MACROCYLIC INHIBITORS OF HEPATITIS C VIRUS

The present invention is concerned with macrocylic compounds having inhibitory activity on the replication of the hepatitis C virus (HCV). It further concerns compositions comprising these compounds as active ingredients as well as processes for preparing these compounds and compositions.

Hepatitis C virus is the leading cause of chronic liver disease worldwide and has become a focus of considerable medical research. HCV is a member of the *Flaviviridae* family of viruses in the *hepacivirus* genus, and is closely related to the *flavivirus* genus, which includes a number of viruses implicated in human disease, such as dengue virus and yellow fever virus, and to the animal *pestivirus* family, which includes bovine viral diarrhea virus (BVDV). HCV is a positive-sense, single-stranded RNA virus, with a genome of around 9,600 bases. The genome comprises both 5' and 3' untranslated regions, which adopt RNA secondary structures, and a central open reading frame that encodes a single polyprotein of around 3,010-3,030 amino acids. The polyprotein encodes ten gene products, which are generated from the precursor polyprotein by an orchestrated series of co- and posttranslational endoproteolytic cleavages mediated by both host and viral proteases. The viral structural proteins include the core nucleocapsid protein, and two envelope glycoproteins E1 and E2. The non-structural (NS) proteins encode some essential viral enzymatic functions (helicase, polymerase, protease), as well as proteins of unknown function. Replication of the viral genome is mediated by an RNA-dependent RNA polymerase, encoded by non-structural protein 5b (NS5B). In addition to the polymerase, the viral helicase and protease functions, both encoded in the bifunctional NS3 protein, have been shown to be essential for replication of HCV RNA. In addition to the NS3 serine protease, HCV also encodes a metalloproteinase in the NS2 region.

Following the initial acute infection, a majority of infected individuals develop chronic hepatitis because HCV replicates preferentially in hepatocytes but is not directly cytopathic. In particular, the lack of a vigorous T-lymphocyte response and the high propensity of the virus to mutate appear to promote a high rate of chronic infection. Chronic hepatitis can progress to liver fibrosis leading to cirrhosis, end-stage liver disease, and HCC (hepatocellular carcinoma), making it the leading cause of liver transplantations.

There are 6 major HCV genotypes and more than 50 subtypes, which are differently distributed geographically. HCV type 1 is the predominant genotype in Europe and the

US. The extensive genetic heterogeneity of HCV has important diagnostic and clinical implications, perhaps explaining difficulties in vaccine development and the lack of response to therapy.

Transmission of HCV can occur through contact with contaminated blood or blood products, for example following blood transfusion or intravenous drug use. The introduction of diagnostic tests used in blood screening has led to a downward trend in post-transfusion HCV incidence. However, given the slow progression to the end-stage liver disease, the existing infections will continue to present a serious medical and economic burden for decades.

Current HCV therapies are based on (pegylated) interferon-alpha (IFN-α) in combination with ribavirin. This combination therapy yields a sustained virologic response in more than 40% of patients infected by genotype 1 viruses and about 80% of those infected by genotypes 2 and 3. Beside the limited efficacy on HCV type 1, this combination therapy has significant side effects and is poorly tolerated in many patients. Major side effects include influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms. Hence there is a need for more effective, convenient and better tolerated treatments.

Recently, two peptidomimetic HCV protease inhibitors have gained attention as clinical candidates, namely BILN-2061 disclosed in WO00/59929 and VX-950 disclosed in WO03/87092. A number of similar HCV protease inhibitors have also been disclosed in the academic and patent literature. It has already become apparent that the sustained administration of BILN-2061 or VX-950 selects HCV mutants which are resistant to the respective drug, so called drug escape mutants. These drug escape mutants have characteristic mutations in the HCV protease genome, notably D168V, D168A and/or A156S. Accordingly, additional drugs with different resistance patterns are required to provide failing patients with treatment options, and combination therapy with multiple drugs is likely to be the norm in the future, even for first line treatment.

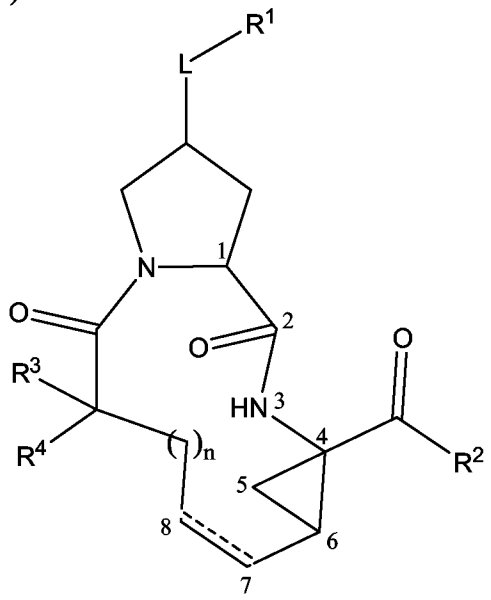
Experience with HIV drugs, and HIV protease inhibitors in particular, has further emphasized that sub-optimal pharmacokinetics and complex dosage regimes quickly result in inadvertent compliance failures. This in turn means that the 24 hour trough concentration (minimum plasma concentration) for the respective drugs in an HIV regime frequently falls below the IC_{90} or ED_{90} threshold for large parts of the day. It is considered that a 24 hour trough level of at least the IC_{50}, and more realistically, the IC_{90} or ED_{90}, is essential to slow down the development of drug escape mutants.

Achieving the necessary pharmacokinetics and drug metabolism to allow such trough levels provides a stringent challenge to drug design. The strong peptidomimetic nature of prior art HCV protease inhibitors, with multiple peptide bonds poses pharmacokinetic hurdles to effective dosage regimes.

There is a need for HCV inhibitors which may overcome the disadvantages of current HCV therapy such as side effects, limited efficacy, the emerging of resistance, and compliance failures.

The present invention concerns inhibitors of HCV replication which are attractive not only in terms of their activity as HCV inhibitors but also for their good cell permeability and concomitant bioavailability.

The present invention concerns inhibitors of HCV replication, which can be represented by formula (I):



(I)

the *N*-oxides, salts, and stereochemically isomeric forms thereof, wherein the dashed line represents an optional double bond between atoms C7 and C8;

R^1 is aryl or a saturated, a partially unsaturated or completely unsaturated 5 or 6 membered monocyclic or 9 to 12 membered bicyclic heterocyclic ring system wherein said ring system contains one nitrogen, and optionally one to three additional heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and wherein the remaining ring members are carbon atoms; wherein said

ring system may be optionally substituted on any carbon or nitrogen ring atom with one, two, three, or four substituents each independently selected from C_{3-7}cycloalkyl, aryl, Het, -C(=O)$NR^{5a}R^{5b}$, -C(=O)R^7, -C(=O)OR^{6a}, and C_{1-6}alkyl optionally substituted with C_{3-7}cycloalkyl, aryl, Het, -C(=O)$NR^{5a}R^{5b}$, -$NR^{5a}R^{5b}$, -C(=O)R^7, -NR^{5a}C(=O)R^7, -$NR^{5a}SO_pR^8$, -SO_pR^8, -$SO_pNR^{5a}R^{5b}$, -C(=O)OR^6, or -NR^{5a}C(=O)OR^{6a}; and wherein the substituents on any carbon atom of the heterocyclic ring may also be selected from –OR^8, -SR^8, halo, polyhalo-C_{1-6}alkyl, oxo, thio, cyano, nitro, azido, -$NR^{5a}R^{5b}$, -NR^{5a}C(=O)R^7, -$NR^{5a}SO_pR^8$, -SO_pR^8, -$SO_pNR^{5a}R^{5b}$, -C(=O)OH, and -NR^{5a}C(=O)OR^{6a};

L is a direct bond, –O–, -O-C_{1-4}alkanediyl-, –O-CO–, –O-C(=O)-NR^{5a}- or –O-C(=O)-NR^{5a}-C_{1-4}alkanediyl-;

$\mathbf{R^2}$ represents hydrogen, -OR^6, -C(=O)OR^6, -C(=O)R^7, -C(=O)$NR^{5a}R^{5b}$, -C(=O)NHR^{5c}, -$NR^{5a}R^{5b}$, -NHR^{5c}, -$NHSO_pNR^{5a}R^{5b}$, -$NR^{5a}SO_pR^8$, or -$B(OR^6)_2$;

$\mathbf{R^3}$ and $\mathbf{R^4}$ are hydrogen or C_{1-6}alkyl; or $\mathbf{R^3}$ and $\mathbf{R^4}$ taken together may form a C_{3-7}cycloalkyl ring;

n is 3, 4, 5, or 6;

p is 1 or 2;

each $\mathbf{R^{5a}}$ and $\mathbf{R^{5b}}$ are, independently, hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted with halo, C_{1-6}alkoxy, cyano, polyhaloC_{1-6}alkoxy, C_{3-7}cycloalkyl, aryl, or with Het; or $\mathbf{R^{5a}}$ and $\mathbf{R^{5b}}$ taken together with the nitrogen atom to which they are attached form pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl; wherein the morpholinyl and piperidinyl groups may be optionally substituted with one or with two C_{1-6}alkyl radicals;

$\mathbf{R^{5c}}$ is C_{3-7}cycloalkyl, aryl, Het, -O-C_{3-7}cycloalkyl, -O-aryl, -O-Het, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein said C_{1-6}alkyl or C_{1-6}alkoxy may be each optionally substituted with –C(=O)OR^6, C_{3-7}cycloalkyl, aryl, or Het;

$\mathbf{R^6}$ is hydrogen; C_{2-6}alkenyl; Het; C_{3-7}cycloalkyl optionally substituted with C_{1-6}alkyl; or C_{1-6}alkyl optionally substituted with C_{3-7}cycloalkyl, aryl or Het;

$\mathbf{R^{6a}}$ is C_{2-6}alkenyl, C_{3-7}cycloalkyl, Het, or C_{1-6}alkyl optionally substituted with C_{3-7}cycloalkyl, aryl or Het;

$\mathbf{R^7}$ is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, or aryl;

$\mathbf{R^8}$ is hydrogen, polyhaloC_{1-6}alkyl, aryl, Het, C_{3-7}cycloalkyl optionally substituted with C_{1-6}alkyl, or C_{1-6}alkyl optionally substituted with C_{3-7}cycloalkyl, aryl or Het;

aryl as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydronaphthyl, each of which may be optionally substituted with one, two or three substituents selected from halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxy-

carbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, aminocarbonyl, mono- or diC_{1-6}alkylaminocarbonyl, azido, mercapto, C_{3-7}cycloalkyl, phenyl, pyridyl, thiazolyl, pyrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl; wherein the morpholinyl and piperidinyl groups may be optionally substituted with one or with two C_{1-6}alkyl radicals; and the phenyl, pyridyl, thiazolyl, pyrazolyl groups may be optionally substituted with 1, 2 or 3 substituents each independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, halo, amino, mono- or diC_{1-6}alkylamino;

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, said heterocyclic ring being optionally condensed with a benzene ring, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhalo-C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, aminocarbonyl, mono- or diC_{1-6}alkylaminocarbonyl, C_{3-7}cycloalkyl, phenyl, pyridyl, thiazolyl, pyrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl; wherein the morpholinyl and piperidinyl groups may be optionally substituted with one or with two C_{1-6}alkyl radicals; and the phenyl, pyridyl, thiazolyl, pyrazolyl groups may be optionally substituted with 1, 2 or 3 substituents each independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, halo, amino, mono- or diC_{1-6}alkylamino.

The compounds of the present invention are surprising because despite their decreasing structural flexibility, they are active drugs against HCV. This is contrary to the currently prevailing opinion which expects less active drugs with less flexible macrocylic rings.

In addition, the compounds of the present invention having relatively low molecular weight are easy to synthesize, starting from starting materials that are commercially available or readily available through art-known synthesis procedures.

The invention further relates to methods for the preparation of the compounds of formula (I), the *N*-oxides, addition salts, quaternary amines, metal complexes, and stereochemically isomeric forms thereof, their intermediates, and the use of the intermediates in the preparation of the compounds of formula (I).

The invention relates to the compounds of formula (I) *per se*, the *N*-oxides, addition salts, quaternary amines, metal complexes, and stereochemically isomeric forms thereof, for use as a medicament. The invention further relates to pharmaceutical compositions comprising a carrier and an anti-virally effective amount of a compound of formula (I) as specified herein. The pharmaceutical compositions may comprise combinations of the aforementioned compounds with other anti-HCV agents. The invention further relates to the aforementioned pharmaceutical compositions for administration to a subject suffering from HCV infection.

The invention also relates to the use of a compound of formula (I), or a *N*-oxide, addition salt, quaternary amine, metal complex, or stereochemically isomeric forms thereof, for the manufacture of a medicament for inhibiting HCV replication. Or the invention relates to a method of inhibiting HCV replication in a warm-blooded animal said method comprising the administration of an effective amount of a compound of formula (I), or a *N*-oxide, addition salt, quaternary amine, metal complex, or stereochemically isomeric forms thereof.

As used in the foregoing and hereinafter, the following definitions apply unless otherwise noted.

The term halo is generic to fluoro, chloro, bromo and iodo.

The term "polyhaloC_{1-6}alkyl" as a group or part of a group, e.g. in polyhaloC_{1-6}alkoxy, is defined as mono- or polyhalo substituted C_{1-6}alkyl, in particular C_{1-6}alkyl substituted with up to one, two, three, four, five, six, or more halo atoms, such as methyl or ethyl with one or more fluoro atoms, for example, difluoromethyl, trifluoromethyl, trifluoroethyl. Preferred is trifluoromethyl. Also included are perfluoroC_{1-6}alkyl groups, which are C_{1-6}alkyl groups wherein all hydrogen atoms are replaced by fluoro atoms, e.g. pentafluoroethyl. In case more than one halogen atom is attached to an alkyl group within the definition of polyhaloC_{1-6}alkyl, the halogen atoms may be the same or different.

As used herein "C_{1-4}alkyl" as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as for example methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-1-propyl; "C_{1-6}alkyl" encompasses C_{1-4}alkyl radicals and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, 1-pentyl, 2-pentyl, 3-pentyl, 1-hexyl, 2-hexyl, 2-methyl-1-butyl, 2-methyl-1-pentyl, 2-ethyl-1-butyl, 3-methyl-2-pentyl, and the like. Of interest amongst C_{1-6}alkyl is C_{1-4}alkyl.

The term "C_{2-6}alkenyl" as a group or part of a group defines straight and branched chained hydrocarbon radicals having saturated carbon-carbon bonds and at least one double bond, and having from 2 to 6 carbon atoms, such as, for example, ethenyl (or vinyl), 1-propenyl, 2-propenyl (or allyl), 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 2-methyl-2-butenyl, 2-methyl-2-pentenyl and the like. Of interest amongst C_{2-6}alkenyl is C_{2-4}alkenyl.

The term "C_{2-6}alkynyl" as a group or part of a group defines straight and branched chained hydrocarbon radicals having saturated carbon-carbon bonds and at least one triple bond, and having from 2 to 6 carbon atoms, such as, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 2-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl and the like. Of interest amongst C_{2-6}alkynyl is C_{2-4}alkynyl.

C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. C_{3-7}cycloalkyl when substituted on aryl or Het in particular is cyclopropyl.

C_{1-6}alkanediyl defines bivalent straight and branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methylene, ethylene, 1,3-propanediyl, 1,4-butanediyl, 1,2-propanediyl, 2,3-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the like. Of interest amongst C_{1-6}alkanediyl is C_{1-4}alkanediyl.

C_{1-6}alkoxy means C_{1-6}alkyloxy wherein C_{1-6}alkyl is as defined above.

As used herein before, the term (=O) or oxo forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom. Whenever a ring or ring system is substituted with an oxo group, the carbon atom to which the oxo is linked is a saturated carbon.

The bivalent radical L can be -O-C_{1-4}alkanediyl-, –O-CO–, –O-C(=O)-NR^{5a}- or –O-C(=O)-NR^{5a}-C_{1-4}alkanediyl-; these bivalent radicals in particular are linked to the pyrrolidine moiety by their oxygen atom.

The radical Het is a heterocycle as specified in this specification and claims. Examples of Het comprise, for example, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazinolyl, isothiazinolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl (including 1,2,3-triazolyl, 1,2,4-triazolyl), tetrazolyl, furanyl, thienyl, pyridyl, pyrimidyl, pyridazinyl, triazinyl,

or any of such heterocycles condensed with a benzene ring, such as indolyl, indazolyl (in particular 1H-indazolyl), indolinyl, quinolinyl, tetrahydroquinolinyl (in particular 1,2,3,4-tetrahydroquinolinyl), isoquinolinyl, tetrahydroisoquinolinyl (in particular 1,2,3,4-tetrahydroisoquinolinyl), quinazolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazinolyl, benzisothiazinolyl, benzothiazolyl, benzoxadiazolyl, benzothiadiazolyl, benzo-1,2,3-triazolyl, benzo-1,2,4-triazolyl, benzotetrazolyl, benzofuranyl, benzothienyl, benzopyrazolyl, and the like. Of interest amongst the Het radicals are those which are non-saturated, in particular those having an aromatic character. Of further interest are those Het radicals which are monocyclic.

Each of the Het or R^1 radicals mentioned in the previous and the following paragraph may be optionally substituted with the number and kind of substituents mentioned in the definitions of the compounds of formula (I) or any of the subgroups of compounds of formula (I). Some of the Het or R^1 radicals mentioned in this and the following paragraph may be substituted with one, two or three hydroxy substituents. Such hydroxy substituted rings may occur as their tautomeric forms bearing keto groups. For example a 3-hydroxypyridazine moiety can occur in its tautomeric form 2*H*-pyridazin-3-one. Some examples keto-substituted Het or R^1 radicals are 1,3-dihydro-benzimidazol-2-one, 1,3-dihydro-indol-2-one, 1*H*-indole-2,3-dione, 1*H*-benzo[*d*]isoxazole, 1*H*-benzo[*d*]isothiazole, 1*H*-quinolin-2-one, 1*H*-quinolin-4-one, 1*H*-quinazolin-4-one, 9*H*-carbazole, and 1*H*-quinazolin-2-one. Where Het is piperazinyl, it preferably is substituted in its 4-position by a substituent linked to the 4-nitrogen with a carbon atom, e.g. 4-C_{1-6}alkyl, 4-polyhaloC_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{3-7}cycloalkyl.

R^1 can be a saturated, a partially unsaturated or completely unsaturated 5 or 6 membered monocyclic or 9 to 12 membered bicyclic heterocyclic ring system as specified in this specification and claims. Examples of said monocyclic or bicyclic ring system comprise any of the rings mentioned in the above paragraph as examples of the radical Het and additionally any of the monocyclic heterocycles mentioned in the above paragraph that are condensed with pyridyl or pyrimidinyl such as, for example, pyrrolopyridine (in particular 1*H*-pyrrolo[2,3]-*b*]pyridine, 1*H*-pyrrolo[2, 3-*c*]pyridine), naphtyridine (in particular 1,8-naphtyridine), imidazopyridine (in particular 1*H*-imidazo[4, 5-*c*]pyridine, 1*H*-imidazo[4,5-*b*]pyridine), pyridopyrimidine, purine (in particular 7*H*-purine) and the like.

Interesting Het or R^1 radicals comprise, for example pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl (including 1,2,3-triazolyl, 1,2,4-triazolyl), tetrazolyl, furanyl, thienyl, pyridyl, pyrimidyl, pyridazinyl, pyrazolyl, triazinyl, or any of such heterocycles condensed with a benzene ring, such as indolyl, indazolyl (in particular 1H-indazolyl), indolinyl, quinolinyl, tetrahydroquinolinyl (in particular 1,2,3,4-tetrahydroquinolinyl), isoquinolinyl, tetrahydroisoquinolinyl (in particular 1,2,3,4-tetrahydroisoquinolinyl), quinazolinyl, phthalazinyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoxadiazolyl, benzothiadiazolyl, benzofuranyl, benzothienyl.

The Het radicals pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-substituted piperazinyl preferably are linked via their nitrogen atom (i.e. 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, 4-substituted 1-piperazinyl).

Each "aryl" is as specified above and preferably is phenyl substituted with the substituents specified above. This applies equally to arylC_{1-6}alkyl, which in particular can be arylmethyl, e.g. benzyl.

It should be noted that the radical positions on any molecular moiety used in the definitions may be anywhere on such moiety as long as it is chemically stable.

Radicals used in the definitions of the variables include all possible isomers unless otherwise indicated. For instance pyridyl includes 2-pyridyl, 3-pyridyl and 4-pyridyl; pentyl includes 1-pentyl, 2-pentyl and 3-pentyl.

When any variable occurs more than one time in any constituent, each definition is independent.

Whenever used hereinafter, the term "compounds of formula (I)", or "the present compounds" or similar terms, it is meant to include the compounds of formula (I), each and any of the subgroups thereof, their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes, and stereochemically isomeric forms. One embodiment comprises the compounds of formula (I) or any subgroup of compounds of formula (I) specified herein, as well as the *N*-oxides, salts, as the possible stereoisomeric forms thereof. Another embodiment comprises the compounds of formula (I) or any subgroup of compounds of formula (I) specified herein, as well as the salts as the possible stereoisomeric forms thereof.

The compounds of formula (I) have several centers of chirality and exist as stereochemically isomeric forms. The term "stereochemically isomeric forms" as used herein defines all the possible compounds made up of the same atoms bound by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formula (I) may possess.

With reference to the instances where (*R*) or (*S*) is used to designate the absolute configuration of a chiral atom within a substituent, the designation is done taking into consideration the whole compound and not the substituent in isolation.

Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms, which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of the present invention both in pure form or mixed with each other are intended to be embraced within the scope of the present invention.

Pure stereoisomeric forms of the compounds and intermediates as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term "stereoisomerically pure" concerns compounds or intermediates having a stereoisomeric excess of at least 80% (i.e. minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in particular having a stereoisomeric excess of 97% up to 100%. The terms "enantiomerically pure" and "diastereomerically pure" should be understood in a similar way, but then having regard to the enantiomeric excess, and the diastereomeric excess, respectively, of the mixture in question.

Pure stereoisomeric forms of the compounds and intermediates of this invention may be obtained by the application of art-known procedures. For instance, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids or bases. Examples thereof are tartaric acid, dibenzoyl-tartaric acid, ditoluoyltartaric acid and camphosulfonic acid. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting

materials, provided that the reaction occurs stereospecifically. Preferably, if a specific stereoisomer is desired, said compound is synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The diastereomeric racemates of the compounds of formula (I) can be obtained separately by conventional methods. Appropriate physical separation methods that may advantageously be employed are, for example, selective crystallization and chromatography, e.g. column chromatography.

For some of the compounds of formula (I), their *N*-oxides, salts, solvates, quaternary amines, or metal complexes, and the intermediates used in the preparation thereof, the absolute stereochemical configuration was not experimentally determined. A person skilled in the art is able to determine the absolute configuration of such compounds using art-known methods such as, for example, X-ray diffraction.

The present invention is also intended to include all isotopes of atoms occurring on the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

The term "prodrug" as used throughout this text means the pharmacologically acceptable derivatives such as esters, amides and phosphates, such that the resulting *in vivo* biotransformation product of the derivative is the active drug as defined in the compounds of formula (I). The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th ed, McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p 13–15) describing prodrugs generally is hereby incorporated. Prodrugs preferably have excellent aqueous solubility, increased bioavailability and are readily metabolized into the active inhibitors *in vivo*. Prodrugs of a compound of the present invention may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either by routine manipulation or *in vivo*, to the parent compound.

Preferred are pharmaceutically acceptable ester prodrugs that are hydrolysable *in vivo* and are derived from those compounds of formula (I) having a hydroxy or a carboxyl group. An *in vivo* hydrolysable ester is an ester, which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl

esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyl-oxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyl-oxyethyl which may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxy-methoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4-position of the benzoyl ring.

For therapeutic use, salts of the compounds of formula (I) are those wherein the counter-ion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic (i.e. hydroxybutanedioic acid), tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids.

Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

The compounds of formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

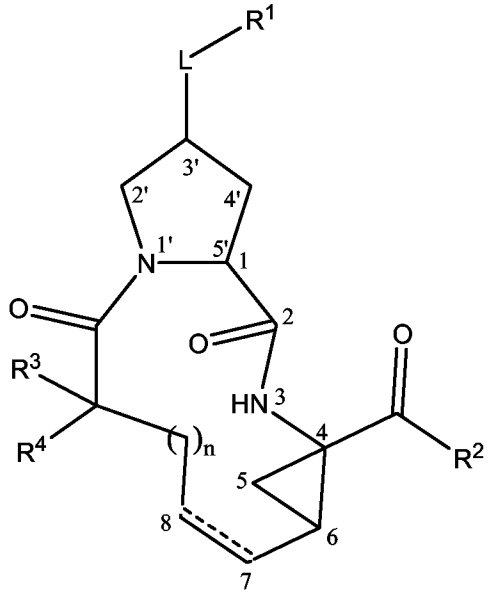
The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of formula (I) are able to form by reaction between a basic nitrogen of a compound of formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyliodide or benzyliodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary amine has a positive charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

It will be appreciated that the compounds of formula (I) may have metal binding, chelating, complex forming properties and therefore may exist as metal complexes or metal chelates. Such metalated derivatives of the compounds of formula (I) are intended to be included within the scope of the present invention.

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

As mentioned above, the compounds of formula (I) have several asymmetric centers. In order to more efficiently refer to each of these asymmetric centers, the numbering system as indicated in the following structural formula will be used.

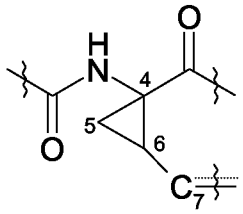


(I)

Asymmetric centers are present at positions 1, 4 and 6 of the macrocycle as well as at the carbon atom 3' in the pyrrolidine moiety, or proline residue, bearing the –L-R^1 group. Each of these asymmetric centers can occur in their R or S configuration.

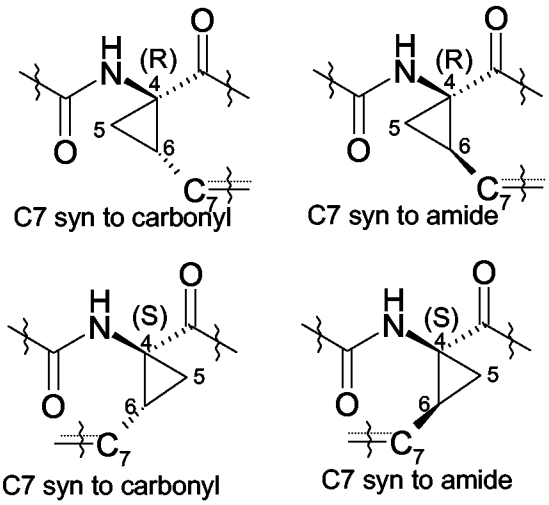
The stereochemistry at position 1 preferably corresponds to that of an L-amino acid configuration, i.e. that of L-proline.

The compounds of formula (I) include a cyclopropyl group as represented in the structural fragment below:



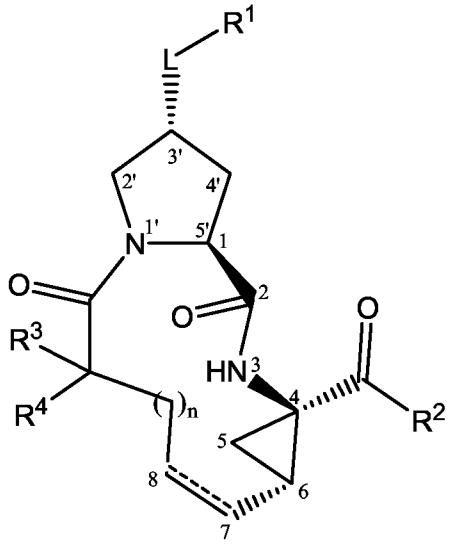
wherein C_7 represents the carbon at position 7 and carbons at position 4 and 6 are asymmetric carbon atoms of the cyclopropane ring.

Notwithstanding other possible asymmetric centers at other segments of the compounds of the invention, the presence of these two asymmetric centers means that the compounds can exist as mixtures of diastereomers, such as the diastereomers of compounds of formula (I) wherein the carbon at position 7 is configured either syn to the carbonyl or syn to the amide as shown below.



One embodiment concerns compounds of formula (I) wherein the carbon at position 7 is configured syn to the carbonyl. Another embodiment concerns compounds of formula (I) wherein the configuration at the carbon at position 4 is R. A specific subgroup of compounds of formula (I) are those wherein the carbon at position 7 is configured syn to the carbonyl and wherein the configuration at the carbon at position 4 is R.

The compounds of formula (I) also include a proline residue. Preferred are the compounds of formula (I) wherein the substituent at the 1 (or 5') position and the substituent –L-R^1 (at position 3') are in a trans configuration. Of particular interest are the compounds of formula (I) wherein position 1 has the configuration corresponding to L-proline and the –L-R^1 substituent is in a trans configuration in respect of position 1. Preferably the compounds of formula (I) have the stereochemistry as indicated in the structure of formula (I-a) as depicted below:



(I-a)

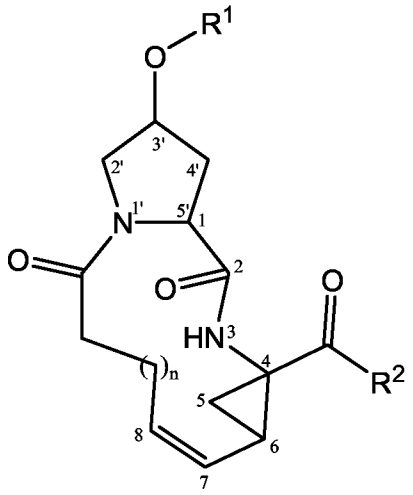
One embodiment of the present invention concerns compounds of formula (I) or of formula (I-a), or of any subgroup of compounds of formula (I), wherein one or more of the following conditions apply:

(a) R^3 and R^4 are both hydrogen;

(b) L is –O-;

(c) a double bond is present between carbon atoms 7 and 8.

A particular subgroup of compounds of formula (I) are those represented by the following structural formula:

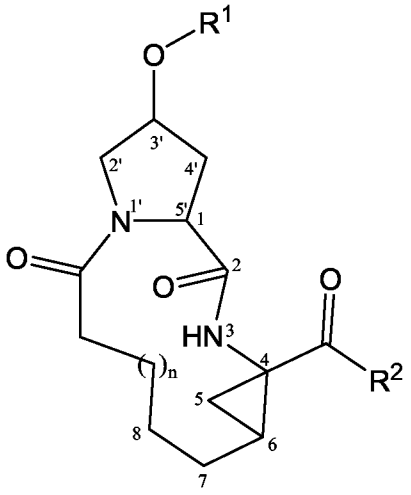


(I-b)

Amongst the compounds of formula (I-b), those having the stereochemical configuration of the compounds of formula (I-a) are of particular interest.

The double bond between carbon atoms 7 and 8 in the compounds of formula (I), or in any subgroup of compounds of formula (I), may be in a *cis* or in a *trans* configuration. Preferably the double bond between carbon atoms 7 and 8 is in a *cis* configuration, as depicted in formula (I-b).

Yet another particular subgroup of compounds of formula (I) are those represented by the following structural formula:



(I-c)

Amongst the compounds of formula (I-c), those having the stereochemical configuration of the compounds of formula (I-a) are of particular interest.

In (I-a), (I-b) and (I-c), where applicable, L, n, R^1, R^2, R^3 and R^4 are as specified in the definitions of the compounds of formula (I) or in any of the subgroups of compounds of formula (I) specified herein.

It is to be understood that the above defined subgroups of compounds of formulae (I-a), (I-b) or (I-c) as well as any other subgroup defined herein, are meant to also comprise any *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms of such compounds.

When n is 2, the moiety $-CH_2-$ bracketed by "n" corresponds to ethanediyl in the compounds of formula (I) or in any subgroup of compounds of formula (I). When n is 3, the moiety $-CH_2-$ bracketed by "n" corresponds to propanediyl in the compounds of formula (I) or in any subgroup of compounds of formula (I). When n is 4, the moiety $-CH_2-$ bracketed by "n" corresponds to butanediyl in the compounds of formula (I) or in any subgroup of compounds of formula (I). When n is 5, the moiety $-CH_2-$ bracketed by "n" corresponds to pentanediyl in the compounds of formula (I) or in any subgroup of compounds of formula (I). When n is 6, the moiety $-CH_2-$ bracketed by "n" corresponds to hexanediyl in the compounds of formula (I) or in any subgroup of compounds of formula (I). Particular subgroups of the compounds of formula (I) are those compounds wherein n is 4 or 5.

Further subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein R^1 is phenyl, naphthyl, pyridyl, pyridazinyl, triazolyl, tetrazolyl, quinolinyl, isoquinolinyl, quinazolinyl, pyrimidinyl, [1,8]naphthyridinyl, indolinyl, 1,2,3,4-tetrahydroquinolinyl,

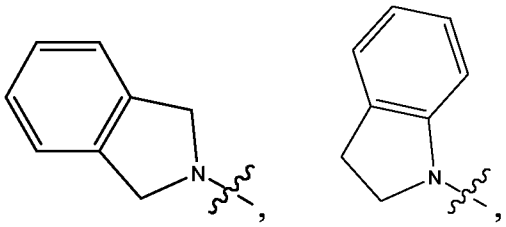
1,2,3,4-tetrahydroisoquinolinyl; all optionally substituted with one, two or three substituents selected from those mentioned in relation to R^1 in the definitions of the compounds of formula (I) or any of the subgroups of compounds of formula (I).

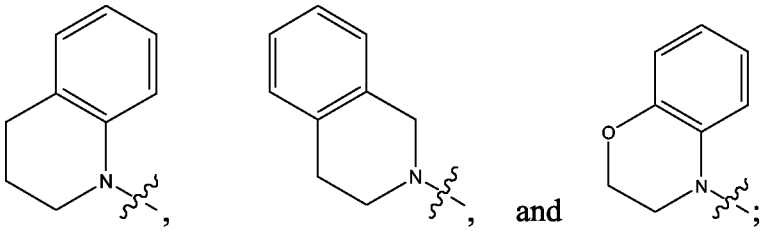
Other subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein

(a) R^1 is phenyl, naphthyl (such as naphth-1-yl or naphth-2-yl), quinolinyl (in particular quinolin-4-yl), isoquinolinyl (in particular isoquinolin-1-yl), quinazolinyl (in particular quinazolin-4-yl), pyridyl (in particular 3-pyridyl), pyrimidinyl (in particular pyrimidin-4-yl), pyridazinyl (in particular pyridazin-3-yl and pyridazin-2-yl), [1,8]naphtyridinyl (in particular [1,8]naphthyridin-4-yl);

(b) R^1 is triazolyl (in particular triazol-1-yl, triazol-2-yl), tetrazolyl (in particular tetrazol-1-yl, tetrazol-2-yl), 6-oxo-pyridazin-1-yl, pyrazolyl (in particular pyrazol-1-yl), or imidazolyl (in particular imidazol-1-yl, imidazol-2-yl);

(c) R^1 is a heterocycle selected from





and

;

and wherein each of the above mentioned R^1 radicals may be optionally substituted with one, two or three substituents selected from those mentioned in relation to R^1 in the definitions of the compounds of formula (I) or any of the subgroups of compounds of formula (I).

