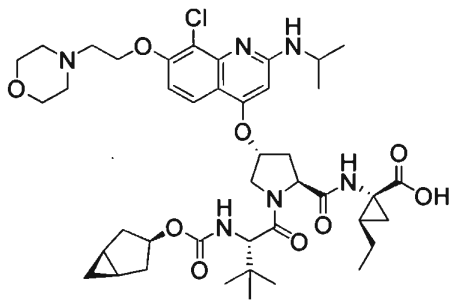


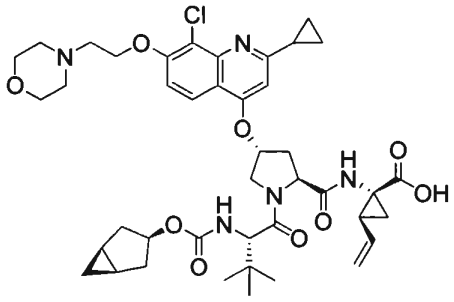
Example 114:

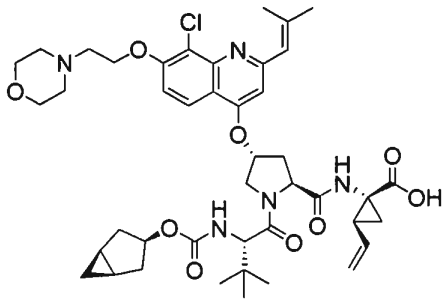
Using procedures similar to those described herein, the following compounds of formula (I) can also be prepared.

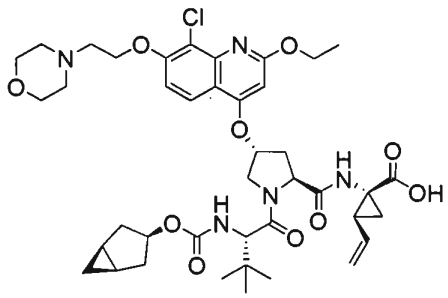












Example 115:

The following illustrate representative pharmaceutical dosage forms, containing a compound of formula I ("Compound X'), for therapeutic or prophylactic use in humans.

(i) Tablet 1	mg/tablet
Compound X=	100.0
Lactose	77.5
Povidone	15.0
Croscarmellose sodium	12.0
Microcrystalline cellulose	92.5
Magnesium stearate	3.0
	300.0

(ii) Tablet 2	mg/tablet
Compound X=	20.0
Microcrystalline cellulose	410.0
Starch	50.0
Sodium starch glycolate	15.0
Magnesium stearate	5.0
	500.0

(iii) Capsule	mg/capsule
Compound X=	10.0
Colloidal silicon dioxide	1.5
Lactose	465.5
Pregelatinized starch	120.0
Magnesium stearate	3.0
	600.0

(iv) Injection 1 (1 mg/ml)	mg/ml
Compound X= (free acid form)	1.0
Dibasic sodium phosphate	12.0
Monobasic sodium phosphate0.7	
Sodium chloride	4.5
1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(v) Injection 2 (10 mg/ml)	mg/ml
Compound X= (free acid form)	10.0
Monobasic sodium phosphate0.3	
Dibasic sodium phosphate	1.1
Polyethylene glycol 400	200.0
01 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(vi) Aerosol	mg/can
Compound X=	20.0
Oleic acid	10.0
Trichloromonofluoromethane	5,000.0
Dichlorodifluoromethane	10,000.0
Dichlorotetrafluoroethane	5,000.0

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art.

BIOLOGICAL ASSAYS

NS3 Enzymatic Potency: Purified NS3 protease is complexed with NS4A peptide and then incubated with serial dilutions of the compounds (DMSO used as solvent). Reactions are started by addition of dual-labeled peptide substrate and the resulting kinetic increase in fluorescence is measured. Non-linear regression of velocity data is performed to calculate IC_{50}s. Activity is initially tested against genotype 1b protease. Depending on the potency obtained against genotype 1b, additional genotypes (1a, 2a, 3) and or protease inhibitor resistant enzymes (D168Y, D168V, or A156T mutants) may be tested. BILN-2061 is used as a control during all assays. The compounds of Examples 1-81 were evaluated in this assay and were found to have IC_{50} values of less than about 1 μM.

Replicon Potency and Cytotoxicity: Huh-luc cells (stably replicating Bartenschlager's I389luc-ubi-neo/NS3-3'/ET genotype 1b replicon) is treated with serial dilutions of compound (DMSO is used as solvent) for 72 hours. Replicon copy number is measured by bioluminescence and non-linear regression is performed to calculate EC_{50}s. Parallel plates treated with the same drug dilutions are assayed for cytotoxicity using the Promega CellTiter-Glo cell viability assay. Depending on the potency achieved against the 1b replicon, compounds may be tested against a genotype 1a replicon and/or inhibitor resistant replicons encoding D168Y or A156T mutations. BILN-2061 is used as a control during all assays. The compounds of Examples 1-81 were evaluated in this assay and were found to have EC_{50} values of less than about 5 μM.

Effect of serum proteins on replicon potency

Replicon assays are conducted in normal cell culture medium (DMEM + 10%FBS) supplemented with physiologic concentrations of human serum albumin (40 mg/mL) or a-acid glycoprotein (1 mg/mL). EC_{50}s in the presence of human serum proteins are compared to the EC_{50} in normal medium to determine the fold shift in potency.

Enyzmatic Selectivity: The inhibition of mammalian proteases including Porcine Pancreatic Elastase, Human Leukocyte Elastase, Protease 3, and Cathepsin D are measured at K_m for the respective substrates for each enzyme. IC_{50} for each enzyme is compared to the IC_{50} obtained with NS3 1b protease to calculate selectivity.

MT-4 Cell Cytotoxicity: MT4 cells are treated with serial dilutions of compounds for a five day period. Cell viability is measured at the end of the treatment period using the Promega CellTiter-Glo assay and non-linear regression is performed to calculate CC_{50}.

Compound Concentration Associated with Cells at EC_{50}: Huh-luc cultures are incubated with compound at concentrations equal to EC_{50}. At multiple time points (0 – 72 hours), cells are washed 2X with cold medium and extracted with 85% acetonitrile; a sample of the media at each time-point is also extracted. Cell and media extracts are analyzed by LC/MS/MS to determine the molar concentration of compounds in each fraction

Solubility and Stability: Solubility is determined by taking an aliquot of 10 mM DMSO stock solution and preparing the compound at a final concentration of 100 μM in the test

media solutions (PBS, pH 7.4 and 0.1 N HCl, pH 1.5) with a total DMSO concentration of 1%. The test media solutions are incubated at room temperature with shaking for 1 hr. The solutions are then centrifuged and the recovered supernatants are assayed on the HPLC/UV. Solubility will be calculated by comparing the amount of compound detected in the defined test solution compared to the amount detected in DMSO at the same concentration. The stability of compounds after a 1 hour incubation in the test media at 37°C is also determined.

Stability in Cryopreserved Human, Dog, and Rat Hepatocytes: Each compound is incubated for up to 1 hour in hepatocyte suspensions (100 µl, 80,000 cells per well) at 37°C. Cryopreserved hepatocytes are reconstituted in the serum-free incubation medium. The suspension is transferred into 96-well plates (50 µL/well). The compounds are diluted to 2 µM in incubation medium and then are added to hepatocyte suspensions to start the incubation. Samples are taken at 0, 10, 30 and 60 minutes after the start of incubation and reaction will be quenched with a mixture consisting of 0.3% formic acid in 90% acetonitrile/10% water. The concentration of the compound in each sample is analyzed using LC/MS/MS. The disappearance half-life of the compound in hepatocyte suspension is determined by fitting the concentration-time data with a monophasic exponential equation. The data is also scaled up to represent intrinsic hepatic clearance and/or total hepatic clearance.

Stability in Hepatic S9 Fraction from Human, Dog, and Rat: Each compound is incubated for up to 1 hour in S9 suspension (500 µl, 3 mg protein/mL) at 37°C (n = 3). The compounds are added to the S9 suspension to start the incubation. Samples are taken at 0, 10, 30, and 60 minutes after the start of incubation. The concentration of the compound in each sample is analyzed using LC/MS/MS. The disappearance half-life of the compound in S9 suspension is determined by fitting the concentration-time data with a monophasic exponential equation.

Caco-2 Permeability: Both forward (A-to-B) and reverse (B-to-A) permeability is measured. Caco-2 monolayers are grown to confluence on collagen-coated, microporous, polycarbonate membranes in 12-well Costar Transwell® plates. The compounds are

dosed on the apical side for forward permeability (A-to-B), and are dosed on the basolateral side for reverse permeability (B-to-A). The cells are incubated at 37°C with 5% CO_2 in a humidified incubator. At the beginning of incubation, at 1 hr and 2 hr after incubation, a 200-μL aliquot is taken from the receiver chamber and replaced with fresh assay buffer. The concentration of the compound in each sample is determined with LC/MS/MS. The apparent permeability, Papp, is calculated.

Plasma Protein Binding:

Plasma protein binding is measured by equilibrium dialysis. Each compound is spiked into blank plasma at a final concentration of 2 μM. The spiked plasma and phosphate buffer is placed into opposite sides of the assembled dialysis cells, which is then rotated slowly in a 37°C water bath. At the end of the incubation, the concentration of the compound in plasma and phosphate buffer is determined. The percent unbound is calculated using the following equation:

$$\% \text{ Unbound} = 100 \bullet \left(\frac{C_f}{C_b + C_f} \right)$$

Where C_f and C_b are free and bound concentrations determined as the post-dialysis buffer and plasma concentrations, respectively

CYP450 Profiling:

Each compound is incubated with each of 5 recombinant human CYP450 enzymes, including CYP1A2, CYP2C9, CYP3A4, CYP2D6 and CYP2C19 in the presence and absence of NADPH. Serial samples will be taken from the incubation mixture at the beginning of the incubation and at 5, 15, 30, 45 and 60 min after the start of the incubation. The concentration of the compound in the incubation mixture is determined by LC/MS/MS. The percentage of the compound remaining after incubation at each time point is calculated by comparing with the sampling at the start of incubation.

Stability in Rat, Dog, Monkey and Human Plasma:

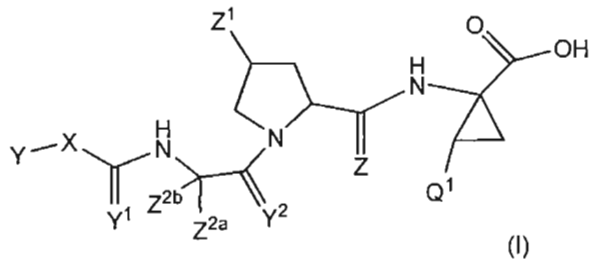
Compounds are incubated for up to 2 hour in plasma (rat, dog, monkey, or human) at 37°C. Compounds are added to the plasma at final concentrations of 1 and 10 ug/mL. Aliquots are taken at 0, 5, 15, 30, 60, and 120 min after adding the compound.

Concentration of compounds and major metabolites at each timepoint are measured by LC/MS/MS.

All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

What is claimed:

1. A compound of formula I:



(I)

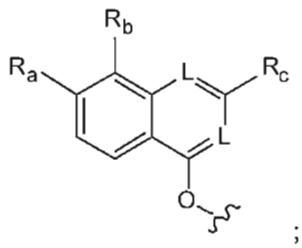
or a pharmaceutically acceptable salt, thereof, wherein:

Y^1 is O,

Y^2 is O,

Z is O,

Z^1 is



;

R_a is R^1, H, trifluoromethoxy, NR_sR_t, $C(=O)NR_sR_t$, $S(=O)_2NR_sR_t$ or (C1-10)alkyl, wherein one or more carbon atoms of said (C1-10)alkyl is optionally replaced by O, S, S(=O), $S(=O)_2$ or NR_g and which (C1-10)alkyl is optionally substituted with one or more hydroxy, halo, cyano, NR_nR_p, $C(=O)NR_nR_p$, (C1-10)alkoxy, carboxy, (C1-10)alkoxycarbonyl, aryl, heteroaryl, or heterocyclyl and which heterocyclyl is optionally substituted with one or more A^3; or R_a and R_b taken together with the atoms to which they are attached form a 5 or 6 membered heterocyclic ring containing one or more O, S, or NR_g;

R_b is R^1, H, F, Cl, Br, I, CF_3, (C1-10)alkyl, or XR^3;

R_c is R^1, H, cyano, F, Cl, Br, I, $-C(=O)NR_dR_e$, $C(=O)NR_sR_t$, NR_sR_t, $S(=O)_2NR_sR_t$, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkoxy, cycloalkyl, OR_r, SR_r, $S(O)R_r$, $S(O)_2R_r$,

aryl, or heteroaryl, which (C1-10)alkyl, (C1-10)alkoxy, cycloalkyl, aryl or heteroaryl is optionally substituted with one or more groups independently selected from halo, hydroxy, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p; SR_r, $S(O)R_r$, or $S(O)_2R_r$;

R_d and R_e are each independently H or (C1-10)alkyl;

each R_g is H, NR_sR_t, $C(=O)NR_sR_t$, $S(=O)_2NR_sR_t$, A^2, hydroxy, carboxy, cyano, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p, SR_r, $S(O)R_r$, or $S(O)_2R_r$;

each L is independently CH or N;

Z^{2a} is H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, haloalkyl, (C1-10)alkyl, $-S(=O)_2$-(C1-10)alkyl, wherein any carbon atom of Z^{2a} may optionally be replaced with a heteroatom selected from O, S or NR_g ;

Z^{2b} is H;

Q^1 is (C1-10)alkyl, (C2-10)alkenyl, or (C2-10)alkynyl which Q^1 is optionally substituted with R^1 or R_c;

X is independently a bond or O;

Y is a polycarbocycle;

each R^1 is independently $-P(Y^3)(OA^2)(OA^2)$, $-P(Y^3)(OA^2)(N(A^2)_2)$, $-P(Y^3)(A^2)(OA^2)$, $-P(Y^3)(A^2)(N(A^2)_2)$, or $P(Y^3)(N(A^2)_2)(N(A^2)_2)$;

each A^2 is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)haloalkyl, (C3-10)cycloalkyl, aryl, or heteroaryl;

each Y^3 is independently O, S, or NR^3;

each R_n and R_p is independently H, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, which (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, is optionally substituted with one or more R^1, halo, hydroxy, carboxy, cyano, or (C1-10)alkoxy; or R_n and R_p together with the nitrogen to which they are attached form a pyrrolidine, piperidine, piperazine, morpholino, or thiomorpholino ring; which ring is optionally substituted with one or more (C1-10)alkyl or (C1-10)alkoxy, and which (C1-10)alkyl or (C1-10)alkoxy is optionally substituted with one or more halo;

each R_r is independently H, (C1-10)alkyl, cycloalkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, aryl, heteroaryl, or (C1-10)alkoxycarbonyl;

R_s and R_t are independently H, (C1-10)alkyl, cycloalkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, $S(=O)_2A^2$, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl,

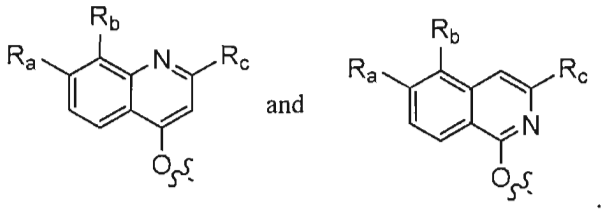
which (C1-10)alkyl, cycloalkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, or (C1-10)alkoxycarbonyl, is optionally substituted with one or more R^1, halo hydroxy, carboxy, cyano, or (C1-10)alkoxy; or R_s and R_t together with the nitrogen to which they are attached form a pyrrolidine, piperidine, piperazine, morpholino, or thiomorpholino ring wherein one or more carbon atoms of said pyrrolidine, piperidine, piperazine, morpholino or thiomorpholino ring is optionally replaced by S(=O), $S(=O)_2$, or C(=O);

each A^3 is independently selected from halo, hydroxy, carboxy, cyano, (C1-10)alkyl, (C2-10)alkenyl, (C2-10)alkynyl, (C1-10)alkanoyl, (C1-10)alkoxy, (C1-10)alkanoyloxy, (C1-10)alkoxycarbonyl, NR_nR_p, SR_r, $S(O)R_r$, or $S(O)_2R_r$; and

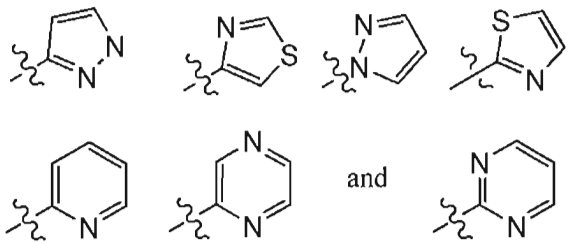
R^3 is H or (C1-10)alkyl.

2. The compound of claim 1, or pharmaceutiacally acceptable salt thereof, wherein X is O.

3. The compound of claim 2, or pharmaceutiacally acceptable salt thereof, wherein Z^1 is selected from the following structures:

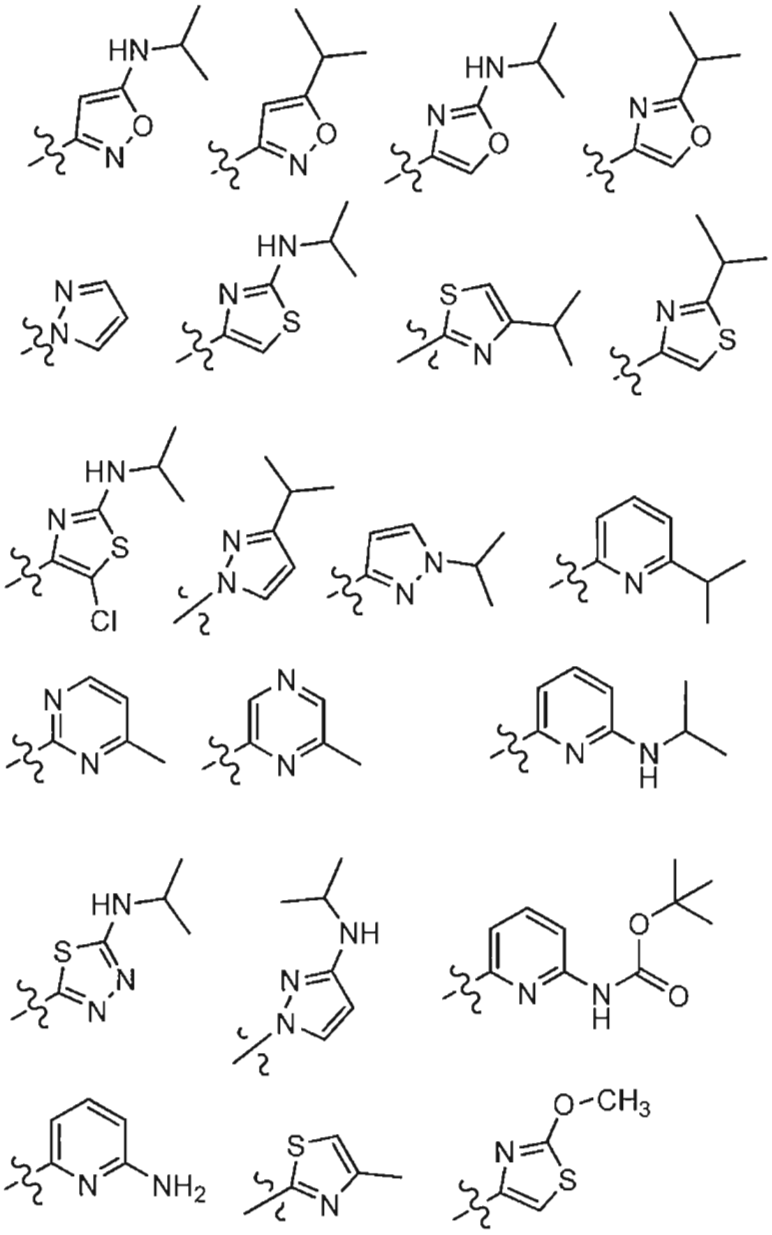


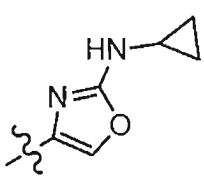
4. The compound of claim 2, or pharmaceutiacally acceptable salt thereof, wherein R_c is a heteroaryl ring selected from:

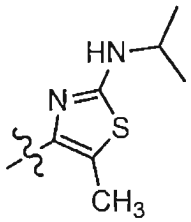


which heteroaryl ring is optionally substituted with one or more (C1-10)alkyl, halo, or NR_nR_p; wherein each R_n and R_p is independently H or (C1-10)alkyl.

5. The compound of claim 2,or pharmaceutiacally acceptable salt thereof, wherein each R_c is selected from:





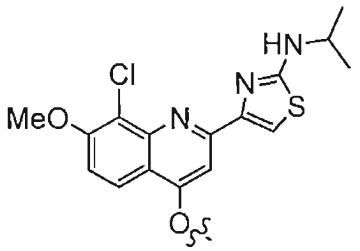
and


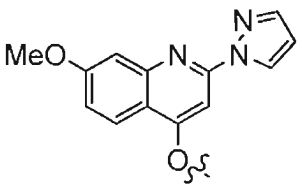
6. The compound of claim 3,or pharmaceutiacally acceptable salt thereof, wherein R_b is H or Cl.

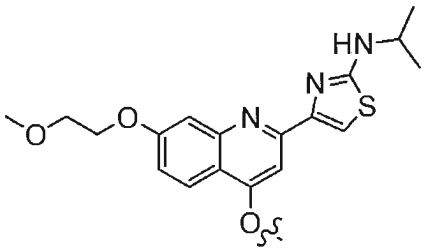
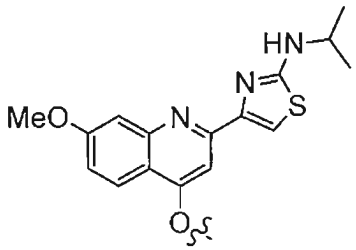
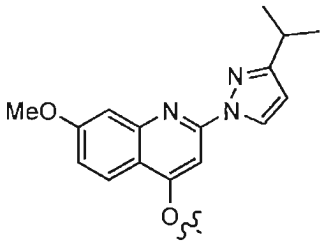
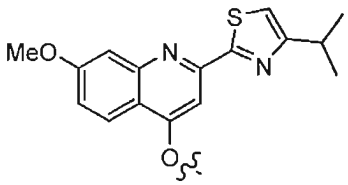
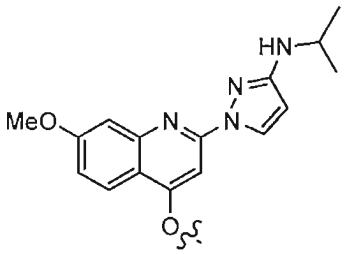
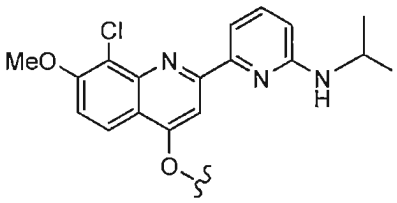
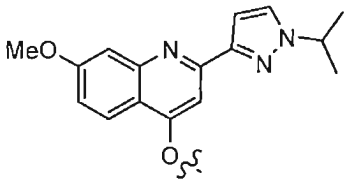
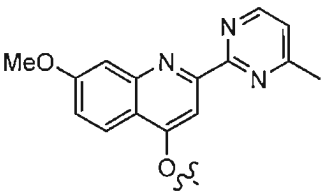
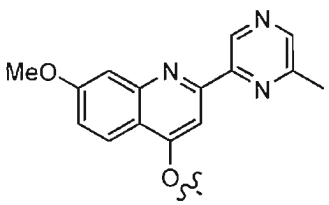
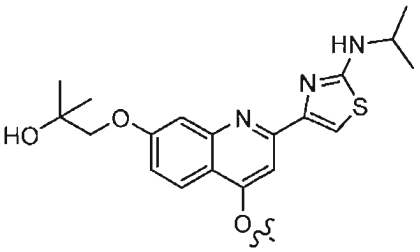
7. The compound of claim 3,or pharmaceutiacally acceptable salt thereof wherein R_a is H, methoxy, N-(2-cyanoethyl)amino, N-(3,3,3-trifluoroethyl)amino, 2-methoxyethoxy, 2-hydroxyethoxy, 2-hydroxy-2-methylpropoxy, 2-amino-2-methylpropoxy, N,N-dimethylaminocarbonylmethoxy, morpholinocarbonylmethoxy, 2-[N-(2,2,2-trifluoroethyl)amino]ethoxy, 2-morpholinoethoxy, cyanomethoxy, 2-piperazin-1-ylethoxy, 2-(N,N-dimentylamino)ethoxy, 2-(3,3-dimethylmorpholino)ethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, or carboxymethoxy.

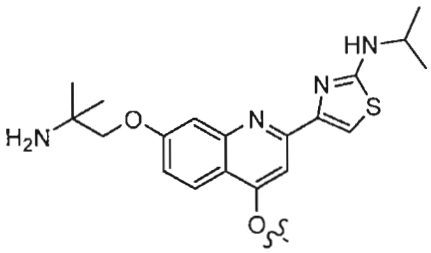
8. The compound of claim 3,or pharmaceutiacally acceptable salt thereof wherein R_a is H, methoxy, N-(2-cyanoethyl)amino, N-(3,3,3-trifluoroethyl)amino, 2-methoxyethoxy, 2-hydroxyethoxy, 2-hydroxy-2-methylpropoxy, 2-amino-2-methylpropoxy, N,N-dimethylaminocarbonylmethoxy, morpholinocarbonylmethoxy, 2-[N-(2,2,2-trifluoroethyl)amino]ethoxy, or 2-morpholinoethoxy.

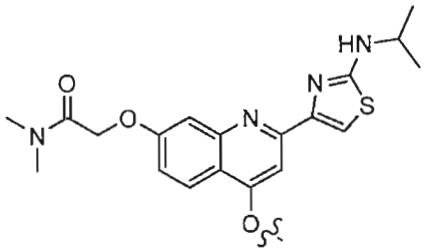
9. The compound of claim 2,or pharmaceutiacally acceptable salt thereof, wherein Z^1 is selected from the following structures:

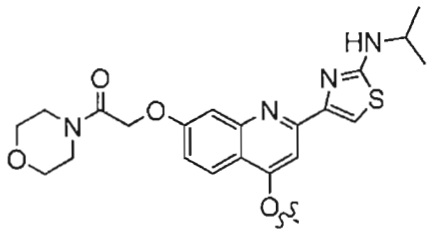


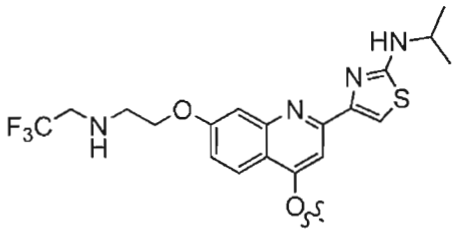


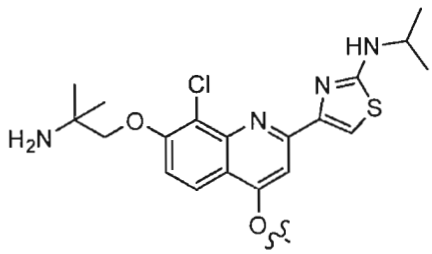











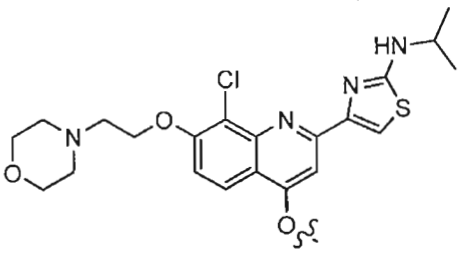


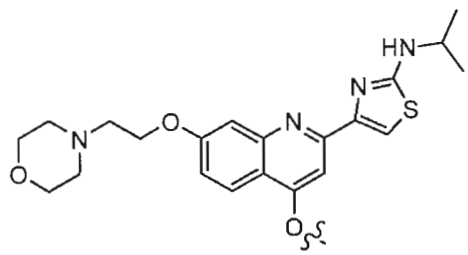


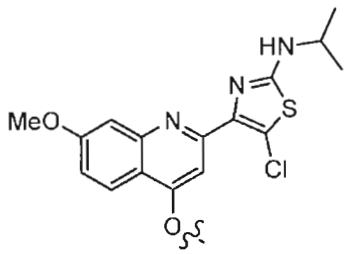


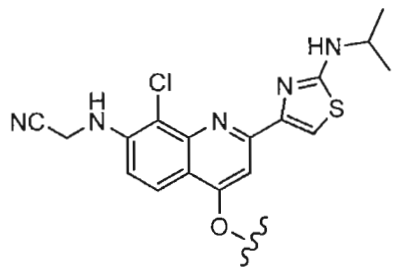


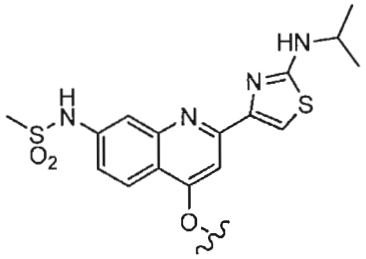


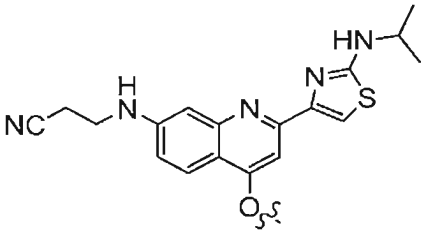


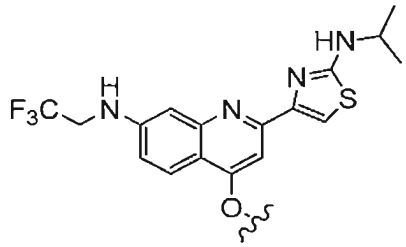


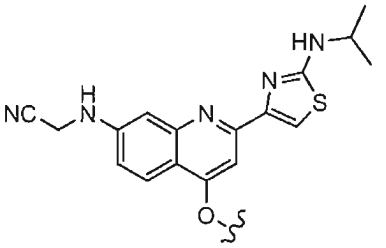


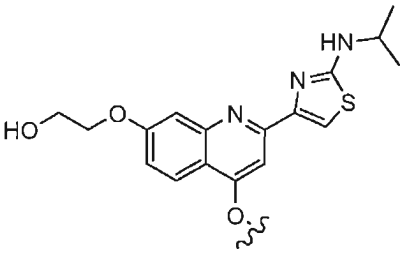


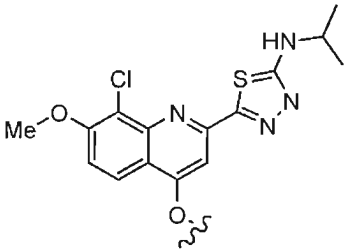


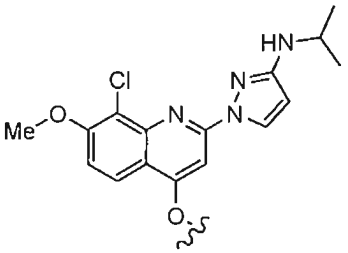


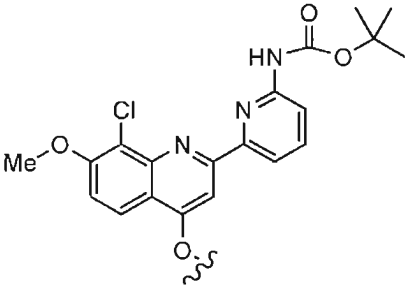


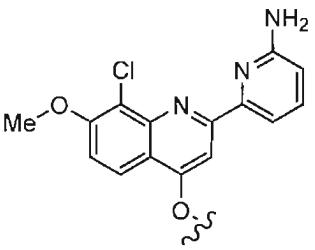


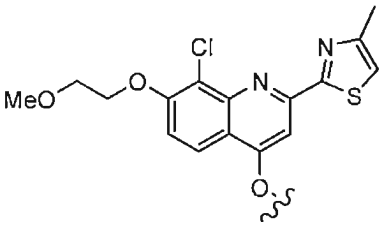


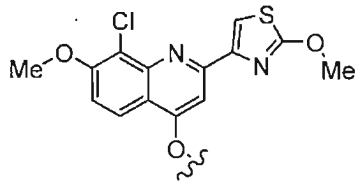


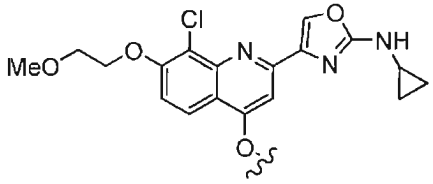


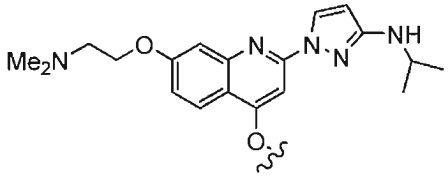


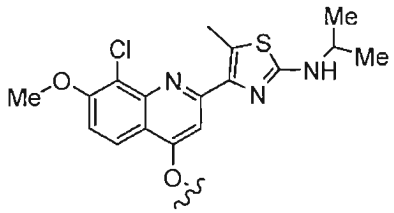


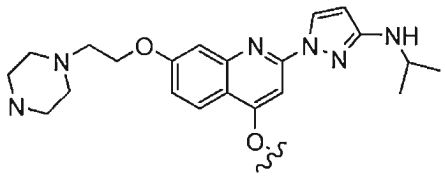


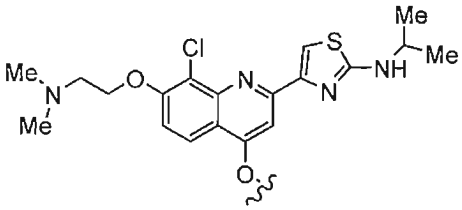


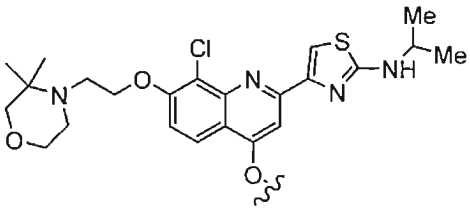


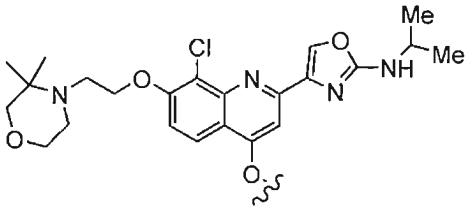


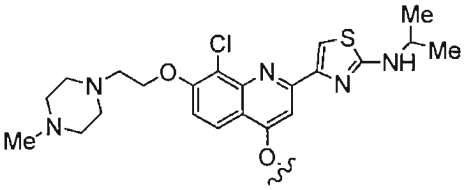


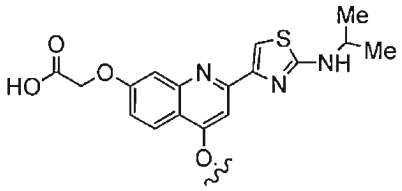


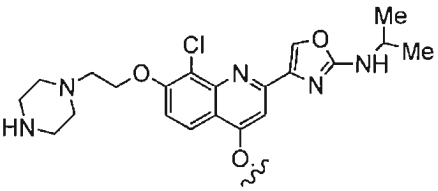


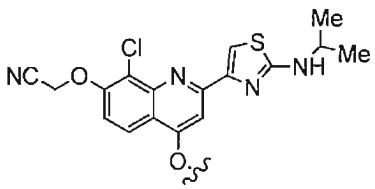


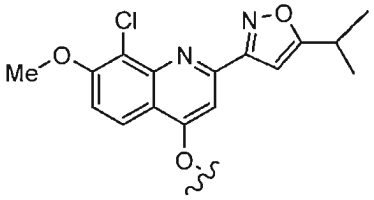


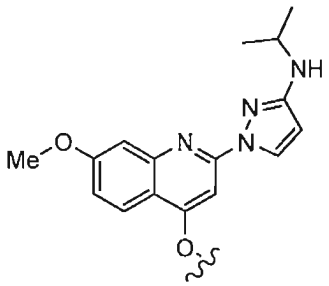


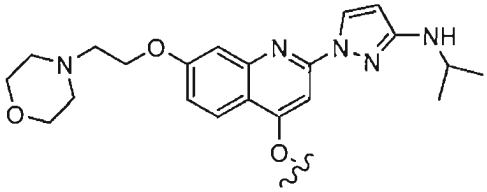


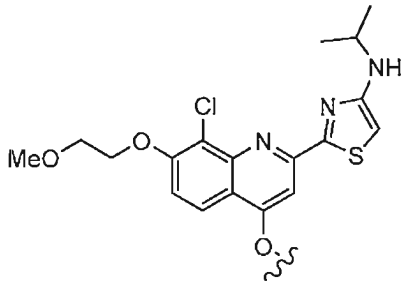


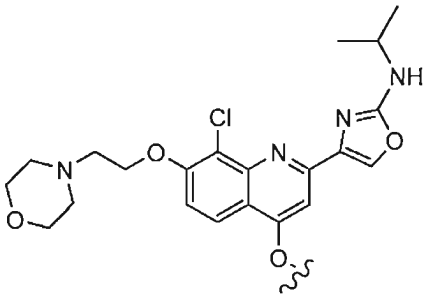


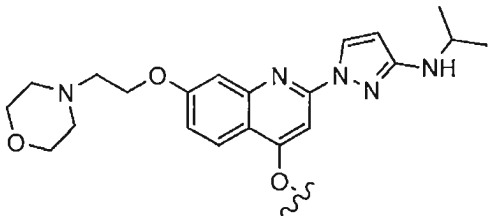


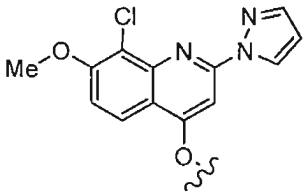


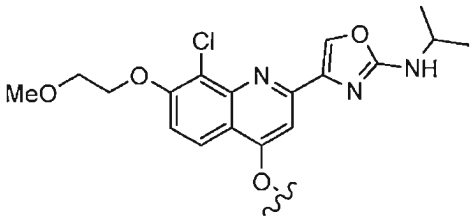


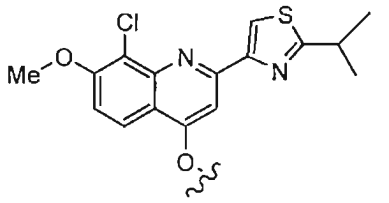


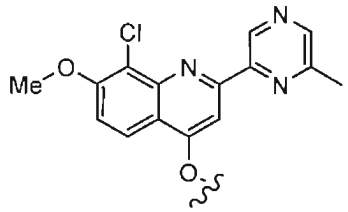


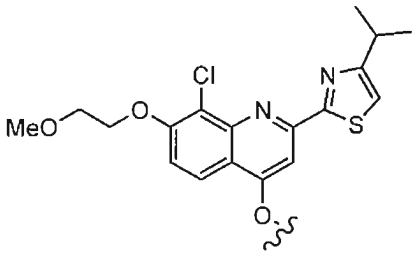


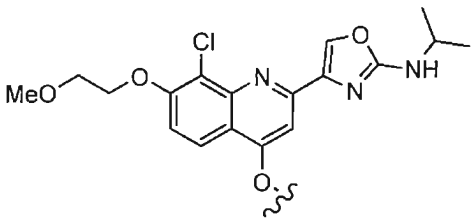


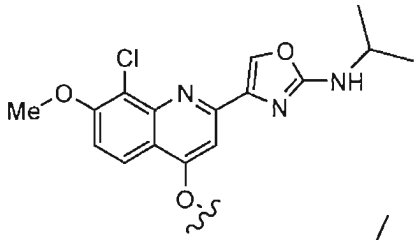


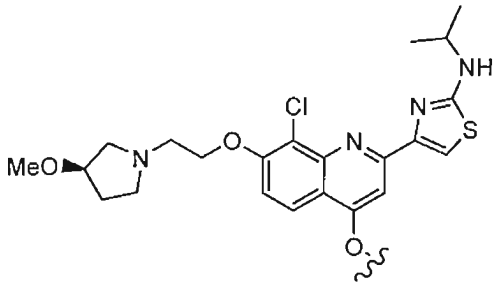


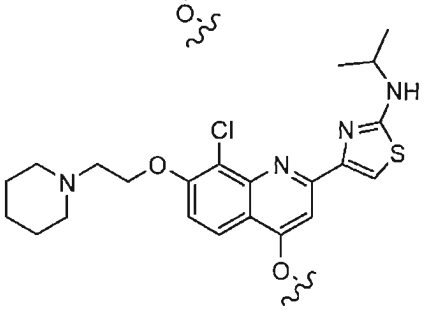


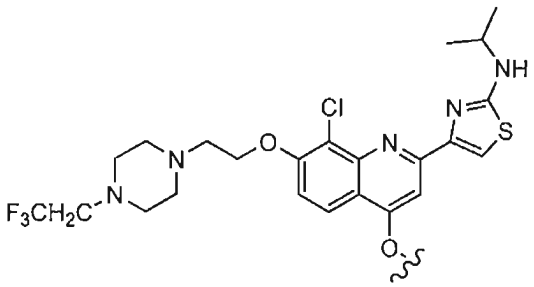


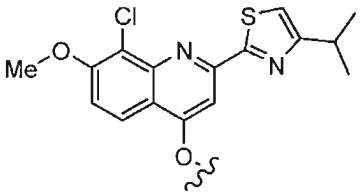




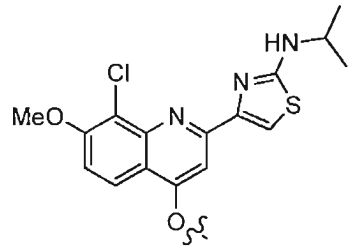
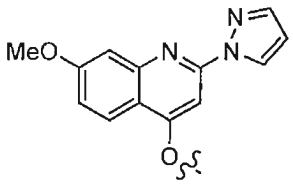
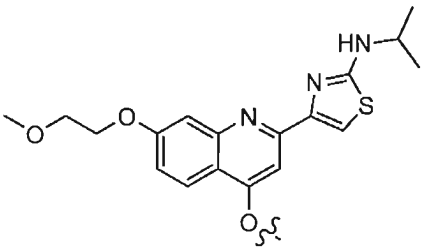
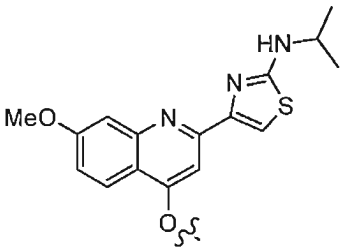
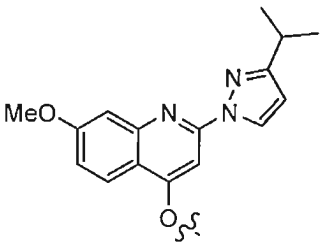
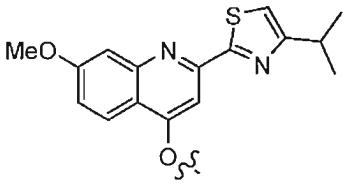
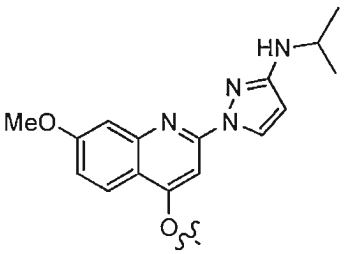
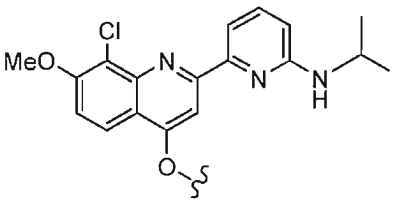
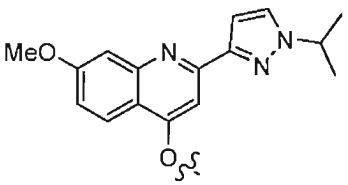
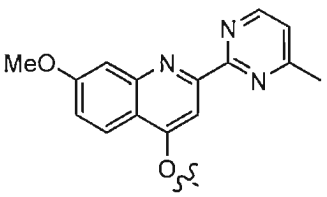


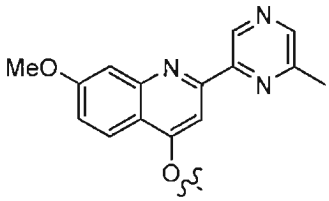
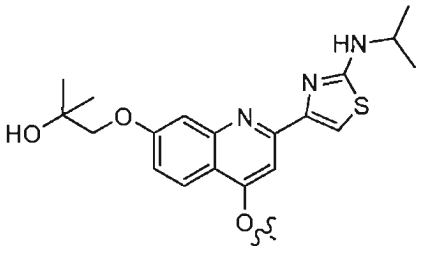
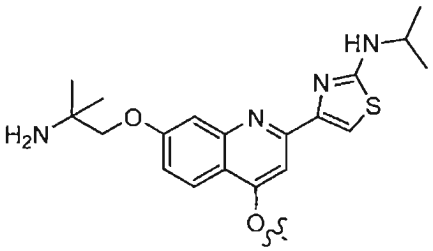
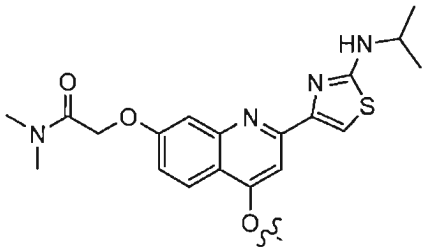
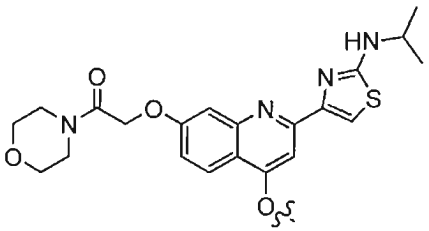
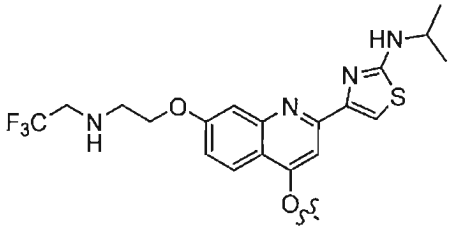
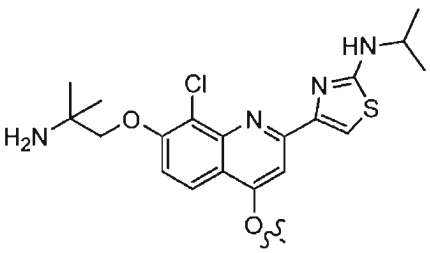
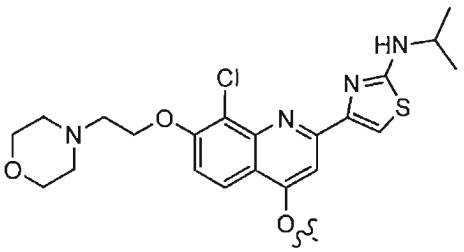


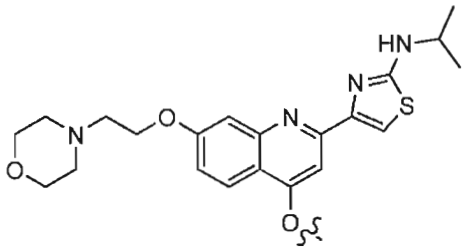
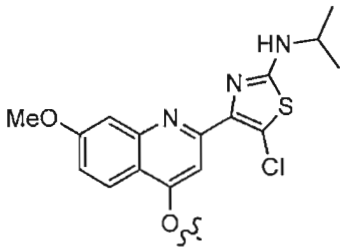
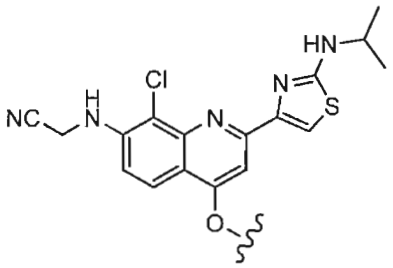
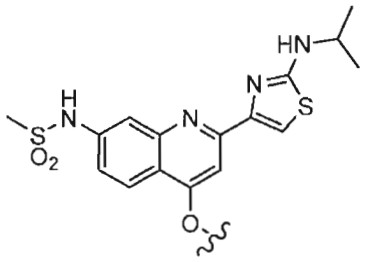
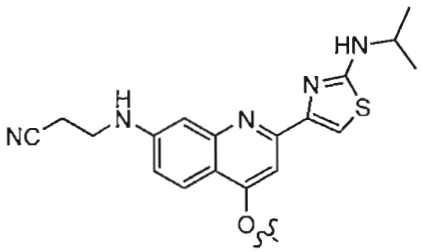
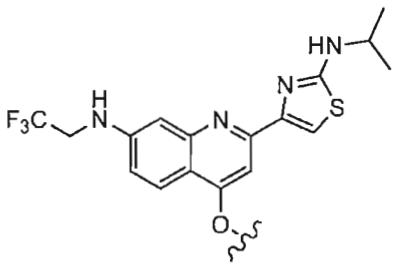
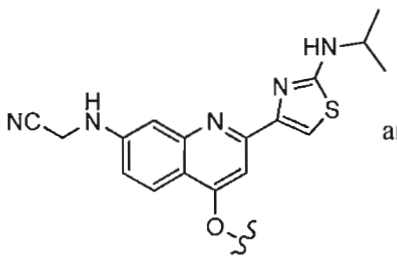
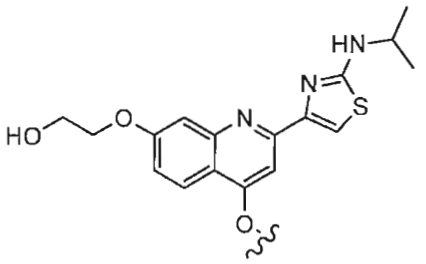