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is a direct bond, –O–, –OC(=O) –, or –OC(=O)NR^{5a}–, or in particular wherein L is –OC(=O)NH– or –O-, or more in particular wherein L is –O-.

Preferably L is –O–, and R^1 is as specified above in (a). Preferably L is a direct bond, and R^1 is as specified above in (b). Preferably L is a bivalent radical –OC(=O)–, and R^1 is as specified above in (c).

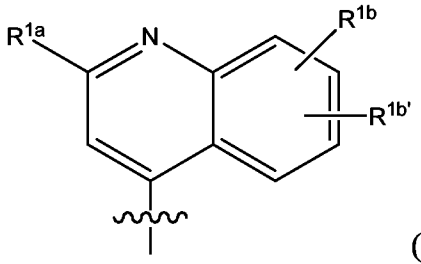
Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is –O– and R^1 is quinolinyl (in particular quinolin-4-yl), isoquinolinyl (in particular isoquinolin-1-yl), quinazolinyl (in particular quinazolin-4-yl), or pyrimidinyl (in particular pyrimidin-4-yl), either of which is, independently, optionally mono, di, or tri substituted with C_{1-6}alkyl, C_{1-6}alkoxy, nitro, hydroxy, halo, trifluoromethyl, -$NR^{5a}R^{5b}$, -$C(=O)NR^{5a}R^{5b}$, C_{3-7}cycloalkyl, aryl, Het, -C(=O)OH, or –$C(=O)OR^{6a}$; wherein aryl or Het are each, independently, optionally substituted with halo, C_{1-6}alkyl, C_{1-6}alkoxy, amino, mono- or diC_{1-6}alkylamino, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl (e.g.4-methylpiperazinyl), thiomorpholinyl or morpholinyl; and wherein the morpholinyl, thiomorpholinyl and piperidinyl groups may optionally substituted with one or two C_{1-6}alkyl radicals.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is –O– and R^1 is quinolinyl (in particular quinolin-4-yl), isoquinolinyl (in particular isoquinolin-1-yl), quinazolinyl (in particular quinazolin-4-yl), or pyrimidinyl (in particular pyrimidin-4-yl), either of which is, independently, optionally mono, di, or tri substituted with methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, fluoro, chloro, bromo, -$NR^{5a}R^{5b}$, -$C(=O)NR^{5a}R^{5b}$, phenyl, methoxyphenyl, cyanophenyl, halophenyl, pyridyl, C_{1-4}alkylpyridyl, pyrimidinyl, piperidinyl, morpholinyl, piperazinyl, C_{1-4}alkyl-piperazinyl, pyrrolidinyl, pyrazolyl, C_{1-4}alkyl-pyrazolyl, thiazolyl, C_{1-4}alkylthiazolyl, cyclopropylthiazolyl, or mono- or diC_{1-4}alkyl-aminothiazolyl; and wherein the morpholinyl, thiomorpholinyl and piperidinyl groups may optionally be substituted with one or two C_{1-6}alkyl (in particular one or two methyl) radicals.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^1 is quinolinyl, optionally substituted with 1, 2, 3 or 4 (or with 1, 2 or 3) substituents selected from those mentioned as possible substituents on the monocyclic or bicyclic ring systems of R^1, as specified in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I).

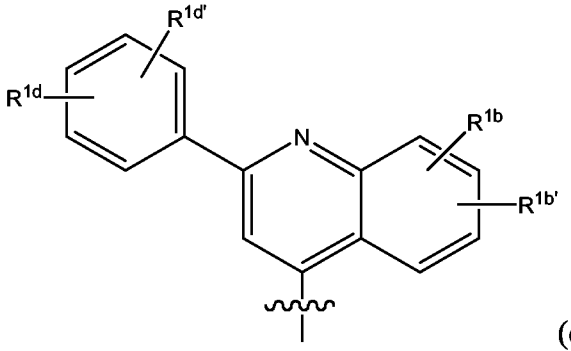
Specific embodiments of the invention are those compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^1 is

(d-1) a radical of formula



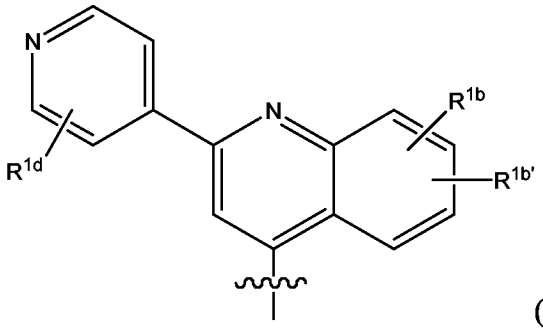
(d-1)

(d-2) a radical of formula



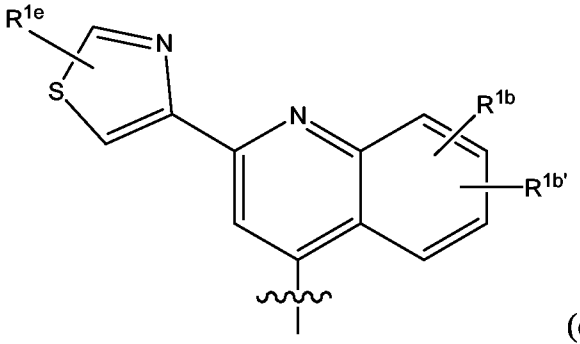
(d-2)

(d-3) a radical of formula



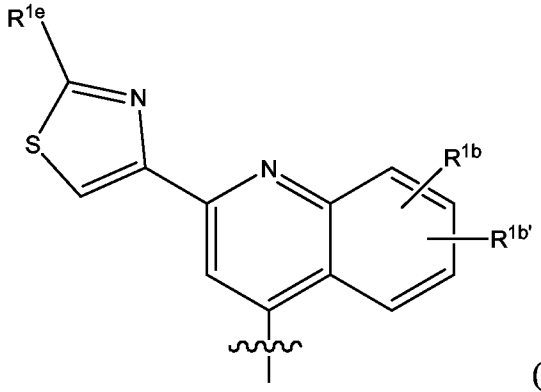
(d-3)

(d-4) a radical of formula



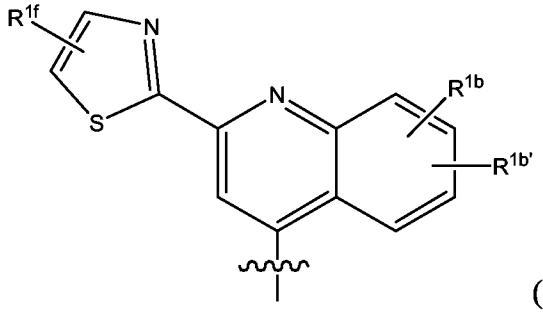
(d-4)

or in particular, (d-4-a) a radical of formula



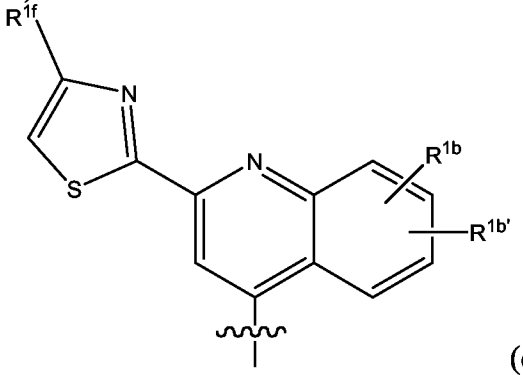
(d-4-a)

(d-5) a radical of formula



(d-5)

or in particular, (d-5-a) a radical of formula



(d-5-a)

wherein in radicals (d-1) – (d-5), as well as in (d-4-a) and (d-5-a):
each R^{1a}, R^{1b}, $R^{1b'}$, R^{1d}, $R^{1d'}$, R^{1e}, R^{1f} are independently any of the substituents selected from those mentioned as possible substituents on the monocyclic or bicyclic ring systems of R^1, as specified in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I);

or, in particular, wherein in radicals (d-1) – (d-5), as well as in (d-4-a) and (d-5-a):

R^{1b} and $R^{1b'}$ may, independently, be hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, $-NR^{5a}R^{5b}$ (in particular amino or mono- or diC_{1-6}alkylamino), $-C(=O)NR^{5a}R^{5b}$, (in particular

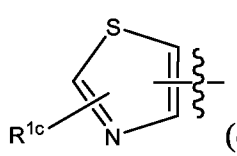
aminocarbonyl or mono- or diC_{1-6}alkylaminocarbonyl), nitro, hydroxy, halo, trifluoromethyl, –C(=O)OH, or –C(=O)OR^{6a} (in particular wherein R^{6a} is C_{1-6}alkyl);

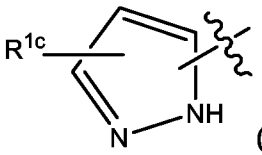
wherein each R^{5a}, R^{5b}, R^{6a} mentioned above or hereinafter independently is as defined in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I);

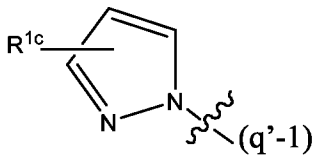
or, in particular, wherein in radicals (d-1) – (d-5), as well as in (d-4-a) and (d-5-a): R^{1a} is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, monoC_{1-6}alkylamino, amino, C_{3-7}cycloalkyl, aryl, or Het;

more specifically R^{1a} is C_{1-6}alkoxy, aryl, or Het; of interest are embodiments wherein R^{1a} is methoxy, ethoxy, propoxy, phenyl, pyridyl, thiazolyl, pyrazolyl, each substituted as specified in the definitions of the compounds of formula (I) or of any of the subgroups of the compounds of formula (I); in specific embodiments said aryl or Het may each, independently, optionally substituted with C_{1-6}alkyl, C_{1-6}alkoxy, amino, mono- or diC_{1-6}alkylamino, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl; and wherein the morpholinyl, and piperidinyl groups may optionally substituted with one or two C_{1-6}alkyl radicals; and in particular R^{1a} can be a radical Het; wherein Het may include pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl; and wherein the morpholinyl, thiomorpholinyl and piperidinyl groups may optionally substituted with one or two C_{1-6}alkyl radicals;

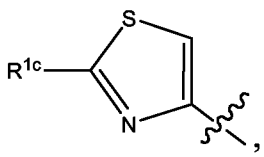
Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^{1a} is a radical

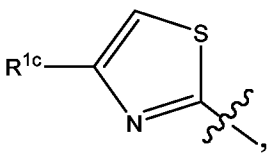

(q)

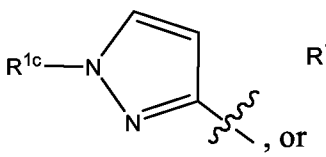

(q')

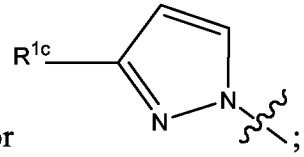

(q'-1)

or, in particular, wherein R^{1a} is selected from the group consisting of:


(q-1)


(q-2)


, or (q-3)


; (q-4)

wherein, where possible a nitrogen may bear an R^{1c} substituent or a link to the remainder of the molecule; each R^{1c} is any of the R^1 substituents may be selected from those mentioned as possible substituents on the monocyclic or bicyclic ring systems of R^1, as specified in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I);

specifically each R^{1c} may be hydrogen, halo, C_{1-6}alkyl, C_{1-6}alkoxy, polyhaloC_{1-6}alkyl (in particular trifluoromethyl), -$NR^{5a}R^{5b}$ (in particular amino or mono- or diC_{1-6}alkyl-amino), -C(=O)$NR^{5a}R^{5b}$, (in particular aminocarbonyl or mono- or diC_{1-6}alkylamino-carbonyl), nitro, hydroxy, –C(=O)OH, or –C(=O)OR^{6a} (in particular wherein R^{6a} is C_{1-6}alkyl), phenyl, pyridyl, thiazolyl, pyrazolyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl (in particular 4-methylpiperazinyl); and wherein the morpholinyl and piperidinyl groups may optionally substituted with one or two C_{1-6}alkyl radicals;

more specifically each R^{1c} may be hydrogen, halo, C_{1-6}alkyl, amino, or mono- or di-C_{1-6}alkylamino, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-C_{1-6}alkyl-piperazinyl; and wherein the morpholinyl and piperidinyl groups may optionally substituted with one or two C_{1-6}alkyl radicals; and the phenyl, pyridyl, thiazolyl, pyrazolyl groups may be optionally substituted with 1, 2 or 3 (in particular with 1 or 2) substituents each independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, halo, amino, mono- or diC_{1-6}alkylamino;

more specifically each R^{1c} may be hydrogen, halo, C_{1-6}alkyl, amino, or mono- or di-C_{1-6}alkylamino, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-C_{1-6}alkyl-piperazinyl; and wherein the morpholinyl and piperidinyl groups may optionally substituted with one or two C_{1-6}alkyl radicals;

and where R^{1c} is substituted on a nitrogen atom, it preferably is a carbon containing substituent that is connected to the nitrogen via a carbon atom or one of its carbon atoms;

specifically each R^{1d} and $R^{1d'}$ independently may be hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, or halo;

or more specifically each R^{1d} in (d-3) may be hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy or halo;

specifically R^{1e} may be hydrogen, C_{1-6}alkyl, amino, mono- or diC_{1-6}alkylamino, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl (in particular

4-methylpiperazinyl); and wherein the morpholinyl and piperidinyl groups may optionally substituted with one or two C_{1-6}alkyl radicals;

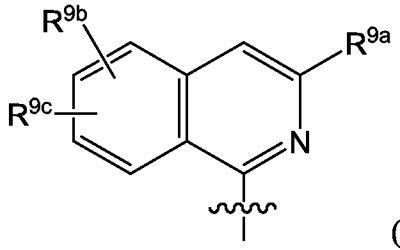
preferably each R^{1b} is C_{1-6}alkoxy, more preferably methoxy;

specifically R^{1f} may be hydrogen, C_{1-6}alkyl, amino, mono- or diC_{1-6}alkylamino, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl (in particular 4-methyl-piperazinyl), or morpholinyl.

Specific embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^1 is 7-methoxy-2-phenyl-quinolin-4-yl and L is –O-.

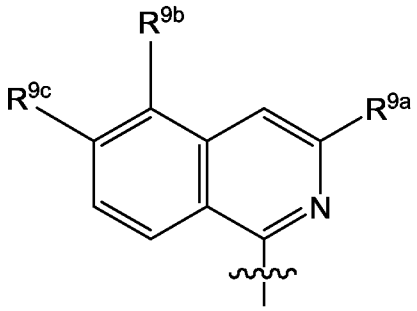
Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^1 is
(e) isoquinolinyl (in particular 1-isoquinolinyl), optionally substituted with 1, 2, 3 or 4 (or with 1, 2 or 3) substituents selected from those mentioned as possible substituents on the monocyclic or bicyclic ring systems of R^1, as specified in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I).

Specific such embodiments are those wherein R^1 is
(e-1) a radical of formula:



(e-1)

or in particular (e-1-a) a radical of formula:



(e-1-a)

wherein R^{9a}, R^{9b}, R^{9c} independently form one another are any of the substituents selected from those mentioned as possible substituents on the monocyclic or bicyclic

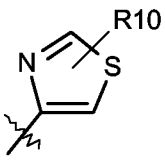
ring systems of R^1, as specified in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I); in particular

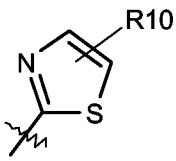
R^{9a} may have the same meanings as R^{1a} as specified above; in particular it may be aryl or Het, either of which is optionally substituted with any of the radicals mentioned as substituents of aryl or of Het as specified definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I) (including the number of substituents); specifically said aryl or Het may be substituted with 1, 2 or 3 (in particular with one) radical or radicals R^{10}; wherein said R^{10} is any of the radicals mentioned as substituents of aryl or Het as specified definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I) as defined above; or in particular R^{10} is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, phenyl, pyridyl, thiazolyl, pyrazolyl, amino optionally mono or disubstituted with C_{1-6}alkyl, or aminocarbonyl or mono- or diC_{1-6}alkylaminocarbonyl; wherein Het also includes pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl (e.g. 4-methylpiperazinyl) or morpholinyl; and wherein the morpholinyl or piperidinyl groups may optionally be substituted with one or two C_{1-6}alkyl radicals; and the phenyl, pyridyl, thiazolyl, pyrazolyl groups may be optionally substituted with 1, 2 or 3 (in particular with 1 or 2) substituents each independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, halo, amino, mono- or diC_{1-6}alkylamino;

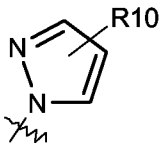
R^{9b} may have the same meanings as R^{1b} as specified above; in particular it may be hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, Het, halo (e.g. bromo, chloro or fluoro);
R^{9c} may have the same meanings as R^{1c} as specified above; in particular it may be hydrogen or C_{1-6}alkoxy.

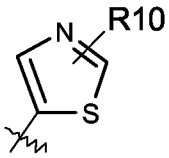
In particular R^{9a} in the isoquinolinyl radical specified under (e-1) or (1-e-a) includes phenyl, pyridyl, thiazolyl, oxazolyl or pyrazolyl either of which is optionally substituted with R^{10} as defined above, in particular optionally substituted whith an R^{10} which may be hydrogen, C_{1-6}alkyl (e.g. methyl, ethyl, isopropyl, tert-butyl), amino, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl (e.g. 4-methylpiperazinyl), or morpholinyl, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, aminocarbonyl, or mono- or diC_{1-6}alkylaminocarbonyl; and wherein the morpholinyl and piperidinyl groups may optionally substituted with one or two C_{1-6}alkyl radicals.

Preferably R^{9a} in the isoquinolinyl radical specified under (e-1) or (e-1-a) includes any of radicals (q), (q'), (q'-1), (q-1), (q-2), (q-3), (q-4) specified above as well as:


(q-5)

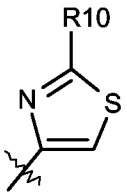

(q-6)

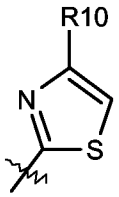

(q-7)

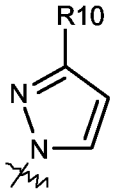

(q-8)

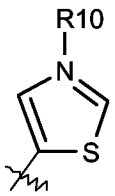
wherein each R^{10} is any of the radicals mentioned as substituents of Het as specified in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I); or in particular R^{10} is as defined above; especially R^{10} is hydrogen, C_{1-6}alkyl (e.g. methyl, ethyl, isopropyl, tert-butyl), amino, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl (e.g. 4-methylpiperazinyl), morpholinyl, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, aminocarbonyl, or mono- or diC_{1-6}alkylaminocarbonyl; and wherein the morpholine and piperidine may optionally substituted with one or two C_{1-6}alkyl radicals.

Also preferably R^{9a} in the isoquinolinyl radical specified under (e-1) or (e-1-a) includes:







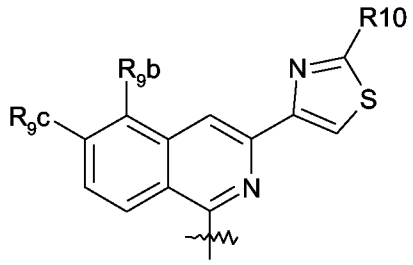


wherein each R^{10} is as defined above, and especially is hydrogen, halo, C_{1-6}alkyl (e.g. methyl, ethyl, isopropyl, tert-butyl), amino, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl (e.g. 4-methylpiperazinyl), morpholinyl, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, aminocarbonyl, or mono- or diC_{1-6}alkylaminocarbonyl; and wherein the morpholinyl and piperidinyl groups may optionally substituted with one or two C_{1-6}alkyl radicals.

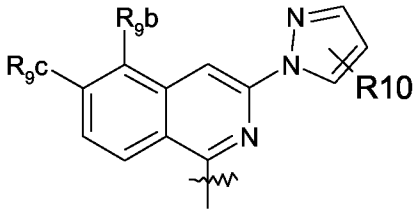
R^{9b} in the isoquinolinyl radical specified under (e-2) may be hydrogen, C_{1-6}alkyl, halo (e.g. bromo, chloro or fluoro), especially hydrogen or bromo.

R^{9b} in the isoquinolinyl radical specified under (e-2) may be hydrogen or C_{1-6}alkoxy (e.g. methoxy).

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^1 is



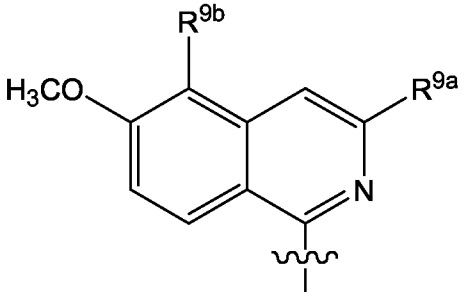
(e-2)



(e-3)

wherein R^{9b} is hydrogen or halo (e.g. bromo) and R^{9c} is hydrogen or C_{1-6}alkoxy (e.g. methoxy).

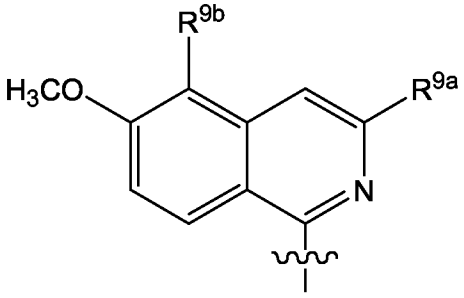
Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^1 is



(e-4)

wherein R^{9a} is as defined in any of the groups or subgroups of compounds of formula (I); and
R^{9b} is hydrogen, halo, or trifluoromethyl.

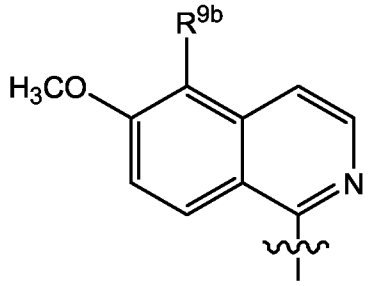
Further preferred embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^1 is:



(e-4)

wherein R^{9a} is methoxy, ethoxy or propoxy; and
R^{9b} is hydrogen, fluoro, bromo, chloro, iodo, methyl, ethyl, propyl, or trifluoromethyl.

Further embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^1 is:



(e-5)

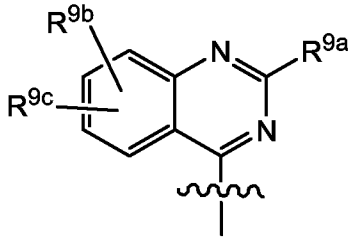
wherein R^{9b} is hydrogen, halo, or trifluoromethyl.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^1 is

(f) quinazolinyl (in particular quinazolin-4-yl), optionally substituted with 1, 2, 3 or 4 (or with 1, 2 or 3) substituents selected from those mentioned as possible substituents on the monocyclic or bicyclic ring systems of R^1, as specified in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I).

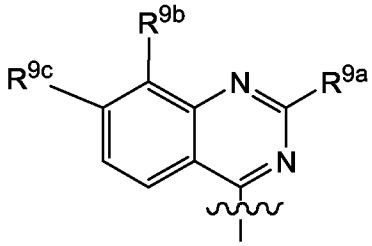
Quinazoline embodiments of R^1 include

(f-1) a radical :



(f-1)

or in particular (f-1-a) a radical :



(f-1-a)

wherein R^{9a}, R^{9b} and R^{9c} have the meanings stated above in relation to R^1 being isoquinolinyl (such as in radicals (e-1), (e-1-a), etc).

wherein specifically R^{9a} is C_{3-7}cycloalkyl, aryl or Het, any of which is optionally substituted with one, two or three (in particular with one) R^{10}; wherein

R^{10} is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, phenyl, pyridyl, thiazolyl, pyrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl, thiomorpholinyl or morpholinyl, aminocarbonyl, mono or di C_{1-6}alkylaminocarbonyl; wherein the piperidinyl or morpholinyl may be optionally substituted with one or two C_{1-6}alkyl radicals; and the phenyl, pyridyl, thiazolyl, pyrazolyl groups may be optionally substituted with 1, 2 or 3 (or with 1 or 2) substituents each independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, halo, amino, mono- or diC_{1-6}alkylamino (in particular selcted from C_{1-6}alkyl);

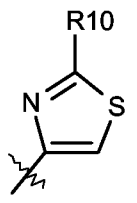
R^{9b} is hydrogen, halogen, C_{1-6}alkyl (in particular methyl), C_{3-7}cycloalkyl, aryl, Het, halo (in particular bromo, chloro or fluoro);
R^{9c} is hydrogen or C_{1-6}alkoxy.

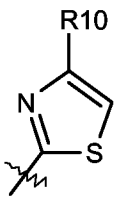
Favoured embodiments of R^{9a} for quinazolines include aryl or Het, especially wherein R^{9a} is phenyl, pyridyl, thiazolyl, oxazolyl or pyrazolyl either of which is optionally substituted with one, two or three (in particular with one) R^{10} as defined.

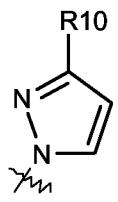
Embodiments of R^{10} for quinazoline include is hydrogen, methyl, ethyl, isopropyl, tert-butyl, halo (including dihalo, such as difluoro), pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl (e.g. 4-methylpiperazinyl) or morpholinyl, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, amino carbonyl, mono or diC_{1-6}alkylaminocarbonyl, or C_{3-7}cyclo-alkyl (in particular cyclopropyl).

Preferably R^{9a} in the quinazolyl radical specified under (f-1) or (f-1-a) includes any of radicals (q), (q'), (q'-1), (q-1), (q-2), (q-3), (q-4), (q-5), (q-6), (q-7), (q-8) specified above;
wherein in these radicals R^{10} is as defined above or in particular is hydrogen, C_{1-6}alkyl (such as methyl, ethyl, isopropyl, tert-butyl), pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, N-methylpiperazinyl or morpholinyl, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino or amino carbonyl, mono or diC_{1-6}alkylaminocarbonyl.

R^{9a} for quinazolines may include







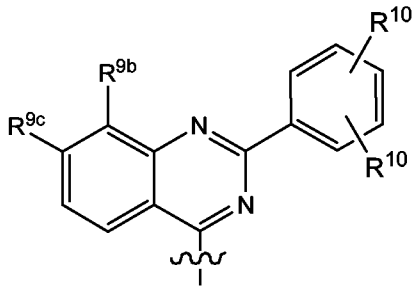
wherein R^{10} is hydrogen, halogen, C_{1-6}alkyl (such as methyl, ethyl, isopropyl, tert-butyl), C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylamido, morpholinyl or piperidin-1-yl, the morpholinyl and piperidinyl being optionally substituted with one or two C_{1-6}alkyl groups.

Additional R^{9a} embodiments for quinazolines include phenyl substited with one or two R^{10} groups such as is hydrogen, methyl, ethyl, isopropyl, tert-butyl, methoxy, saturated monocyclic amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino or aminocarbonyl, mono- and diC_{1-6}alkylaminocarbonyl or halo (in particular fluoro).

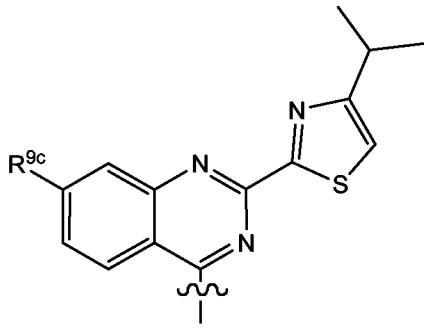
Embodiments of R^{9b} for quinazolines include hydrogen, C_{1-6}alkyl (in particular methyl), halo (e.g. bromo, chloro or fluoro) especially wherein R^{9b} is hydrogen or bromo.

Embodiments of R^{9c} for quinazolines include hydrogen or C_{1-6}alkoxy (in particular methoxy).

Specific embodiments of the compounds of formula (I) or any of the subgroups of compounds of formula (I) are those wherein R^1 is :



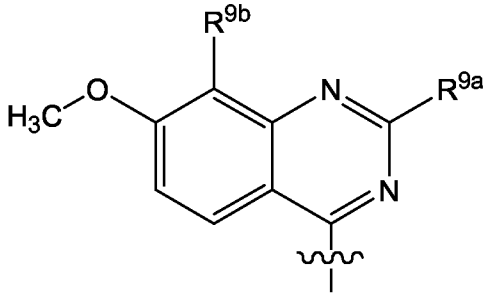
(f-2)



(f-3)

wherein R^{9b} is hydrogen or methyl; and each R^{10} and R^{9c} are as specified above and in particular and R^{9c} is hydrogen or C_{1-6}alkoxy (e.g. methoxy).

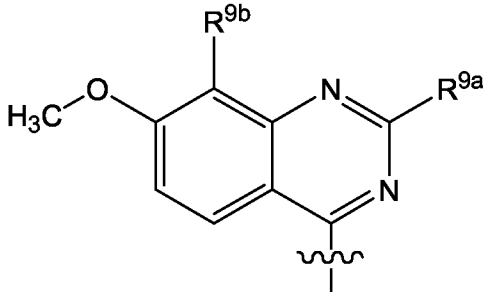
Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^1 is



(g-1)

wherein R^{9a} is as defined in any of the groups or subgroups of compounds of formula (I), preferably R^{9a} is p-methoxyphenyl or p-fluoromethyl; and
R^{9b} is hydrogen, halo, methyl, or trifluoromethyl.

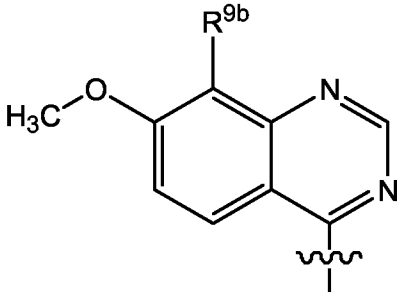
Further preferred embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^1 is:



(g-1)

wherein R^{9a} is methoxy, ethoxy or propoxy; and
R^{9b} is hydrogen, fluoro, bromo, chloro, iodo, methyl, ethyl, propyl, or trifluoromethyl.

Further embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^1 is:



(g-2)

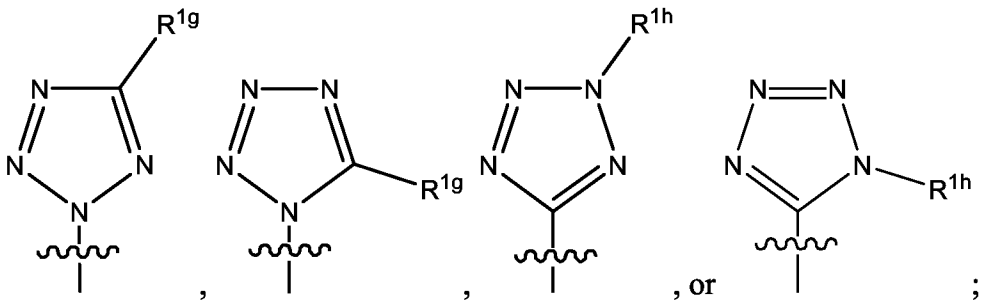
wherein R^{9b} is hydrogen, halo, or trifluoromethyl.

Preferred amongst the subgroups of compounds of the embodiments wherein R^1 is a radical (d-1) – (d-5), (e-1) – (e-3), (f-1) – (f-3), (g-1) – (g-2) as specified above, are those compounds whithin these subgroups wherein is L is –O-.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is a direct bond and R^1 is selected from the group consisting of 1*H*-pyrrole, 1*H*-imidazole, 1*H*-pyrazole, furan, thiophene, oxazole, thiazole, isoxazole, isothiazole, pyridine, pyridazine, pyrimidine, pyrazine, phthalazine, quinoxaline, quinazoline, quinoline, cinnoline, 1*H*-pyrrolo[2,3]-*b*]pyridine, 1*H*-indole, 1*H*-benzoimidazole, 1*H*-indazole, 7*H*-purine, benzothiazole, benzoxazole, 1*H*-imidazo[4, 5-*c*]pyridine, 1*H*-imidazo[4,5-*b*]pyridine, 1, 3-dihydro-benzimidazol-2-one, 1, 3-dihydro-benzimidazol-2-thione, 2, 3-dihydro-1*H*-indole, 1,3-dihydro-indol-2-one, 1*H*-indole-2,3-dione, , 1*H*-pyrrolo[2, 3-*c*]pyridine, benzofuran, benzo[*b*]thiophene, benzo[*d*]isoxazole, benzo[*d*]isothiazole, 1H-quinotin-2-one, 1*H*-quinolin-4-one, 1*H*-quinazolin-4-one, 9*H*-carbazole, and 1*H*-quinazolin-2-one, each optionally substituted with the R^1 substituents specified in the definitions of the compounds of formula (I) or any of the subgroups of compounds of formula (I).

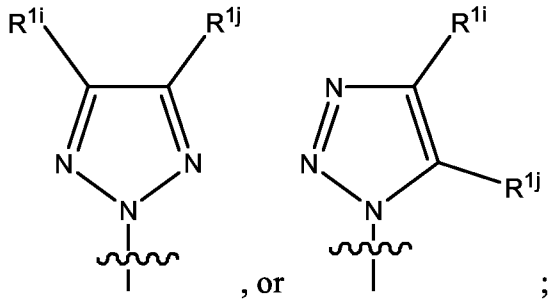
Further embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is a direct bond and R^1 is selected from the group consisting of pyrrolidine, 4,5-dihydro-1*H*-pyrazole, pyrazolidine, imidazolidin-2-one, pyrrolidin-2-one, pyrrolidine-2,5-dione, piperidine-2,6-dione, piperidin-2-one, piperazine-2,6-dione, piperazin-2-one, piperazine, morpholine, pyrazolidin-3-one, imidazolidine-2,4-dione, piperidine, tetrahydrofuran, tetrahydropyran, 1,4-dioxane, and 1,2,3,6-tetrahydropyridine, each optionally substituted with the R^1 substituents specified in the definitions of the compounds of formula (I) or any of the subgroups of compounds of formula (I).

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is a direct bond and R^1 is optionally substituted tetrazolyl as depicted below:



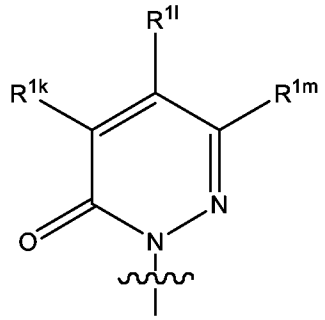
wherein R^{1g} is hydrogen, C_{1-6}alkoxy, hydroxy, $-NR^{5a}R^{5b}$, $-C(=O)R^7$, $-SO_pR^8$, C_{3-7}cycloalkyl, aryl, Het, or C_{1-6}alkyl optionally substituted with C_{3-7}cycloalkyl, aryl, or Het;
R^{1h} is hydrogen, $-NR^{5a}R^{5b}$, C_{3-7}cycloalkyl, aryl, Het, or C_{1-6}alkyl optionally substituted with C_{3-7}cycloalkyl, aryl, or Het; and
R^{5a}, R^{5b}, R^7, and R^8 are as defined above.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is a direct bond and R^1 is optionally substituted triazolyl as depicted below:



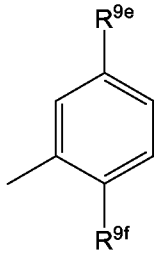
wherein R^{1i} and R^{1j} are each, independently, selected from the group consisting of hydrogen, halo, $-C(=O)NR^{5a}R^{5b}$, $-C(=O)R^7$, C_{3-7}cycloalkyl, aryl, Het, and C_{1-6}alkyl optionally substituted with $-NR^{5a}R^{5b}$, or aryl; or alternatively, R^{1i} and R^{1j} taken together with the carbon atoms to which they are attached, may form a cyclic moiety selected from the group consisting of aryl and Het.

Further preferred substituents for R^1 when L is a direct bond, include pyridazinone and derivatives thereof as shown below:



wherein R^{1k}, R^{1l} and R^{1m} are independently selected from the group consisting of hydrogen, azido, halo, C_{1-6}alkyl, $-NR^{5a}R^{5b}$, C_{3-7}cycloalkyl, aryl, and Het; or alternatively, R^{1k} and R^{1l} or R^{1l} and R^{1m} taken together with the carbon atoms to which they are attached, may form a phenyl moiety, which in turn may be optionally substituted with azido, halo, C_{1-6}alkyl, $-NR^{5a}R^{5b}$, C_{3-7}cycloalkyl, aryl or Het.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is –O-(C=O)-NR^{5a}- or in particular wherein L is -O-(C=O)-NH- and R^1 is aryl as defined above; or R^1 is phenyl optionally substituted with 1, 2 or three substituents selected from those mentioned as possible substituents of the radical aryl as in the definitions of the compounds of formula (I) or of any of the subgroups of compounds of formula (I); specifically R^1 is a radical of formula:



wherein

R^{9e} is hydrogen, C_{1-6}alkyl, polyhaloC_{1-6}alkyl or halo;

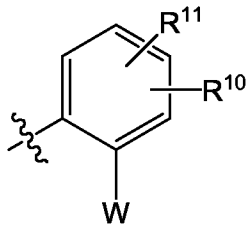
R^{9f} is –COOH, -C(=O)OR^{6a}, halo, Het or aryl; wherein Het and aryl are as defined herein and

R^{6a} is C_{1-6}alkyl, preferably R^{6a} is methyl or ethyl;

In particular, R^{9e} may be hydrogen, fluoro or trifluoromethyl.

In particular, R^{9f} may be -COOC_{1-6}alkyl (e.g. -C(=O)OEt), phenyl, thiazolyl, 1-piperidinyl or 1-pyrazolyl, the phenyl, piperidinyl and pyrazolyl groups being optionally substituted with C_{1-6}alkyl, in particular with methyl.

Other embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein L is –O-(C=O)-NR^{5a}- or, in particular, wherein L is –O-(C=O)-NH- and R^1 is a radical of formula:



wherein R^{10} and R^{11} independently from one another are hydrogen, halo, hydroxy, nitro, cyano, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxy-carbonyl, amino, azido, mercapto, C_{1-6}alkylthio, polyhaloC_{1-6}alkyl, aryl or Het; especially R^{10} and R^{11} independently from one another are hydrogen, halo, nitro,

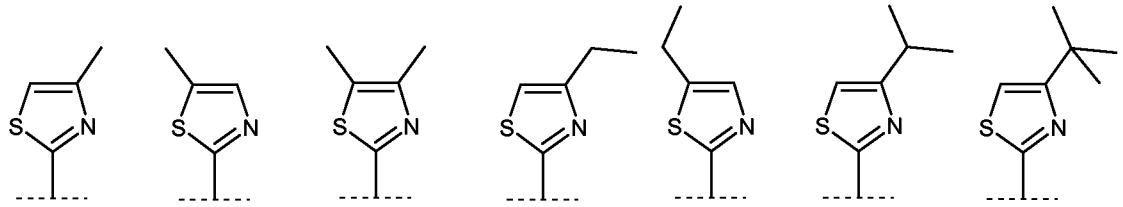
carboxyl, methyl, ethyl, isopropyl, t-butyl, methoxy, ethoxy, isopropoxy, t-butoxy, methylcarbonyl, ethylcarbonyl, isopropylcarbonyl, t-butyl-carbonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, t-butoxycarbonyl, methylthio, ethylthio, isopropylthio, t-butylthio, trifluoromethyl, or cyano;

W is aryl or Het, or W is –COOH or –$COOR^{6a}$, wherein R^{6a} is C_{1-6}alkyl, preferably methyl or ethyl.

Other subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein W is phenyl, naphthyl (in particular naphth-1-yl, or naphth-2-yl), pyrrolyl (in particular pyrrol-1-yl), pyridyl (in particular 3-pyridyl), pyrimidinyl (in particular pyrimidin-4-yl), pyridazinyl (in particular pyridazin-3-yl and pyridazin-2-yl), 6-oxo-pyridazin-1-yl, triazolyl (in particular 1,2,3-triazolyl, 1,2,4-triazolyl, more in particular 1,2,3-triazol-2-yl, 1,2,4-triazol-3-yl), tetrazolyl (in particular tetrazol-1-yl, tetrazol-2-yl), pyrazolyl (in particular pyrazol-1-yl, pyrazol-3-yl), imidazolyl (in particular imidazol-1-yl, imidazol-2-yl), thiazolyl (in particular thiazol-2-yl), pyrrolidinyl (in particular pyrrolidin-1-yl), piperidinyl (in particular piperidin-1-yl), piperazinyl (in particular 1-piperazinyl), 4-C_{1-6}alkylpiperazinyl (in particular 4-C_{1-6}alkylpiperazin-1-yl, more in particular 4-methyl-piperazin-1-yl), furanyl (in particular furan-2-yl), thienyl (in particular thien-3-yl), morpholinyl (in particular morpholin-4-yl); all optionally substituted with one or two substituents selected from C_{1-6}alkyl, polyhaloC_{1-6}alkyl, or C_{1-6}alkoxycarbonyl.

In particular W may be phenyl, naphth-1-yl, naphth-2-yl, pyrrol-1-yl, 3-pyridyl, pyrimidin-4-yl, pyridazin-3-yl, pyridazin-2-yl, 6-oxo-pyridazin-1-yl, 1,2,3-triazol-2-yl, 1,2,4-triazol-3-yl, tetrazol-1-yl, tetrazol-2-yl, pyrazol-1-yl, pyrazol-3-yl, imidazol-1-yl, imidazol-2-yl, thiazol-2-yl, pyrrolidin-1-yl, piperidin-1-yl, furan-2-yl, thien-3-yl, morpholin-4-yl; all optionally substituted with one or two substituents selected from C_{1-6}alkyl, polyhaloC_{1-6}alkyl (such as trifluoromethyl) and C_{1-6}alkoxycarbonyl.

Further subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein W is thiazol-2-yl substituted with one or two C_{1-6}alkyl, such as methyl, ethyl, isopropyl or tert-butyl. Preferred subgroups of the compounds of formula (I) are those compounds of formula (I), or any subgroup of compounds of formula (I) specified herein, wherein W is selected from the following structures:



Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^{10} and R^{11} independently from one another are hydrogen, halo, nitro, carboxyl, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxy-carbonyl, C_{1-6}alkylthio, polyhaloC_{1-6}alkyl, cyano, aryl or Het.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^{10} and R^{11} independently from one another are hydrogen, halo, nitro, carboxyl, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, ethoxy, isopropoxy, *tert* -butoxy, methylcarbonyl, ethylcarbonyl, isopropylcarbonyl, *tert* -butyl-carbonyl, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, *tert*–butoxycarbonyl, methylthio, ethylthio, isopropylthio, *tert* -butylthio, trifluoromethyl, or cyano.

Preferred embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein one of R^{10} and R^{11} is hydrogen.

Preferred embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein one of R^{10} and R^{11} is halo (in particular fluoro), trifluoromethyl or C_{1-6}alkyl (in particular methyl). Other preferred embodiments are those wherein one of R^{10} and R^{11} is halo (in particular fluoro), trifluoromethyl or methyl, and the other of R^{10} and R^{11} is hydrogen.

Preferred embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein one of R^{10} and R^{11} is in para position in respect of the W group. Further preferred embodiments are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein one of R^{10} and R^{11} is halo (in particular fluoro), trifluoromethyl or methyl, and is in para position in respect of the W group; the other of R^{10} and R^{11} may be as defined above or may be hydrogen.

Embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein

(a) R^2 is –NHR^{5c}, in particular wherein R^{5c} is C_{1-6}alkyl, aryl, Het, C_{1-6}alkoxy, -O-aryl, or –O-Het;

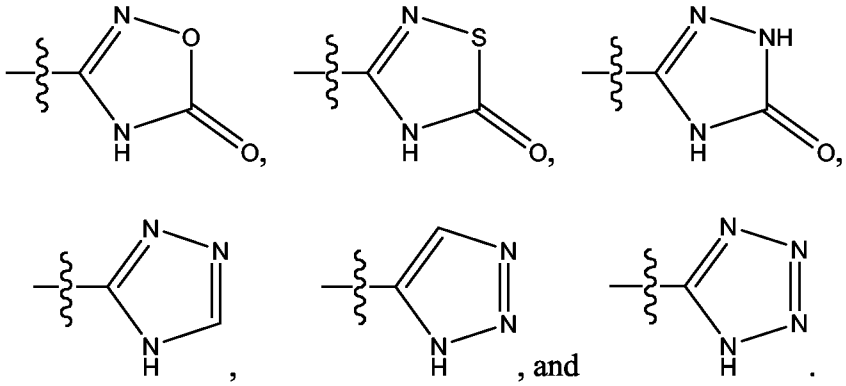
(b) R^2 is $-OR^6$, in particular wherein R^6 is C_{1-6}alkyl, such as methyl, ethyl, or *tert*-butyl and preferably wherein R^6 is hydrogen;

(c) R^2 is $-NHS(=O)_2R^8$, in particular wherein R^8 is C_{1-6}alkyl, C_3-C_7cycloalkyl optionally substituted with C_{1-6}alkyl, or aryl, e.g. wherein R^8 is methyl, cyclopropyl, methylcyclopropyl, or phenyl;

(d) R^2 is $-C(=O)OR^6$, $-C(=O)R^7$, $-C(=O)NR^{5a}R^{5b}$, or $-C(=O)NHR^{5c}$, wherein R^{5a}, R^{5b}, R^{5c}, R^6, or R^7 are as defined above, and R^2 preferably is $-C(=O)NHR^{5c}$ wherein R^{5c} is cyclopropyl;

(e) R^2 is $-NHS(=O)_2NR^{5a}R^{5b}$, in particular wherein R^{5a} and R^{5b} are, each independently, hydrogen, C_{3-7}cycloalkyl or C_{1-6}alkyl, e.g. $NHS(=O)_2N(C_{1-3}alkyl)_2$.

Further embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^2 is $-NHR^{5c}$, and R^{5c} is a Het group selected from



Further embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein R^2 is $-NHR^{5c}$, and R^{5c} is a C_{1-6}alkyl substituted with $-C(=O)OR^6$.

Further embodiments of the invention are compounds of formula (I) or any of the subgroups of compounds of formula (I) wherein

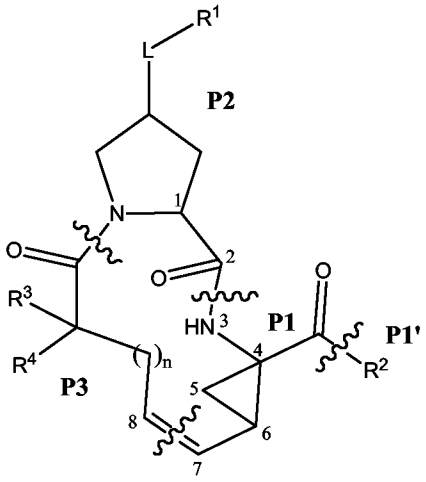
(a) R^3 and R^4 are both hydrogen;

(b) R^3 and R^4 are both C_{1-6}alkyl;

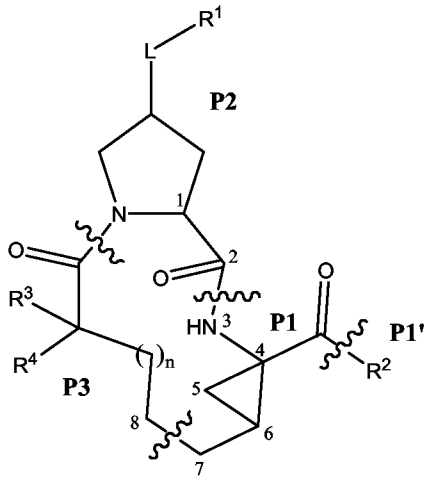
(c) R^3 and R^4 taken together with the carbon atom to which they are linked form a cyclopropyl, a cyclobutyl, a cyclopentyl, or a cyclohexyl group.

The compounds of formula (I) having a double or a single bond in the macrocycle (i.e. between carbon atoms 7 and 8), represented by formula (I-d) or (I-e) herebelow, consist of three building blocks P1, P2, P3. The building block P1 further contains a P1' tail.

The linking of building blocks P1 with P2, P3 with P2, and optionally P1 with P1', involves forming an amide bond. The linking of building blocks P1, P1', P2 and P3 to prepare compounds (I-d) or (I-c) can be done in any given sequence. One of the steps involves a cyclization whereby the macrocycle is formed. Compounds of formula (I-e) can be prepared from compound of formula (I-b) by reduction of the double bond.



(I-d)

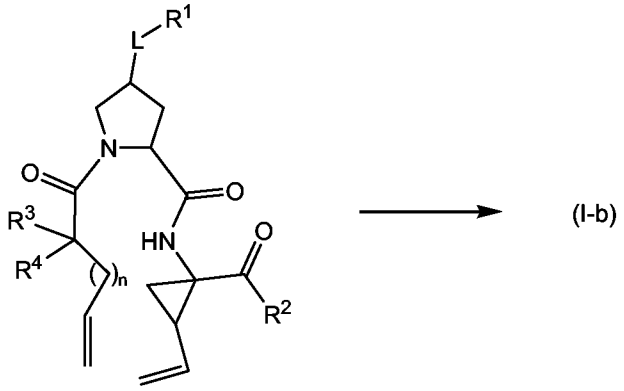


(I-e)

The synthesis procedures described hereinafter are meant to be applicable for as well the racemates, stereochemically pure intermediates or end products, as any stereoisomeric mixtures. The racemates or stereochemical mixtures may be separated into stereoisomeric forms at any stage of the synthesis procedures. In one embodiment, the intermediates and end procucts have the stereochemistry specified above in the compounds of formula (I-a).

In one embodiment, compounds (I-d) are prepared by first forming the amide bonds and subsequent forming the double bond linkage between P3 and P1 with concomitant cyclization to the macrocycle.

In a preferred embodiment, compounds (I) wherein the bond between C_7 and C_8 is a double bond, which are compounds of formula (I-a), as defined above, may be prepared as outlined in the following reaction scheme:



(II)

Formation of the macrocycle can be carried out via an olefin metathesis reaction in the presence of a suitable metal catalyst such as e.g. the Ru-based catalyst reported by Miller, S.J., Blackwell, H.E., Grubbs, R.H. J. Am. Chem. Soc. 118, (1996), 9606-9614; Kingsbury, J. S., Harrity, J. P. A., Bonitatebus, P. J., Hoveyda, A. H., J. Am. Chem. Soc. 121, (1999), 791-799; and Huang et al., J. Am. Chem. Soc. 121, (1999), 2674-2678; for example a Hoveyda-Grubbs catalyst.

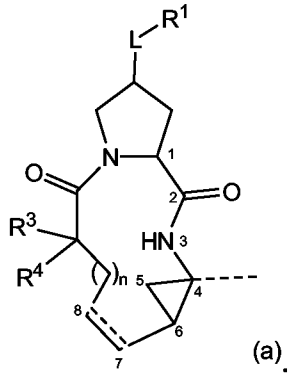
Air-stable ruthenium catalysts such as bis(tricyclohexylphosphine)-3-phenyl-1H-inden-1-ylidene ruthenium chloride (Neolyst M1®) or bis(tricyclohexylphosphine)-[(phenylthio)methylene]ruthenium (IV) dichloride can be used. Other catalysts that can be used are Grubbs first and second generation catalysts, i.e. Benzylidene-bis(tricyclohexylphosphine)dichlororuthenium and (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium, respectively. Of particular interest are the Hoveyda-Grubbs first and second generation catalysts, which are dichloro(*o*-isopropoxyphenylmethylene)(tricyclohexylphosphine)-ruthenium(II) and 1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium respectively. Also other catalysts containing other transition metals such as Mo can be used for this reaction.

The metathesis reactions may be conducted in a suitable solvent such as for example ethers, e.g. THF, dioxane; halogenated hydrocarbons, e.g. dichoromethane, $CHCl_3$, 1,2-dichloroethane and the like. In a preferred embodiment, the metathesis reaction is conducted in toluene. These reactions are conducted at increased temperatures under nitrogen atmosphere.

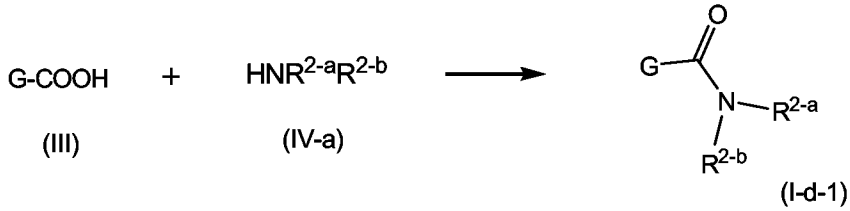
Compounds of formula (I) wherein the link between C7 and C8 in the macrocycle is a single bond, i.e. compounds of formula (I-e), can be prepared from the compounds of formula (I-d) by a reduction of the C7-C8 double bond in the compounds of formula (I-a). This reduction may be conducted by catalytic hydrogenation with hydrogen in the

presence of a noble metal catalyst such as, for example, Pt, Pd, Rh, Ru or Raney nickel. Of interest is Rh on alumina. The hydrogenation reaction preferably is conducted in a solvent such as, e.g. an alcohol such as methanol, ethanol, or an ether such as THF, or mixtures thereof. Water can also be added to these solvents or solvent mixtures.

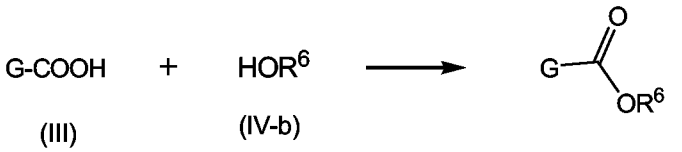
The R^2 group can be connected to the P1 building block at any stage of the synthesis, i.e. before or after the cyclization, or before or after the cyclization and reduction as descibed herein above. The compounds of formula (I) wherein R^2 represents $-NR^{5a}R^{5b}$, $-NHR^{5c}$, $-NHSO_pNR^{5a}R^{5b}$, $-NR^{5a}SO_pR^8$, these groups being collectively represented by $-NR^{2-a}R^{2-b}$, said compounds being represented by formula (I-d-1), can be prepared by linking the R^2 group to P1 by forming an amide bond between both moieties. Similarly, the compounds of formula (I) wherein R^2 represents $-OR^6$, i.e. compounds (I-d-2), can be prepared by linking the R^2 group to P1 by forming an ester bond. In one embodiment, the $-NR^{2-a}R^{2-b}$ or $-OR^6$ groups are introduced in the last step of the synthesis of the compounds (I) as outlined in the following reaction schemes wherein G represents a group:



(a)



(I-d-1)

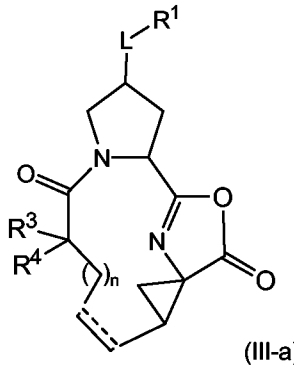


(I-d-2)

Intermediate (III) can be coupled with the amine (IV-a) by an amide forming reaction such as any of the procedures for the formation of an amide bond described hereinafter. In particular, (III) may be treated with a coupling agent, for example *N,N'*-carbonyl-diimidazole (CDI), EEDQ, IIDQ, EDCI, or benzotriazol-1-yl-oxy-tris-pyrrolidino-

phosphonium hexafluorophosphate (commercially available as PyBOP®), in a solvent such as an ether, e.g. THF, or a halogenated hydrocarbon, e.g. dichloromethane, chlorophorm, dichloroethane, followed by reaction with the desired (IV-a), preferably after reacting (III) with the coupling agent. The reactions of (III) with (IV-a) preferably are conducted in the presence of a base, for example a trialkylamine such as triethylamine or diisopropylethylamine, or 1,8-diazabicycle[5.4.0]undec-7-ene (DBU). Intermediate (III) can also be converted into an activated form, e.g. an activated form of general formula G-CO-Z, wherein Z represents halo, or the rest of an active ester, e.g. Z is an aryloxy group such as phenoxy, p.nitrophenoxy, pentafluorophenoxy, trichlorophenoxy, pentachlorophenoxy and the like; or Z can be the rest of a mixed anhydride. In one embodiment, G-CO-Z is an acid chloride (G-CO-Cl) or a mixed acid anhydride (G-CO-O-CO-R or G-CO-O-CO-OR, R in the latter being e.g. C_{1-4}alkyl, such as methyl, ethyl, propyl, i.propyl, butyl, t.butyl, i.butyl, or benzyl). The activated form G-CO-Z is reacted with the desired (IV-a).

The activation of the carboxylic acid in (III) as described in the above reactions may lead to an internal cyclization reaction to an azalactone intermediate of formula



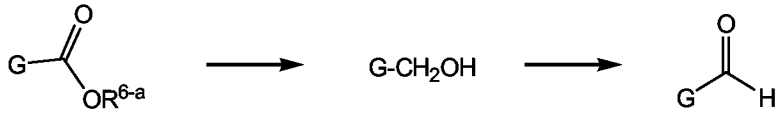
(III-a),

wherein L, R^1, R^3, R^4, n are as specified above and wherein the stereogenic centers may have the stereochemical configuration as specified above, for example as in (I-a) or (I-b). The intermediates (III-a) can be isolated from the reaction mixture, using conventional methodology, and the isolated intermediate (III-a) is then reacted with (IV-a), or the reaction mixture containing (III-a) can be reacted further with (IV-a) without isolation of (III-a). In one embodiment, where the reaction with the coupling agent is conducted in a water-immiscible solvent, the reaction mixture containing (III-a) may be washed with water or with slightly basic water in order to remove all water-soluble side products. The thus obtained washed solution may then be reacted with (IV-a) without additional purification steps. The isolation of intermediates (III-a) on the other hand may provide certain advantages in that the isolated product, after

optional further purification, may be reacted with (IV-a), giving rise to less side products and an easier work-up of the reaction.

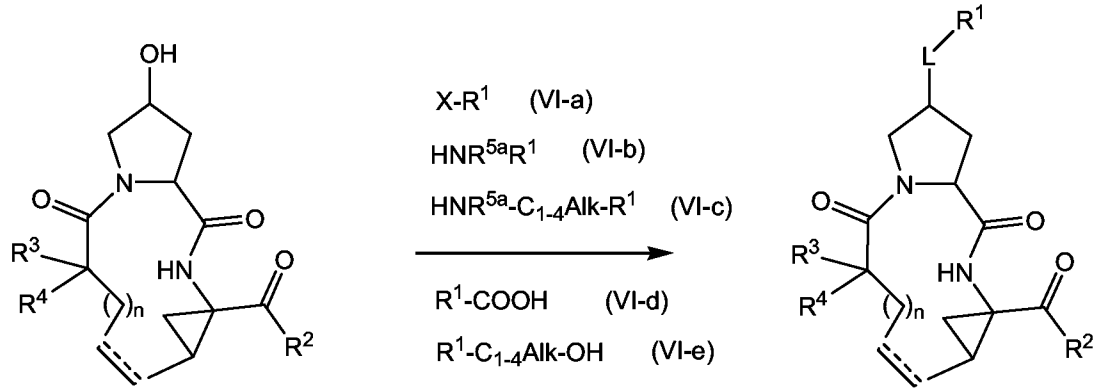
Intermediate (III) can be coupled with the alcohol (IV-b) by an ester forming reaction. For example, (III) and (IV-b) are reacted together with removal of water either physically, e.g. by azeotropical water removal, or chemically by using a dehydrating agent. Intermediate (III) can also be converted into an activated form G-CO-Z, such as the activated forms mentioned above, and subsequently reacted with the alcohol (IV-b). The ester forming reactions preferably are conducted in the presence of a base such as an alkali metal carbonate or hydrogen carbonate, e.g. sodium or potassium hydrogen carbonate, or a tertairy amine such as the amines mentioned herein in relation to the amide forming reactions, in particular a trialkylamine, e.g. triethylamine. Solvents that can be used in the ester forming recations comprise ethers such as THF; halogenated hydrocarbons such as dichoromethane, $CHCl_3$; hydrocarbons such as toluene; polar aprotic solvents such as DMF, DMSO, DMA; and the like solvents.

The compounds of formula (I) wherein R^2 represents hydrogen, i.e. compounds (I-d-4), can be prepared from the esters (I-d-2-a), which are intermediates of formula (I-d-2) wherein R^6 is C_{1-4}alkyl, can be obtained by a reduction reaction to the corresponding alcohols (I-d-3), e.g. with a complex metal hydride such as $LiAlH_4$ or $NaBH_4$, followed by an oxidation reaction with a mild oxidant, e.g. with MnO_2, thus obtaining intermediates (I-d-4).



(I-d-2-a) (I-d-3) (I-d-4)

The compounds of formula (I) can also be prepared by reacting an intermediate (V) with intermediates (VI-a) – (VI-e) as outlined in the following reaction scheme wherein the various radicals have the meanings specified above and C_{1-4}Alk represents C_{1-4}alkanediyl:



X in (VI-a) represents hydroxy or a leaving group such as a halide, e.g. bromide or chloride, or an arylsulfonyl group, e.g. mesylate, triflate or tosylate and the like.

In one embodiment, the reaction of (V) with (VI-a) is an O-arylation reaction and X represents a leaving group. This reaction can be conducted following the procedures described by E. M. Smith et al. (J. Med. Chem. (1988), 31, 875-885). In particular, this reaction is conducted in the presence of a base, preferably a strong base, in a reaction-inert solvent, e.g. one of the solvents mentioned for the formation of an amide bond.

In a particular embodiment, starting material (V) is reacted with (VI-a) in the presence of a base which is strong enough to detract a hydrogen from the hydroxy group, for example an alkali of alkaline metal hydride such as LiH or sodium hydride, or alkali metal alkoxide such as sodium or potassium methoxide or ethoxide, potassium *tert*-butoxide, in a reaction inert solvent like a dipolar aprotic solvent, e.g. DMA, DMF and the like. The resulting alcoholate is reacted with the arylating agent (VII), wherein X is a suitable leaving group as mentioned above. The conversion of (V) to (I) using this type of O-arylation reaction does not change the stereochemical configuration at the carbon bearing the hydroxy or -L-R^1 group.

Alternatively, the reaction of (V) with (VI-a) can also be conducted via a Mitsunobu reaction (Mitsunobu, 1981, Synthesis, January, 1-28; Rano et al., Tetrahedron Lett., 1995, 36, 22, 3779-3792; Krchnak et al., Tetrahedron Lett., 1995, 36, 5, 6193-6196; Richter et al., Tetrahedron Lett., 1994, 35, 27, 4705-4706). This reaction comprises treatment of intermediate (V) with (VI-a) wherein X is hydroxyl, in the presence of triphenylphosphine and an activating agent such as a dialkyl azocarboxylate, e.g. diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD) or the like. The Mitsunobu reaction changes the stereochemical configuration at the carbon bearing the hydroxy or -L-R^1 group.

Compounds of formula (I) wherein L is a urethane group (L is –O-C(=O)-NR^{5a}-) can be prepared by reacting (V) with (VI-b) or (VI-c) in the presence of a carbonyl introducing agent. The latter comprise reagents such as phosgene or phosgene derivatives such as carbonyl diimidazole (CDI). In one embodiment, (V) is reacted with phosgene thus providing the corresponding chloroformate which upon reaction with an amine, R^1-NH_2, or H-NR^1R^{5a}, provides carbamates i.e. L is -OC(=O)NH- or -OC(=O)NR^{5a}-. The reactions of the chloroformate with the amine preferably are conducted using the same solvents and bases as those mentioned for an amide bond formation, mentioned hereinafter, in particular those mentioned in relation to the reaction of (III) with (IV-a). Particular bases are alkali metal carbonates or hydrogen carbonates, e.g. sodium or potassium hydrogen carbonate, or tertairy amines, such as a trialkylamine, e.g. triethylamine.

The reaction of alcohol (V) with an acid (VI-d) yields esters, i.e. L is –O-C(=O)-. This ester forming reaction can be conducted using similar procedures as those described for the reaction of (III) and (IV-b). In particular the acid (VI-d) is converted to a corresponding acylating agent, e.g. an acid anhydride or acid halide, e.g. an acid chloride (R^1-C(=O)Cl).

Compounds of formula (I) wherein L is –O-C_{1-4}alkanediyl–, can be prepared by an ether forming reaction with (VI-e). Ether formation can be by azeotropical water removal, or chemically, e.g. by a Williamson reaction.

Alternatively, in order to prepare the compounds of formula (I), first an amide bond between building blocks P2 and P1 is formed, followed by coupling of the P3 building block to the P1 moiety in P1-P2, and a subsequent amide bond formation between P3 and the P2 moiety in P2-P1-P3 with concomitant ring closure. Yet again, the tail P1' can be bonded to the P1 building block at any stage of the synthesis of the compounds of formula (I), for example before or after coupling the building blocks P2 and P1; before or after coupling the P3 building block to P1; or before or after coupling building blocks P3 and P2 and the concomitant ring closure.

Yet another alternative synthetic methodology is the formation of an amide bond between building blocks P2 and P3, followed by the coupling of building block P1 to P3, and a last amide bond formation between P1 and P2 with concomitant ring closure. Yet again, the tail P1' can be bonded to the P1 building block at any stage of the synthesis of the compounds of formula (I), i.e. in the present case, before or after coupling the building blocks P2 and P3; before or after coupling the building blocks P1 and P3; before or after coupling P1 and P2 with concomitant ring closure.

Building blocks P1 and P3 can be linked via double bond formation at carbons 7 and 8, if desired, followed by a reduction of the C7-C8 double bond. The thus formed P1-P3 block can be coupled to building block P2 and subsequently cyclized, by forming amide bonds. In a preferred embodiment, building block P1-P3 is not reduced and coupled as such with P2 and cyclized, yielding compounds (I-1).

Building blocks P1 and P3 in any of the previous approaches can be linked via double bond formation, e.g. by the olefin metathesis reaction described hereinafter, or a Wittig type reaction.

The individual building blocks can first be prepared and subsequently coupled together or alternatively, precursors of the building blocks can be coupled together and modified at a later stage to the desired molecular composition.

The functionalities in each of the building blocks may be protected to avoid side reactions.

The formation of amide bonds can be carried out using standard procedures such as those used for coupling amino acids in peptide synthesis. The latter involves the dehydrative coupling of a carboxyl group of one reactant with an amino group of the other reactant to form a linking amide bond. The amide bond formation may be performed by reacting the starting materials in the presence of a coupling agent or by converting the carboxyl functionality into an active form such as an active ester, mixed anhydride or a carboxyl acid chloride or bromide. General descriptions of such coupling reactions and the reagents used therein can be found in general textbooks on peptide chemistry, for example, M. Bodanszky, "Peptide Chemistry", 2nd rev. ed., Springer-Verlag, Berlin, Germany, (1993).

Examples of coupling reactions with amide bond formation include the azide method, mixed carbonic-carboxylic acid anhydride (isobutyl chloroformate) method, the carbodiimide (dicyclohexylcarbodiimide, diisopropylcarbodiimide, or water-soluble carbodiimide such as *N*-ethyl-*N'*-[(3-dimethylamino)propyl]carbodiimide) method, the active ester (*p*-nitrophenyl ester, *N*-hydroxysuccinic imido ester) method, the Woodward reagent K-method, the 1,1-carbonyldiimidazole (CDI or N,N'-carbonyl-diimidazole) method, the phosphorus reagents or oxidation-reduction methods. Some of these methods can be enhanced by adding suitable catalysts, e.g. in the carbodiimide method by adding 1-hydroxybenzotriazole, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), or 4-DMAP. Further coupling agents are (benzotriazol-1-yloxy)tris-(dimethylamino)

phosphonium hexafluorophosphate, either by itself or in the presence of 1-hydroxy-benzotriazole or 4-DMAP; or 2-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetra-methyluronium tetrafluoroborate, or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate. These coupling reactions can be performed in either solution (liquid phase) or solid phase.

A preferred amide bond formation is performed employing N-ethyloxycarbonyl-2-ethyloxy-1,2-dihydroquinoline (EEDQ) or N-isobutyloxy-carbonyl-2-isobutyloxy-1,2-dihydroquinoline (IIDQ). Unlike the classical anhydride procedure, EEDQ and IIDQ do not require base nor low reaction temperatures. Typically, the procedure involves reacting equimolar amounts of the carboxyl and amine components in an organic solvent (a wide variety of solvents can be used). Then EEDQ or IIDQ is added in excess and the mixture is allowed to stir at room temperature.

The coupling reactions preferably are conducted in an inert solvent, such as halogenated hydrocarbons, e.g. dichloromethane, chloroform, dipolar aprotic solvents such as acetonitrile, dimethylformamide, dimethylacetamide, DMSO, HMPT, ethers such as tetrahydrofuran (THF).

In many instances the coupling reactions are done in the presence of a suitable base such as a tertiary amine, e.g. triethylamine, diisopropylethylamine (DIPEA), *N*-methyl-morpholine, *N*-methylpyrrolidine, 4-DMAP or 1,8-diazabicycle[5.4.0]undec-7-ene (DBU). The reaction temperature may range between 0 °C and 50 °C and the reaction time may range between 15 min and 24 h.

The functional groups in the building blocks that are linked together may be protected to avoid formation of undesired bonds. Appropriate protecting groups that can be used are listed for example in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1999) and "The Peptides: Analysis, Synthesis, Biology", Vol. 9, Academic Press, New York (1987).

Carboxyl groups can be protected as an ester that can be cleaved off to give the carboxylic acid. Protecting groups that can be used include 1) alkyl esters such as methyl, trimethylsilyl and *tert*-butyl; 2) arylalkyl esters such as benzyl and substituted benzyl; or 3) esters that can be cleaved by a mild base or mild reductive means such as trichloroethyl and phenacyl esters.

Amino groups can be protected by a variety of N-protecting groups, such as:

1) acyl groups such as formyl, trifluoroacetyl, phthalyl, and *p*-toluenesulfonyl;

2) aromatic carbamate groups such as benzyloxycarbonyl (Cbz or Z) and substituted benzyloxycarbonyls, and 9-fluorenylmethyloxycarbonyl (Fmoc);
3) aliphatic carbamate groups such as *tert*-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxy-carbonyl, and allyloxycarbonyl;
4) cyclic alkyl carbamate groups such as cyclopentyloxycarbonyl and adamantyloxycarbonyl;
5) alkyl groups such as triphenylmethyl, benzyl or substituted benzyl such as 4-methoxybenzyl;
6) trialkylsilyl such as trimethylsilyl or t.Bu dimethylsilyl; and
7) thiol containing groups such as phenylthiocarbonyl and dithiasuccinoyl.