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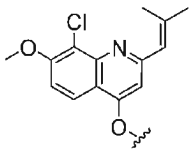
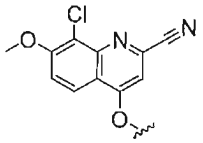
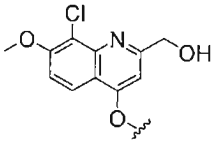
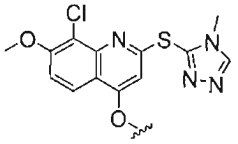
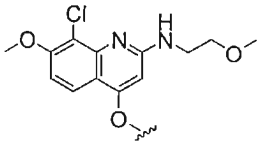
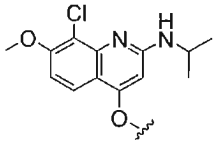
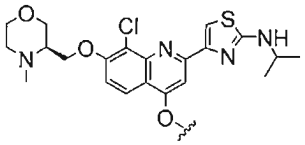
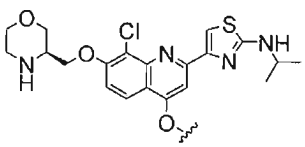
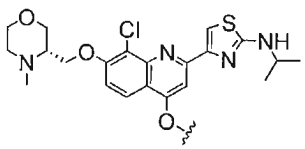
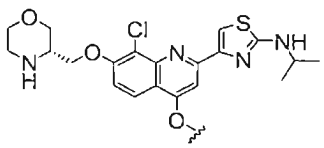
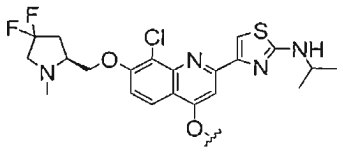
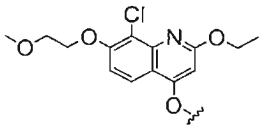
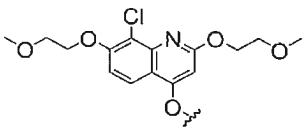
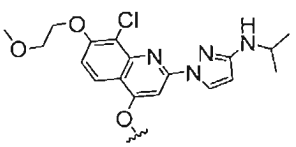
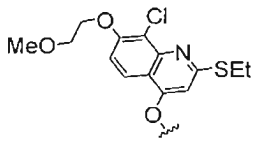
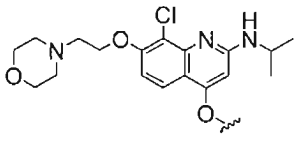
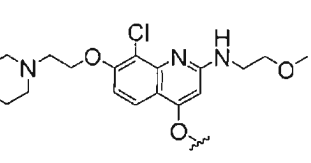
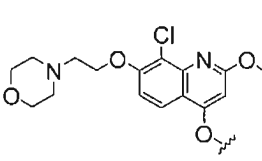
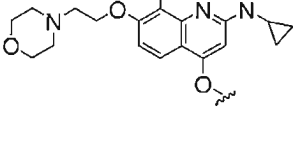
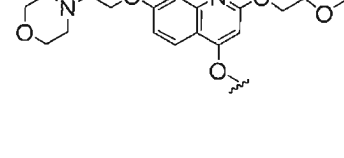
10. The compound of claim 2, or pharmaceutiacally acceptable salt thereof, wherein Z^1 is selected from the following structures:

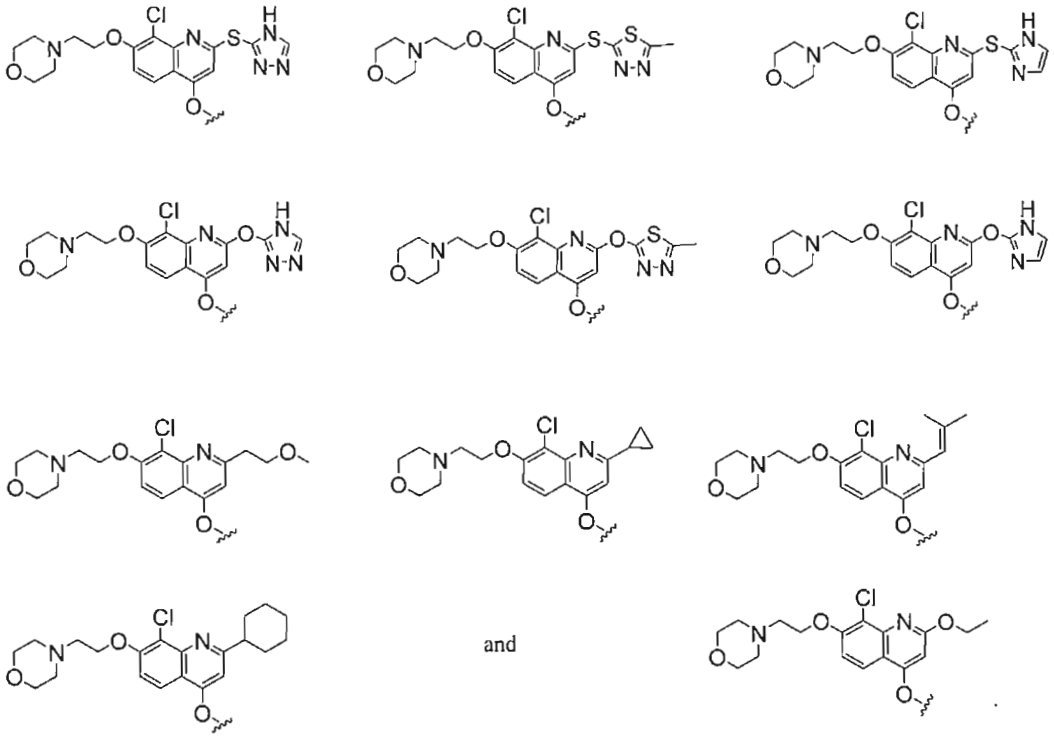


















and


11. The compound of claim 2, or pharmaceutiacally acceptable salt thereof, wherein Z^1 is selected from the following structures:



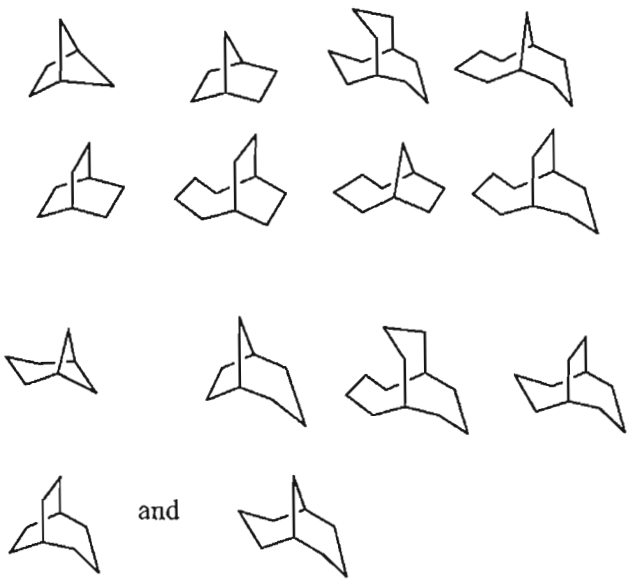
and

12. The compound of claim 1, or pharmaceutiacally acceptable salt thereof, wherein Q^1 is vinyl or ethyl.

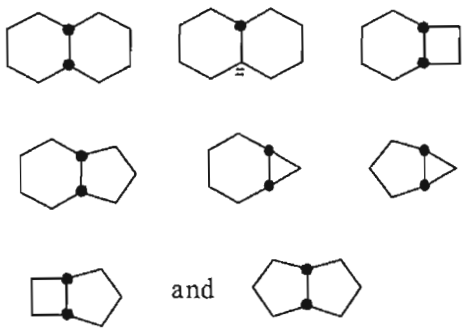
13. The compound of claim 2, or pharmaceutiacally acceptable salt thereof, wherein Z^{2a} is *tert*-butyl.

14. The compound of claim 2, or pharmaceutiacally acceptable salt thereof, wherein Y is a bridged carbocyclic ring system.

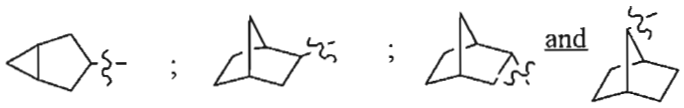
15. The compound of claim 2, or pharmaceutiacally acceptable salt thereof, wherein Y comprises a bridged ring system selected from:



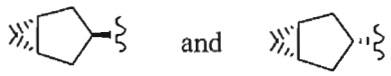
16. The compound of claim 2, or pharmaceutiacally acceptable salt thereof, wherein Y comprises a fused ring system selected from:



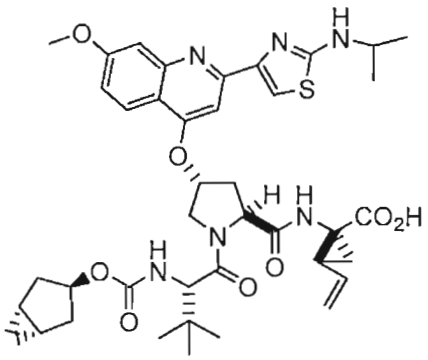
17. The compound of claim 2, or pharmaceutiacally acceptable salt thereof, wherein Y is selected from:

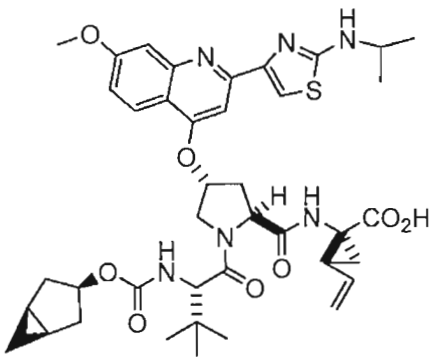


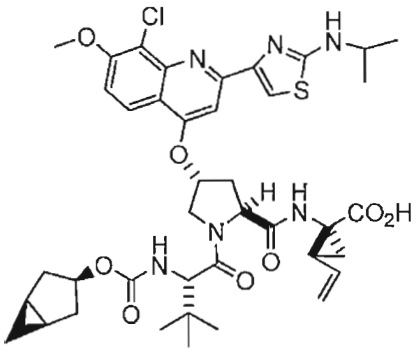
18. The compound of claim 2, or pharmaceutiacally acceptable salt thereof, wherein Y is selected from:

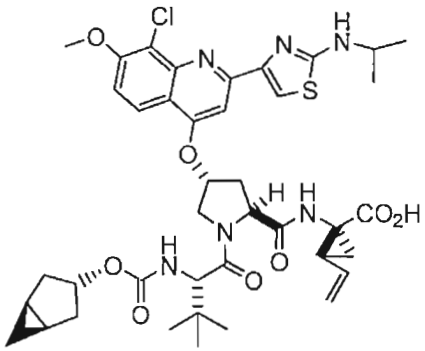


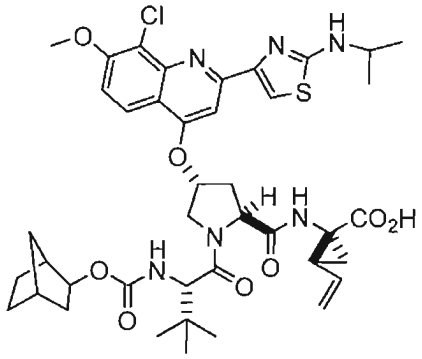
19. The compound of claim 1 which is selected from:

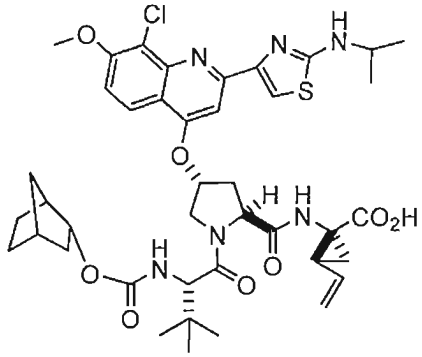


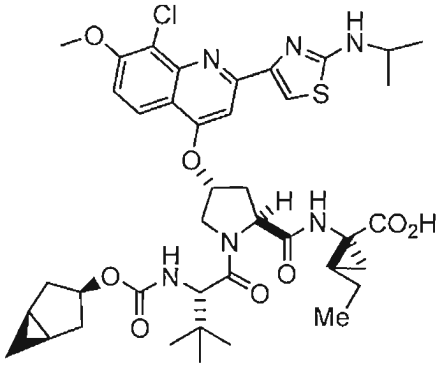


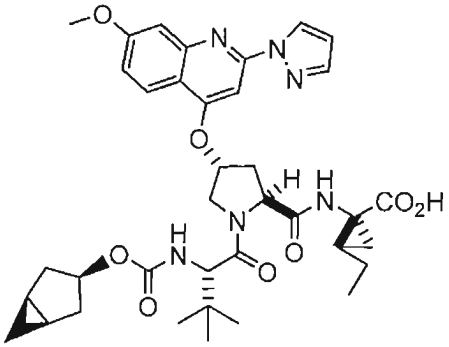


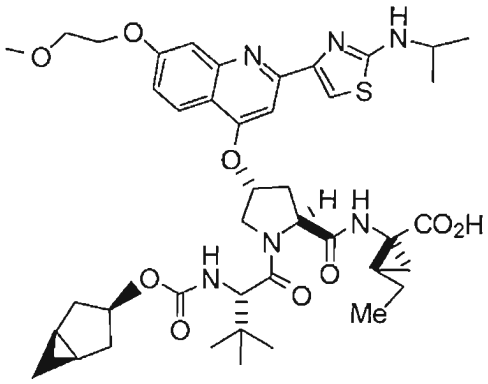


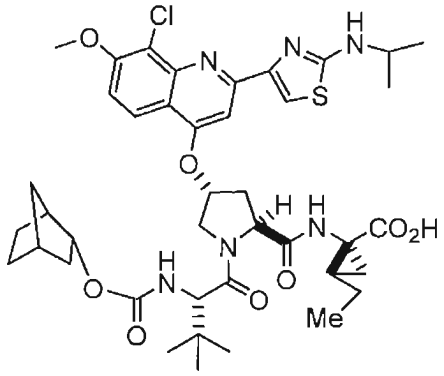


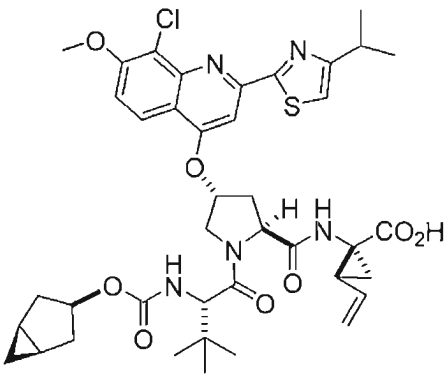


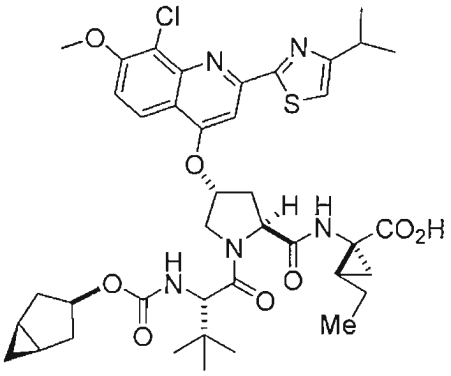


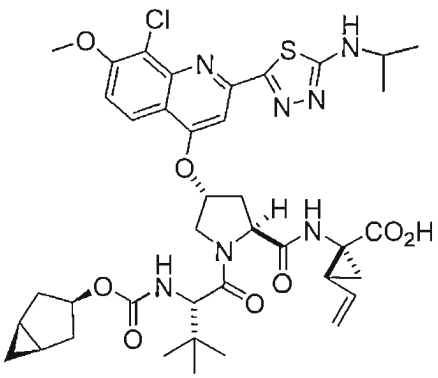


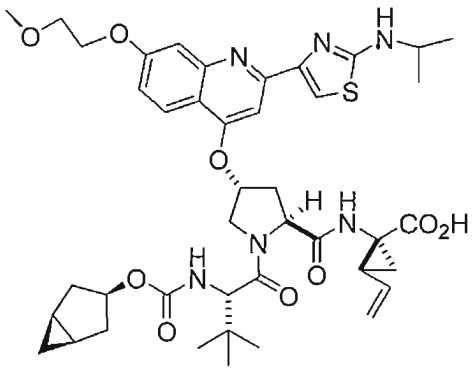


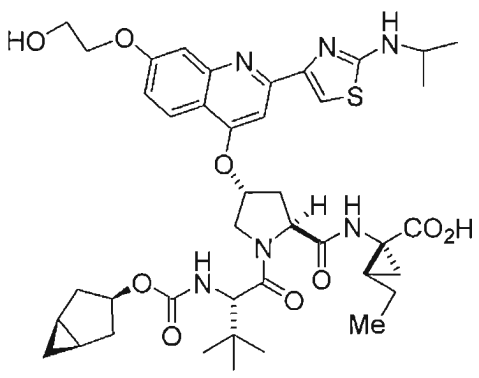


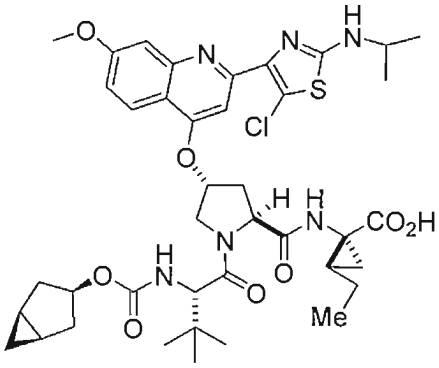


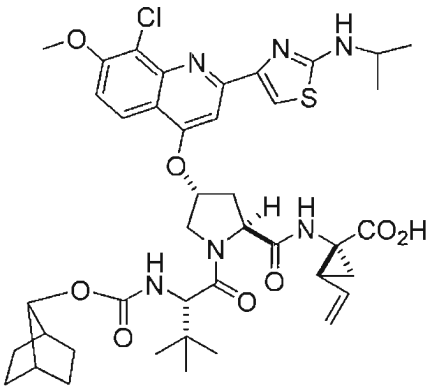


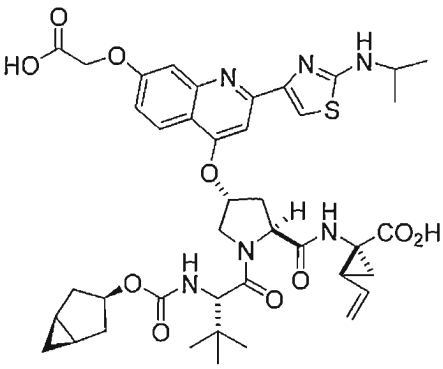




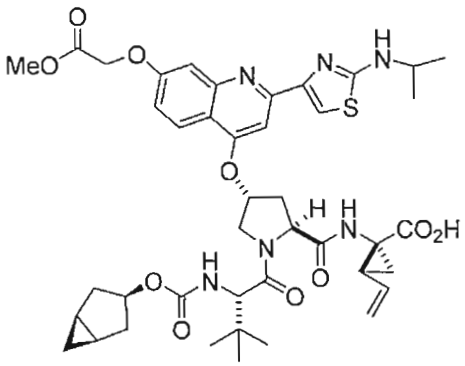






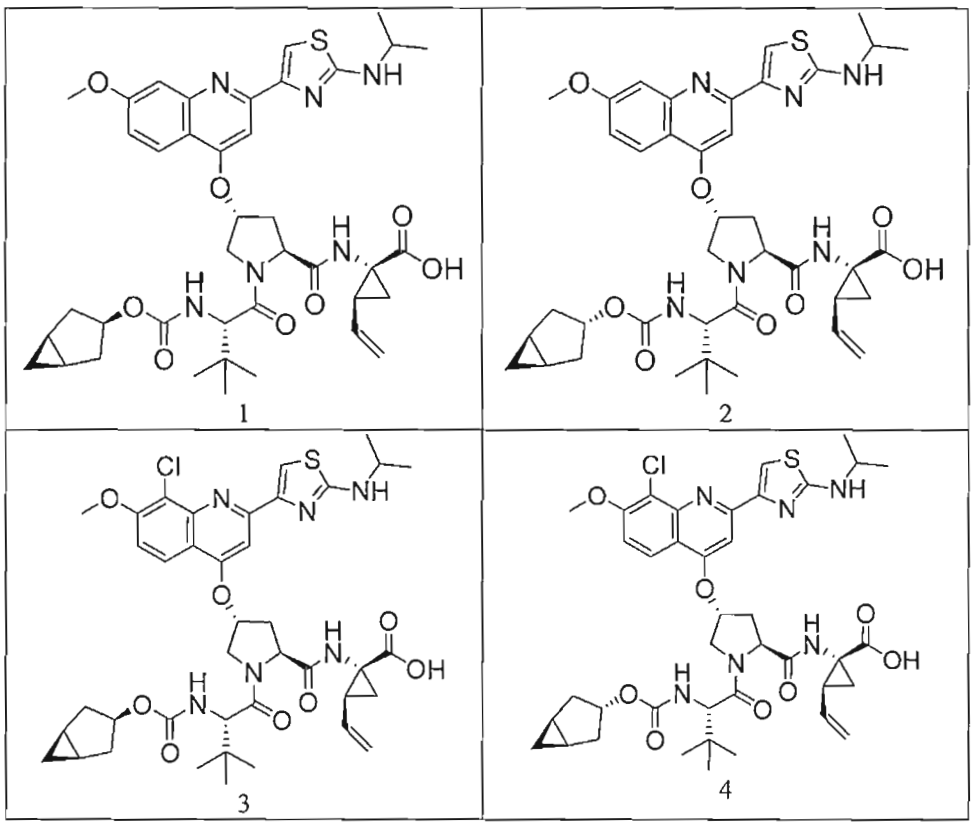


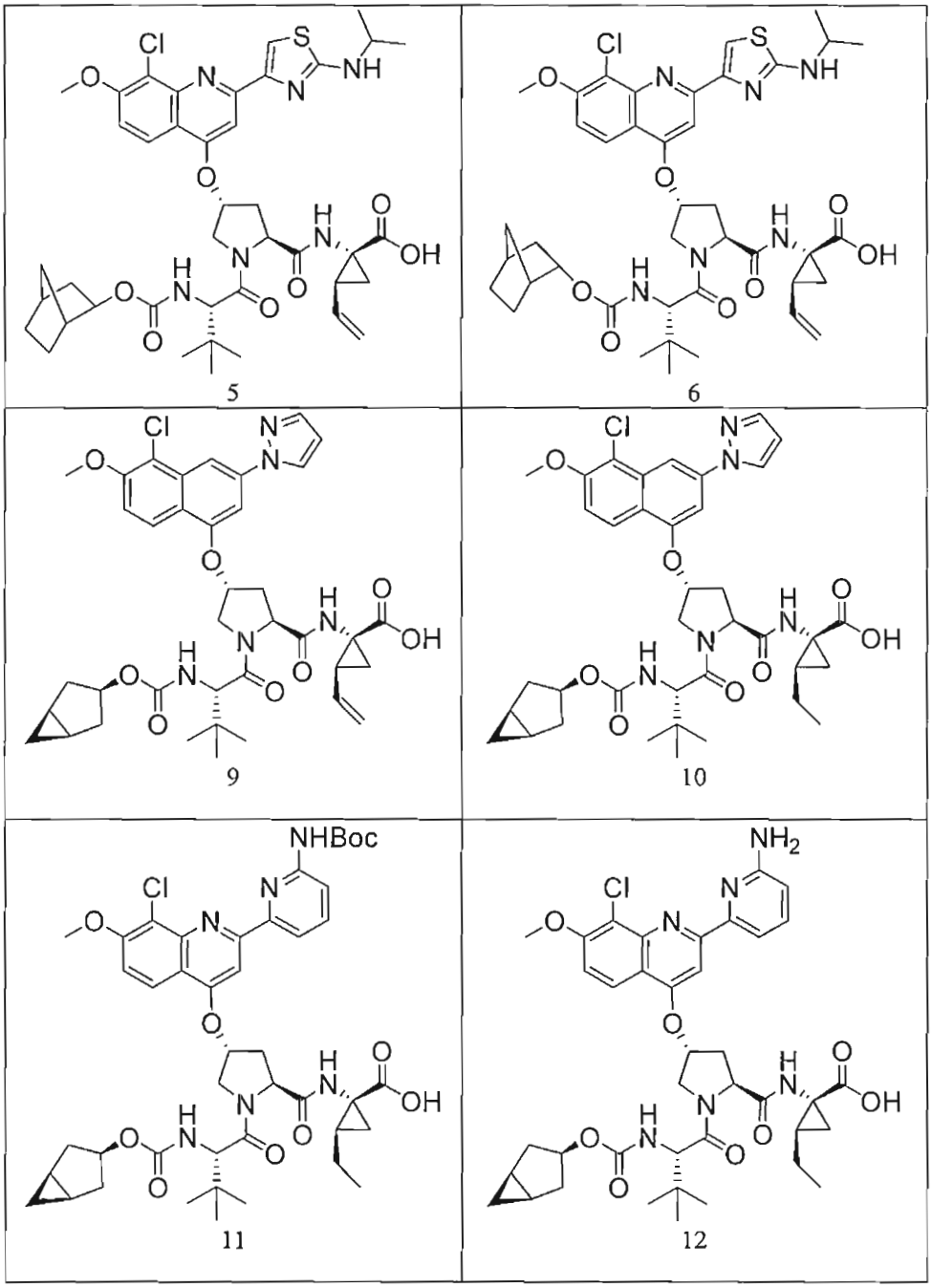
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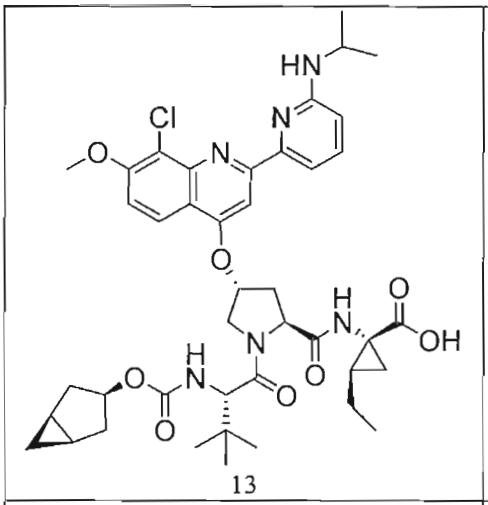


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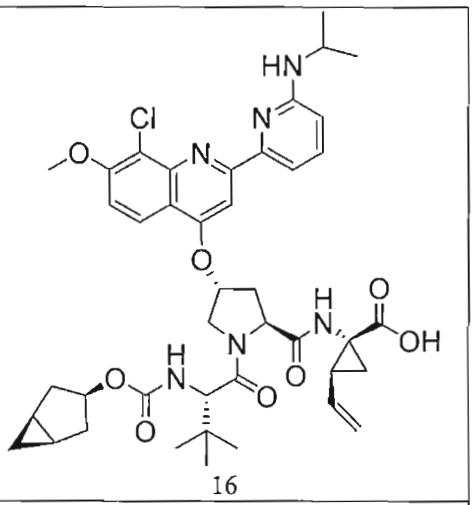
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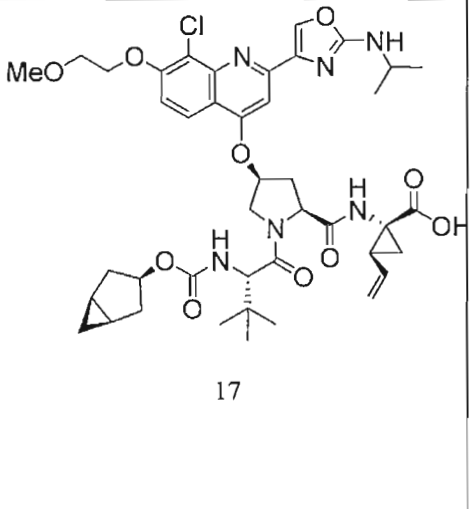

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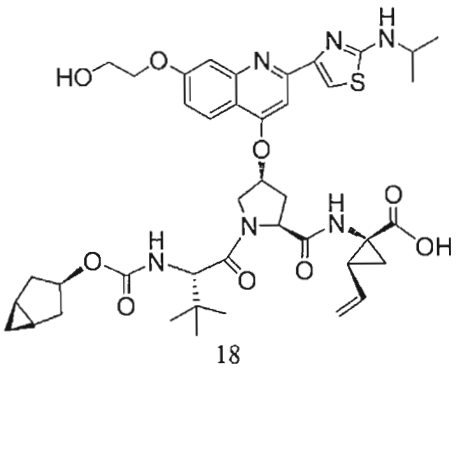
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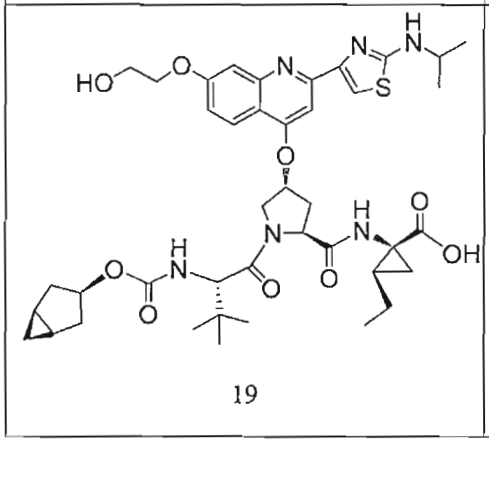
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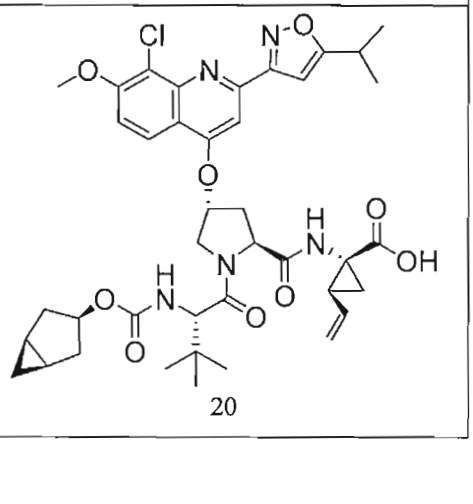
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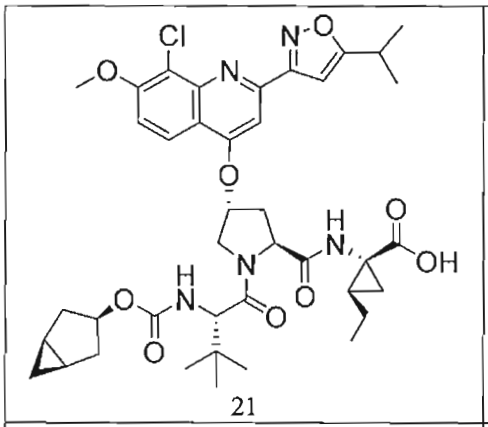
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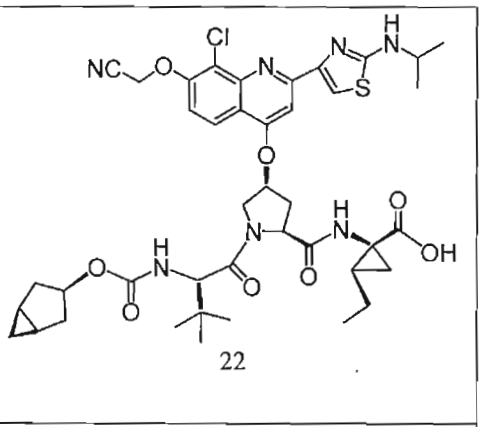
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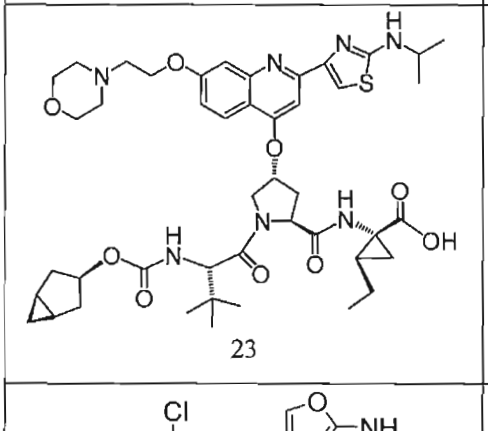
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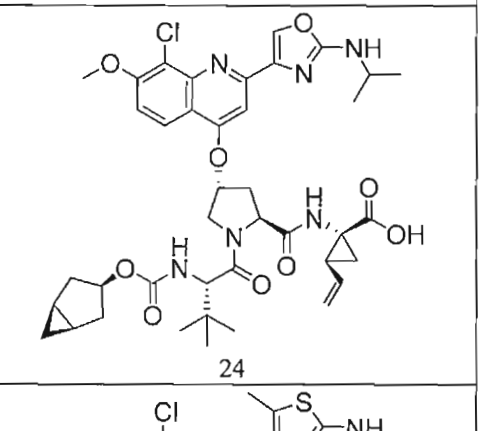
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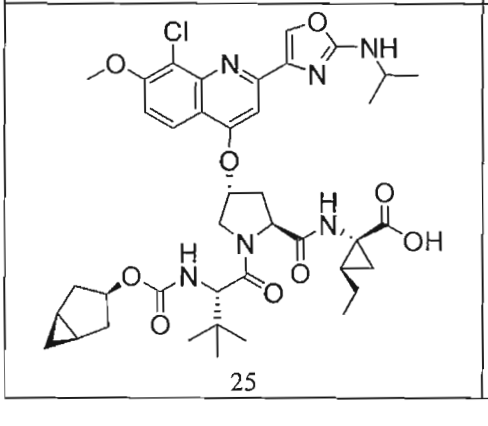
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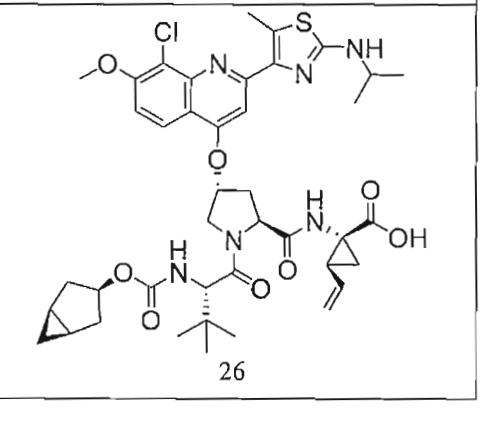
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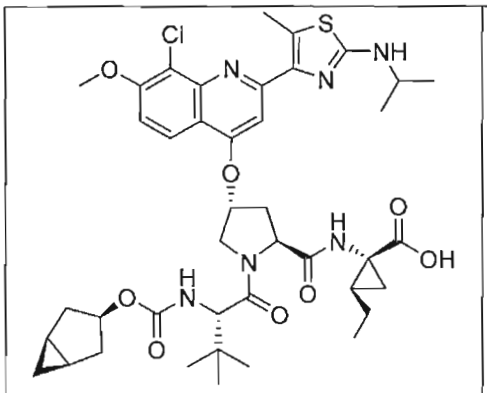
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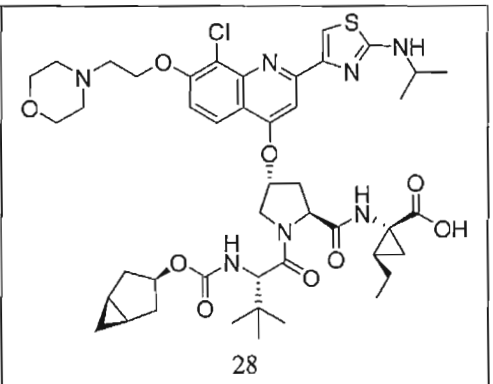
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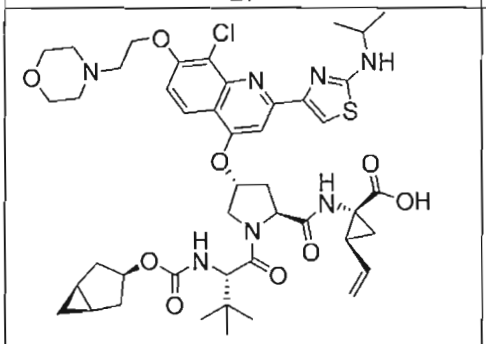
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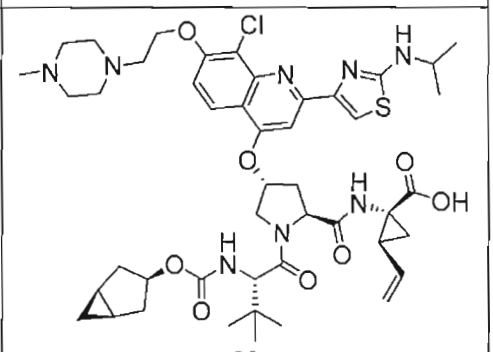
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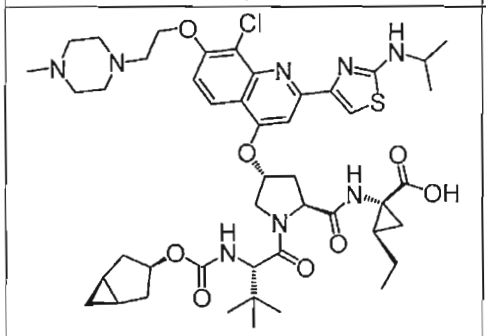
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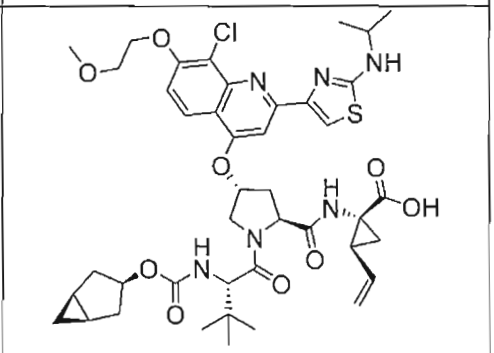
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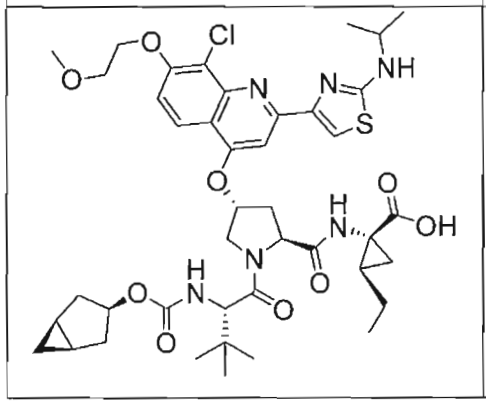
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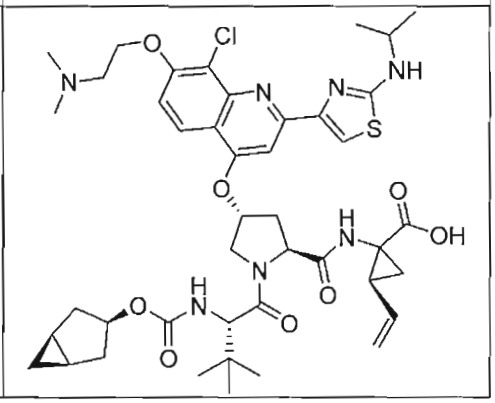