Interesting amino protecting groups are Boc and Fmoc.

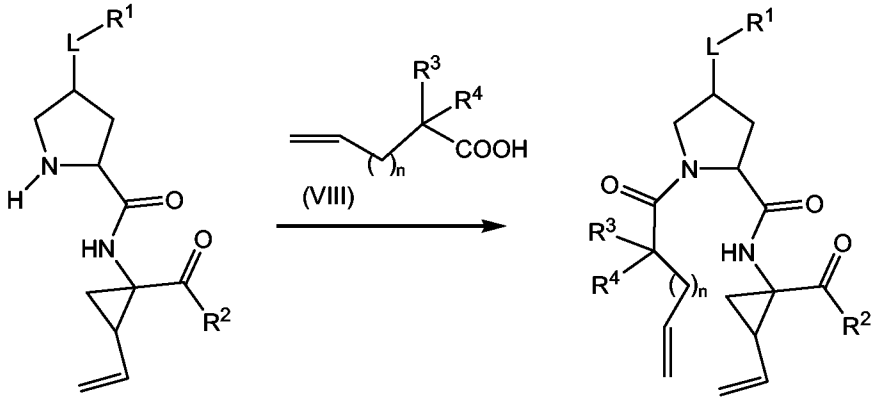
Preferably the amino protecting group is cleaved off prior to the next coupling step. Removal of N-protecting groups can be done following art-known procedures. When the Boc group is used, the methods of choice are trifluoroacetic acid, neat or in dichloromethane, or HCl in dioxane or in ethyl acetate. The resulting ammonium salt is then neutralized either prior to the coupling or in situ with basic solutions such as aqueous buffers, or tertiary amines in dichloromethane or acetonitrile or dimethyl-formamide. When the Fmoc group is used, the reagents of choice are piperidine or substituted piperidine in dimethylformamide, but any secondary amine can be used. The deprotection is carried out at a temperature between 0 °C and room temperature, usually around 15-25 °C, or 20-22 °C.

Other functional groups that can interfere in the coupling reactions of the building blocks may also be protected. For example hydroxyl groups may be protected as benzyl or substituted benzyl ethers, e.g. 4-methoxybenzyl ether, benzoyl or substituted benzoyl esters, e.g. 4-nitrobenzoyl ester, or with trialkylsilyl goups (e.g. trimethylsilyl or *tert*-butyldimethylsilyl).

Further amino groups may be protected by protecting groups that can be cleaved off selectively. For example, when Boc is used as the α-amino protecting group, the following side chain protecting groups are suitable: p-toluenesulfonyl (tosyl) moieties can be used to protect further amino groups; benzyl (Bn) ethers can be used to protect hydroxy groups; and benzyl esters can be used to protect further carboxyl groups. Or when Fmoc is chosen for the α-amino protection, usually *tert*-butyl based protecting groups are acceptable. For instance, Boc can be used for further amino groups; *tert*-butyl ethers for hydroxyl groups; and *tert*-butyl esters for further carboxyl groups.

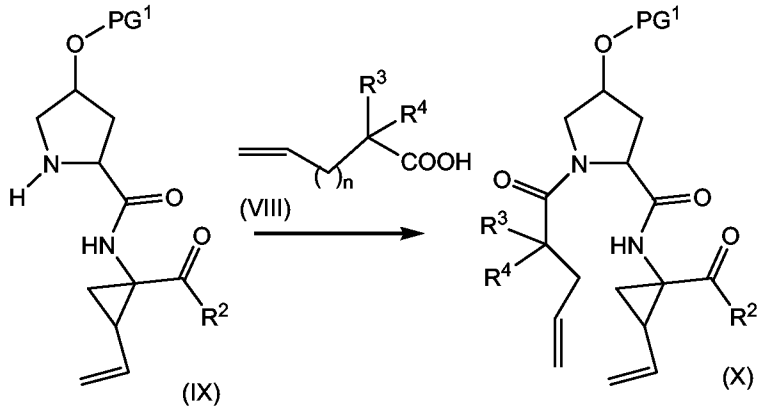
Any of the protecting groups may be removed at any stage of the synthesis procedure but preferably, the protecting groups of any of the functionalities not involved in the reaction steps are removed after completion of the build-up of the macrocycle. Removal of the protecting groups can be done in whatever manner is dictated by the choice of protecting groups, which manners are well known to those skilled in the art.

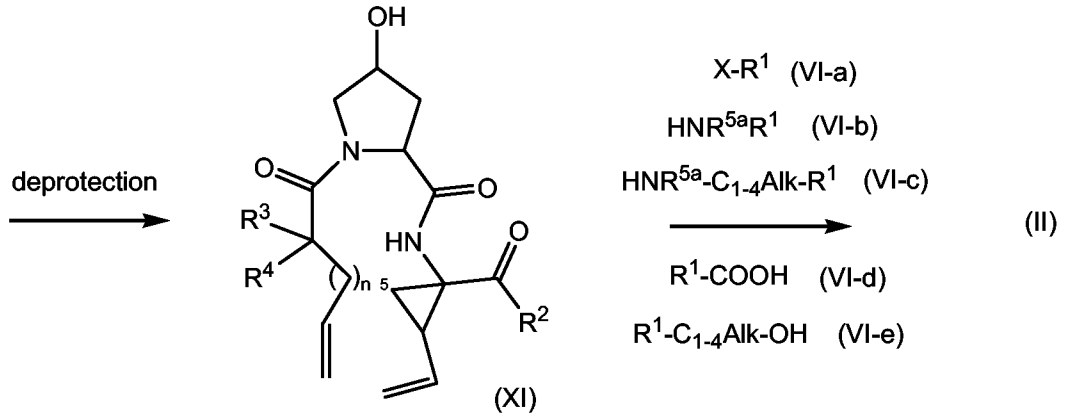
The intermediates of formula (II) may be prepared by reacting an intermediate (VII) with an alkene carboxylic acid or a derivative thereof (VIII) as outlined in the following reaction scheme.



Intermediate (VII) is reacted with alkenyl acid (VIII) applying the reaction procedures for amide bond formation as described above.

The intermediates (II) can alternatively be prepared as follows:

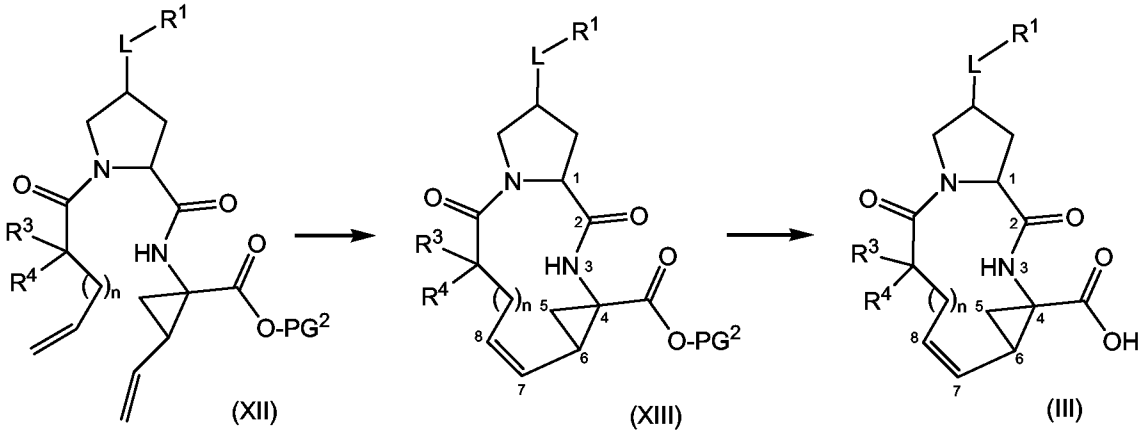




PG^1 is an O-protecting group, which can be any of the groups mentioned herein and in particular is a benzoyl or substituted benzoyl group such as 4-nitrobenzoyl.

Reaction of (VIII) with (IX) yields intermediates (X). These are deprotected, in particular using the reaction conditions mentioned above. For example where PG^1 is benzoyl or substituted benzoyl this group is removed by reaction with a an alkali metal hydroxide (LiOH, NaOH, KOH), in particular where PG^1 is 4-nitrobenzoyl, with LiOH, in an aqueous medium comprising water and a water-soluble organic solvent such as an alkanol (methanol, ethanol) and THF. The resulting alcohol (XI) is reacted with intermediates (VI-a) – (VI-e) as described above for the reaction of (V) with (VI-a) – (VI-e) and this reaction results in intermediates (II).

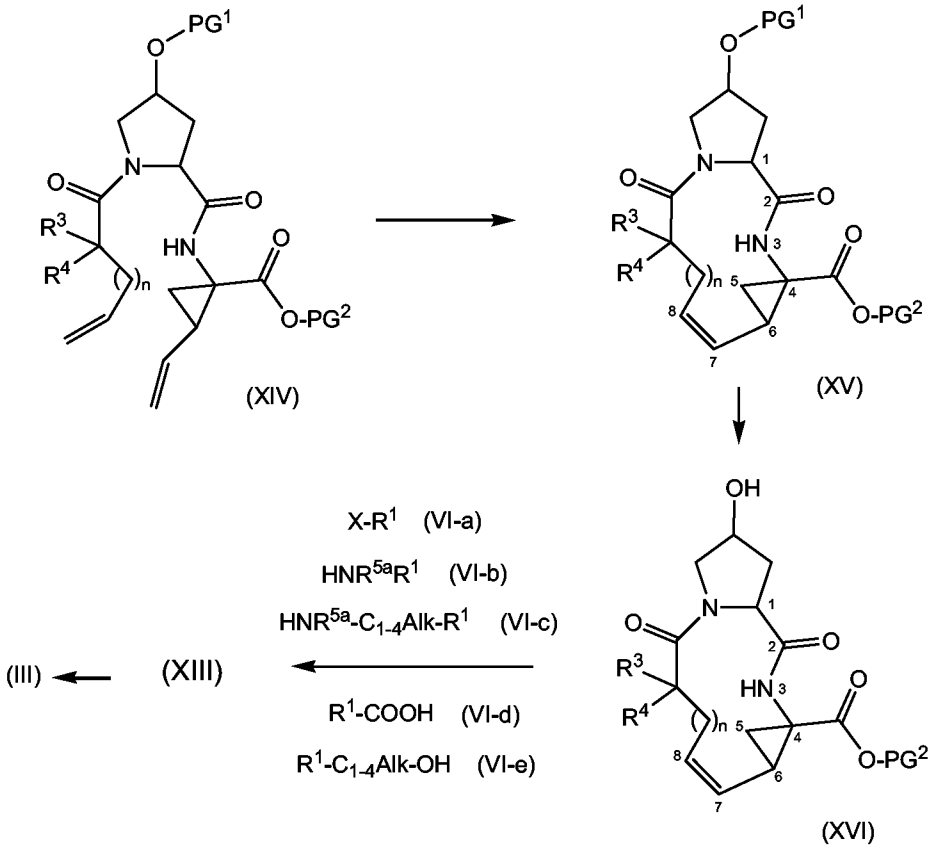
The intermediates of formula (III) may be prepared by first cyclizing the open ester (XII) to a macrocyclic ester (XIII), which in turn is converted to the corresponding macrocyclic carboxylic acid (III) as follows:



L is as specified above and PG^2 is a carboxyl protecting group, e.g. one of the carboxyl protecting groups mentioned above, in particular a C_{1-4}alkyl or benzyl ester, e.g. a methyl, ethyl or t.butyl ester. The reaction of (X) to (XI) is a metathesis reaction and is conducted as described above. The group PG^2 is removed following procedures also

described above. Where PG^1 is a C_{1-4}alkyl ester, it is removed by alkaline hydrolysis, e.g. with NaOH or preferably LiOH, in an aqueous solvent, e.g. a C_{1-4}alkanol/water mixture. A benzyl group can be removed by catalytic hydrogenation.

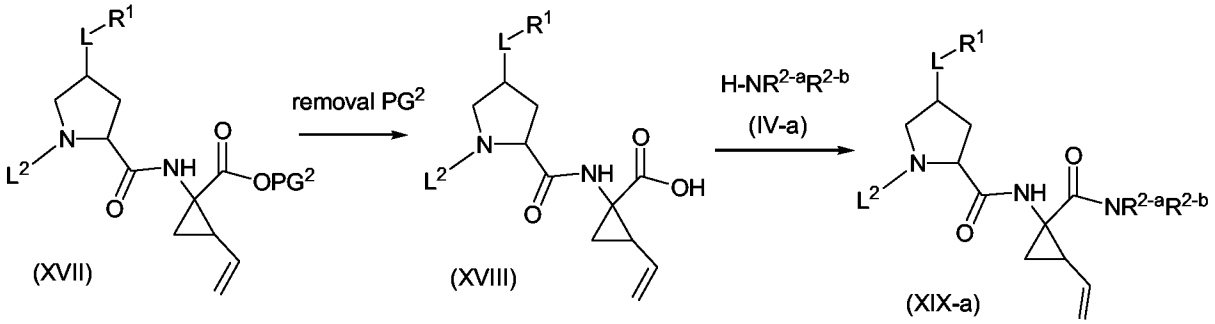
In an alternative synthesis, intermediates (III) can be prepared as follows:

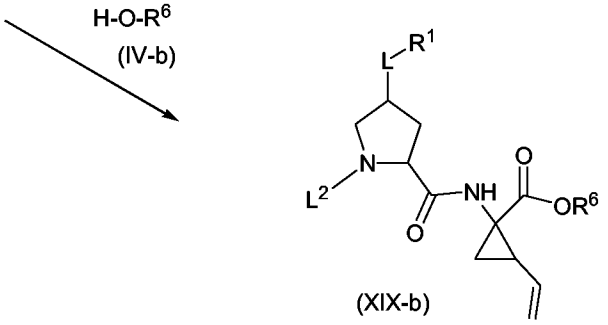


The PG^1 group may be removed using art-known methodologies, e.g. methyl or ethyl esters by treatment with an alkali metal hydroxide in an aqueous medium, t.butyl esters with weak acid and benzyl esters with strong acid or by catalytic hydrogenation. Where L is a radical (a) this reaction sequence yields intermediates (III). These can also prepared by removing L being an O-protecting group and etherifying the thus formed alcohol with intermediate (VI-a) as described above.

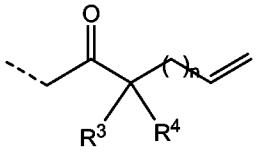
First, intermediates (XIV) are cyclized to the macrocyclic ester (XV), (XV) is deprotected by removal of the PG^1 group to (XVI), from which is reacted with intermediates (VI-a) – (VI-e) to intermeiates (XIII), followed by removal of carboxyl protecting group PG^2 yielding intermediates (III). The cyclization, deprotection of PG^1 and PG^2 and the coupling with (VI-a) – (VI-e) can be done as described above.

The R^2 groups can be introduced at any stage of the synthesis, either as the last step as described above, or earlier, before the macrocycle formation. In the following scheme the group $-NR^{2-a}R^{2-b}$ is as specified above:





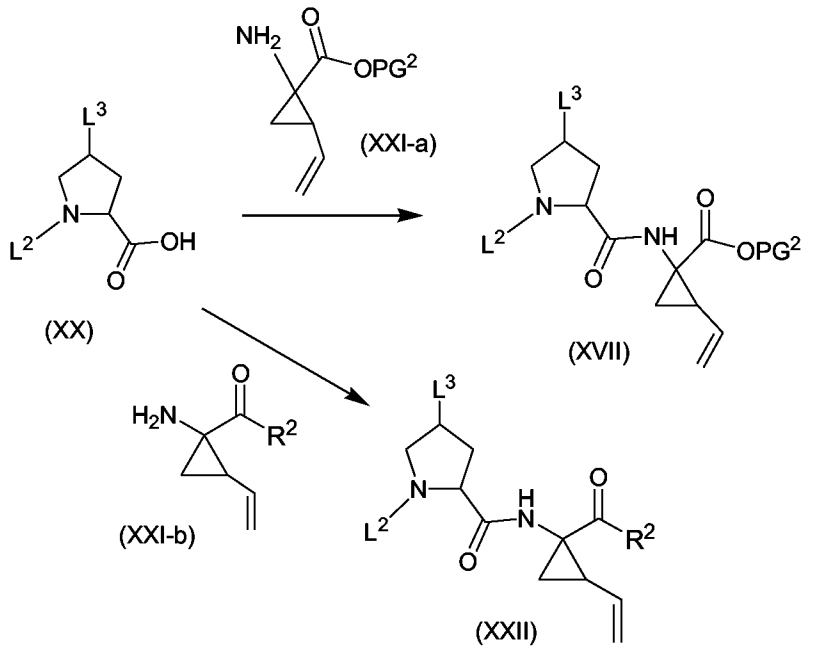
L and PG^2 are as defined above and L^2 is a nitrogen-protecting group (PG, as defined above), or L^2 is a group



(b), wherein R^3, R^4 and n are as defined above. The intermediates (XIX-a) and (XIX-b) wherein L^1 represents a group (b) correspond to the intermediates (II) and may be processed further as specified above.

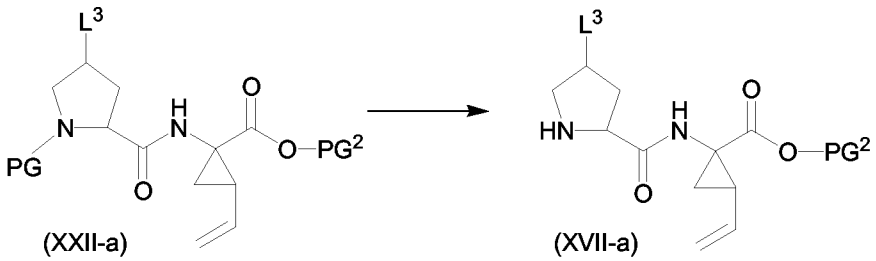
Coupling of P1 and P2 building blocks

The P1 and P2 building blocks are linked using an amide forming reaction following the procedures described above. The P1 building block may have a carboxyl protecting group PG2 (as in (XVI-a)) or may already be linked to P1' group (as in (XVI-b)). L^3 is hydroxy, $-OPG^1$ or a group $-L-R^1$ as specified above. Where in any of the following reaction schemes L^3 is hydroxy, prior to each step it may be protected to a group $-OPG^1$ and, if desired, subsequently deprotected back to a free hydroxy function. Similarly, an hydroxy function may be converted to a group $-L-R^1$.



In the procedure of the above scheme, a cyclopropyl amino acid (XXI-a) or (XXI-b) is coupled to the acid function of the P2 building block using an amide forming reaction such as the standard peptide coupling conditions described above. Intermediates (XVII) or (XXII) are obtained. Some of the latter correspond to intermediates (XIX-a) or (XIX-b) in the previous reaction scheme. Removal of the acid protection group in (XVII), using the appropriate conditions for the protecting group used, followed by coupling with an amine $HNR^{2-a}R^{2-b}$ (IV-a) or with HOR^6 (IV-b) as described above, again yields the intermediates (XXII), wherein $-COR^2$ are amide or ester groups.

In one embodiment, L^2 is a group (b) and these reactions involve coupling P1 to P2-P3, which results in the intermediates (X) or (II) mentioned above. In another embodiment, L^2 is a N-protecting group PG, which is as specified above, and the coupling reaction results in an intermediate (XXII-a), from which the group PG can be removed obtaining intermediates (XVII-a), which are intermediates (XVII) as specified above wherein L^2 is hydrogen, using reaction conditions also mentioned above:

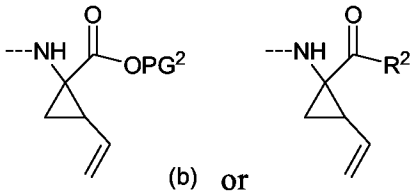


In one embodiment, PG in this reaction is a BOC group. Where additionally L^3 is hydroxy, the starting material is Boc-L-hydroxyproline.

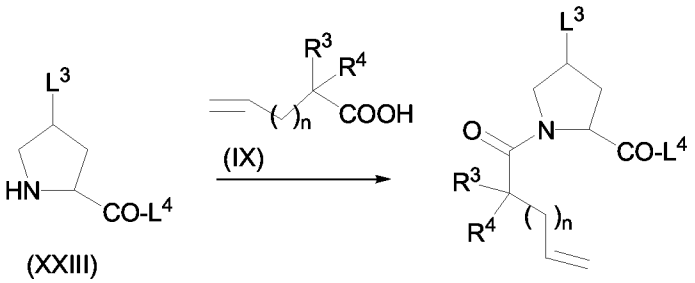
In the above schemes, the group L^3 can be a group -O-PG^1 which is introduced on a starting material (XX), wherein L^3 is hydroxy. In this instance PG^1 is chosen such that it is selectively cleavable towards group PG.

Coupling of P3 and P2 building blocks

The P3 and P2 building blocks are linked using an amide forming reaction following the procedures described above for the coupling of (VII) with (VIII). A general procedure is represented in the following reaction scheme wherein L^3 is as specified above and L^4 is a group -O-PG^2, or a group



(b) or (c).



(XXIII) (XXIV)

Where L^4 in (XXIII) is a group –OPG^2, the PG^2 group may be removed and the resulting acid coupled with cyclopropyl amino acids (XXI-a) or (XXI-b), yielding intermediates (XVII) or (XXII) wherein L^2 is a radical (b).

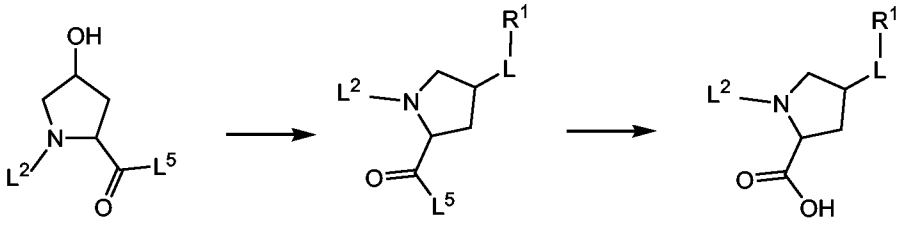
The building blocks P1, P1', P2 and P3 used in the preparation of the compounds of formula (I) can be prepared starting from art-known intermediates. A number of such syntheses are described hereafter in more detail.

Synthesis of P2 building blocks

The P2 building blocks contain a pyrrolidine moiety substituted with a group –L-R^1. The R^1 group can be coupled to the pyrrolidine ring at any convenient stage of the synthesis of compounds according to the present invention. One approach is to first couple the R^1 group to the pyrrolidine ring and subsequently add the other desired building blocks, i.e. P1 (optionally with the P1' tail) and P3, followed by the macrocycle formation. Another approach is to couple the building blocks P2, bearing

no R^1 substituent, with each P1 and P3, and to add the R^1 group either before or after the macrocycle formation.

Building blocks P2 can be prepared by reacting a hydroxyproline derivative (XXV) with intermediates (VI-a) – (VI-e) as described above for the synthesis of (I) starting from (V). This reaction is represented in the scheme below, wherein L^5 is hydroxy or a group -OPG^2, or L^5 may represent a P1 group such as the groups (b) and (c) as specified above, and wherein further the groups L^2 and PG^2 are as mentioned above. In one embodiment L^2 is PG, i.e. an N-protecting group



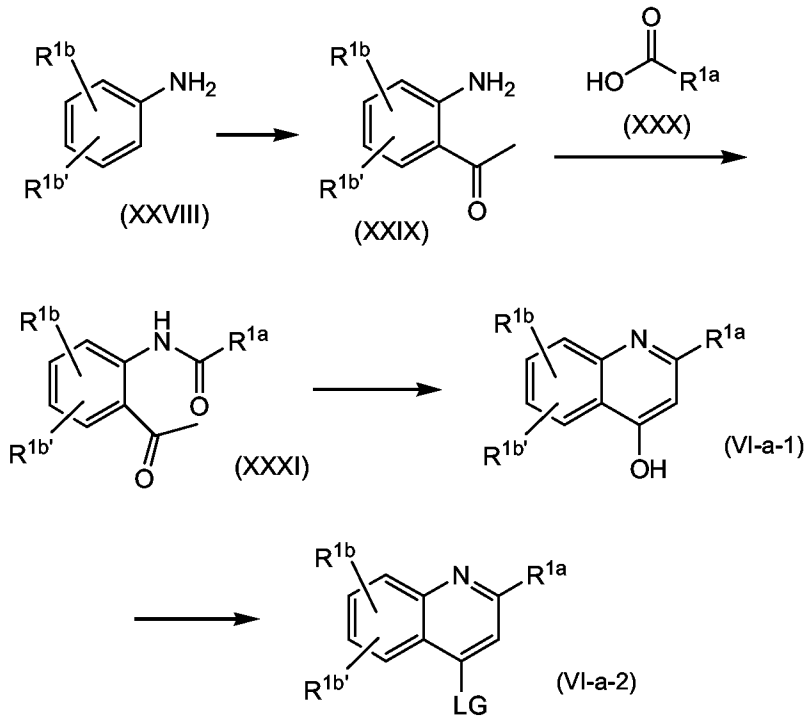
(XXV) (XXVI) (XXVII)

In one embodiment the group L^2 is PG, wherin the latter is t.butoxycarbonyl (Boc), L^5 is hydroxy and the starting material (XXV) is the commercially available Boc-hydroxyproline, or any other stereoisomeric form thereof, e.g. Boc-L-hydroxyproline, in particular the trans isomer of the latter.

Where L^5 in (XXVI) is -OPG^2, the carboxyl protecting group may be removed following procedures described above to hydroxyproline derivatives (XXVII). In one embodiment L^2 is Boc and L^5 is -OPG^2, wherein PG^2 is a lower alkyl ester, in particular a methyl or ethyl ester. Hydrolysis of the latter ester to the acid can be done by standard procedures, e.g. acid hydrolysis with hydrochloric acid in methanol or ethanol with an alkali metal hydroxide such as NaOH, in particular with LiOH.

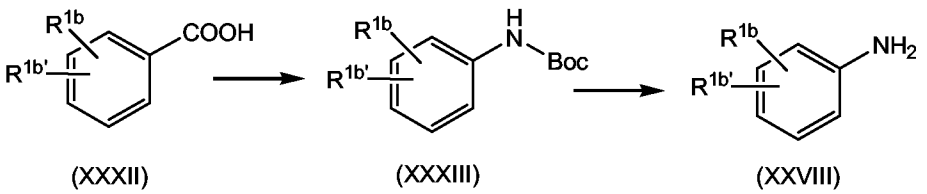
The intermediates (VI-a), (VI-b), (VI-c), (VI-d) and (VI-e) are art-known compounds or can be prepared following art-known methods using known starting materials.

Intermediates (VI-a) which are quinoline derivatives, such as those wherein R^1 is a radical (d-1), (d-2), (d-3), (d-4), (d-4-a), (d-5) or (d-5-a) as specified above, may be prepared as shown below:



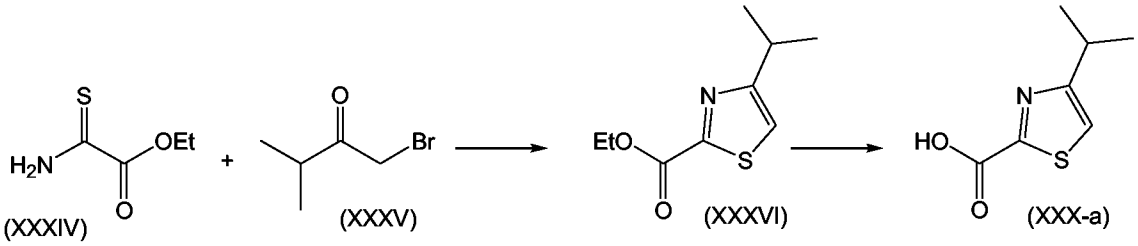
Friedel-Craft acylation of a 3-methoxyaniline (XXVIII), available either commercially or via art-known procedures, using an acylating agent such as acetyl chloride or the like in the presence of one or more Lewis acids such as boron trichloride and aluminium trichloride in a solvent like dichloromethane provides (XXIX). Coupling of (XXIX) with 4-isopropyl-thiazole-2-carboxylic acid (XXX), preferably under basic conditions, such as in pyridine, in the presence of an activating agent for the carboxylate group, for instance $POCl_3$, followed by ring closure and dehydration under basic conditions like potassium *tert*-butoxide in *tert*-butanol yields quinoline derivative (VI-a-1). The latter can be converted to (VI-a-2) wherein LG is a leaving group, e.g. by reaction of (VI-a-1) with a halogenating agent, for example phosphoryl chloride or the like, or with an arylsulfonyl chloride, e.g. with tosyl chloride.

Substituted anilines (XXVIII) are available commercially or may be prepared from a suitable substituted benzoic acid (XXXII), which is reacted with diphenylphosphoryl-azide at increased temperature and subsequently treated with a C_{1-4}alkanol, in particular t.butanol, affording C_{1-4}alkoxycarbonylamines such as compound (XXXIII). Deprotection of compound (XXXIII) yields substituted anilines (XXVIII).



Alternatively, substituted anilines (XXVIII) may be prepared from the corresponding substituted nitrobenzenes by reducing the latter with elemental zinc, tin or iron in the presence of an acid.

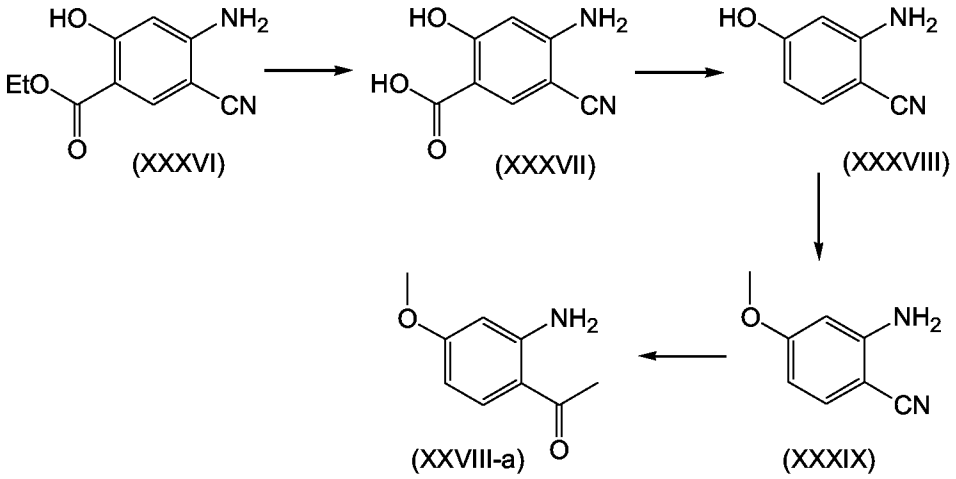
A variety of carboxylic acids with the general structure (XXX) can be used in the above synthesis. These acids are available either commercially or can be prepared via art-known procedures. An example of the preparation of 2-(substituted)aminocarboxy-aminothiazole derivatives, following the procedure described by Berdikhina et al. in Chem. Heterocycl. Compd. (Engl. Transl.) (1991), 427-433, is shown the following reaction scheme which illustrates the preparation of 2-carboxy-4-isopropyl-thiazole (XXX-a):



Ethyl thiooxamate (XXXIV) is reacted with the β-bromoketone (XXXV) to form the thiazolyl carboxylic acid ester (XXXVI) which is hydrolyzed to the corresponding acid (XXX-a). The ethyl ester in these intermediates may be replaced by other carboxyl protecting groups PG^2, as defined above.

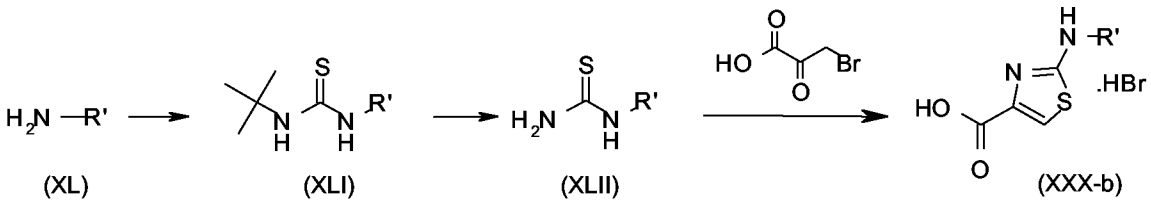
The bromoketone (XXXV) may be prepared from 3-methyl-butan-2-one (MIK) with a sililating agent (such as TMSCl) in the presence of a suitable base (in particular LiHMDS) and bromine.

Intermediates (XXVIII) having a methoxy substituent, said intermediates being represented by formula (XXVIII-a), may be prepared as described by Brown et al. J. Med. Chem. 1989, 32, 807- 826, or as outlined in the following scheme.



Starting materials ethylacetyl acetate and ethoxymethylene malononitrile, which are commercially available, are reacted in the presence of a suitable base, such as sodium ethoxide, and a solvent, such as ethanol and the like. This reaction affords intermediate (XXXVI). The latter is hydrolyzed, e.g. with a base such as an alkali metal hydroxide, e.g. NaOH or LiOH, in a suitable solvent such as ethanol/water to produce (XXXVII). Decarboxylation of intermediate (XXXVII) into intermediate (XXXVIII) is performed at increased temperature until effervescence ceases, preferably in the presence of a basic solvent such as quinoline. Methylation of intermediate (XXXVIII), in particular with a methylating agent such as MeI in the presence of a suitable base (e.g. K_2CO_3) in a suitable solvent (such as DMF and the like) yields (XXXIX). The latter is reacted with a Grignard reagent such as MeMgBr in the presence of a suitable solvent (e.g. THF), followed by hydrolysis, for instance with aqueous HCl, affording intermediate (XXVIII-a).

The synthesis of further carboxylic acids (XXX), in particular of substituted amino thiazole carboxylic acids (XXX-b) is illustrated herebelow:



Thiourea (XLII) with various alkyl substituents R' can be formed by reaction of the appropriate amine (XL) with *tert*-butylisothiocyanate in the presence of a base like diisopropylethylamine in a solvent like dichloromethane followed by removal of the *tert*-butyl group under acidic conditions. Subsequent condensation of thiourea derivative (XLII) with 3-bromopyruvic acid provides the thiazole carboxylic acid (XXX-b).

Compounds of the present invention or building blocks P2 wherein a heterocyclic R^1 group is attached via a ring nitrogen directly to the pyrrolidine ring, i.e. L is a direct bond in general formula (I), can be prepared for example by using a replacement reaction wherein a suitable leaving group on the pyrrolidine ring is replaced by a nitrogen-containing cyclic group. This can be done at the building block stage or after assembling and/or cyclizing the building blocks. In one procedure the pyrrolidine derivative (V), (XI), (XVI), (XXV) or any intermediate having an L^3 group that is hydroxy, is reacted with a leaving group introducing reagent, such as with a halogenating agent, for example phosphoryl chloride or the like, or with an arylsulfonyl chloride, e.g. with tosyl chloride. The thus formed intermediate is then reacted with a heterocycle having a ring nitrogen substituted with hydrogen (i.e. N-H).

Compounds of formula (I) wherein L is a direct bond and R^1 is a ring system connected to the pyrrolidine moiety via a carbon atom can be prepared by building up the ring starting from the hydroxy compounds. This can either be done at the building block stage or after assembling and/or cyclizing the building blocks. For example, the hydroxy function may be converted into a leaving group which in turn is substituted by a cyano group. This cyano group in turn can be further converted into the desired heterocycles. For example, compounds wherein a tetrazole derivative is attached through a carbon atom of the tetrazolic ring are conveniently prepared by building up the tetrazole moiety directly onto the pyrrolidine-ring precursor. This can be achieved for instance by condensing the thus introduced cyano group followed by reaction with an azide reagent like sodium azide. Triazole derivatives can also be built up directly onto the nitrogen-ring precursor for example by transforming the hydroxy group of the nitrogen-ring precursor into an azide group followed by a 3+2 cycloaddition reaction of the obtained azide with a suitable alkyne derivative.

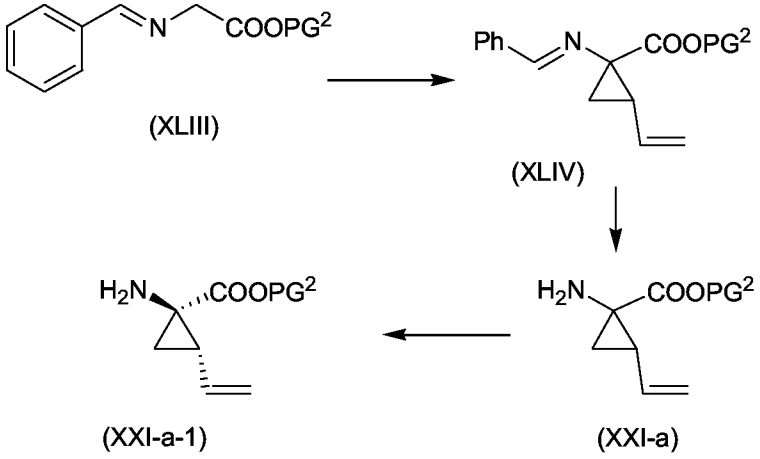
Structurally diverse tetrazoles for use in the above reactions to introduce a R^1 group can be prepared by reacting commercially available nitrile compounds with sodium azide. Triazole derivatives can be prepared by reaction of an alkyne compound and trimethylsilyl azide. Useful alkyne compounds are either commercially available or they can be prepared for instance according to the Sonogashira reaction, i.e. reaction of a primary alkyne, an aryl halide and triethylamine in the presence of $PdCl_2(PPh)_3$ and CuI as described for example in A. Elangovan, Y.-H. Wang, T.-I. Ho, Org. Lett., 2003, *5*, 1841-1844. The heterocyclic substituent can also be modified when attached to the P2 building block either before or after coupling of the P2 building block to the other building blocks.

Further alternatives for the preparation of compounds wherein L is a bond and R^1 is an optionally substituted heterocycle can be found for example in WO2004/072243.

Synthesis of P1 building blocks

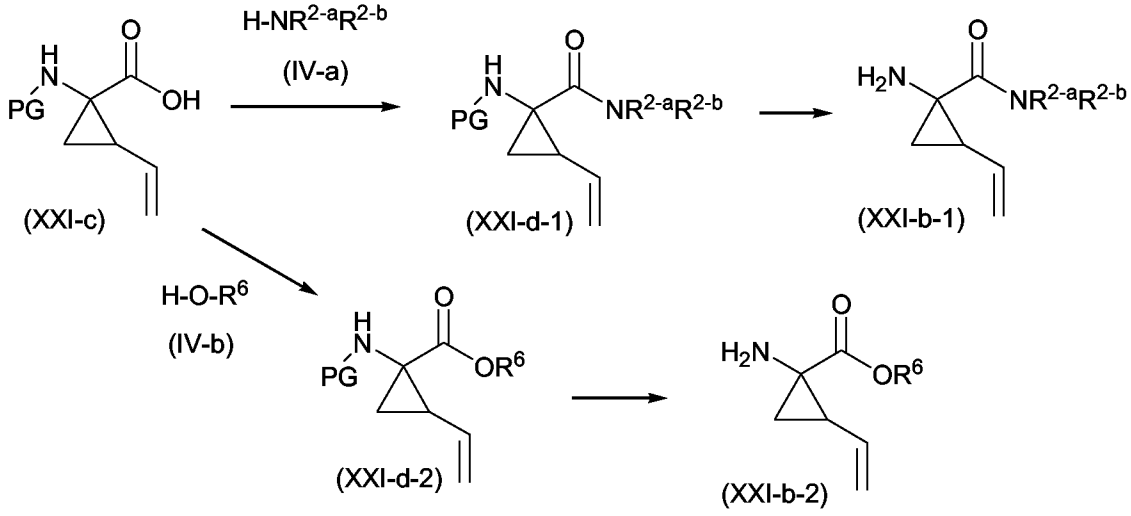
The cyclopropane amino acid used in the preparation of the P1 fragment is commercially available or can be prepared using art-known procedures.

The amino-vinyl-cyclopropyl ethyl ester (XXI-a) may be obtained according to the procedure described in WO 00/09543 or as illustrated in the following scheme, wherein PG^2 is a carboxyl protecting group as specified above:



Treatment of commercially available or easily obtainable imine (XLIII) with 1,4-dihalobutene in presence of a base produces (XLIV), which after hydrolysis yields cyclopropyl amino acid (XXI-a), having the allyl substituent *syn* to the carboxyl group. Resolution of the enantiomeric mixture (XXI-a) results in (XXI-a-1). The resolution is performed using art-known procedures such as enzymatic separation; crystallization with a chiral acid; or chemical derivatization; or by chiral column chromatography. Intermediates (XXI-a) or (XXI-a-1) may be coupled to the appropriate proline derivatives as described above.

Introduction of a N-protecting group PG and removal of PG^2 results in cyclopropyl amino acids (XXI-c) which are converted to the amides (XXI-b-1) or esters (XXI-b-2) as outlined in the following reaction scheme, wherein R^{2-a}, R^{2-b} and PG are as specified above.



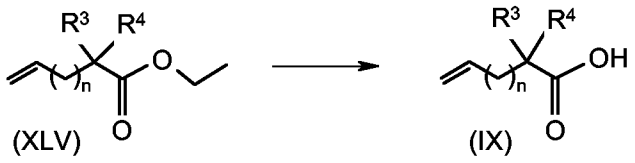
The reaction of (XXI-c) with amine (IV-a) is an amide forming procedure. The similar reaction with (IV-b) is an ester forming reaction. Both can be performed following the procedures described above. This reaction yields intermediates (XXI-d-1) or (XXI-d-2) from which the amino protecting group is removed by standard methods such as those described above. This in turn results in the desired intermediate (XXI-b-1). Starting materials (XXI-c) may be prepared from intermediates (XXI-a) by first introducing a N-protecting group PG and subsequent removal of the group PG^2.

In particular the reaction of (XXI-c) with (IV-a) is done by treatment of the amino acid with a coupling agent, for example N,N'-carbonyl-diimidazole (CDI) or the like, in a solvent like THF followed by reaction with (IV-a) in the presence of a base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Alternatively the amino acid can be treated with (IV-a) in the presence of a base like diisopropylethylamine followed by treatment with a coupling agent such as benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (commercially available as PyBOP®) to effect the introduction of the sulfonamide group.

Intermediates (XXI-b-1) or (XXI-b-2) in turn may be coupled to the appropriate proline derivatives as described above.

Synthesis of the P3 building blocks

The P3 building blocks are available commercially or can be generated according to methodologies known to the skilled in the art. The following scheme illustrates the preparation of P3 building blocks.



The ester (XLV) can be transformed into the corresponding acid (IX) by hydrolysis in the presence of an acid or a base. R^3, R^4, and n are as defined above.

Coupling of the appropriate P3 building block to the P2-P1 moiety or the P2 moiety alone may be accomplished by forming an amide bond as explained above (reaction of (XXIII) with (IX)).

Coupling of a P3 building block to a P1 moiety alone (with or without the P1' tail) can be achieved via an olefin metathesis reaction as described herein above.

Compounds of formula (I) may be converted into each other following art-known functional group transformation reactions.

The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarbo-peroxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzene-carboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. *tert*-butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Pure stereochemically isomeric forms of the compounds of formula (I) may be obtained by the application of art-known procedures. Diastereomers may be separated by physical methods such as selective crystallization and chromatographic techniques, e.g., counter-current distribution, liquid chromatography and the like.

The compounds of formula (I) may be obtained as racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I), which are sufficiently basic or acidic may be

converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid, respectively chiral base. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali or acid. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound may be synthesized by stereospecific methods of preparation. These methods may advantageously employ enantiomerically pure starting materials.

In a further aspect, the present invention concerns a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) as specified herein, or a compound of any of the subgroups of compounds of formula (I) as specified herein, and a pharmaceutically acceptable carrier. A therapeutically effective amount in this context is an amount sufficient to prophylactically act against, to stabilize or to reduce viral infection, and in particular HCV viral infection, in infected subjects or subjects being at risk of being infected. In still a further aspect, this invention relates to a process of preparing a pharmaceutical composition as specified herein, which comprises intimately mixing a pharmaceutically acceptable carrier with a therapeutically effective amount of a compound of formula (I), as specified herein, or of a compound of any of the subgroups of compounds of formula (I) as specified herein.

Therefore, the compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form or metal complex, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions

and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin.

The compounds of the present invention may also be administered via oral inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compounds of the present invention may be administered to the lungs in the form of a solution, a suspension or a dry powder, a solution being preferred. Any system developed for the delivery of solutions, suspensions or dry powders via oral inhalation or insufflation are suitable for the administration of the present compounds.

Thus, the present invention also provides a pharmaceutical composition adapted for administration by inhalation or insufflation through the mouth comprising a compound of formula (I) and a pharmaceutically acceptable carrier. The compounds of the present invention may be administered via inhalation of a solution in nebulized or aerosolized doses.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including

scored or coated tablets), capsules, pills, suppositories, powder packets, wafers, injectable solutions or suspensions and the like, and segregated multiples thereof.

The compounds of formula (I) show antiviral properties. Viral infections and their associated diseases treatable using the compounds and methods of the present invention include those infections brought on by HCV and other pathogenic flaviviruses such as Yellow fever, Dengue fever (types 1-4), St. Louis encephalitis, Japanese encephalitis, Murray valley encephalitis, West Nile virus and Kunjin virus. The diseases associated with HCV include progressive liver fibrosis, inflammation and necrosis leading to cirrhosis, end-stage liver disease, and HCC; and for the other pathogenic flaviruses the diseases include yellow fever, dengue fever, hemorraghic fever and encephalitis. A number of the compounds of this invention moreover are active against mutated strains of HCV. Additionally, many of the compounds of this invention show a favorable pharmacokinetic profile and have attractive properties in terms of bioavailability, including an acceptable half-life, AUC (area under the curve) and peak values and lacking unfavourable phenomena such as insufficient quick onset and tissue retention.

The *in vitro* antiviral activity against HCV of the compounds of formula (I) was tested in a cellular HCV replicon system based on Lohmann et al. (1999) Science 285:110-113, with the further modifications described by Krieger et al. (2001) Journal of Virology 75: 4614-4624, which is further exemplified in the examples section. This model, while not a complete infection model for HCV, is widely accepted as the most robust and efficient model of autonomous HCV RNA replication currently available. Compounds exhibiting anti-HCV activity in this cellular model are considered as candidates for further development in the treatment of HCV infections in mammals. It will be appreciated that it is important to distinguish between compounds that specifically interfere with HCV functions from those that exert cytotoxic or cytostatic effects in the HCV replicon model, and as a consequence cause a decrease in HCV RNA or linked reporter enzyme concentration. Assays are known in the field for the evaluation of cellular cytotoxicity based for example on the activity of mitochondrial enzymes using fluorogenic redox dyes such as resazurin. Furthermore, cellular counter screens exist for the evaluation of non-selective inhibition of linked reporter gene activity, such as firefly luciferase. Appropriate cell types can be equipped by stable transfection with a luciferase reporter gene whose expression is dependent on a constitutively active gene promoter, and such cells can be used as a counter-screen to eliminate non-selective inhibitors.

Due to their antiviral properties, particularly their anti-HCV properties, the compounds of formula (I) or any subgroup thereof, their *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms, are useful in the treatment of individuals experiencing a viral infection, particularly a HCV infection, and for the prophylaxis of these infections. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses, in particular flaviviruses such as HCV.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines. Said use as a medicine or method of treatment comprises the systemic administration to viral infected subjects or to subjects susceptible to viral infections of an amount effective to combat the conditions associated with the viral infection, in particular the HCV infection.

The present invention also relates to the use of the present compounds or any subgroup thereof in the manufacture of a medicament for the treatment or the prevention of viral infections, particularly HCV infection.

The present invention furthermore relates to a method of treating a warm-blooded animal infected by a virus, or being at risk of infection by a virus, in particular by HCV, said method comprising the administration of an anti-virally effective amount of a compound of formula (I), as specified herein, or of a compound of any of the subgroups of compounds of formula (I), as specified herein.

Also, the combination of previously known anti-HCV compound, such as, for instance, interferon-α (IFN-α), pegylated interferon-α and/or ribavirin, and a compound of formula (I) can be used as a medicine in a combination therapy. The term "combination therapy" relates to a product containing mandatory (a) a compound of formula (I), and (b) optionally another anti-HCV compound, as a combined preparation for simultaneous, separate or sequential use in treatment of HCV infections, in particular, in the treatment of infections with HCV.

Anti-HCV compounds encompass agents selected from an HCV polymerase inhibitor, an HCV protease inhibitor, an inhibitor of another target in the HCV life cycle, and immunomodulatory agent, an antiviral agent, and combinations thereof.

HCV polymerase inhibitors include, but are not limited to, NM283 (valopicitabine), R803, JTK-109, JTK-003, HCV-371, HCV-086, HCV-796 and R-1479.

Inhibitors of HCV proteases (NS2-NS3 inhibitors and NS3-NS4A inhibitors) include, but are not limited to, the compounds of WO02/18369 (see, e.g., page 273, lines 9-22 and page 274, line 4 to page 276, line 11); BILN-2061, VX-950, GS-9132 (ACH-806), SCH-503034, and SCH-6. Further agents that can be used are those disclosed in WO98/17679, WO-00/056331 (Vertex); WO 98/22496 (Roche); WO 99/07734, (Boehringer Ingelheim), WO 2005/073216, WO2005073195 (Medivir) and structurally similar agents.

Inhibitors of other targets in the HCV life cycle, including NS3 helicase; metallo-protease inhibitors; antisense oligonucleotide inhibitors, such as ISIS-14803, AVI-4065 and the like; siRNA's such as SIRPLEX-140-N and the like; vector-encoded short hairpin RNA (shRNA); DNAzymes; HCV specific ribozymes such as heptazyme, RPI.13919 and the like; entry inhibitors such as HepeX-C, HuMax-HepC and the like; alpha glucosidase inhibitors such as celgosivir, UT-231B and the like; KPE-02003002; and BIVN 401.

Immunomodulatory agents include, but are not limited to; natural and recombinant interferon isoform compounds, including α-interferon, β-interferon, γ-interferon, ω-interferon and the like, such as Intron A®, Roferon-A®, Canferon-A300®, Advaferon®, Infergen®, Humoferon®, Sumiferon MP®, Alfaferone®, IFN-beta®, Feron® and the like; polyethylene glycol derivatized (pegylated) interferon compounds, such as PEG interferon-α-2a (Pegasys®), PEG interferon-α-2b (PEG-Intron®), pegylated IFN-α-con1 and the like; long acting formulations and derivatizations of interferon compounds such as the albumin-fused interferon albuferon α and the like; compounds that stimulate the synthesis of interferon in cells, such as resiquimod and the like; interleukins; compounds that enhance the development of type 1 helper T cell response, such as SCV-07 and the like; TOLL-like receptor agonists such as CpG-10101 (actilon), isatoribine and the like; thymosin α-1; ANA-245; ANA-246; histamine dihydrochloride; propagermanium; tetrachlorodecaoxide; ampligen; IMP-321; KRN-7000; antibodies, such as civacir, XTL-6865 and the like; and prophylactic and therapeutic vaccines such as InnoVac C, HCV E1E2/MF59 and the like.

Other antiviral agents include, but are not limited to, ribavirin, amantadine, viramidine, nitazoxanide; telbivudine; NOV-205; taribavirin; inhibitors of internal ribosome entry; broad-spectrum viral inhibitors, such as IMPDH inhibitors (e.g., compounds of US5,807,876, US6,498,178, US6,344,465, US6,054,472, WO97/40028, WO98/40381,

WO00/56331, and mycophenolic acid and derivatives thereof, and including, but not limited to VX-950, merimepodib (VX-497), VX-148, and/or VX-944); or combinations of any of the above.

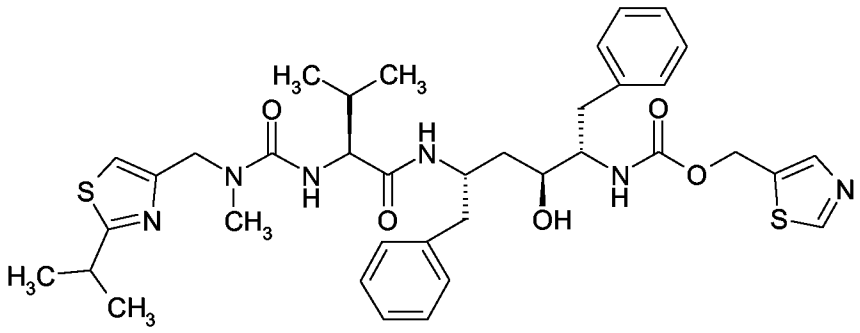
Thus, to combat or treat HCV infections, the compounds of formula (I) may be co-administered in combination with for instance, interferon-α (IFN-α), pegylated interferon-α and/or ribavirin, as well as therapeutics based on antibodies targeted against HCV epitopes, small interfering RNA (Si RNA), ribozymes, DNAzymes, antisense RNA, small molecule antagonists of for instance NS3 protease, NS3 helicase and NS5B polymerase.

Accordingly, the present invention relates to the use of a compound of formula (I) or any subgroup thereof as defined above for the manufacture of a medicament useful for inhibiting HCV activity in a mammal infected with HCV viruses, wherein said medicament is used in a combination therapy, said combination therapy preferably comprising a compound of formula (I) and another HCV inhibitory compound, e.g. (pegylated) IFN-α and/or ribavirin.

In still another aspect there are provided combinations of a compound of formula (I) as specified herein and an anti-HIV compound. The latter preferably are those HIV inhibitors that have a positive effect on drug metabolism and/or pharmacokinetics that improve bioavailabilty. An example of such an HIV inhibitor is ritonavir.

As such, the present invention further provides a combination comprising (a) an HCV NS3/4a protease inhibitor of formula (I) or a pharmaceutically acceptable salt thereof; and (b) ritonavir or a pharmaceutically acceptable salt thereof.

The compound ritonavir, and pharmaceutically acceptable salts thereof, and methods for its preparation are described in WO94/14436. For preferred dosage forms of ritonavir, see US6,037, 157, and the documents cited therein: US5,484, 801, US08/402,690, and WO95/07696 and WO95/09614. Ritonavir has the following formula:



In a further embodiment, the combination comprising (a) an HCV NS3/4a protease inhibitor of formula (I) or a pharmaceutically acceptable salt thereof; and (b) ritonavir or a pharmaceutically acceptable salt thereof; further comprises an additional anti-HCV compound selected from the compounds as described herein.

In one embodiment of the present invention there is provided a process for preparing a combination as described herein, comprising the step of combining an HCV NS3/4a protease inhibitor of formula (I) or a pharmaceutically acceptable salt thereof, and ritonavir or a pharmaceutically acceptable salt thereof. An alternative embodiment of this invention provides a process wherein the combination comprises one or more additional agent as described herein.

The combinations of the present invention may be used as medicaments. Said use as a medicine or method of treatment comprises the systemic administration to HCV-infected subjects of an amount effective to combat the conditions associated with HCV and other pathogenic flavi- and pestiviruses. Consequently, the combinations of the present invention can be used in the manufacture of a medicament useful for treating, preventing or combating infection or disease associated with HCV infection in a mammal, in particular for treating conditions associated with HCV and other pathogenic flavi- and pestiviruses.

In one embodiment of the present invention there is provided a pharmaceutical composition comprising a combination according to any one of the embodiments described herein and a pharmaceutically acceptable excipient. In particular, the present invention provides a pharmaceutical composition comprising (a) a therapeutically effective amount of an HCV NS3/4a protease inhibitor of the formula (I) or a pharmaceutically acceptable salt thereof, (b) a therapeutically effective amount of ritonavir or a pharmaceutically acceptable salt thereof, and (c) a pharmaceutically acceptable excipient. Optionally, the pharmaceutical composition further comprises an additional agent selected from an HCV polymerase inhibitor, an HCV protease inhibitor, an inhibitor of another target in the HCV life cycle, and immunomodulatory agent, an antiviral agent, and combinations thereof.

The compositions may be formulated into suitable pharmaceutical dosage forms such as the dosage forms described above. Each of the active ingredients may be formulated separately and the formulations may be co-administered or one formulation containing both and if desired further active ingredients may be provided.

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

In one embodiment the combinations provided herein may also be formulated as a combined preparation for simultaneous, separate or sequential use in HIV therapy. In such a case, the compound of general formula (I) or any subgroup thereof, is formulated in a pharmaceutical composition containing other pharmaceutically acceptable excipients, and ritonavir is formulated separately in a pharmaceutical composition containing other pharmaceutically acceptable excipients. Conveniently, these two separate pharmaceutical compositions can be part of a kit for simultaneous, separate or sequential use.

Thus, the individual components of the combination of the present invention can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The present invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly. In a preferred embodiment, the separate dosage forms are administered about simultaneously.

In one embodiment, the combination of the present invention contains an amount of ritonavir, or a pharmaceutically acceptable salt thereof, which is sufficient to clinically improve the bioavailability of the HCV NS3/4a protease inhibitor of formula (I) relative to the bioavailability when said HCV NS3/4a protease inhibitor of formula (I) is administered alone.

In another embodiment, the combination of the present invention contains an amount of ritonavir, or a pharmaceutically acceptable salt thereof, which is sufficient to increase at least one of the pharmacokinetic variables of the HCV NS3/4a protease inhibitor of formula (I) selected from $t_{1/2}$, C_{min}, C_{max}, C_{ss}, AUC at 12 hours, or AUC at 24 hours, relative to said at least one pharmacokinetic variable when the HCV NS3/4a protease inhibitor of formula (I) is administered alone.

A further embodiment relates to a method for improving the bioavailability of a HCV NS3/4a protease inhibitor comprising administering to an individual in need of such improvement a combination as defined herein, comprising a therapeutically effective amount of each component of said combination.

In a further embodiment, the invention relates to the use of ritonavir or a pharmaceutically acceptable salt thereof, as an improver of at least one of the pharmacokinetic variables of a HCV NS3/4a protease inhibitor of formula (I) selected from $t_{1/2}$, C_{min}, C_{max}, C_{ss}, AUC at 12 hours, or AUC at 24 hours; with the proviso that said use is not practised in the human or animal body.

The term "individual" as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

Bioavailability is defined as the fraction of administered dose reaching systemic circulation. $t_{1/2}$ represents the half life or time taken for the plasma concentration to fall to half its original value. C_{ss} is the steady state concentration, i.e. the concentration at which the rate of input of drug equals the rate of elimination. C_{min} is defined as the lowest (minimum) concentration measured during the dosing interval. C_{max}, represents the highest (maximum) concentration measured during the dosing interval. AUC is defined as the area under the plasma concentration-time curve for a defined period of time.

The combinations of this invention can be administered to humans in dosage ranges specific for each component comprised in said combinations. The components comprised in said combinations can be administered together or separately. The NS3/4a protease inhibitors of formula (I) or any subgroup thereof, and ritonavir or a pharmaceutically acceptable salt or ester thereof, may have dosage levels of the order of 0.02 to 5.0 grams-per-day.

When the HCV NS3/4a protease inhibitor of formula (I) and ritonavir are administered in combination, the weight ratio of the HCV NS3/4a protease inhibitor of formula (I) *to* ritonavir is suitably in the range of from about 40:1 to about 1:15, or from about 30:1 to about 1:15, or from about 15: 1 to about 1: 15, typically from about 10: 1 to about 1:10, and more typically from about 8:1 to about 1:8. Also useful are weight ratios of the HCV NS3/4a protease inhibitors of formula (I) *to* ritonavir ranging from about 6:1 to about 1:6, or from about 4:1 to about 1:4, or from about 3:1 to about 1:3, or from about 2:1 to about 1:2, or from about 1.5:1 to about 1:1.5. In one aspect, the amount by weight of the HCV NS3/4a protease inhibitors of formula (I) is equal to or greater than that of ritonavir, wherein the weight ratio of the HCV NS3/4a protease inhibitor of formula (I) to ritonavir is suitably in the range of from about 1: 1 to about 15: 1, typically from about 1: 1 to about 10: 1, and more typically from about 1: 1 to about 8: 1. Also useful are weight ratios of the HCV NS3/4a protease inhibitor of formula (I) *to* ritonavir ranging from about 1: 1 to about 6: 1, or from about 1: 1 to about 5: 1, or from

about 1: 1 to about 4:1, or from about 3:2 to about 3:1, or from about 1:1 to about 2:1 or from about 1:1 to about 1.5:1.

The term "therapeutically effective amount" as used herein means that amount of active compound or component or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought, in the light of the present invention, by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated. Since the instant invention refers to combinations comprising two or more agents, the "therapeutically effective amount" is that amount of the agents taken together so that the combined effect elicits the desired biological or medicinal response. For example, the therapeutically effective amount of a composition comprising (a) the compound of formula (I) and (b) ritonavir, would be the amount of the compound of formula (I) and the amount of ritonavir that when taken together have a combined effect that is therapeutically effective.

In general it is contemplated that an antiviral effective daily amount would be from 0.01 mg/kg to 500 mg/kg body weight, more preferably from 0.1 mg/kg to 50 mg/kg body weight. It may be appropriate to administer the required dose as one, two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines.

According to one embodiment, the HCV NS3/4a protease inhibitor of formula (I) and ritonavir may be co-administered once or twice a day, preferably orally, wherein the amount of the compounds of formula (I) per dose is from about 1 to about 2500 mg, and the amount of ritonavir per dose is from 1 to about 2500 mg. In another embodiment, the amounts per dose for once or twice daily co-administration are from about 50 to about 1500 mg of the compound of formula (I) and from about 50 to about

1500 mg of ritonavir. In still another embodiment, the amounts per dose for once or twice daily co-administration are from about 100 to about 1000 mg of the compound of formula (I) and from about 100 to about 800 mg of ritonavir. In yet another embodiment, the amounts per dose for once or twice daily co-administration are from about 150 to about 800 mg of the compound of formula (I) and from about 100 to about 600 mg of ritonavir. In yet another embodiment, the amounts per dose for once or twice daily co-administration are from about 200 to about 600 mg of the compound of formula (I) and from about 100 to about 400 mg of ritonavir. In yet another embodiment, the amounts per dose for once or twice daily co-administration are from about 200 to about 600 mg of the compound of formula (I) and from about 20 to about 300 mg of ritonavir. In yet another embodiment, the amounts per dose for once or twice daily co-administration are from about 100 to about 400 mg of the compound of formula (I) and from about 40 to about 100 mg of ritonavir.

Exemplary combinations of the compound of formula (I) (mg)/ritonavir (mg) for once or twice daily dosage include 50/100, 100/100, 150/100, 200/100, 250/100, 300/100, 350/100, 400/100, 450/100, 50/133, 100/133, 150/133, 200/133, 250/133, 300/133, 50/150, 100/150, 150/150, 200/150, 250/150, 50/200, 100/200, 150/200, 200/200, 250/200, 300/200, 50/300, 80/300, 150/300, 200/300, 250/300, 300/300, 200/600, 400/600, 600/600, 800/600, 1000/600, 200/666, 400/666, 600/666, 800/666, 1000/666, 1200/666, 200/800, 400/800, 600/800, 800/800, 1000/800, 1200/800, 200/1200, 400/1200, 600/1200, 800/1200, 1000/1200, and 1200/1200. Other exemplary combinations of the compound of formula (I) (mg)/ritonavir (mg) for once or twice daily dosage include 1200/400, 800/400, 600/400, 400/200, 600/200, 600/100, 500/100, 400/50, 300/50, and 200/50.

In one embodiment of the present invention there is provided an article of manufacture comprising a composition effective to treat an HCV infection or to inhibit the NS3 protease of HCV; and packaging material comprising a label which indicates that the composition can be used to treat infection by the hepatitis C virus; wherein the composition comprises a compound of the formula (I) or any subgroup thereof, or the combination as described herein.

Another embodiment of the present invention concerns a kit or container comprising a compound of the formula (I) or any subgroup thereof, or a combination according to the invention combining an HCV NS3/4a protease inhibitor of formula (I) or a pharmaceutically acceptable salt thereof, and ritonavir or a pharmaceutically acceptable salt thereof, in an amount effective for use as a standard or reagent in a test or assay for

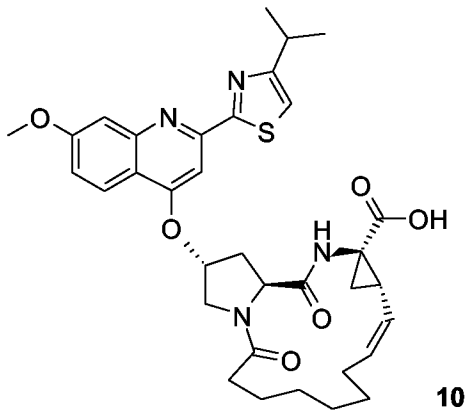
determining the ability of potential pharmaceuticals to inhibit HCV NS3/4a protease, HCV growth, or both. This aspect of the invention may find its use in pharmaceutical research programs.

The compounds and combinations of the present invention can be used in high-throughput target-analyte assays such as those for measuring the efficacy of said combination in HCV treatment.

Examples

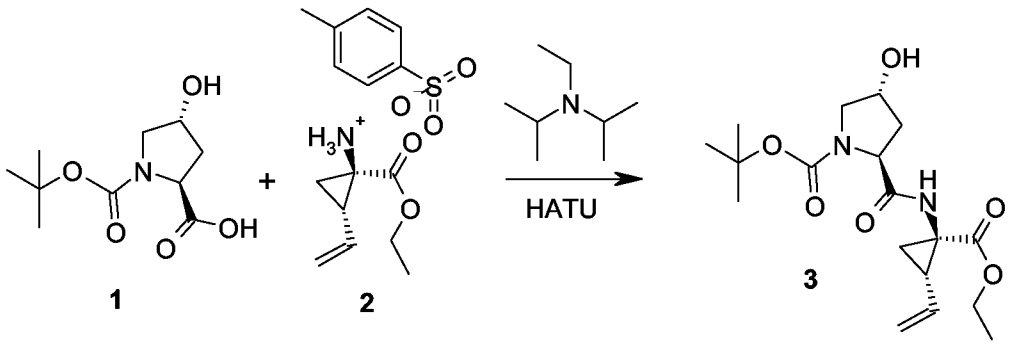
The following examples are intended to illustrate the present invention and not to limit it thereto.

Example 1: Synthesis of 18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid 10.



10

Step A

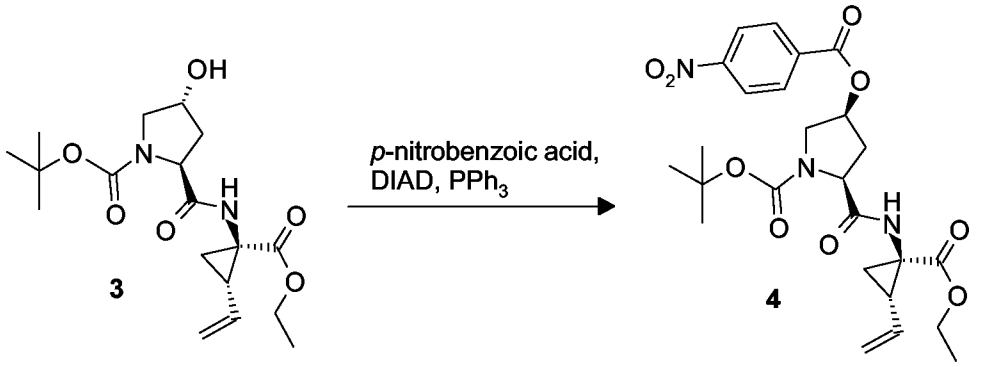


1 2 3

To a stirred solution of Boc-hydroxyproline **1** (5g, 22 mmol) in dry DMF (200 mL) were added 1-amino-2-vinylcyclopropanecarboxylic acid ethyl ester tosylate **2** (8g, 24 mmol) and diisopropylethylamine (7g, 54 mmol). This solution was cooled to 0°C then HATU (9g, 24 mmol) was added. The reaction mixture was stirred at 0°C for 30 minutes under nitrogen then at RT (room temperature) for 4 h. The reaction mixture

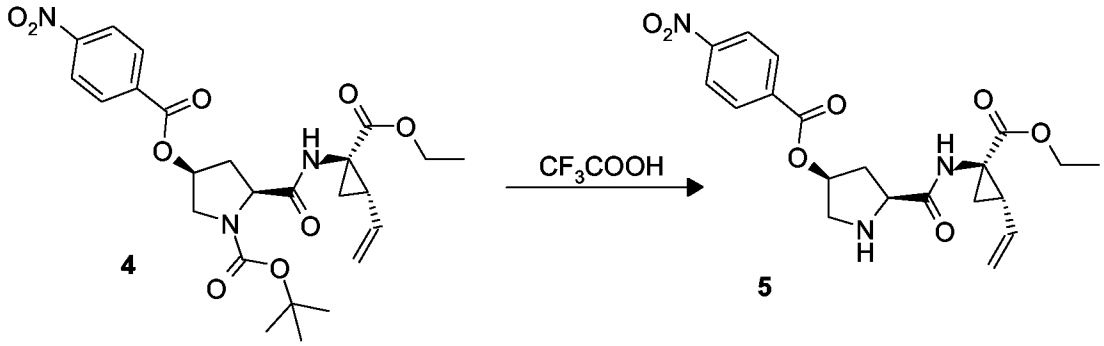
was diluted with water (250 mL) and extracted with EtOAc (3x150 mL). The organic layers were combined and washed with a saturated solution of $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (gradient DCM to EtOAc) afforded 7.7 g (97%) of the desired product **3**: *m/z* = 369 $(M+H)^+$.

Step B



To a solution of alcohol **3** (7.7g, 20.9 mmoles), para-nitrobenzoic acid (5.23 g, 31.3 mmol) and triphenylphosphine (8.22 g, 31.3 mmol) in dry THF (200 mL) was added dropwise at –20 °C, under nitrogen DIAD (6.34 g, 31.35 mmol). After 1h at -20°C the reaction mixture was allowed to warm up to RT. After 3 days, the reaction mixture was filtered off and the precipitate washed with EtOAc. The filtrate was diluted with EtOAc and washed with water, dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography (Gradient of EtOAc (0 to 10%) in CH_2Cl_2) afforded 8.45 g (78%) of the desired product **4** as a colorless oil: *m/z* = 518 $(M+H)^+$.