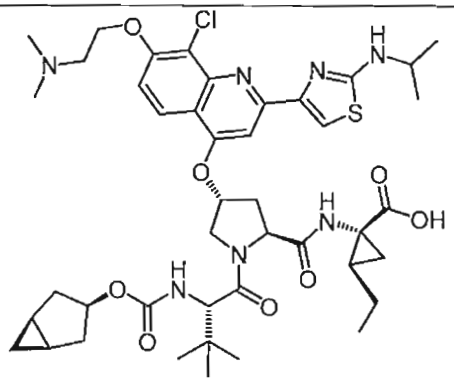
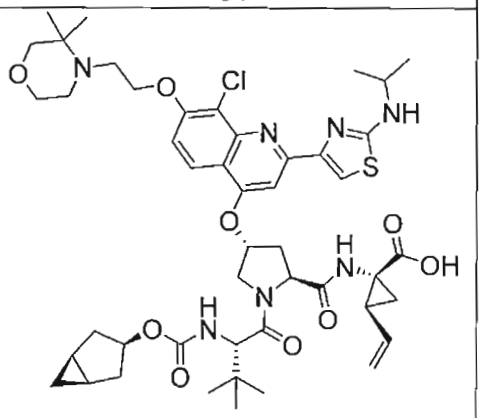
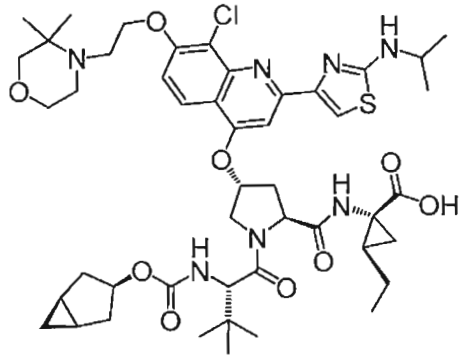
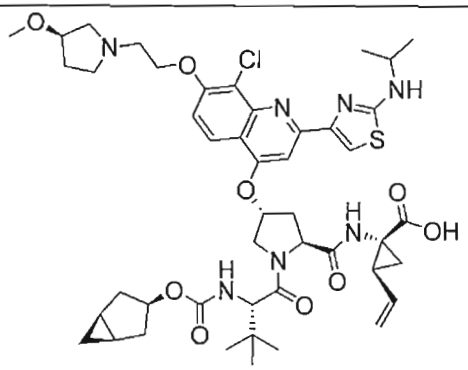
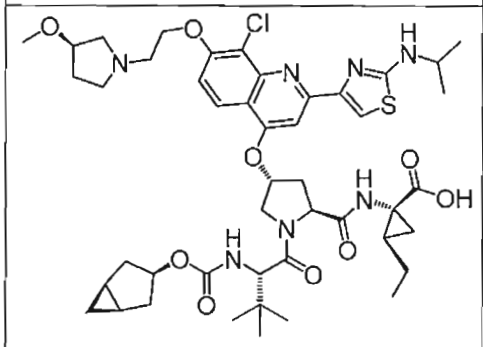
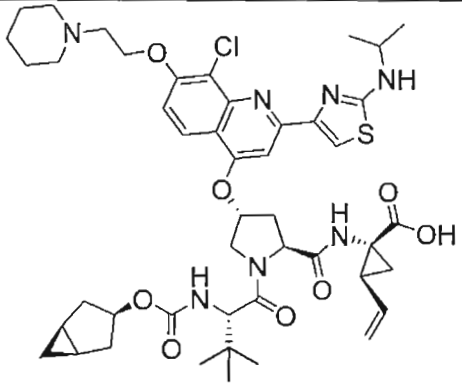
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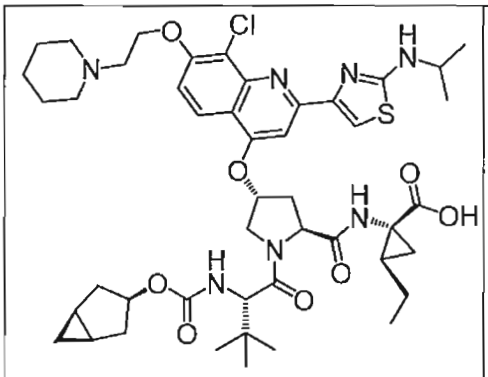


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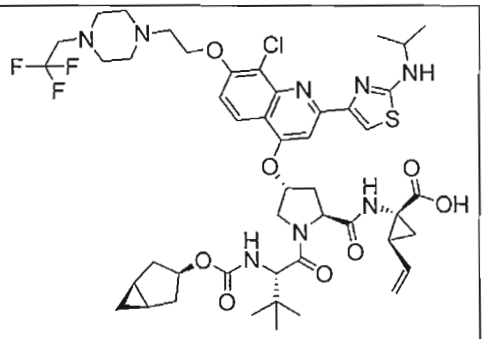