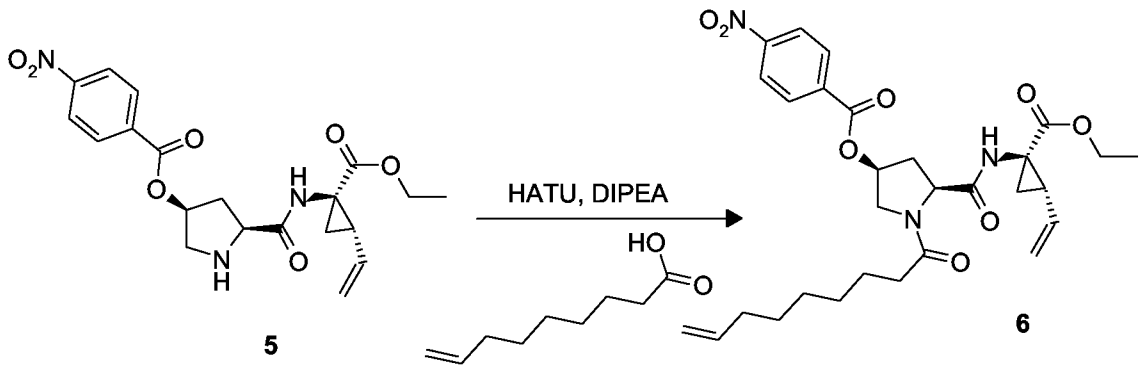
Step C



To a stirred solution of Boc-protected proline derivative **4** (1.25 g, 2.17 mmol) in CH_2Cl_2 (20 mL) was added trifluoroacetic acid (2.48 g, 21.7 mmol). After 30 min at RT, the reaction mixture was concentrated and the residue was partitioned between a

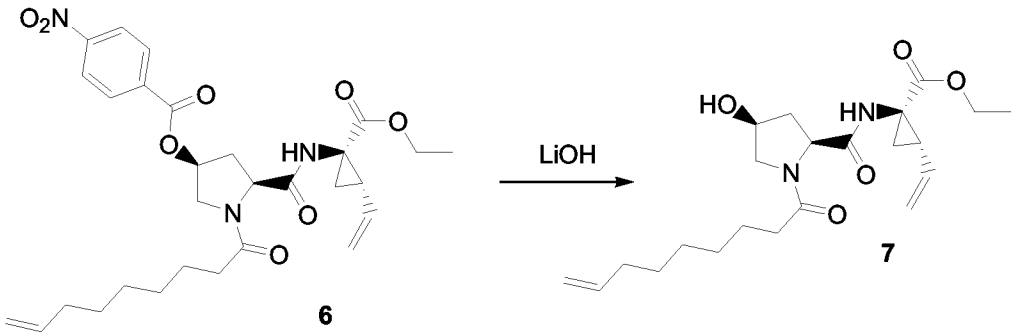
saturated solution of $NaHCO_3$ and EtOAc. The organic layer was dried ($MgSO_4$) filtered and concentrated to give 0.9 g of the desired product **5** as a colorless oil: *m/z* = 418 $(M+H)^+$.

Step D



To a stirred solution of proline derivative **5** (734 mg, 1.76 mmol) in dry DMF (20 mL) was added nonenoic acid (330 mg, 2.11 mmol) and diisopropylethylamine (455 mg, 3.52 mmoles). Then, HATU (802 mg, 2.11 mmol) was added at 0°C under nitrogen. The reaction mixture was stirred at 0°C for 30 minutes then at RT for 4 h, then diluted with water (25 mL) and extracted with EtOAc (3x15 mL). The organic layers were combined and successively washed with a sat. $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered and concentrated. Purification by column chromatography (Gradient of EtOAc (0 to 20%) in DCM) afforded 950 mg (97%) of the desired product **6**: *m/z* = 556 $(M+H)^+$.

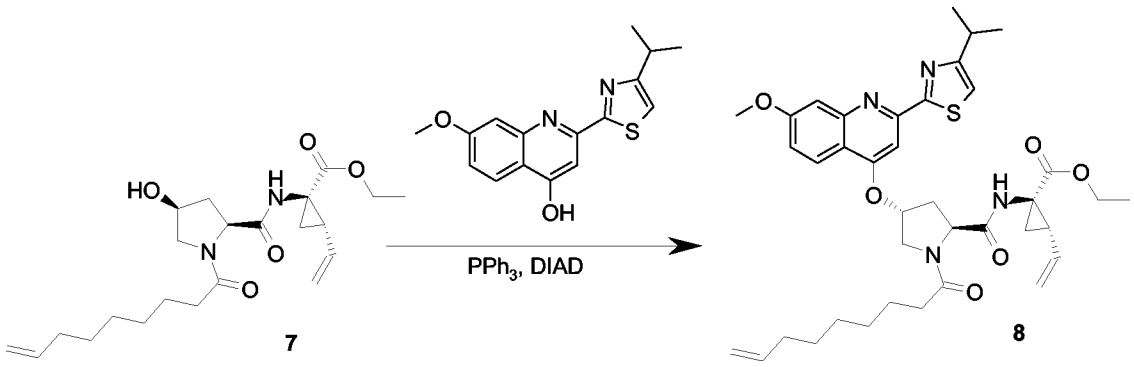
Step E



A solution of lithium hydroxide (300 mg, 7.02 mmol) in water (10 mL) was added at 0°C to a stirred solution of **6** (1.95 g, 3.51 mmol) in THF (30 mL). After 2 h at 0°C, the reaction mixture was acidified with 1M HCl (pH = 6) and extracted with AcOEt. The organic layer was washed with a saturated solution of $NaHCO_3$, dried ($MgSO_4$),

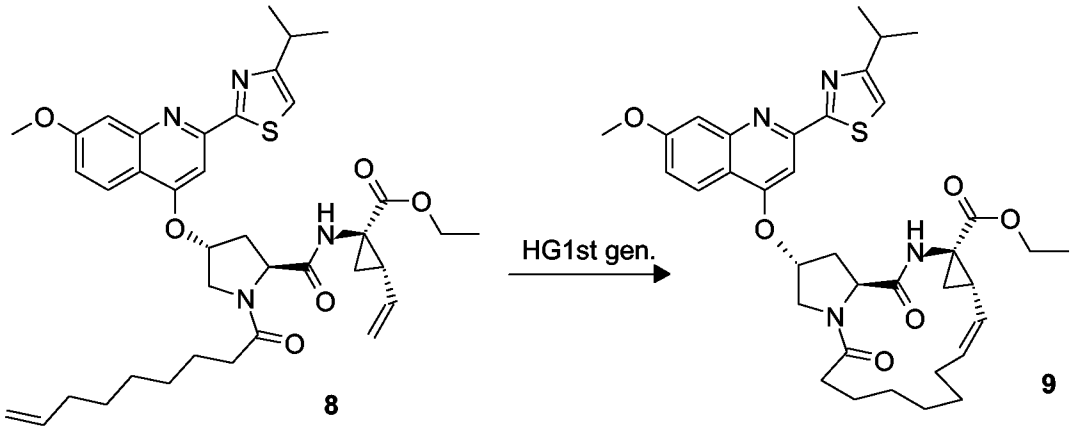
filtered and concentrated to give 1.3g (91%) of the desired product **7** as a colorless oil: *m/z* = 407 $(M+H)^+$.

Step F



To a solution of alcohol **7** (0.5 g, 1.23 mmoles), 2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-ol (0.48 g, 1.6 mmol) and triphenylphosphine (0.45 g, 1.72 mmol) in dry THF (15 mL) was added dropwise DIAD (0.37 g, 1.85 mmoles, 1.5 eq) at –20 °C, under nitrogen. After 1h at –20 °C the reaction mixture was allowed to warm up to RT. After 20h, the mixture was poured in ice/water, and extracted with EtOAc. The organic layers were combined, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (CH_2Cl_2/EtOAc, 80:20) afforded 535 mg (63%) of the desired product **8** as a yellow foam: *m/z* = 689 $(M+H)^+$.

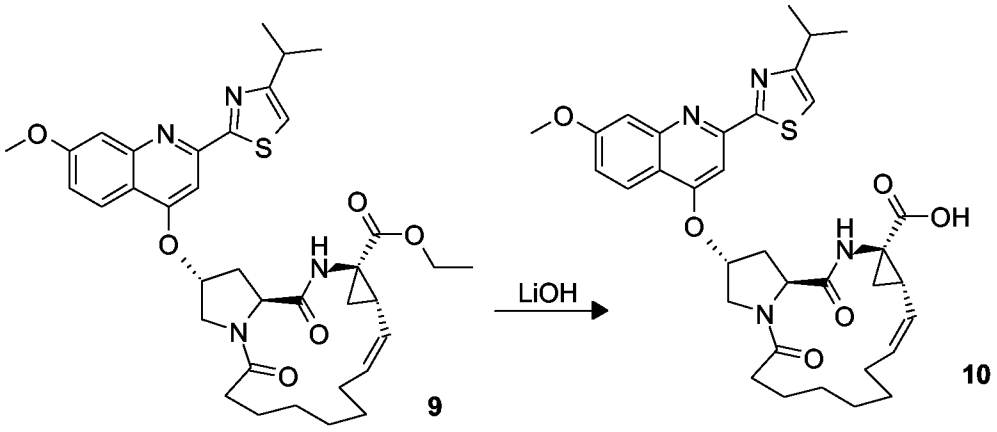
Step G



A solution of **8** (540 mg, 0.78 mmo) and Hoveyda-Grubbs catalyst 1st generation (45 mg, 0.07 mmol) in CH_2Cl_2 (540 mL) was stirred under nitrogen at 70 °C for 19h. The reaction mixture was evaporated and purified by flash chromatography (Gradient

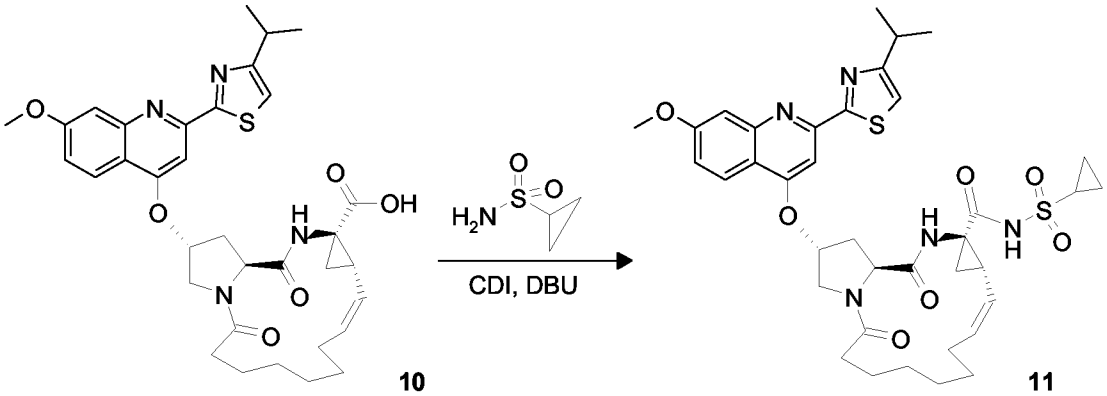
of AcOEt (0 to 20%) in CH_2Cl_2) to afford 390 mg (76%) of the desired macrocycle **9**: *m/z* = 661 $(M+H)^+$.

Step H



A solution of lithium hydroxide (1 g, 23.6 mmol) in water (15 mL) was added to a stirred solution of ester **9** (390 mg, 0.59 mmol) in THF (30 mL) and MeOH (20 mL). After 16 h at room temperature, the reaction mixture was quenched with NH_4Cl sat., concentrated under reduced pressure, acidified to pH 3 with HCl 1N and extracted with CH_2Cl_2, dried ($MgSO_4$) and evaporated to give 325 mg (84%) of 18-[2-[4-(isopropyl)-thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.$0^{4,6}$]-nonadec-7-ene-4-carboxylic acid **10** as an oil that slowly crystallized. The product was recrystallized from ether: *m/z* = 633 $(M+H)^+$.

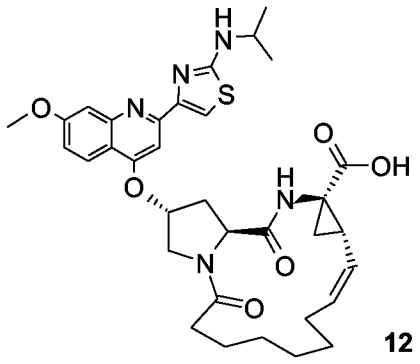
Example 2: Synthesis of *N*-[[18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.$0^{4,6}$]nonadec-7-en-4-yl]carbonyl] (cyclopropyl)sulfonamide 11.



A solution of carboxylic acid **10** (100mg, 0.158 mmol) and carbonyldiimidazole (38 mg, 0.237 mmol) in dry THF (8 mL) was stirred at reflux under nitrogen for 2h.

Optionally, the azalactone derivative, if desired, can be isolated. The reaction mixture was cooled to room temperature and cyclopropylsulfonamide (29 mg, 0.237 mmol) and DBU (36 mg, 0.237 mmol) were added. This solution was heated at 50 °C for 5h. Then, the reaction mixture was cooled down at room temperature and concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and HCl 1N, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give 180 mg of a colorless oil. Purification by flash chromatography (gradient of EtOAc (0 to 20%) in DCM) afforded 90 mg (74%) of the title product **11** as a white powder: *m/z* = 736 $(M+H)^+$. ^1H NMR ($CDCl_3$): 0.9-1.6 (m, 18H), 1.80-1.96 (m, 3H), 2.20-2.28 (m, 1H), 2.37 (t, 1H, *J* = 12 Hz), 2.45-2.72 (m, 4H), 2.88-2.95 (m, 1H), 3.20 (q, 1H, *J* = 6 Hz), 3.96 (s, 3H), 4.0 (d, 1H, *J* = 11 Hz), 4.11 (dd, 1H, *J* = 3.8 Hz, 11 Hz), 4.6 (t, 1H, *J* = 8Hz), 5.0 (t, 1H, *J* = 10 Hz), 5.52 (broad s, 1H), 5.73 (dd, 1H, J = 8 Hz, 18 Hz), 6.68 (s, 1H), 7.05 (s, 1H), 7.12 (dd, 1H, *J* = 2.5 Hz, 9 Hz), 7.38 (d, 1H, *J* = 2.5 Hz), 7.57 (s, 1H), 7.94 (d, 1H, *J* = 9 Hz), 10.23 (s, 1H).

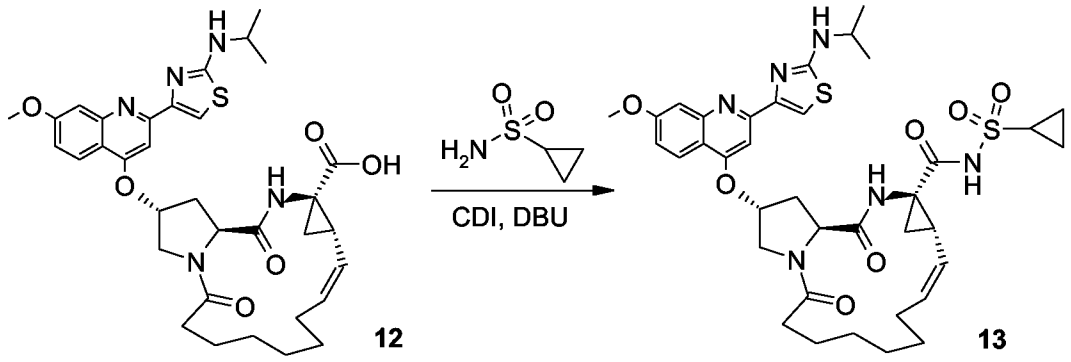
Example 3: Synthesis of 18-[2-[2-(isopropylamino)thiazol-4-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.$0^{4,6}$]nonadec-7-ene-4-carboxylic acid 12



12

The title compound was prepared from 4-hydroxy-2-[2-(isopropylamino)thiazol-4-yl]-7-methoxyquinoline and intermediate **7** following the procedure (Step F-H) reported for 18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.$0^{4,6}$]nonadec-7-ene-4-carboxylic acid **10**: *m/z* = 648 $(M+H)^+$. ^1H NMR ($CDCl_3$): 1.01-1.41 (m, 12H), 1.81-1.95 (m, 3H), 2.11-2.30 (m, 3H), 2.43 (m, 1H), 2.55 (m, 1H), 2.91 (m, 1H), 3.47 (m, 2H), 3.60 (m, 1H), 3.94 (s, 3H), 4.27 (M, 1H) 4.78 (d, *J* = 8.0 Hz, 1H), 5.52-5.70 (m, 3H), 7.10 (d, 1H, *J* = 8.6 Hz), 7.32 (s, 1H), 7.45-7.52 (m, 2H), 7.96 (d, 1H, *J* = 8.6 Hz), 9.5 (s, 1H).

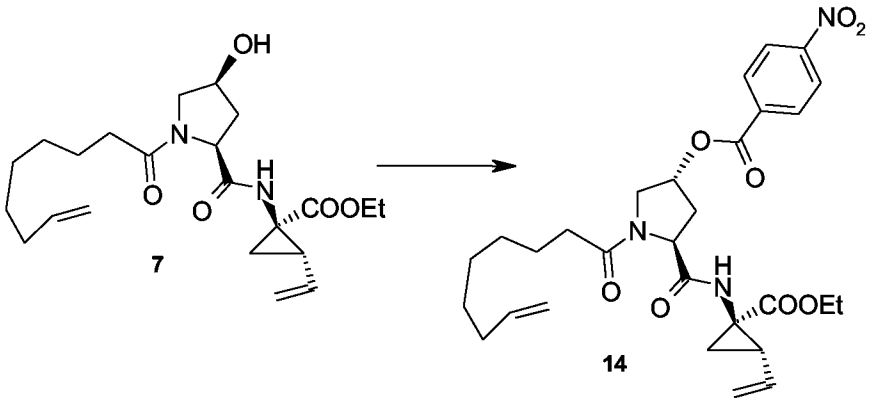
Example 4: Synthesis of *N*-[[18-[2-[2-(isopropylamino) thiazol-4-yl]-7-methoxy-quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo [14.3.0.0^{4,6}]nonadec-7-en-4-yl]carbonyl](cyclopropyl) sulfonamide 13



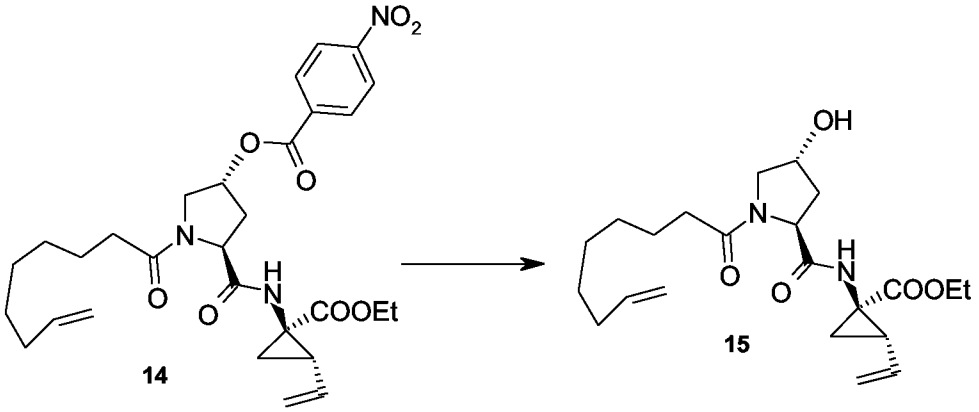
12 13

A solution of 18-[2-[2-(isopropylamino)thiazol-4-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (12, 54 mg, 0.083 mmol) and carbonyldiimidazole (20 mg, 0.125 mmol, 1.5 eq) in dry THF (4 mL) was stirred at reflux under nitrogen for 2h. Optionally, the azalactone derivative, if desired, can be isolated. The reaction mixture was cooled to room temperature and cyclopropylsulfonamide (15 mg, 0.125 mmol) and DBU (19 mg, 0.125 mmol) were added. This solution was heated at 50 °C for 16h. Then, the reaction mixture was cooled down at room temperature and concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and HCl 1N, the organic layer was washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (gradient of EtOAc (0 to 50%) in DCM) afforded 45 mg (72%) of the title product which was recrystallized from water to give 12 mg of the desired product as a slightly yellow powder. *m/z* = 751 $(M+H)^+$. ^1H NMR ($CDCl_3$): 0.8-1.9 (m, 21 H), 2.17 (m, 1H), 2.28-2.56 (m, 4H), 2.65 (m, 1H), 2.86, (m, 1H), 3.55 (m, 1H), 3.87 (m, 4H), 4.10 (m, 1H), 4.57 (m, 1H), 4.94 (t, *J* = 9.5 Hz, 1H), 5.43 (m, 2H), 5.64 (m, 1H), 6.92 (broad s, 1H), 6.98 (dd, *J* = 9.0 Hz, 3.0 Hz, 1H), 7.28 (m, 2H), 7.37 (s, 1H), 7.80 (d, *J* = 9.0 Hz, 1H).

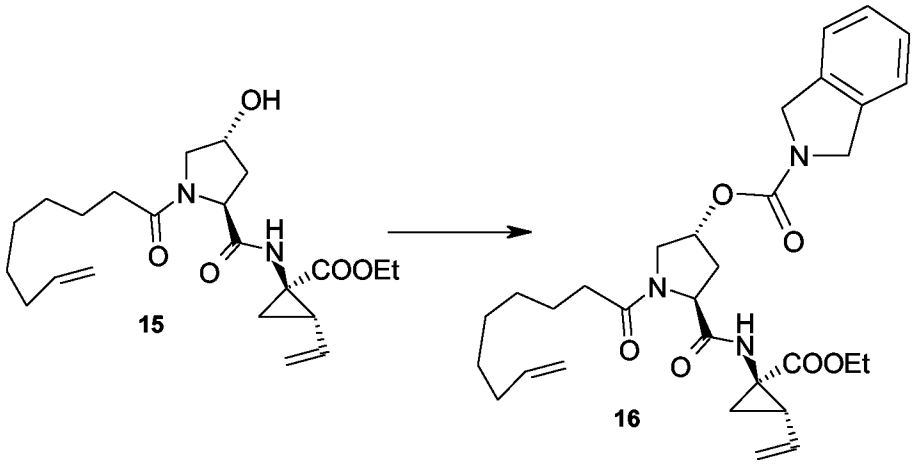
Example 5: Synthesis of 18-[1,3-dihydroisoindol-2-ylcarbonyloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid 18.



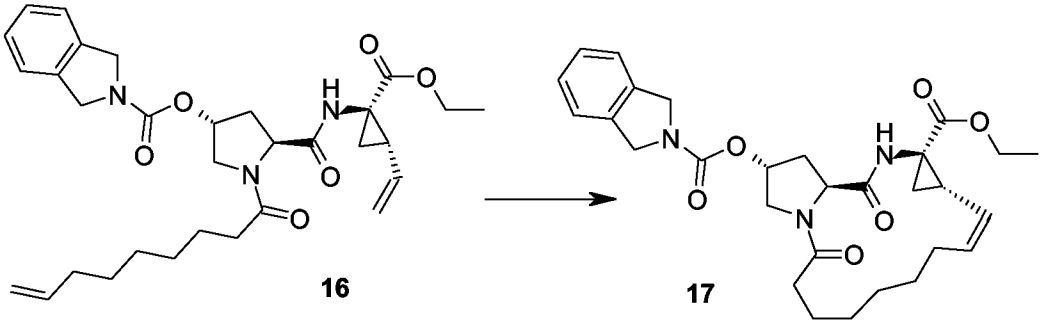
To a solution of alcohol **7** (300 mg, 0.738 mmole), paranitrobenzoic acid (123 mg, 1 eq) and triphenylphosphine (194 mg, 1 eq) in dry THF (10 mL) was added dropwise at -20°C, under nitrogen DIAD (149 mg, 1 eq). After 1h at –20 °C the reaction mixture was allowed to warm up to RT. After 16h, the reaction mixture was diluted with EtOAc and washed with water, dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography (Gradient of EtOAc 0 to 10% in CH_2Cl_2) afforded 200 mg (50%) of the desired product as a colorless oil. *m/z* = 556 ($M+H^+$)



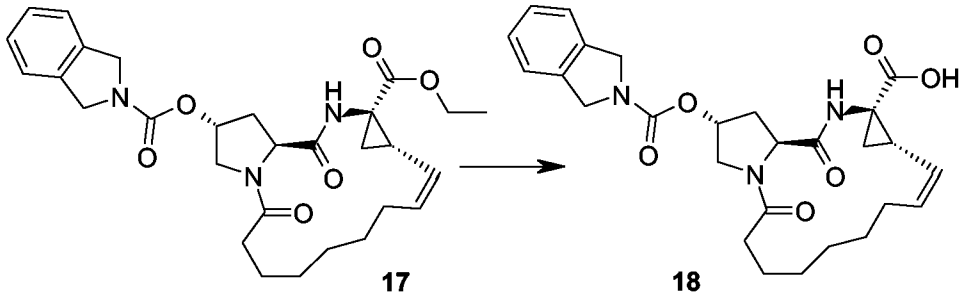
To the paranitrobenzoic ester **14** (200 mg, 0.23 mmole) dissolved in THF (3 mL) and cooled to 0 °C was added LiOH monohydrate (30 mg, 2 eq) dissolved in water (1 mL). The mixture was stirred at 0 °C for 2 h, then it was acidified with a diluted solution of HCl (pH=6) and extracted with AcOEt. The organic layer was extracted with a saturated solution of $NaHCO_3$, washed with brine, dried ($MgSO_4$) and evaporated. The obtained colorless oil was dried under high vacuum to give 140 mg (98%) of the desired product as a white solid. *m/z* = 407 ($M+H^+$).



The alcohol **15** (140 mg, 0.344 mmole) and CDI (56 mg, 1 eq) were mixed in DCM (3 mL) and stirred at RT. After 16h, the amine (45 mg, 2.5 eq) was added and the reaction mixture was stirred at RT until completion as indicated by LC-MS. The RM (reaction mixture) was then extracted with HCl 1M in water, washed with brine, dried, filtered and concentrated. Purification by flash chromatography on silica gel (EtOAc in DCM 0 to 20%) afforded 50 mg of the desired product. m/z = 552 ($M+H^+$).

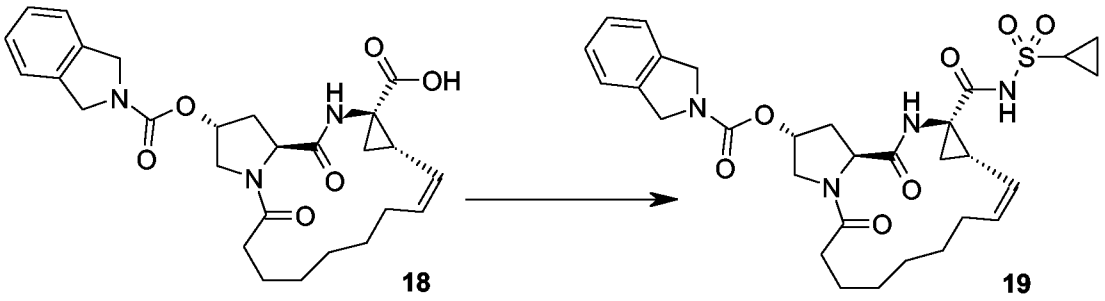


To the diene **16** (50 mg, 0.091 mmole) dissolved in dichloroethane (9 mL - 0.01M) and under N_2, was added Hoveyda-Grubbs 2nd generation catalyst (2.8 mg, 0.05 eq). The reaction mixture was heated at 80 °C with a septum under N_2 overnight. After 15h, the RM was concentrated and purified by flash chromatography on silica gel (EtOAc 0 to 20% in DCM) to give 30 mg (63%) of the desired product **17** as a colorless oil. m/z = 524 ($M+H^+$).



A solution of LiOH monohydrate **17** (98 mg, 2.292 mmoles) in water (1 mL) was added to a solution of ethyl ester (30 mg, 0.057 mmole) in MeOH/THF (1/1). The RM was stirred at RT for 20h. It was then acidified with diluted HCl until pH 4-5 and extracted with EtOAc (3X). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated to give 30 mg of the desired product **18** as a colorless solid. *m/z* = 496 ($M+H^+$).

Example 6: Synthesis of *N*-[18-[1,3-dihydroisoindol-2-ylcarbonyloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.$0^{4,6}$]nonadec-7-ene-4-carbonyl](cyclopropyl)sulfonamide 19.

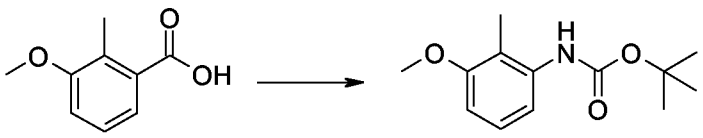


18 **19**

The mixture of carboxylic acid **18** (30 mg, 0.06 mmole) and CDI (20 mg, 2 eq) in dry THF (3 mL) was stirred at reflux for 2h30 under nitrogen. Optionally, the azalactone derivative, if desired, can be isolated. Then, the reaction mixture was cooled at room temperature and cyclopropylsulfonamide (15 mg, 2 eq) and DBU (18 mg, 2 eq) were added. The reaction mixture was stirred at 50°C until completion as indicated by LC-MS. The RM was then concentrated, redissolved in DCM and extracted with HCl 1M then brine, dried and concentrated. Purification by flash chromatography on silica gel afforded the desired product **19**. *m/z* = 599 ($M+H^+$).

Example 7: Synthesis of 18-[2-(thiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.$0^{4,6}$]nonadec-7-ene-4-carboxylic acid 25.

Step A:

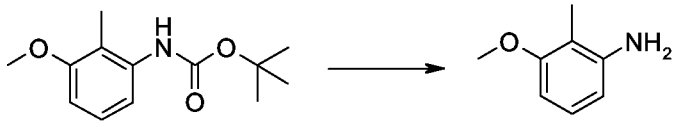


20

Triethylamine (42.4 mL, 302 mmol) was added to a suspension of 3-methoxy-2-methylbenzoic acid (45.6 g, 274 mmol) in dry toluene (800 mL). A clear solution was obtained. Then, diphenylphosphorylazide (dppa) (65.4 mL, 302 mmol) in toluene (100 mL) was slowly added. After 1 h at room temperature, the reaction mixture was

successively heated at 50 °C for 0.5 h, at 70 °C for 0.5 h then at 100 °C for 1 h. To this solution, *t*-BuOH (30.5 g, 411 mmol) in toluene (40 mL) was added at 100 °C and the resulting mixture was refluxed for 7h. The solution was cooled to room temperature then successively washed with water, 0.5 N HCl, 0.5 N NaOH and brine, dried (Na_2SO_4), and evaporated to give 67 g of the target product **20**: *m/z* = 237 $(M)^+$.

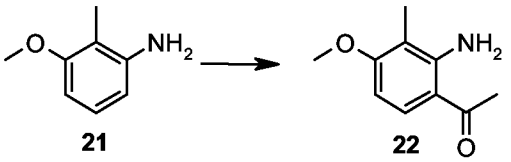
Step B



20 **21**

TFA (40.7 mL, 548 mmol) was added to a solution of *N*-(*tert*-butyloxycarbonyl)-3-methoxy-2-methylaniline (**33**), in dichloromethane (500 mL). After 2 h at room temperature, TFA (40.7 mL, 548 mmol) was added and the resulting mixture was stirred at room temperature overnight. Then, volatiles were evaporated. The residue was triturated with toluene (100 mL) and diisopropylether (250 mL), filtered off and washed with diisopropyl ether (100 mL) to give 56.3 g of the title product **21** as a TFA salt: *m/z* = 138 $(M+H)^+$. The TFA salt was transformed to the free aniline by treatment with $NaHCO_3$.

Step C

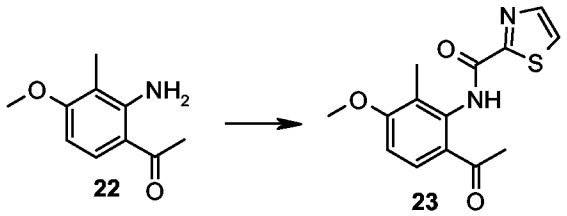


21 **22**

A solution of BCl_3 (1.0 M in CH_2Cl_2, 194 mL) was added dropwise by canula over 20 min, under argon pressure, at 0 °C to a solution of 3-methoxy-2-methylaniline (**21**, 25.4 g, 185 mmol) in xylene (300 mL). The temperature was maintained between 0 °C and 10 °C until the addition was completed. After an additional 30 min at 0 °C, acetonitrile (12.6 mL, 241 mmol) was added dropwise under argon at 0 °C. After 30 min at 0 °C, the resulting suspension was transferred into a dropping funnel, and diluted with CH_2Cl_2 (40 mL). This mixture was added at 0 °C under argon over 20 min to a suspension of $AlCl_3$ (25.9 g, 194 mmol) in CH_2Cl_2 (40 mL). The resulting orange solution was heated in an oil bath at 70 °C under a nitrogen stream for 12 h. Then, the reaction mixture was cooled down to room temperature, and ice-cold water and CH_2Cl_2 were added. This mixture was heated at reflux for 6h, and then cooled to room temperature. After 12h, the pH was adjusted at 0 °C to 3 with 6N NaOH. The solution was extracted with CH_2Cl_2, successively washed with water, 1N NaOH, and brine. The

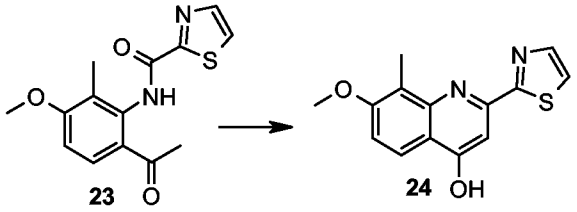
organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was triturated at room temperature in diisopropyl ether (50 mL) for 0.5 h. Then, the suspension was cooled at 0 °C, filtered, and washed with small portion of diisopropyl ether and dried under high vacuum to give 15.4 g (46%) of the desired product **22**: *m/z* = 180 $(M+H)^+$.

Step D



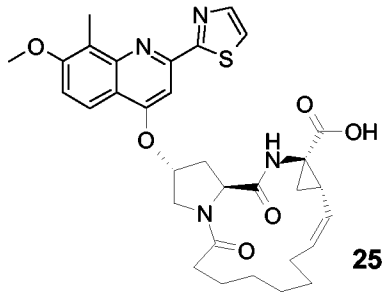
EDCI (257 mg, 1.34 mmol) and HOAt (152 mg, 1.12 mmol) were added to a stirred solution of **22** (200 mg, 1.12 mmol) in CH_2Cl_2 (10 mL) and dry DMF (1 mL). The resulting solution was stirred at room temperature for 3 days. Then, the reaction mixture was partitioned between CH_2Cl_2 and 1N $NaHCO_3$. The organic layer was successively washed with 1N NH_4Cl, and water, dried (Na_2SO_4), and evaporated. Purification by flash chromatography (gradient AcOEt/heptane, 10:90 to 50:50) afforded 62 mg (19%) of the target product **23**: *m/z* = 291 $(M+H)^+$.

Step E. Synthesis of 4-hydroxy-7-methoxy-8-methyl-2-(thiazol-2-yl)quinoline (24)



*t*BuOK (50 mg, 0.448 mmol) was added to a suspension of acetophenone **23** (62 mg, 0.213 mmol) in *t*BuOH (5 mL). The resulting mixture was stirred at 80 °C overnight, then cooled at room temperature. The reaction mixture was diluted with AcOEt, acidified with $KHSO_4$, and successively washed with water and brine. Organic layer was dried (Na_2SO_4) and evaporated to give 43 mg (74%) of the target product **24** as a white powder: *m/z* = 273 $(M+H)^+$.

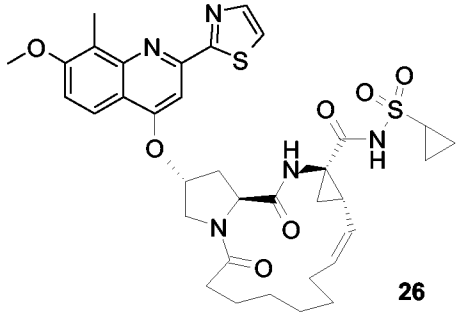
Step F. Synthesis of 18-[2-(thiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.$0^{4,6}$]nonadec-7-ene-4-carboxylic acid **25**.



25

The title compound was prepared from quinoline **24** and intermediate **7** following the procedure (Step F-H) reported for 18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxy-quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.$0^{4,6}$]nonadec-7-ene-4-carboxylic acid **10**: *m/z* = 605 $(M+H)^+$.

Example 8: Synthesis of *N*-[18-[2-(thiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.$0^{4,6}$]nonadec-7-ene-4-carbonyl]-(cyclopropyl)sulfonamide (26)

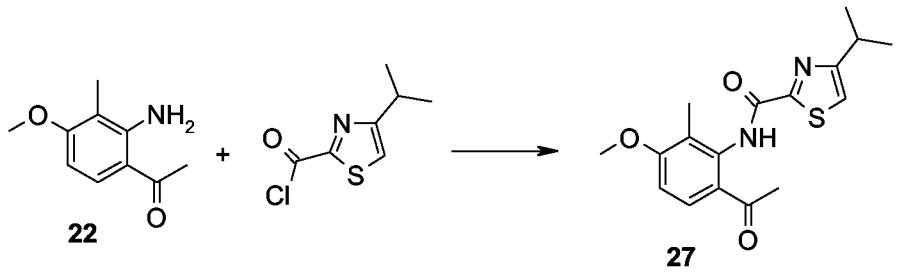


26

The title compound was prepared from 18-[2-(thiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.$0^{4,6}$]nonadec-7-ene-4-carboxylic acid **25** following the procedure reported for synthesis of *N*-[[18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo-[14.3.0.$0^{4,6}$]nonadec-7-en-4-yl]carbonyl](cyclopropyl)sulfonamide **11**: *m/z* = 708 $(M+H)^+$.

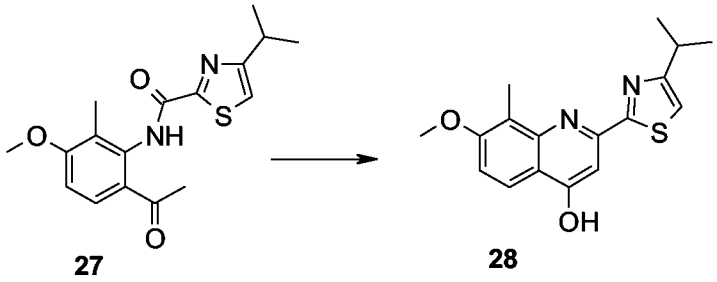
Example 9: Synthesis of 18-[2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.$0^{4,6}$]nonadec-7-ene-4-carboxylic acid (29)

Step A



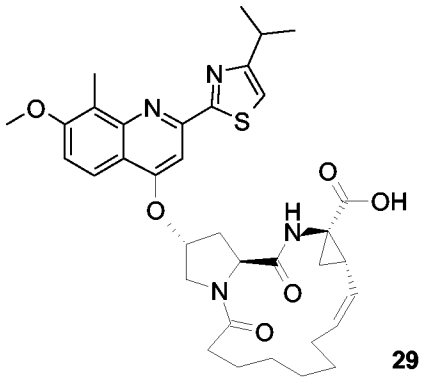
A solution of (2-amino-4-methoxy-3-methylphenyl)(methyl)ketone (**22**, 18.6 g, 104 mmol) in dioxane (50 mL) was added under nitrogen to a suspension of 4-isopropylthiazole-2-carbonyl chloride in dioxane (250 mL). After 2 h at room temperature, the reaction mixture was concentrated to dryness. Then, the residue was partitioned between an aqueous solution of $NaHCO_3$ and AcOEt, organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was triturated in diisopropyl ether, filtered off and washed with diisopropyl ether to give 30.8 g (90 %) of the title product **27**: *m/z* = 333 $(M+H)^+$.

Step B



Potassium *tert*-butoxide (21.8 g, 195 mmol) was added to a suspension of 2'-[[(4-isopropylthiazole-2-yl)(oxo)methyl]amino]-4'-methoxy-3'-methylacetophenone (**27**, 30.8 g, 92.7 mmol) in *tert*-butanol. The resulting reaction mixtures was heated at 100°C overnight. Then, the reaction mixture was cooled at room temperature and diluted with ether (100 mL). The precipitate was filtered off and washed with Et_2O to give a powder (fraction A). The mother liquor was concentrated in vacuo, triturated in ether, filtered off, and washed with ether to give a powder (fraction 2). Fractions 1 and 2 were mixed and poured into water (250 mL). The pH of the resulting solution was adjusted to 6-7 (control with pH paper) with HCl 1N. The precipitate was filtered off, washed with water and dried. Then, the solid was triturated in diisopropyl ether, filtered off and dried to give 26 g (88%) of the title product **28** as a brownish solid: *m/z* = 315 $(M+H)^+$.

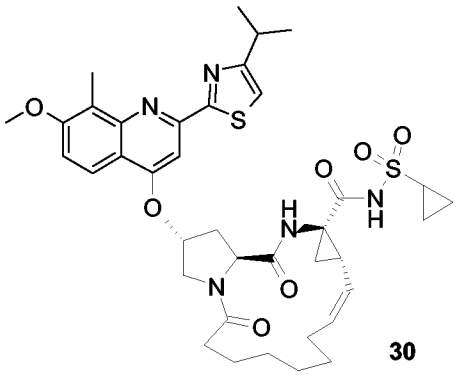
Step C. Synthesis of 18-[2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (**29**)



29

The title compound was prepared from quinoline **28** and intermediate **7** following the procedure (Step F-H) reported for 18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxy-quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid **10**: *m/z* = 647 $(M+H)^+$.

Example 10: Synthesis of *N*-[18-[2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carbonyl](cyclopropyl)sulfonamide (30)

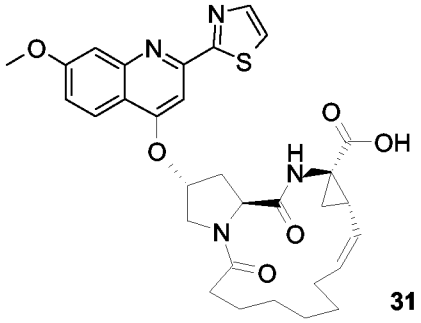


30

The title compound was prepared from 18-[2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (**29**) following the procedure reported for synthesis of *N*-[[18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-en-4-yl]carbonyl](cyclopropyl)sulfonamide **11**: *m/z* = 750 $(M+H)^+$. ^{1}H NMR ($CDCl_3$): 0.90-1.00 (m, 1H), 1.1-1.2 (m, 4H), 1.4 (d, *J* = 6.9 Hz, 6H), 1.4-1.6 (m, 4H), 2.15-2.25 (m, 1H), 2.3-2.4 (m, 1H), 2.45-2.55 (m, 2H), 2.65 (s, 3H), 2.6-2.7 (m, 2H), 2.85-2.95 (m, 1H), 3.15-3.5 (m, 7H), 3.95 (d, *J* = 10.8 Hz, 1H), 3.95 (s, 3H), 4.1 (dd, *J* = 11.5 Hz, *J* = 3.8 Hz, 1H), 4.6 (t, *J* = 8 Hz, 1H), 5.0 (t, *J* =

9 Hz, 1H), 5.5 (t, J = 3.14 Hz, 1H), 5.7-5.8 (dd, J = 18.2 and J = 8.2 Hz, 1H), 6.85 (s, 1H), 7.02 (s, 1H), 7.2 (d, J = 9.5 Hz, 1H), 7.5 (s, 1H), 7.85 (d, J = 9.5 Hz, 1H), 10.5 (br s, 1H).

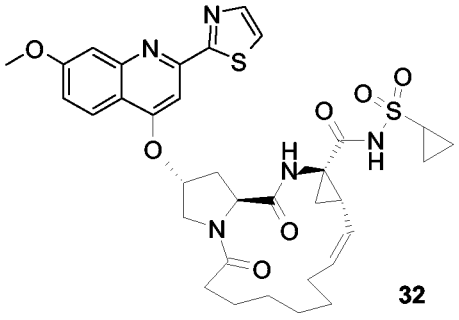
Example 11: Synthesis of 18-[7-methoxy-2-(thiazol-2-yl)quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (31)



31

The title compound was prepared from 4-hydroxy-7-methoxy-2-(thiazol-2-yl)quinoline and intermediate **7** following the procedure (Step F-H) reported for 18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid **10**: m/z = 591 $(M+H)^+$.

Example 12: Synthesis of *N*-[18-[7-methoxy-2-(thiazol-2-yl)quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carbonyl](cyclopropyl)-sulfonamide (32).

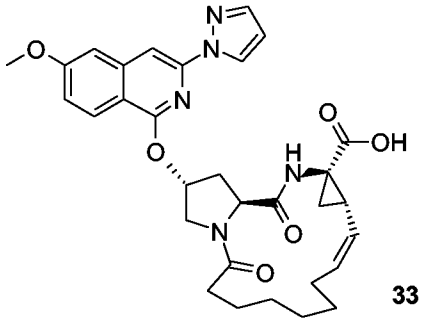


32

The title compound was prepared from 18-[7-methoxy-2-(thiazol-2-yl)quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (**31**) following the procedure reported for synthesis of *N*-[[18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-en-4-yl]carbonyl](cyclopropyl) sulfonamide **11**: m/z = 694 $(M+H)^+$. ^{1}H NMR ($CDCl_3$): 0.90-1.5 (m, 9H), 1.6-1.8 (m, 8H), 2.1-2.4 (m, 2H), 2.45-2.55 (m, 2H), 2.6-2.7 (m, 1H), 2.9-3 (m, 1H), 3.9 (s, 3H), 4.12 (dd, J = 11.6 Hz, J = 3.7 Hz, 1H), 5.1 (t, J = 7.9 Hz, 1H), 5.00 (t, J = 9 Hz, 1H), 5.48 (t, J = 2.9 Hz, 1H), 5.7 (dd, J = 18.2 Hz, J =

8.8 Hz, 1H), 7 (br s, 1H), 7.15 (dd, J = 9.1 Hz, J = 2.4 Hz, 1H), 7.4 (d, J = 2.4 Hz, 1H), 7.5 (d, J = 3.2 Hz, 1H), 7.59 (s, 1H), 7.9 (d, J = 3.2 Hz, 1H), 7.9 (d, J = 9.1 Hz, 1H), 10.3 (br s, 1H).

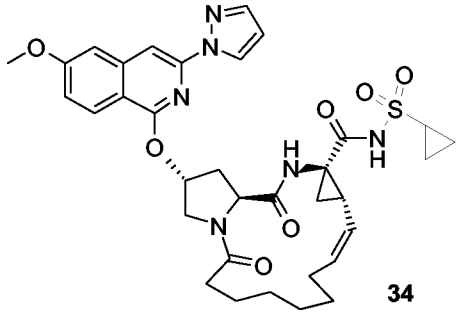
Example 13: Synthesis of 18-[6-methoxy-3-(pyrazol-1-yl)isoquinolin-1-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (33).



33

The title compound was prepared from 1-hydroxy-6-methoxy-3-(pyrazol-1-yl)-isoquinoline and intermediate **7** following the procedure (Step F-H) reported for 18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diaza-tricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid **10**: m/z = 574 $(M+H)^+$.

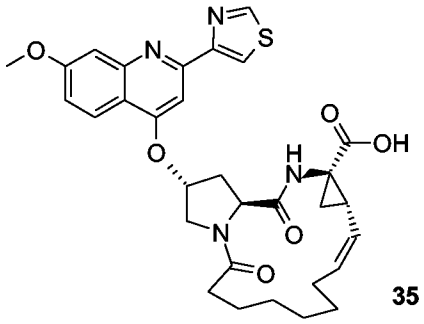
Example 14: Synthesis of *N*-[18-[6-methoxy-3-(pyrazol-1-yl)isoquinolin-1-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carbonyl](cyclopropyl)-sulfonamide (34).



34

The title compound was prepared from 18-[6-methoxy-3-(pyrazol-1-yl)isoquinolin-1-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (**33**) following the procedure reported for synthesis of *N*-[[18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-en-4-yl]carbonyl](cyclopropyl) sulfonamide **11**: m/z = 677 $(M+H)^+$.

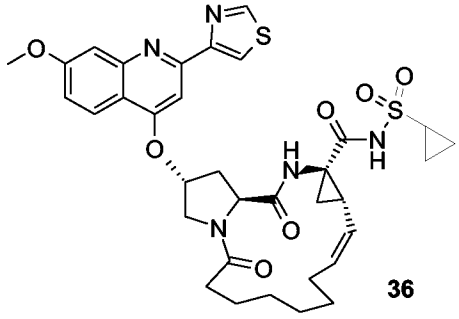
Example 15: Synthesis of 18-[7-methoxy-2-(thiazol-4-yl)quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (35).



35

The title compound was prepared from 4-hydroxy-7-methoxy-2-(thiazol-4-yl)quinoline and intermediate **7** following the procedure (Step F-H) reported for 18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo-[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid **10**: *m/z* = 591 $(M+H)^+$.

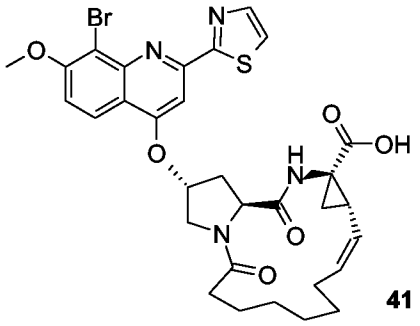
Example 16: Synthesis of *N*-[18-[7-methoxy-2-(thiazol-4-yl)quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carbonyl](cyclopropyl)-sulfonamide (36).



36

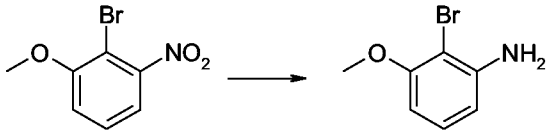
The title compound was prepared from 18-[7-methoxy-2-(thiazol-4-yl)quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (**35**) following the procedure reported for synthesis of *N*-[[18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-en-4-yl]carbonyl](cyclopropyl)sulfonamide **11**: *m/z* = 694 $(M+H)^+$. ^{1}H NMR ($CDCl_3$): 0.80-1.55 (m, 13H), 1.80-1.98 (m, 3H), 2.19-2.28 (m, 1H), 2.30-2.40 (m, 1H), 2.47-2.62 (m, 2H), 2.63-2.75 (m, 2H), 2.88-2.96 (m, 1H), 3.97 (9s, 3H), 4.02 (d, J = 11.5 Hz, 1H), 4.11 (dd, J = 11.4 Hz, J = 3.8 Hz, 1H), 4.60 (t, J = 7.9 Hz, 1H), 5.00 (t, J = 9.5 Hz, 1H), 5.49 (br s, 1H), 5.70-5.77 (m, 1H), 6.68 (s, 1H), 7.12 (dd, J = 2.5 Hz, J = 9.1 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.59 (s, 1H), 7.96 (d, J = 9.1 Hz, 1H), 8.35 (d, J = 2.1 Hz, 1H), 8.94 (d, J = 2.1 Hz, 1H), 9.2 (br s, 1H).

Example 17: Synthesis of 18-[8-bromo-7-methoxy-2-(thiazol-2-yl)quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (41)



41

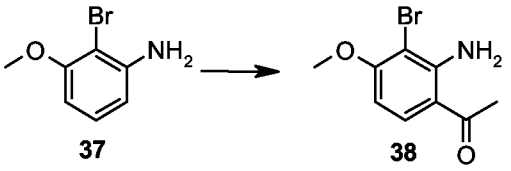
Step A



37

A solution of 2-bromo-1-methoxy-3-nitrobenzene (500 mg, 2.16 mmol) in CH_3OH (5 mL) and THF (5 mL) was added to a solution of NH_4Cl (572 mg, 10.7 mmol) in water (5 mL). Then, iron (325 mesh, 601 mg, 10.7 mmol) was added and the resulting mixture was heated to 70 °C under nitrogen. After 2.5 h, the reaction mixture was cooled to room temperature, filtered over kieselguhr, diluted with AcOEt, and successively washed with a saturated solution of $NaHCO_3$ in water and brine. The organic layer was dried (Na_2SO_4) and evaporated. The residue was triturated in CH_2Cl_2, the filtered to give 390 mg (89 %) of the target product **37** as a beige solid.

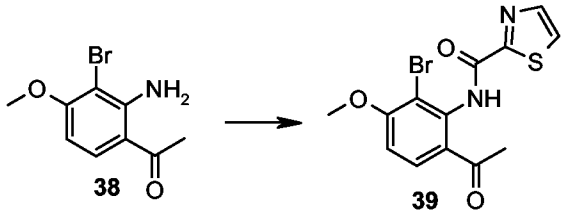
Step B



37 38

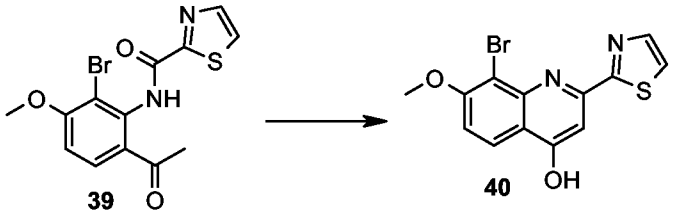
Intermediate **38** was prepared from 2-bromo-*m*-anisidine (**37**) following the procedure reported for synthesis of intermediate **22**.

Step C



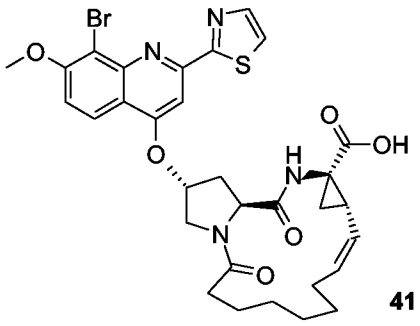
Intermediate **38** (11.2 g, 45.9 mmol) was added under nitrogen to a suspension of thiazole-2-carboxylic chloride .HCl (1.5 eq, 68.8 mmol) in dry dioxane (500 mL). After 12 h at room temperature, the reaction mixture was concentrated under reduced pressure. Then, ether (200 mL) was added and the resulting mixture was cooled down to 0 °C. The precipitate was filtered off and washed with ether to give a solid fraction A. The filtrate was concentrated under reduced pressure. The residue was partitioned between AcOEt and 1N $NaHCO_3$, dried (Na_2SO_4), and evaporated. Purification by column chromatography (heptane/AcOEt, 1:1) provided 9.8 g (60%) of the target product **39** as a yellow powder: *m/z* = 355, 357.

Step D. Synthesis of 8-bromo-4-hydroxy-7-methoxy-2-(thiazol-2-yl)quinoline (40).



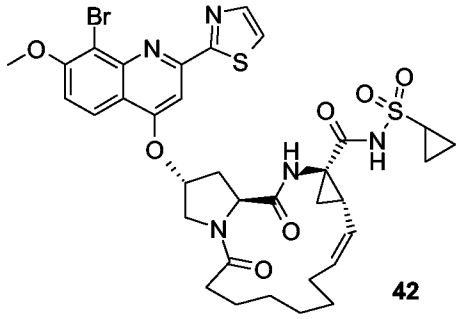
The title compound was prepared from intermediate **39** following the procedure reported for synthesis of 4-hydroxy-7-methoxy-8-methyl-2-(thiazol-2-yl)quinoline (**24**): *m/z* = 337, 339.

Step E. Synthesis of 18-[8-bromo-7-methoxy-2-(thiazol-2-yl)quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.$0^{4,6}$]nonadec-7-ene-4-carboxylic acid (41)



The title compound was prepared from 8-bromo-4-hydroxy-7-methoxy-2-(thiazol-2-yl)quinoline (**40**) and intermediate **7** following the procedure (Step F-H) reported for 18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diaza-tricyclo[14.3.0.0^{4,6}] nonadec-7-ene-4-carboxylic acid **10**: *m/z* = 670 $(M+H)^+$.

Example 18: Synthesis of *N*-[18-[8-bromo-2-(thiazol-2-yl)-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carbonyl]-(cyclopropyl)sulfonamide (42)

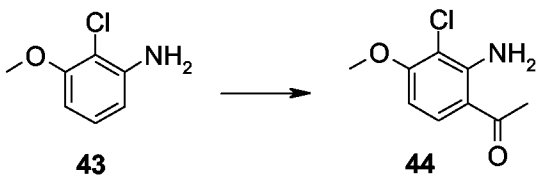


42

The title compound was prepared from 18-[8-bromo-7-methoxy-2-(thiazol-2-yl)-quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (**41**) following the procedure reported for synthesis of *N*-[[18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo-[14.3.0.0^{4,6}]nonadec-7-en-4-yl]carbonyl](cyclopropyl) sulfonamide **11**: *m/z* = 773 $(M+H)^+$. ^{1}H NMR ($CDCl_3$): 0.90-0.98 (m, 1H), 1.05-2.0 (m, 2H), 1.27-1.58 (m, 9H), 1.80-1.97 (m, 3H), 2.18-2.24 (m, 1H), 2.29-2.38 (m, 1H), 2.48-2.62 (m, 2H), 2.69-2.73 (m, 2H), 2.88-2.94 (m, 1H), 4.01 (d, *J* = 11.8 Hz, 1H), 4.08 (s, 3H), 4.12 (dd, *J* = 11.5 Hz, *J* = 3.6 Hz, 1H), 4.61 (t, *J* = 7.9 Hz, 1H), 5.00 (t, *J* = 9.5 Hz, 1H), 5.47-5.60 (m, 1H), 5.70-5.77 (m, 1H), 6.69 (br s, 1H), 7.24 (d, *J* = 9.2 Hz, 1H), 7.55 (d, *J* = 3.2 Hz, 1H), 7.59 (s, 1H), 7.98 (d, *J* = 3.2 Hz, 1H), 8.05 (d, *J* = 9.2 Hz, 1H), 8.20 (br s, 1H).

Example 19: Synthesis of 18-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-14,14-dimethyl-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (49).

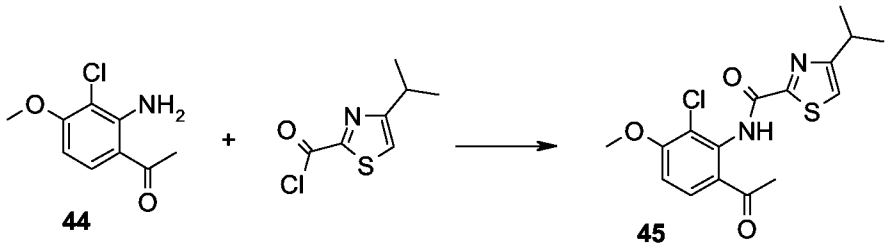
Step A: Synthesis of (2-amino-3-chloro-4-methoxyphenyl)(methyl)ketone (44).



43 **44**

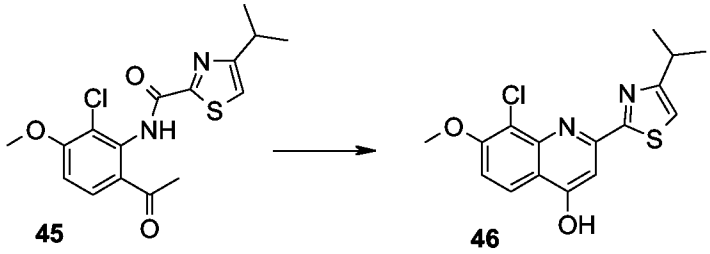
A solution of BCl_3 (1.0 M, 138 mL, 138 mmol) in CH_2Cl_2 was slowly added under nitrogen to a solution of 2-chloro-3-methoxyaniline **43** (20.6 g, 131 mmol) in xylene (225 mL). The temperature was monitored during the addition and was kept below 10°C. The reaction mixture was stirred at 5 °C for 0.5 h. Then, dry acetonitrile (9.0 mL, 170 mmol) was added at 5 °C. After 0.5 h at 5 °C, the solution was transferred into a dropping funnel and slowly added at 5 °C to a suspension of $AlCl_3$ (18.4 g, 138 mmol) in CH_2Cl_2 (80 mL). After 45 min at 5 °C, the reaction mixture was heated at 70 °C under a nitrogen stream. After evaporation of CH_2Cl_2, the temperature of the reaction mixture reached 65 °C. After 12 h at 65 °C, the reaction mixture was cooled to 0 °C, poured onto ice (200 g), and slowly heated to reflux for 7h. After 2 days at room temperature, 6 N NaOH (25 mL) and CH_2Cl_2 (100 mL) were added. The mixture was filtered, the filtered washed with CH_2Cl_2. The organic layer was decanted, and successively washed with water, 1N NaOH, and brine, dried (Na_2SO_4) and evaporated. The residue was triturated in diisopropyl ether at 0 °C, filtered off and washed with diisopropylether to give 19.0 g (73 %) of the title product **44** as a white solid: $m/z = 200$ $(M+H)^+$.

Step B. Synthesis of 2'-[[(4-isopropylthiazole-2-yl)(oxo)methyl]amino]-3'-chloro-4'-methoxyacetophenone (45)



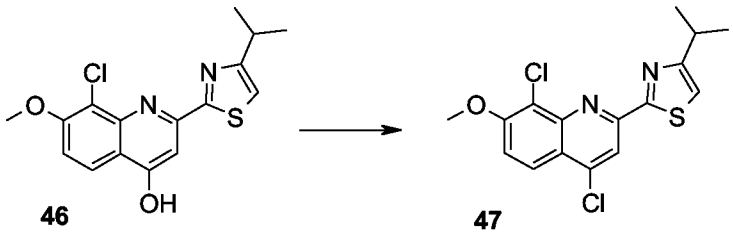
The title product **45** was prepared (79 %) from (2-amino-3-chloro-4-methoxyphenyl)-(methyl)ketone (**44**) following the procedure reported for intermediate **39**: $m/z = 353$ $(M+H)^+$.

Step C. Synthesis of 8-chloro-4-hydroxy-2-(4-isopropylthiazole-2-yl)-7-methoxy-quinoline (46).



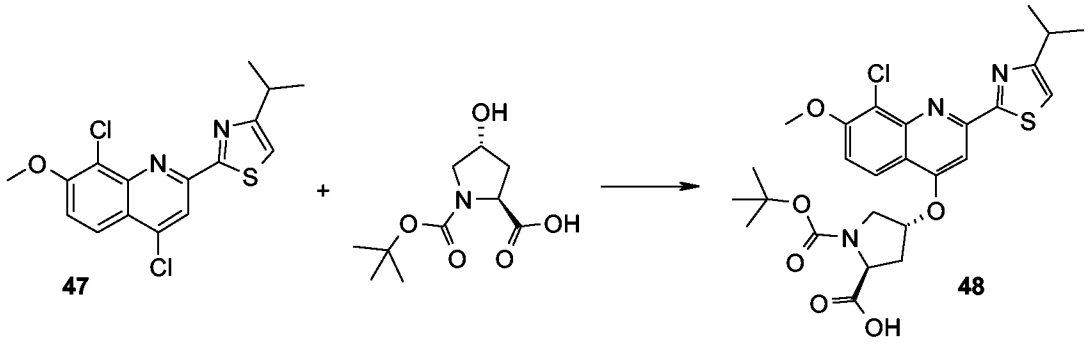
The title product **46** was prepared (58 %) from 2'-[[(4-isopropylthiazole-2-yl)(oxo)-methyl]amino]-3'-chloro-4'-methoxyacetophenone (**45**) following the procedure reported for 4-hydroxy-7-methoxy-8-methyl-2-(thiazol-2-yl)quinoline (**24**): *m/z* = 335 $(M+H)^+$.

Step D: Synthesis of 4,8-dichloro-2-(4-isopropylthiazole-2-yl)-7-methoxyquinoline (47)



A solution of 8-chloro-4-hydroxy-2-(4-isopropylthiazole-2-yl)-7-methoxy-quinoline (**46**, 2.0 g, 5.973 mmol) in $POCl_3$ (10 mL) was heated at 85 °C during 30 min. Then, the reaction mixture was concentrated under reduced pressure. The residue was poured into ice-cooled water (20 mL), the pH was adjusted to 10 with 50% NaOH, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated to give 2.05 g (97%) of the title compound **47** as a yellow solid: *m/z* = 353 $(M+H)^+$.

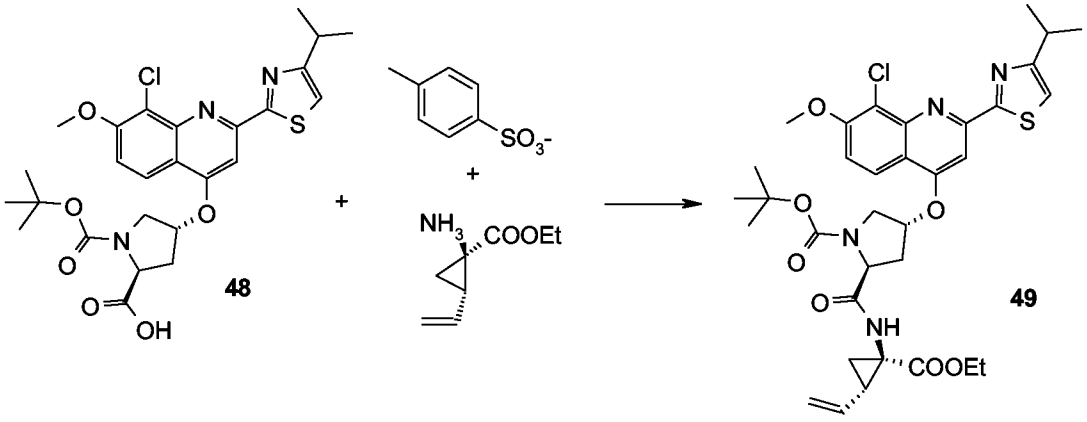
Step E. Synthesis of 4-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (48)



NaH (60% in mineral oil, 679 mg, 17.0 mmol) was added under nitrogen to a solution of Boc-*trans*-hydroxy-L-Proline (2.0 g, 5.66 mmol) in dry DMF (50 mL). After 30 min at room temperature, a solution of 4,8-dichloro-2-(4-isopropylthiazole-2-yl)-7-methoxyquinoline (**47**, 1.38 g, 5.94 mmol) in dry DMF (5 mL) was added. After 12 h at room temperature, the reaction mixture was quenched with diluted HCl until pH 2, extracted twice with EtOAc, washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 3.2 g of crude product. Purification by

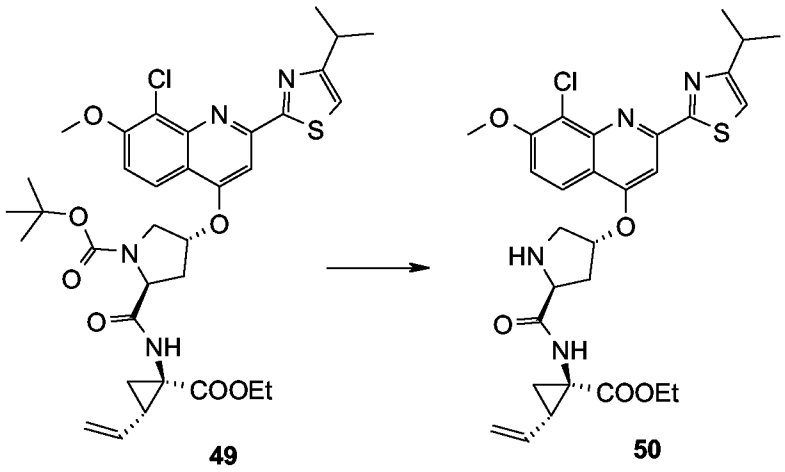
flash chromatography (gradient AcOEt/DCM, 0:100 to 50:50) afforded 2.35 g (75%) of the title product **48**: *m/z* = 549 $(M+H)^+$.

Step F. Synthesis of 4-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-2-(1-ethoxycarbonyl-2-vinylcyclopropylcarbamoyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (49)



To a stirred solution of 4-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (**48**, 3.4 g, 6.20 mmol) in dry DMF (50 mL) was added (*1R,2S*)-1-amino-2-vinylcyclopropanecarboxylic acid ethyl ester tosylate (2.23 g, 6.82 mmol) and diisopropylethylamine (2.70 mL, 17.1 mmol). Then, HATU (2.59 g, 6.82 mmol) was added at 0 °C under nitrogen. After 30 min at 0 °C, the reaction mixture was successively allowed to warm up to room temperature for 4 h, then diluted with water (150 mL) and extracted with EtOAc (3x150 mL). The organic layers were combined and washed with a saturated solution of $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (gradient $EtOAc/CH_2Cl_2$, 0:1 to 2:8) afforded 3.0 g (70%) of the title product **49**: *m/z* = 685 $(M+H)^+$.

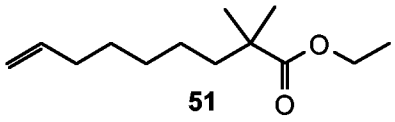
Step G. Synthesis of 1-[[4-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]pyrrolidine-2-carbonyl]amino]-2-vinylcyclopropanecarboxylic acid ethyl ester (**50**).



49 50

To a stirred solution of 4-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-2-(1-ethoxycarbonyl-2-vinylcyclopropylcarbamoyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (**49**, 0.7 g, 1.02 mmol) in CH_2Cl_2 (8 mL) was added trifluoroacetic acid (2.0 mL). After 2h at room temperature, the reaction mixture was concentrated and the residue was partitioned between a saturated solution of $NaHCO_3$ and DCM. The organic layer was dried ($MgSO_4$) filtered and concentrated to give 580 mg (97%) of the title product (**50**) as a colorless oil: m/z = 585 $(M+H)^+$.

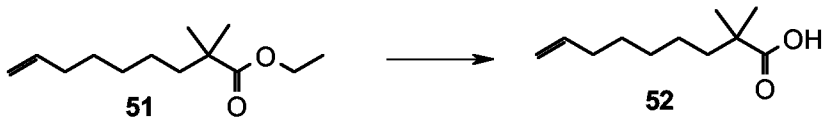
Step H. Synthesis of 2,2-dimethylnon-8-enoic acid ethyl ester (51).