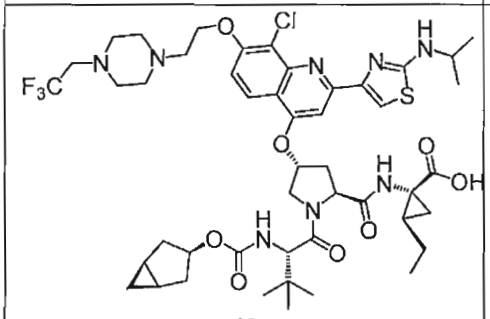
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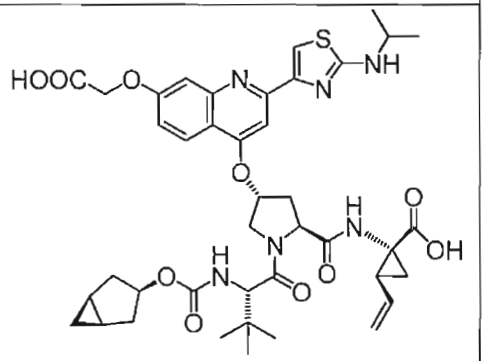
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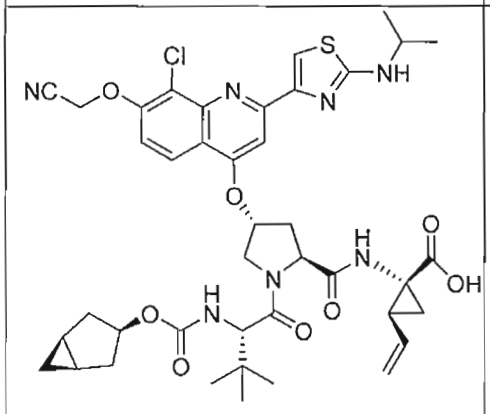
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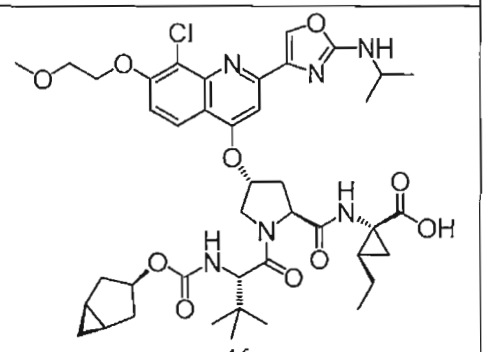
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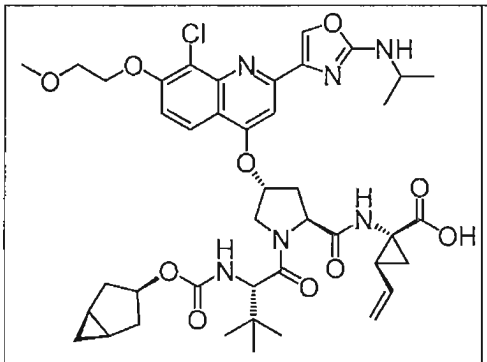
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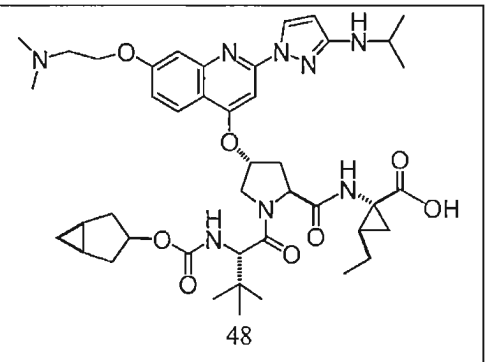
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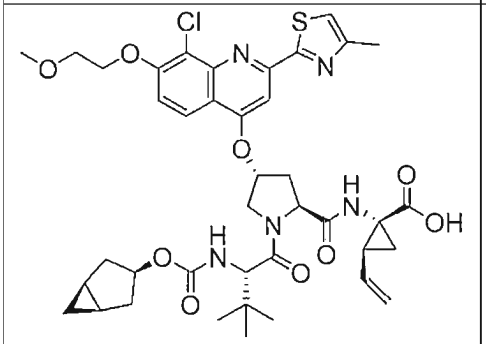
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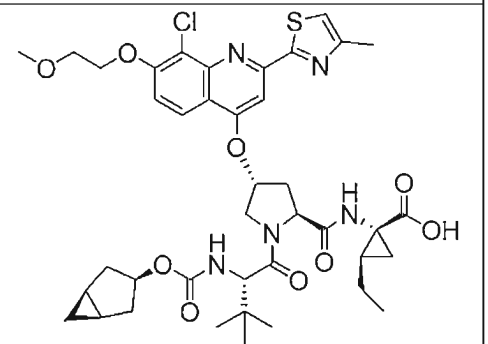
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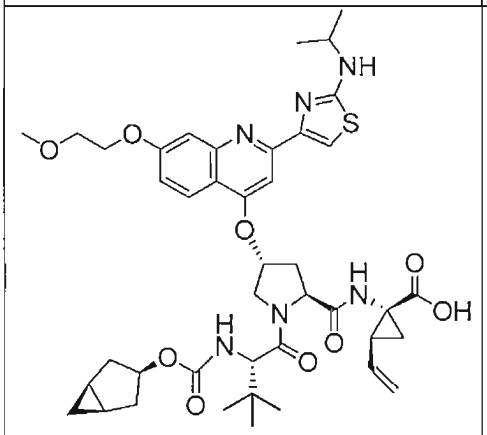
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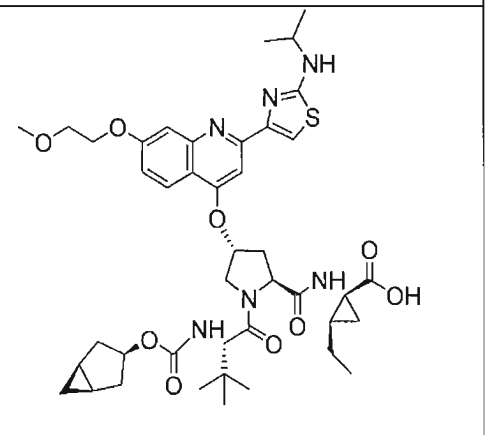
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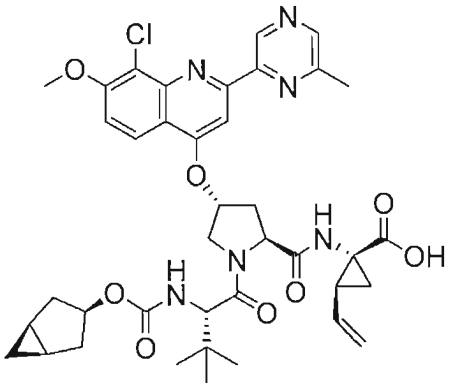
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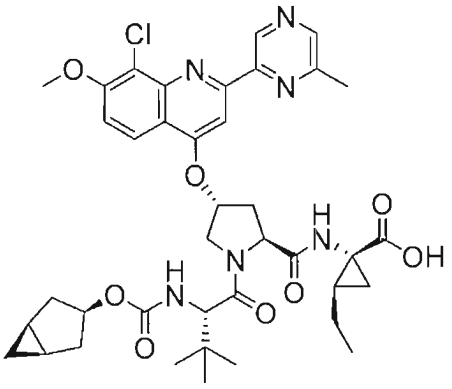
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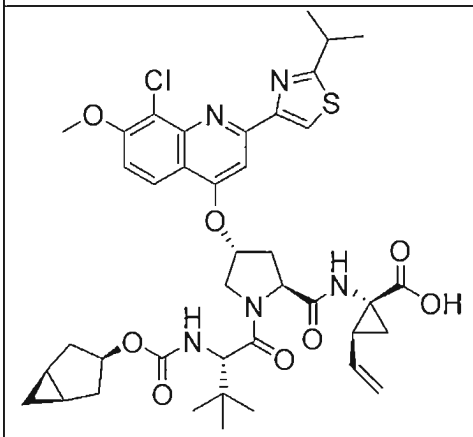
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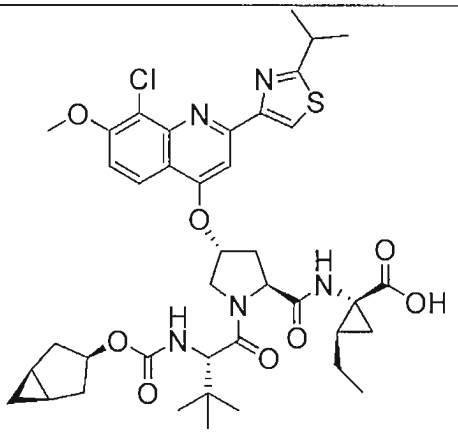
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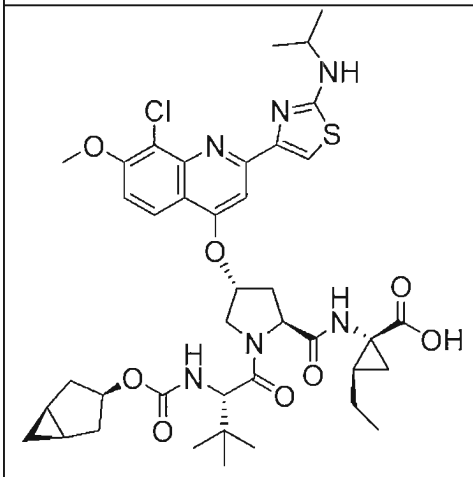
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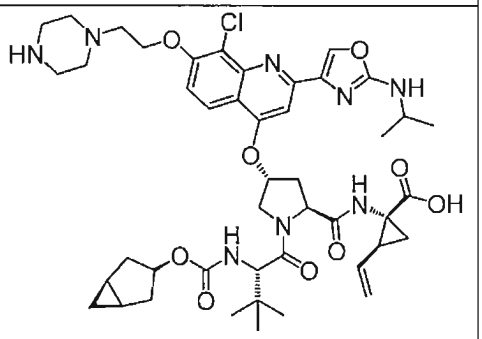
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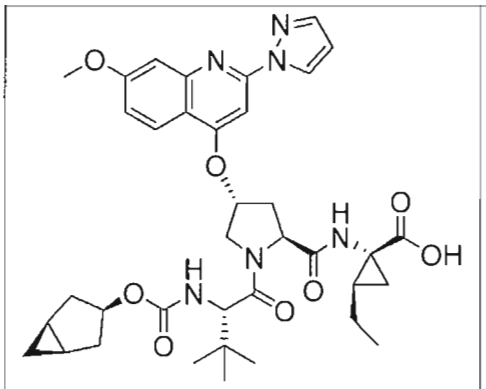
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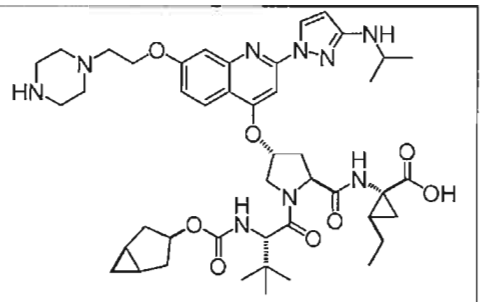
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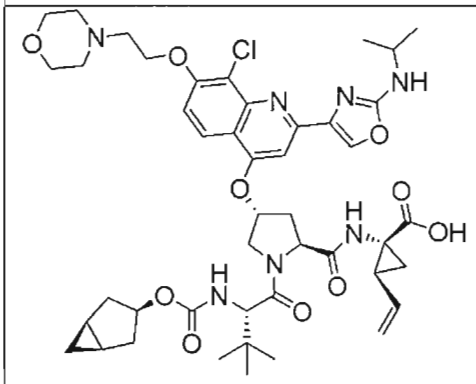
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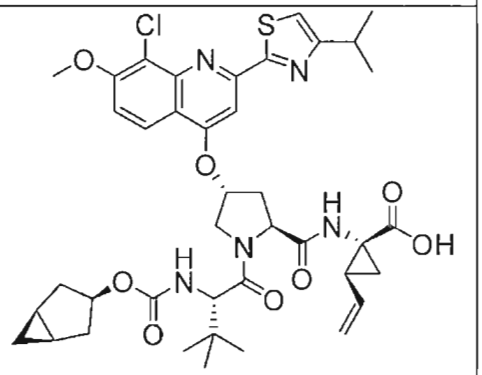
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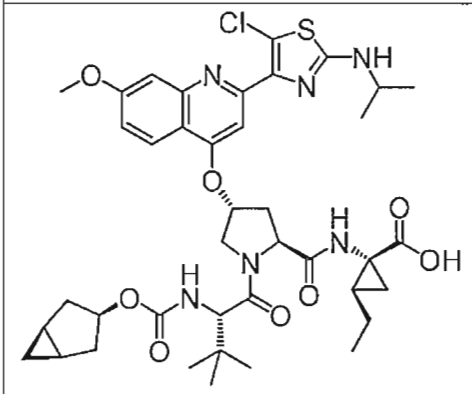
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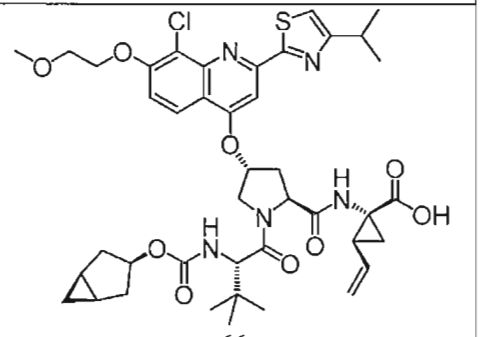
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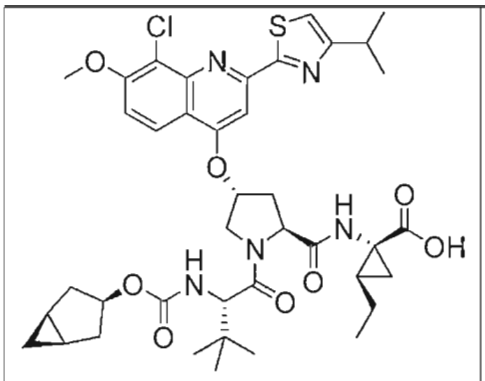
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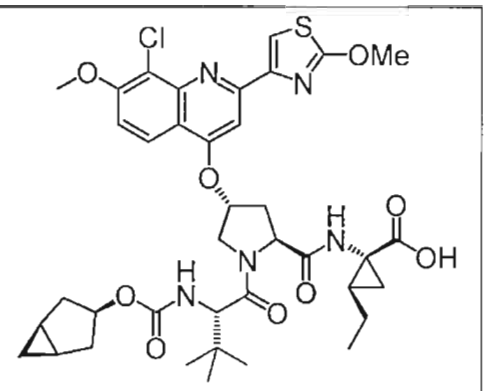
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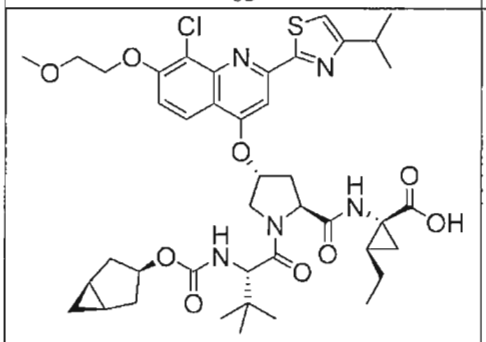
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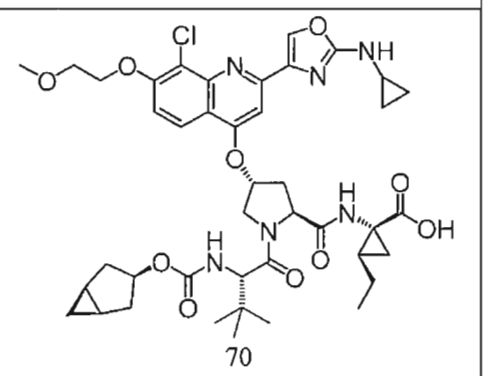
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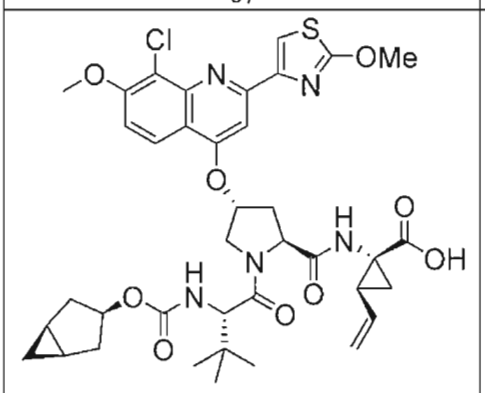
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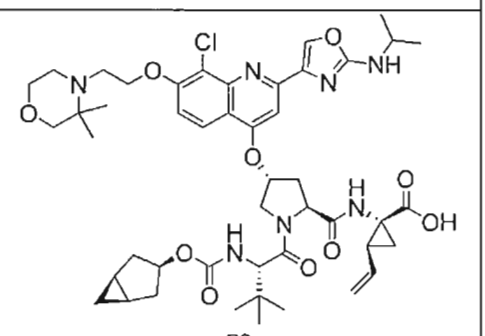
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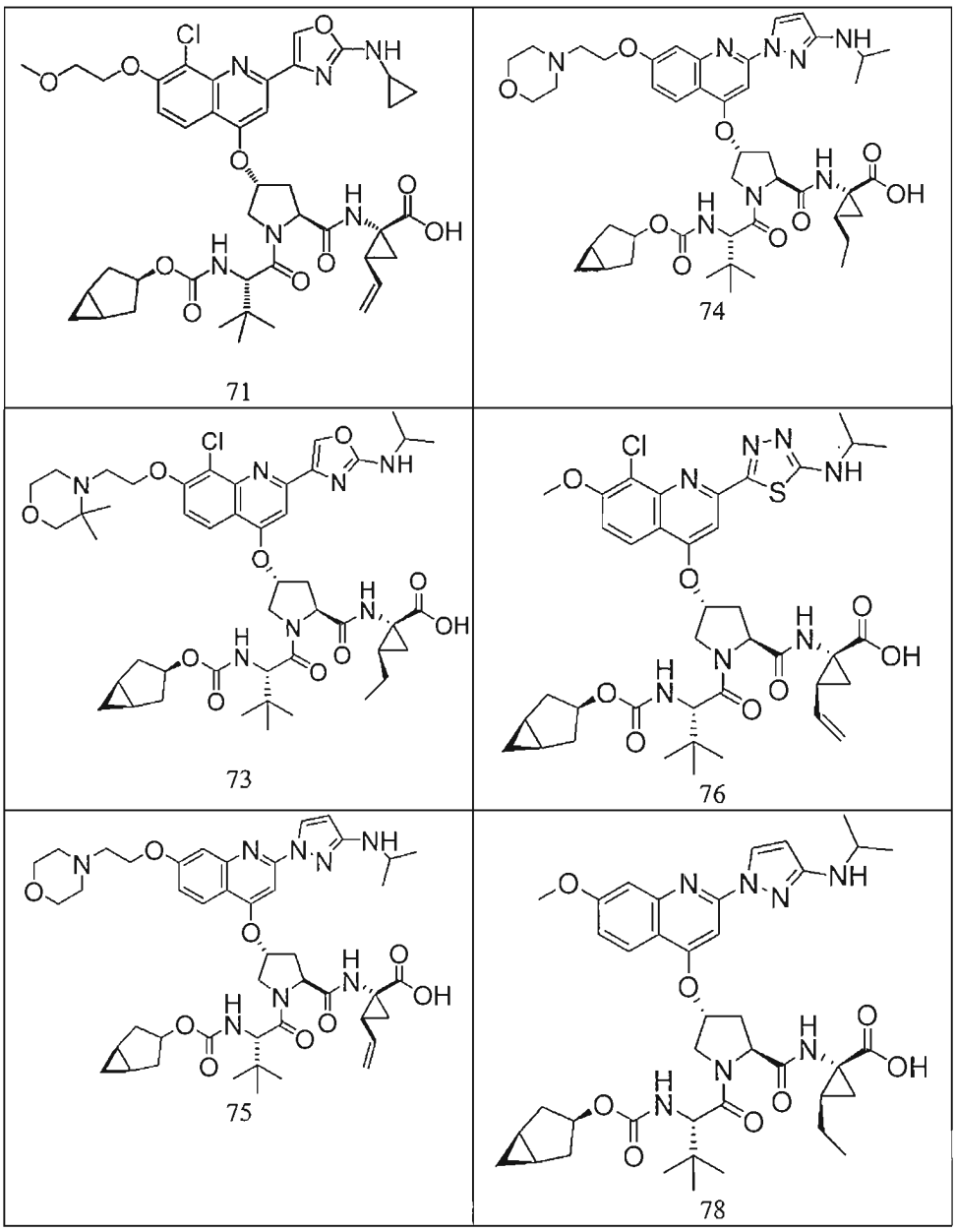
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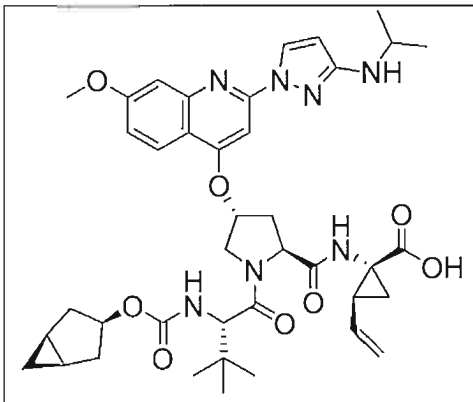
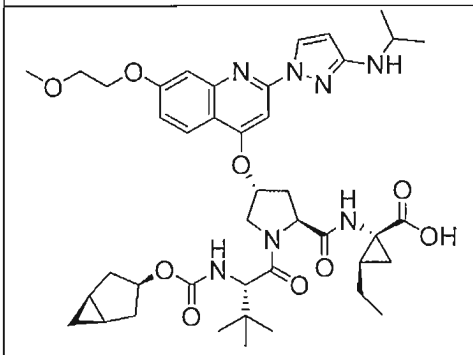


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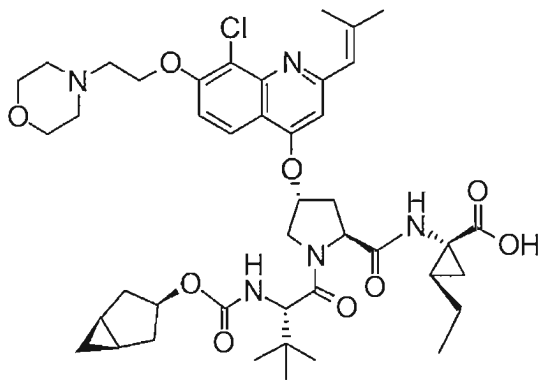
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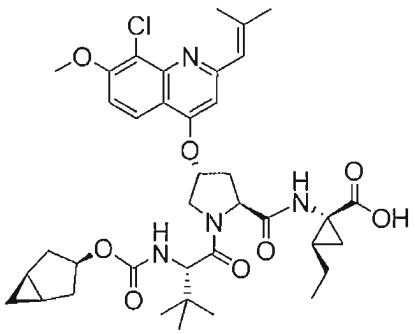

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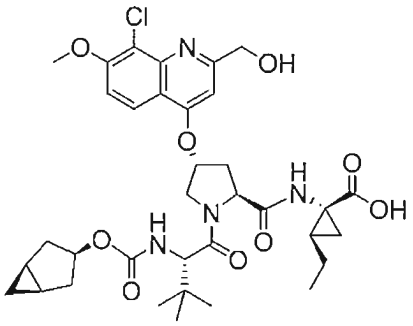
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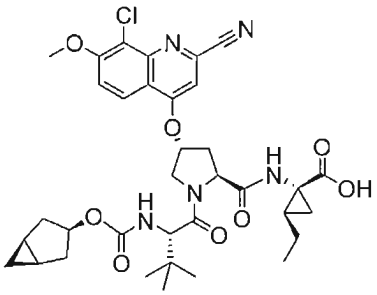
and pharmaceutically acceptable salts thereof.

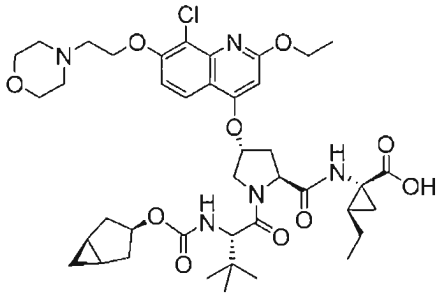
21. The compound of claim 1 which is selected from:

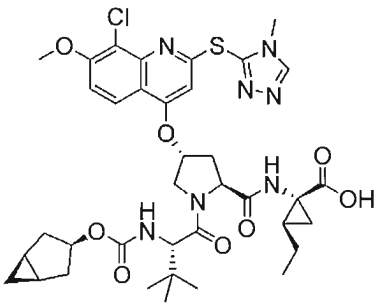


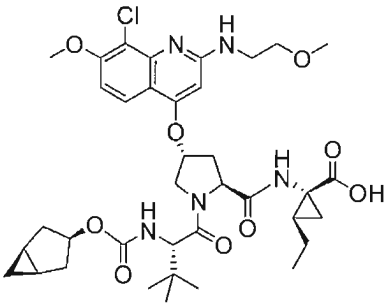


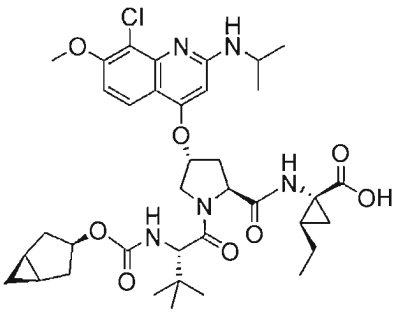


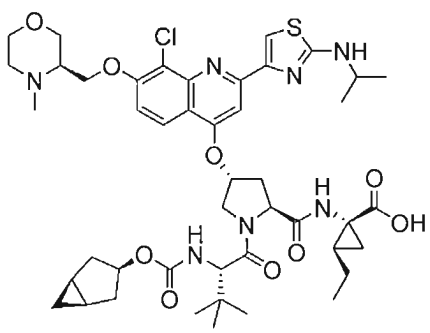


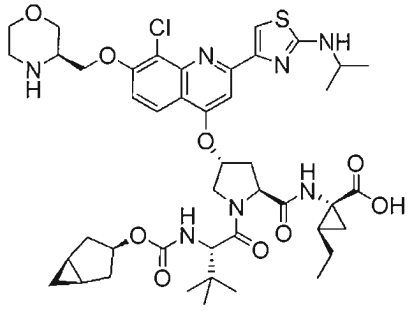


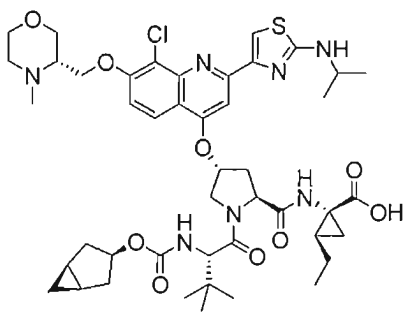


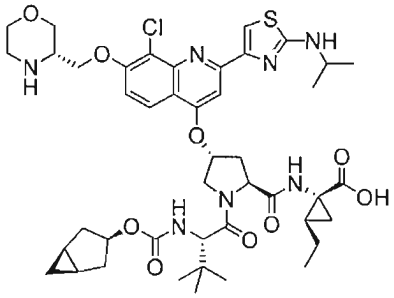


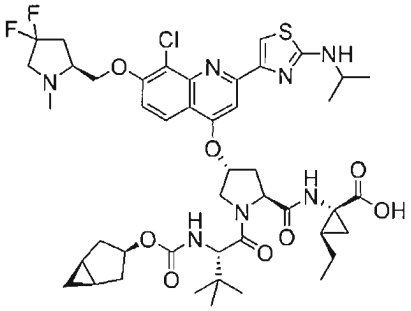


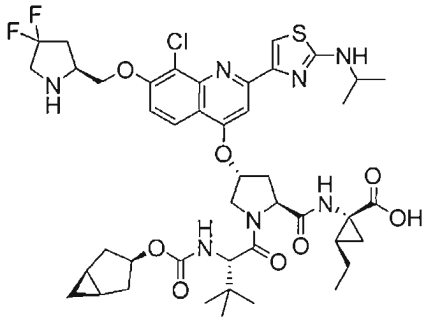


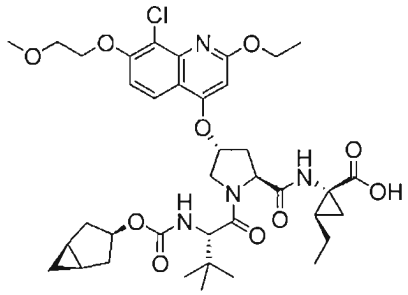


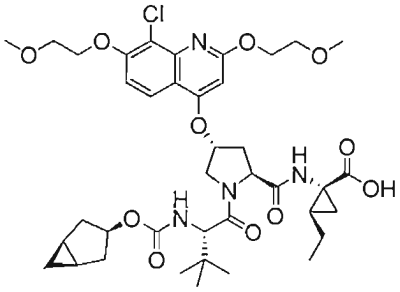


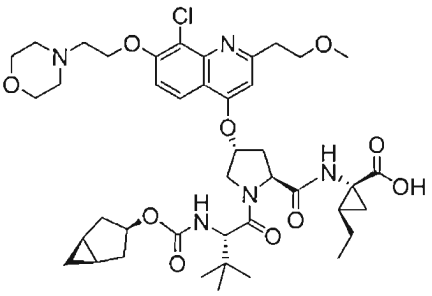


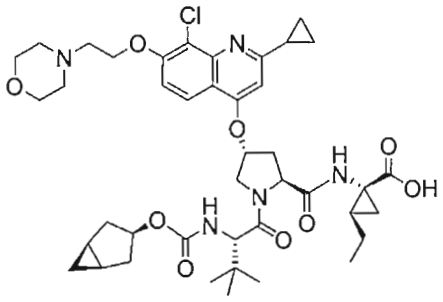


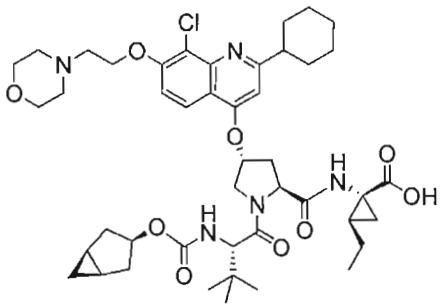


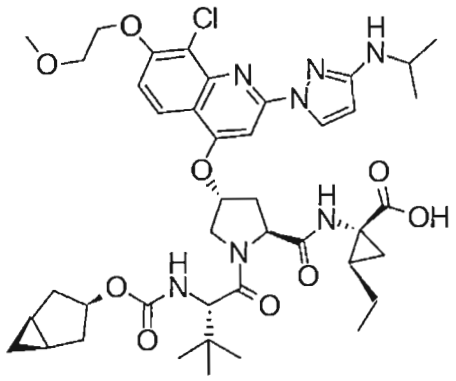


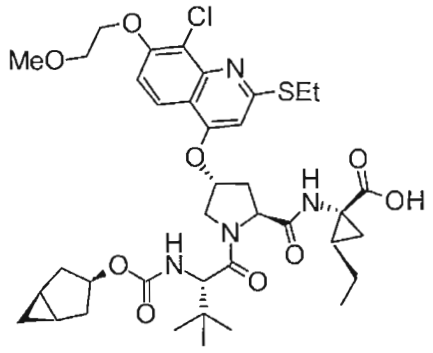




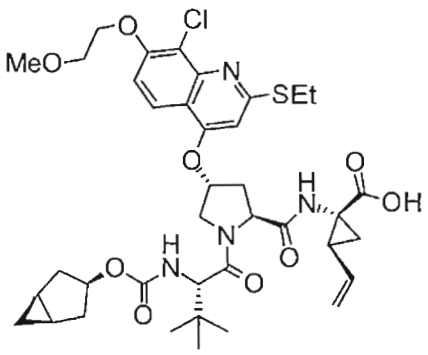






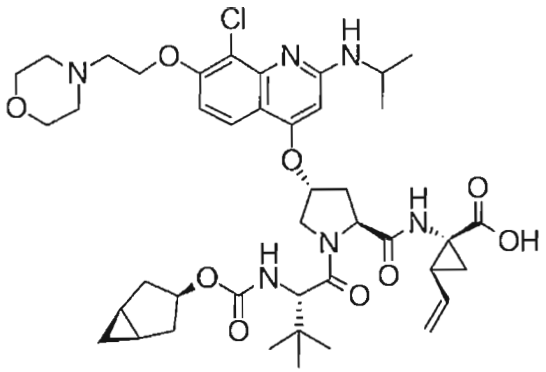


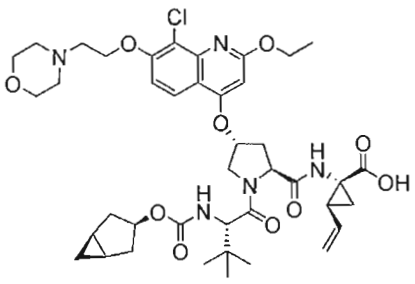
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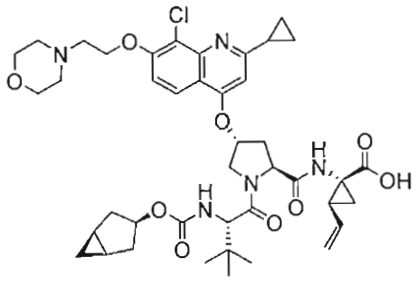


and pharmaceutically acceptable salts thereof.

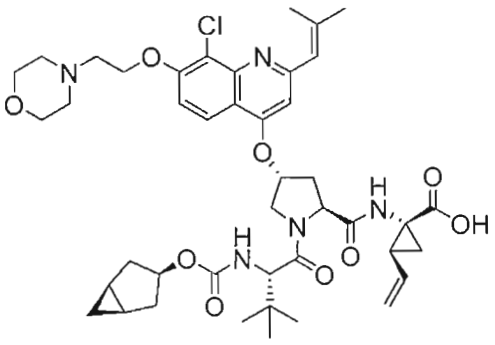
22. The compound of claim 1 which is selected from:





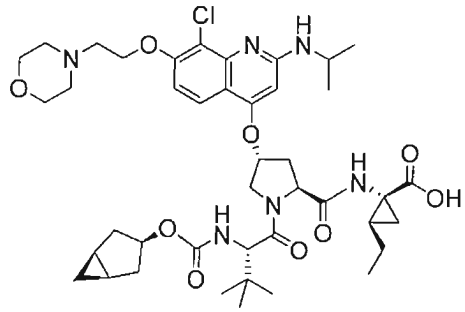


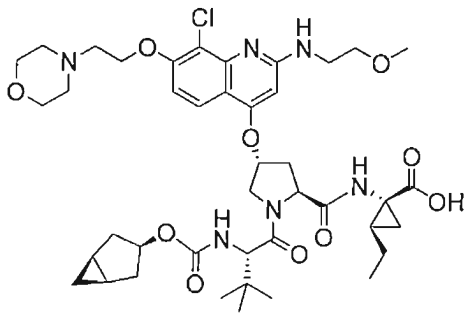
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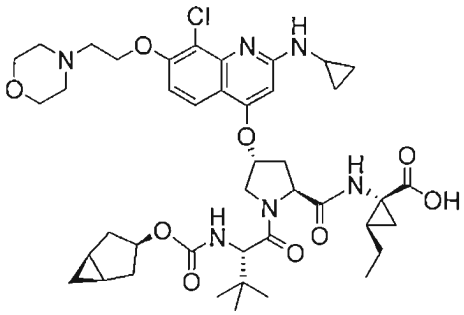


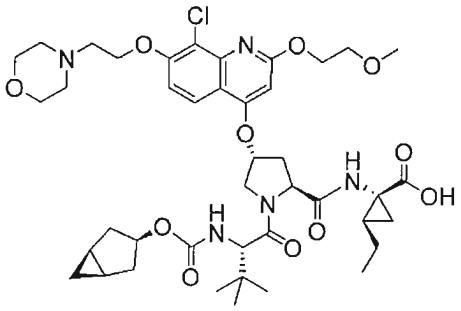
and pharmaceutically acceptable salts thereof.

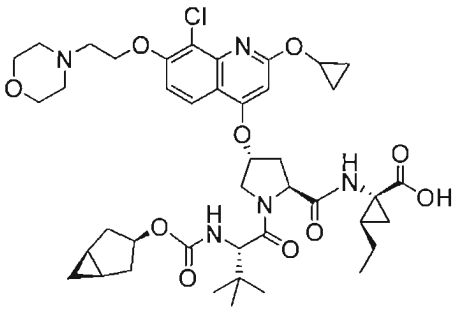
23. The compound of claim 1 which is selected from:

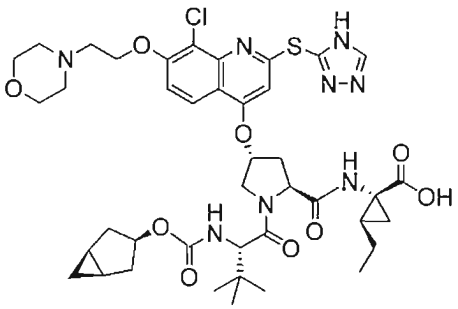


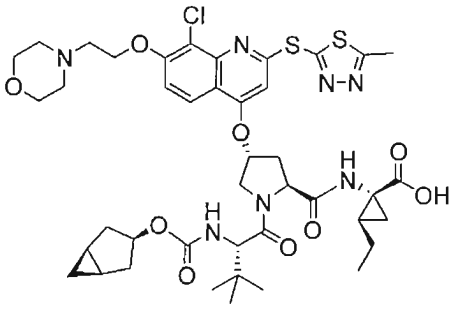


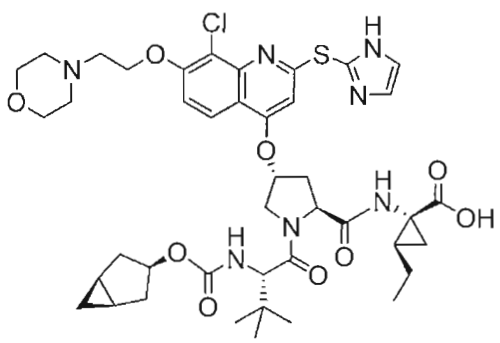


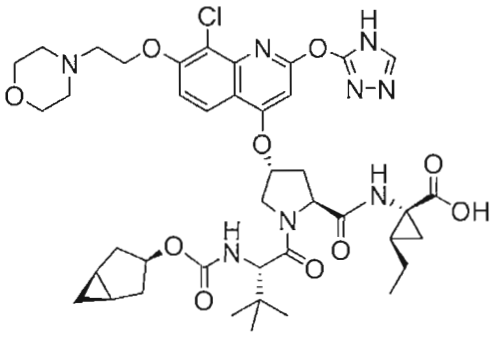


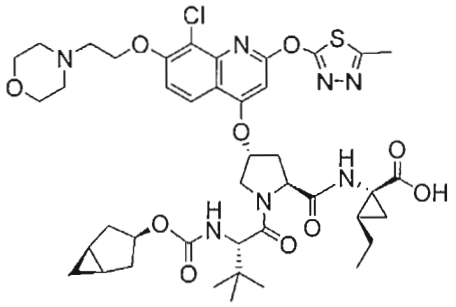




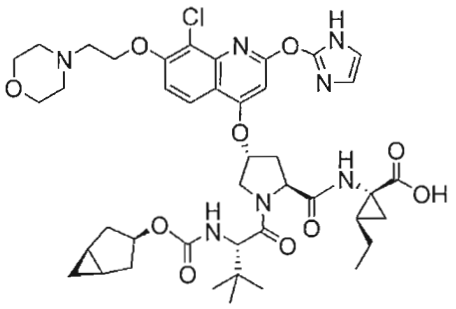








and



and pharmaceutically acceptable salts thereof.

24. The compound of claim 1 which is a pharmaceutically acceptable salt thereof.

25. A pharmaceutical composition comprising the compound of claim 1, or pharmaceutiacally acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

26. The pharmaceutical composition of claim 25, further comprising at least one additional therapeutic agent.

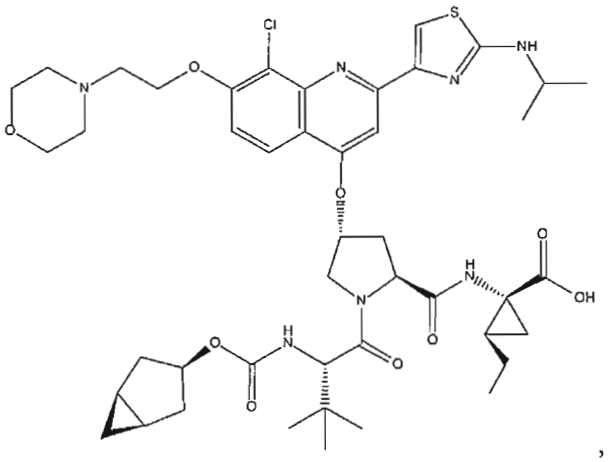
27. The pharmaceutical composition of claim 26, wherein said additional therapeutic agent is selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

28. The pharmaceutical composition according to claim 25, further comprising a nucleoside analogue.

29. The pharmaceutical composition according to claim 28, further comprising an interferon or pegylated interferon.

30. The pharmaceutical composition according to claim 28, wherein said nucleoside analogue is selected from ribavirin, viramidine, levovirin, a L-nucleoside, and isatoribine and said interferon is α-interferon or pegylated interferon.

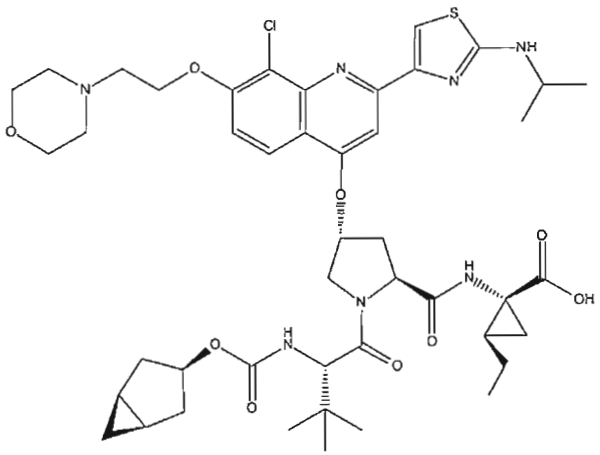
31. A compound which is:



,

or a pharmaceutically acceptable salt thereof.

32. A pharmaceutical composition comprising the compound,



or pharmaceutiacally acceptable salt thereof, and at least one pharmaceutically acceptable carrier.