51

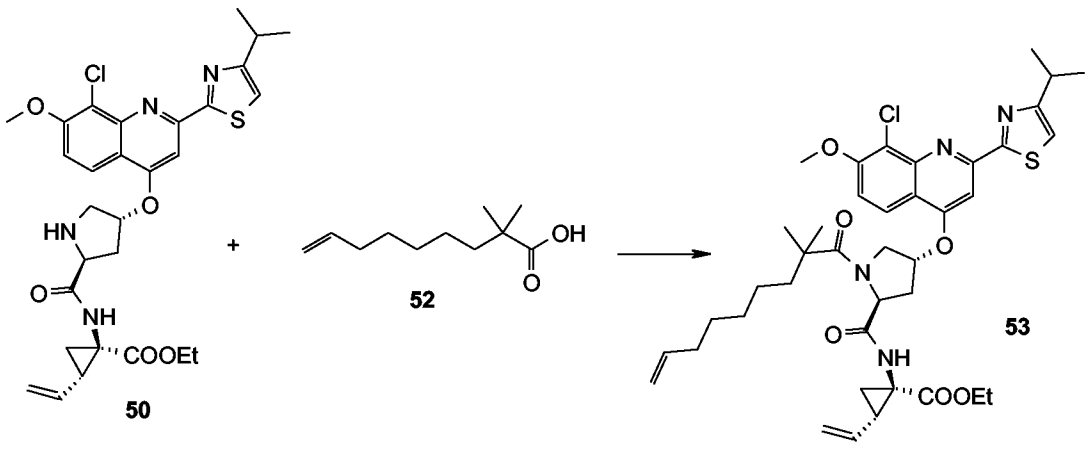
A solution of *n*-BuLi 2.5 M in hexanes (3.79 mL, 9.48 mmol) was added at –78 °C under nitrogen to a solution of diisopropylamine (1.33 mL, 9.46 mmol) in dry THF (10 mL). After 15 min, a solution of ethylisobutyrate (1.0 g, 8.61 mmol) in dry THF (5.0 mL) was slowly added. After 30 min at –78 °C, a solution of 7-bromohept-1-ene (1.68 g, 9.47 mmol) in HMPA (2.0 mL) was added drop wise and the reaction mixture was allowed to warm up to room temperature. After 16 h, the reaction mixture was quenched with diluted HCl, extracted with AcOEt, washed with brine, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (DCM/heptane, 2:8) afforded 800 mg (44%) of the title product (**51**) as a colorless oil. TLC (DCM/hexanes 1/1): Rf = 0.7.

Step I: Synthesis of 2,2-dimethylnon-8-enoic acid (52).



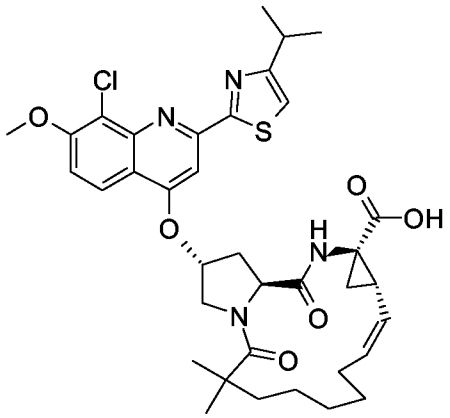
A solution of 2,2-dimethylnon-8-enoic acid ethyl ester (**51**, 800 mg, 3.77 mmol) and LiOH (806 mg, 18.9 mmol) in THF/MeOH/water, 1:1:0.5, was heated at 50 °C for 2.5 h. Then, additional LiOH (1.60 g, 10 eq) was added. After 15 h, the reaction mixture was concentrated under reduced pressure. The pH of the residue was adjusted to 3 with HCl 1N, extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), filtered and concentrated to give 650 mg (94%) of the title product (**52**) as a colorless oil.

Step J. Synthesis of 1-[[4-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-1-(2,2-dimethylnon-8-enoyl)pyrrolidine-2-carbonyl]amino]-2-vinyl-cyclopropanecarboxylic acid ethyl ester (53).



To a solution of 2,2-dimethylnon-8-enoic acid (**52**, 239 mg, 1.3 mmol) in dry CH_2Cl_2 (10 mL) was added oxalyl chloride (165 mg, 2.6 mmol) and 2 drops of DMF. After 3h at room temperature, the reaction mixture was concentrated and co-evaporated with toluene. This crude acid chloride was successively re-dissolved in CH_2Cl_2 and added to a stirred solution of 1-[[4-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]pyrrolidine-2-carbonyl]amino]-2-vinylcyclopropanecarboxylic acid ethyl ester (**50**, 380 mg, 0.65 mmol) and triethylamine (264 µL, 1.95 mmol) in CH_2Cl_2 (30 mL). After 1.5 h, the resulting solution was successively washed with a saturated solution of $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash chromatography (gradient EtOAc/CH_2Cl_2 0:1 to 2:8) afforded the title product (**53**) as a colorless oil (490 mg, 100 %): *m/z* = 751 $(M+H)^+$.

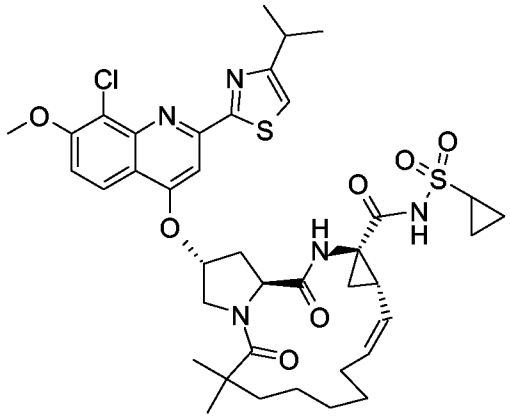
Step K. Synthesis of 18-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-14,14-dimethyl-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (54).



54

The title compound was prepared from 1-[[4-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-1-(2,2-dimethylnon-8-enoyl)pyrrolidine-2-carbonyl]amino]-2-vinylcyclopropanecarboxylic acid ethyl ester (**53**) following the procedure (Steps G and H) reported for 18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxy-quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}] nonadec-7-ene-4-carboxylic acid **10**: *m/z* = 695 $(M+H)^+$.

Example 20: Synthesis of *N*-[18-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxy-quinolin-4-yloxy]-14,14-dimethyl-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carbonyl](cyclopropyl)sulfonamide (55).

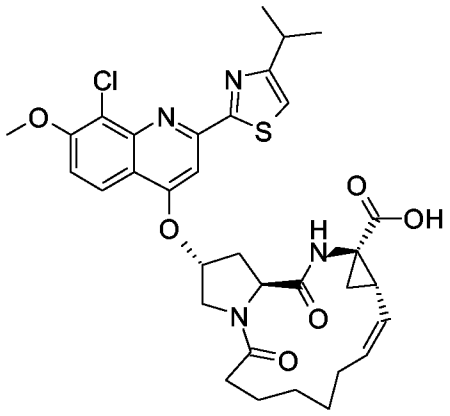


55

The title compound was prepared from 18-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-14,14-dimethyl-2,15-dioxo-3,16-diazatricyclo-[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic acid (**54**) following the procedure reported for synthesis of *N*-[[18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-

2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-en-4-yl]carbonyl](cyclopropyl) sulfonamide **11**: *m/z* = 798 $(M+H)^+$. ^1H NMR ($CDCl_3$): 0.96 (m, 1H), 1.05-1.15 (m, 2H), 1.17 (s, 3H), 1.32 (s, 3H), 1.23-1.36 (m, 7H), 1.38 (d, *J* = 6.8 Hz, 6H), 1.43-1.53 (m, 2H), 1.75-1.94 (m, 3H), 2.39 (m, 1H), 2.56 (m, 3H), 2.85-2.95 (m, 1H), 3.20 (m, 1H), 4.02 (s, 3H), 4.15 (dd, *J* = 3.7 Hz, *J* = 11.6 Hz, 1H), 4.23 (d, *J* = 11.6 Hz, 1H), 4.73 (t, *J* = 7.5 Hz, 1H), 4.99 (t, *J* = 9.4 Hz, 1H), 5.52 (m, 1H), 5.80 (q, *J* = 8.8 Hz, 1H), 7.08 (s, 1H), 7.17 (m, 2H), 7.54 (s, 1H), 7.84 (d, *J* = 9.2 Hz, 1H), 10.3 (s, 1H).

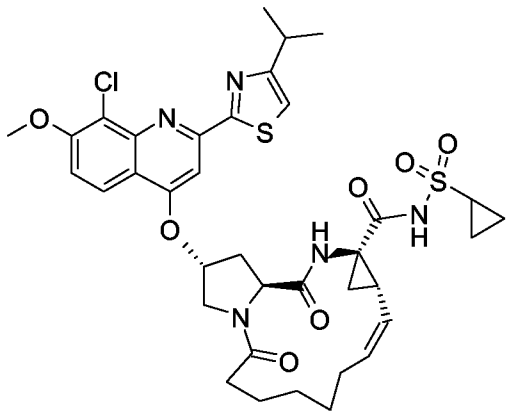
Example 21: Synthesis of 17-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carboxylic acid (56).



56

The title compound was prepared from 8-chloro-4-hydroxy-2-(4-isopropylthiazole-2-yl)-7-methoxyquinoline (**46**), oct-7-enoic acid and intermediate **5** following the procedure (Step D-H) reported for 18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxy-quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}] nonadec-7-ene-4-carboxylic acid **10**: *m/z* = 653 $(M+H)^+$.

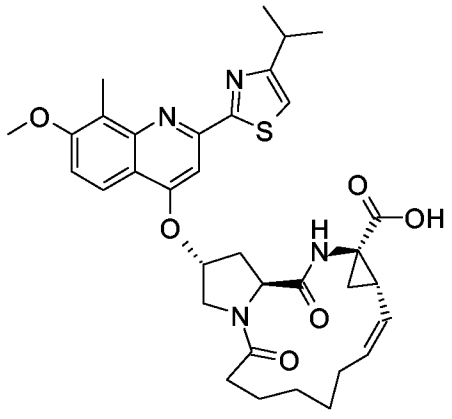
Example 22: Synthesis of *N*-[17-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxy-quinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carbonyl]-(cyclopropyl)sulfonamide (57).



57

The title compound was prepared from 17-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carboxylic acid (**56**) following the procedure reported for synthesis of *N*-[[18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo-[14.3.0.0^{4,6}]nonadec-7-en-4-yl]carbonyl](cyclopropyl)sulfonamide **11**: *m/z* = 756 $(M+H)^+$. ^{1}H NMR ($CDCl_3$): 0.90-0.98 (m, 1H), 1.05-2.0 (m, 2H), 1.3-1.4 (m, 9H), 1.5-1.6 (m, 2H), 1.6-1.65 (m, 1H), 1.75-1.9 (m, 5H), 2.2-2.3 (m, 1H), 2.3-2.4 (m, 1H), 2.45-2.55 (m, 2H), 2.6-2.7 (m, 1H), 2.75-2.85 (m, 1H), 3.15-3.25 (m, 1H), 3.8 (d, *J* = 11.2 Hz, 1H), 4.15 (s, 3H), 3.25 (dd, *J* = 11.15 Hz, *J* = 4.5 Hz, 1H), 4.7 (t, *J* = 7.1 Hz, 1H), 5.2 (t, *J* = 10.4 Hz, 1H), 5.5 (br s, 1H), 5.6-5.7 (m, 1H), 6.9 (br s, 1H), 7.1 (s, 1H), 7.21 (d, *J* = 9.5 Hz, 1H), 7.6 (s, 1H), 8 (d, *J* = 9.5 Hz, 1H), 10.8 (br s, 1H).

Example 23: Synthesis of 17-[2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carboxylic acid (58).

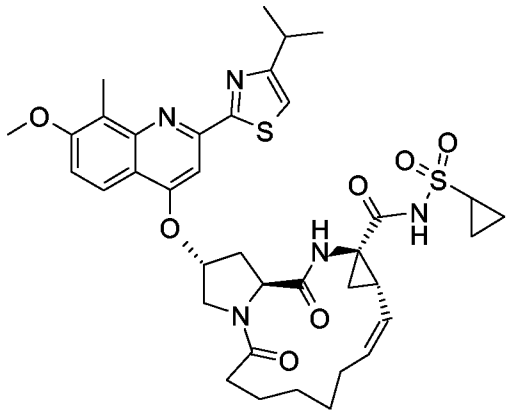


58

The title compound was prepared from 4-hydroxy-2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinoline (**28**), oct-7-enoic acid and intermediate **5** following the procedure (Step D-H) reported for 18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxy-

quinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}] nonadec-7-ene-4-carboxylic acid **10**: *m/z* = 633 $(M+H)^+$.

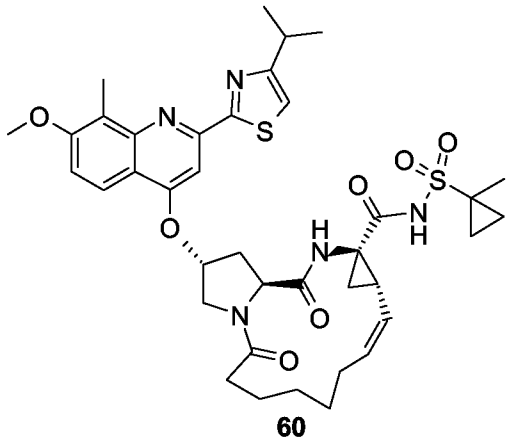
Example 24: Synthesis of *N*-[17-[2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carbonyl]-(cyclopropyl)sulfonamide (59).



59

The title compound was prepared from 17-[2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carboxylic acid (**58**) following the procedure reported for synthesis of *N*-[[18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo-[14.3.0.0^{4,6}]nonadec-7-en-4-yl]carbonyl](cyclopropyl)sulfonamide **11**: *m/z* = 736 $(M+H)^+$. ^{1}H NMR ($CDCl_3$): 0.90-1.01 (m, 1H), 1.05-1.15 (m, 1H), 1.15-1.45 (m, 5H), 1.45 (d, *J* = 6.9 Hz, 6H), 1.4-1.55 (m, 3H), 1.6-1.8 (m, 2H), 2.85-2.95 (m, 1H), 2.15-2.25 (m, 2H), 2.3-2.4 (m, 1H), 2.45-2.55 (m, 1H), 2.6-2.7 (m, 1H), 2.65 (s, 3H), 2.9-3 (m, 1H), 3-3.1 (m, 1H), 3.15-3.25 (m, 1H), 3.85 (d, *J* = 10.8 Hz, 1H), 3.95 (s, 3H), 4.1 (dd, *J* = 11.3 Hz, *J* = 3.6 Hz, 1H), 4.6 (t, *J* = 8.0 Hz, 1H), 5.0 (t, *J* = 10.6 Hz, 1H), 5.5 (t, *J* = 3.2 Hz, 1H), 5.60-5.70 (m, 1H), 6.75 (s, 1H), 7.02 (s, 1H), 7.2 (d, *J* = 9.2 Hz, 1H), 7.5 (s, 1H), 7.9 (d, *J* = 9.2 Hz, 1H), 11 (br s, 1H).

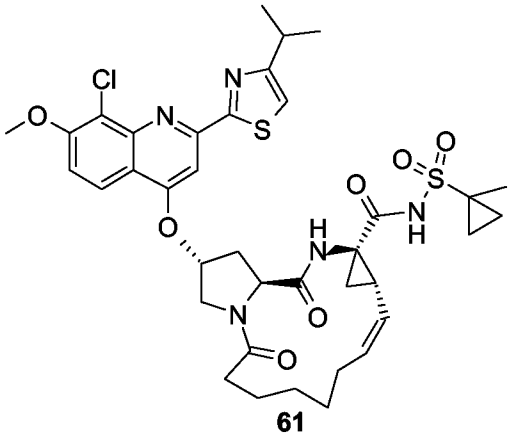
Example 25: Synthesis of *N*-[17-[2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carbonyl]-(1-methylcyclopropyl)sulfonamide (60).



60

The title compound was prepared from 17-[2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carboxylic acid (**58**) and 1-methylcyclopropylsulfonamide following the procedure reported for synthesis of *N*-[[18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-en-4-yl]carbonyl]-(cyclopropyl)sulfonamide **11**: *m/z* = 750 $(M+H)^+$. ^{1}H NMR ($CDCl_3$): 0.90-1.01 (m, 1H), 1.05-1.15 (m, 1H), 1.15-1.45 (m, 4H), 1.45 (d, *J* = 6.9 Hz, 6H), 1.4-1.5 (m, 3H), 1.55 (s, 3H), 1.6-1.8 (m, 2H), 2.85-2.95 (m, 1H), 2.15-2.25 (m, 2H), 2.3-2.4 (m, 1H), 2.45-2.55 (m, 1H), 2.6-2.7 (m, 1H), 2.65 (s, 3H), 2.9-3.0 (m, 1H), 3-3.1 (m, 1H), 3.15-3.25 (m, 1H), 3.85 (d, *J* = 10.8 Hz, 1H), 3.95 (s, 3H), 4.1 (dd, *J* = 11.3 Hz, *J* = 3.6 Hz, 1H), 4.6 (t, *J* = 8.0 Hz, 1H), 5.0 (t, *J* = 10.6 Hz, 1H), 5.5 (t, *J* = 3.3 Hz, 1H), 5.60-5.70 (m, 1H), 6.75 (s, 1H), 7.02 (s, 1H), 7.2 (d, *J* = 9.2 Hz, 1H), 7.5 (s, 1H), 7.9 (d, *J* = 9.2 Hz, 1H), 11 (br s, 1H).

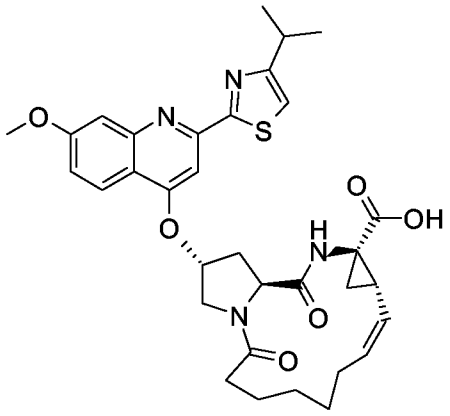
Example 26: Synthesis of *N*-[17-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxy-quinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carbonyl]-(1-methylcyclopropyl)sulfonamide (61).



61

The title compound was prepared from 17-[8-chloro-2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carboxylic acid (**56**) and 1-methylcyclopropylsulfonamide following the procedure reported for synthesis of *N*-[[18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}]nonadec-7-en-4-yl]carbonyl]-(cyclopropyl) sulfonamide **11**: *m/z* = 770 $(M+H)^+$. ^{1}H NMR ($CDCl_3$): 0.90-0.98 (m, 1H), 1.05-2.0 (m, 2H), 1.3-1.4 (d, *J* = 6.9 Hz, 6H), 1.45-1.55 (m, 2H), 1.5 (s, 3H), 1.55-1.7 (m, 2H), 1.75-1.9 (m, 2H), 1.9-2.1 (m, 2H), 2.1-2.4 (m, 2H), 2.4-2.5 (m, 2H), 2.6-2.7 (m, 2H), 3-3.1 (m, 1H), 3.15-3.25 (m, 1H), 3.3-3.4 (m, 1H), 3.6-3.7 (m, 1H), 3.9 (d, *J* = 11.6 Hz, 1H), 4.05 (s, 3H), 4.6 (t, *J* = 8.0 Hz, 1H), 5.2 (t, *J* = 10.6 Hz, 1H), 5.5 (br s, 1H), 5.6-5.7 (m, 1H), 6.9 (br s, 1H), 7.1 (s, 1H), 7.2 (d, *J* = 9.3 Hz, 1H), 7.53 (s, 1H), 7.95 (d, *J* = 9.3 Hz, 1H), 10.8 (br s, 1H).

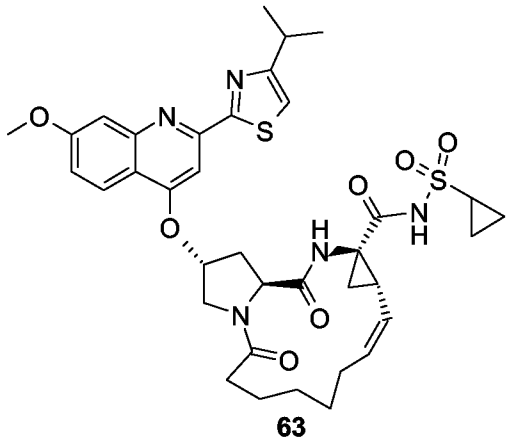
Example 27: Synthesis of 17-[2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methyl-quinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carboxylic acid (62)



62

The title compound was prepared from 4-hydroxy-2-(4-isopropylthiazol-2-yl)-7-methoxyquinoline, oct-7-enoic acid and intermediate **5** following the procedure (Step D-H) reported for 18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo[14.3.0.0^{4,6}] nonadec-7-ene-4-carboxylic acid **10**: *m/z* = 619 $(M+H)^+$.

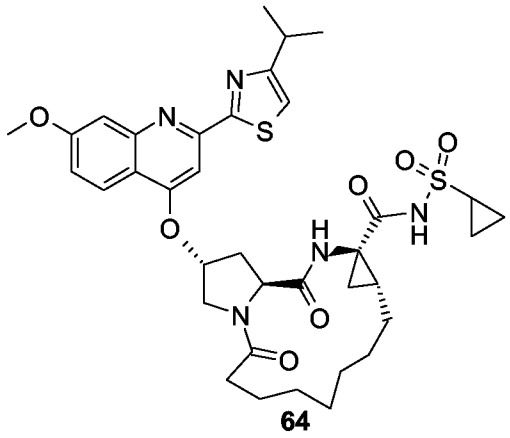
Example 28: Synthesis of *N*-[17-[2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carbonyl]-(cyclopropyl)sulfonamide (63)



63

The title compound was prepared from 17-[2-(4-isopropylthiazol-2-yl)-7-methoxy-8-methylquinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carboxylic acid (**62**) following the procedure reported for synthesis of *N*-[[18-[2-[4-(isopropyl)thiazol-2-yl]-7-methoxyquinolin-4-yloxy]-2,15-dioxo-3,16-diazatricyclo-[14.3.0.0^{4,6}]nonadec-7-en-4-yl]carbonyl](cyclopropyl)sulfonamide **11**: *m/z* = 722 $(M+H)^+$. ^{1}H NMR ($CDCl_3$): 0.99–1.77 (m, 17H), 1.94 (dd, *J* = 6.0 Hz, *J* = 9.7 Hz, 1H), 2.12-2.26 (m, 2H), 2.37 (dd, *J* = 7.3 Hz, 16.4 Hz, 1H), 2.57-2.71 (m, 3H), 2.96 (m, 1H), 3.04 (m, 1H), 3.22 (m, 1H), 3.92 (m, 1H), 3.96 (s, 3H), 4.14 (dd, *J* = 3.7 Hz, 11.3 Hz, 1H), 4.58 (t, *J* = 7.9 Hz, 1H), 5.05 (t, *J* = 10.6 Hz, 1H), 5.53 (m, 1H), 5.66 (m, 1H), 6.58 (s, 1H), 7.06 (s, 1H), 7.12 (dd, *J* = 2.5 Hz, *J* = 9.1 Hz, 1H), 7.37 (d, *J* = 2.5 Hz, 1H), 7.56 (s, 1H), 7.93 (d, *J* = 9.1 Hz, 1H), 10.8 (br s, 1H).

Example 29: Synthesis of *N*-[17-[2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadecane-4-carbonyl]-(cyclopropyl)sulfonamide (64)



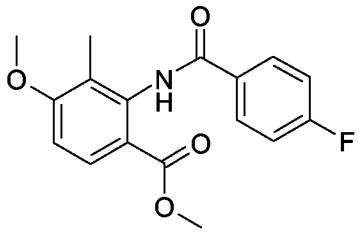
64

To a solution of olefin *N*-[17-[2-(4-isopropylthiazol-2-yl)-7-methoxyquinolin-4-yloxy]-2,14-dioxo-3,15-diazatricyclo[13.3.0.0^{4,6}]octadec-7-ene-4-carbonyl](cyclopropyl)-sulfonamide (**63**, 100 mg, 0.139 mmole) in MeOH (3.0 mL) heated at 80 °C, was added

2,4,6-triisopropylbenzene sulfonohydrazide ($TrisNHNH_2$) and triethylamine portion wise over several hours. Then, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and a saturated solution of $NaHCO_3$, successively washed with HCl 1N and brine, dried ($MgSO_4$), filtered and evaporated. Purification by flash chromatography (gradient of $AcOEt/CH_2Cl_2$, 0:1 to 1:9) followed by recrystallization from isopropylether/petroleum ether, and then preparative HPLC afforded 6 mg (6%) of the title product (**59**) as a white powder: *m/z* = 724 $(M+H)^+$. ^1H NMR ($CDCl_3$): 0.90-1.70 (m, 21H), 1.95-2.03 (m, 2H), 2.25-2.35 (m, 2H), 2.63-2.68 (m, 2H), 2.99 (m, 1H), 3.22 (m, 1H), 3.41 (m, 1H), 3.96 (m, 5H), 4.15 (d, J = 15 Hz, 1H), 4.60 (t, J = 7.9 Hz, 1H), 5.53 (m, 1H), 6.57 (s, 1H), 7.05 (s, 1H), 7.12 (dd, J = 2.5 Hz, 9.1 Hz, 1H), 7.38 (d, J = 2.5 Hz, 1H), 7.56 (s, 1H), 7.93 (d, J = 9.1 Hz, 1H), 10.8 (br s, 1H).

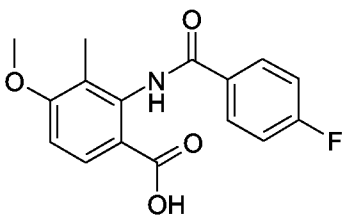
Example 30: Synthesis of a quinazoline as a P2 building block

2-(4-Fluoro-benzoylamino)-4-methoxy-3-methyl-benzoic acid methyl ester (65)



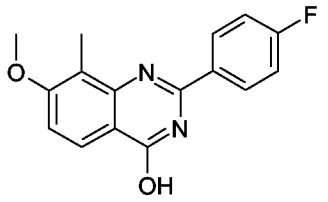
4-Fluoro benzoic acid (700 mg, 5 mmol) was dissolved in dichloromethane (20 ml) and pyridine (2 ml). 2-Amino-4-methoxy-3-methyl-benzoic acid methyl ester (878 mg, 4.5 mmol) was added and the mixture was refluxed for 5 h. Water was added and the mixture was extracted with dichloromethane. The organic phase was dried, filtered and evaporated and the afforded residue was purified by column chromatography on silica gel, eluted with ether-pentane 1:1 which gave pure title compound (870 mg, 61 %). MS $(M+H^+)$ 318.

2-(4-Fluoro-benzoylamino)-4-methoxy-3-methyl-benzoic acid (66)



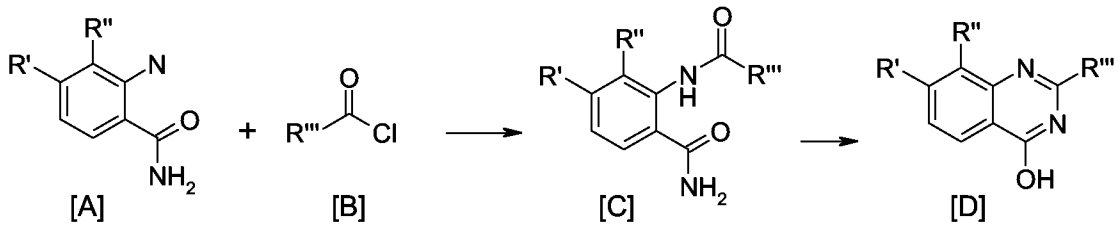
LiOH (1M, 4 mL) was added to a solution of 2-(4-fluoro-benzoylamino)-4-methoxy-3-methyl-benzoic acid methyl ester (65) (870 mg, 2.7 mmol), in tetrahydrofuran (15 ml), water (7.5 ml) and methanol (7.5 ml) . The mixture was heated to 50 °C for 4 h. Water (30 ml) was then added and the volume reduced to half. Acidification with acetic acid followed by filtration gave pure title compound (830 mg, 100 %).
MS ($M+H^+$) 304.

2-(4-Fluoro-phenyl)-7-methoxy-8-methyl-quinazolin-4-ol (67)



2-(4-Fluoro-benzoylamino)-4-methoxy-3-methyl-benzoic acid (66) (830 mg, 2.7 mmol) was heated to 150 °C in formamide (20 ml) for 4 h. The excess formamide was removed by distillation. Water was added and the precipitated product was filtered of to give pure title compound (642 mg, 83 %).
MS ($M+H^+$) 285.

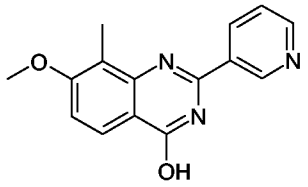
Example 31: General procedure for the preparation of substituted quinazolin-4-ols



To a suspension of a substituted 2-amino-benzamide [A] (1 eq) in dry THF (60 ml) was added pyridine (2 eq) and the mixture was cooled to 5°C. The acid chloride [B] (1.25 eq) was added slowly and the mixture was stirred at room temperature overnight. The mixture was evaporated under reduced pressure and then suspended in water. The compound was left in the water for some hours, filtered and washed with cold water and diethyl ether. The product [C] was dried under vacuum. Yield: 90-100%.
When the acid chloride [B] used was a nicotinyl chloride hydrochloride, then 2.5 eq of pyridine was used and the mixture was stirred for 2-3 days at room temperature instead of over night.
The formed amide [C] (1 eq) was added to a suspension of sodium carbonate (2.5 eq) in a 1:1 mixture of water and EtOH and the mixture was refluxed for two hours. The

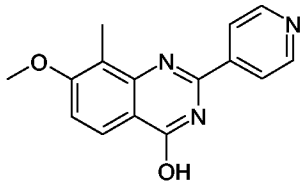
EtOH was removed under reduced pressure, a solution of 5% citric acid was added and the mixture was allowed to stay overnight. The product [D] was isolated by filtration, then washed with water and diethyl ether and dried under vacuum.

Example 32: 7-Methoxy-8-methyl-2-pyridin-3yl-quinazolin-4-ol (68)



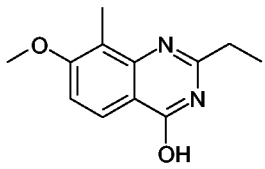
The general procedure described in Example 31 was followed using 2-amino-4-methoxy-3-methyl benzamide as benzamide derivative and nicotinyl chloride hydrochloride as acid chloride, which gave the title compound (2.5g, 92%), [M+H]=268.

Example 33: 7-Methoxy-8-methyl-2-pyridin-4yl-quinazolin-4-ol (69)



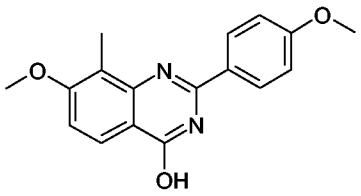
The general procedure described in Example 31 was followed using 2-amino-4-methoxy-3-methyl benzamide as benzamide derivative and isonicotinoyl chloride hydrochloride as acid chloride, which gave the title compound (1.6 g, 60%), [M+H]=268.

Example 34: 7-Methoxy-8-methyl-2-ethyl-quinazolin-4-ol (70)



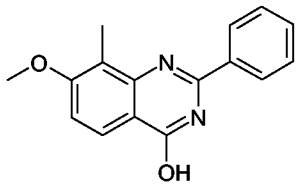
The general procedure described in Example 31 was followed using 2-amino-4-methoxy-3-methyl benzamide as benzamide derivative [A] and acetic acid chloride as acid chloride [B], which gave the title compound (2.2 g, 100%).
^{1}H-NMR DMSO-D_6 δ 1.2 (m, 3H), 2.38 (s, 3H), 2.6 (m, 2H), 3.90 (s, 3H), 7.18 (d, 2H), 7.96 (d, 2H), 11.88 (s, 1H).

Example 35: 7-Methoxy-8-methyl-2-(4-methoxyphenyl)-quiazolin-4-ol (71)



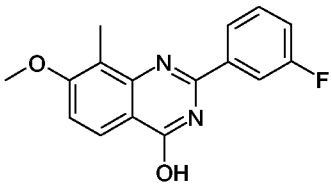
The general procedure described in Example 31 was followed using 2-amino-4-methoxy-3-methyl benzamide as benzamide derivative [A] and 4-methoxybenzoic acid chloride as acid chloride [B], which gave the title compound (5.5 g, 92%).
^{1}H-NMR DMSO-D_6 δ 2.38 (s, 3H), 3.82 (s, 3H), 3.92 (s, 3H), 7.04 (d, 2H), 7.20 (d, 1H), 8.00 (d, 1H), 8.20 (d, 2H), 12.18 (s,1H).

Example 36: 8-Methoxy-2-phenyl-quinazolin-4-ol (72)



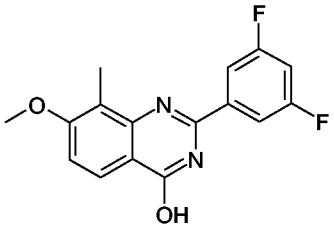
The general procedure described in Example 31 was followed using 2-amino-4-methoxy-3-methyl benzamide as benzamide derivative [A] and benzoyl chloride as acid chloride [B], which gave the title compound (2.0 g, 80%), [M+H]=253.
^{1}H-NMR DMSO-D_6 δ 3.97 (s, 3H), 7.39-7.72 (m, 6H), 8.19 (m, 2H), 12.48 (s, 1H).

Example 37: 2-(3-Fluoro-phenyl)-7-methoxy-8-methyl-quinazolin-4-ol (73)



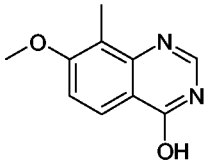
The general procedure described in Example 31 was followed using 2-amino-4-methoxy-3-methyl benzamide as benzamide derivative [A] and 3-fluoro-benzoyl chloride as acid chloride [B], which gave the title compound (2.1 g, 73%), [M+H]=271.

Example 38: 2-(3,5-Difluoro-phenyl)-7-methoxy-8-methyl-quinazolin-4-ol (74)



The general procedure described in Example 31 was followed using 2-amino-4-methoxy-3-methyl benzamide as benzamide derivative [A] and 3,5-difluoro-benzoyl chloride as acid chloride [B], which gave the title compound (2.1 g, 85%), [M+H]=303.

Example 39: 7-Methoxy-8-methyl-quinazolin-4-ol (75)



The title compound was formed as a biproduct when the ring closing reaction, step [B] to [C], in the general procedure was performed in DMF rather than in EtOH.

Example 40: Activity of compounds of formula (I)

Replicon assay

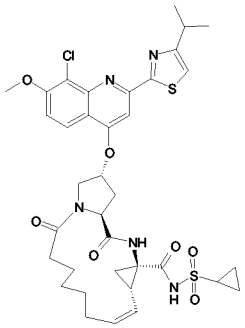
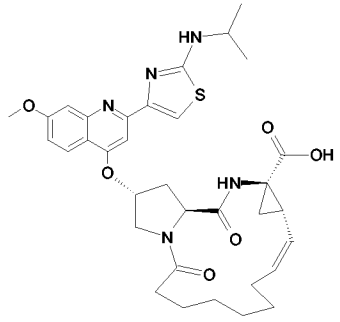
The compounds of formula (I) were examined for activity in the inhibition of HCV RNA replication in a cellular assay. The assay demonstrated that the compounds of formula (I) exhibited activity against HCV replicons functional in a cell culture. The cellular assay was based on a bicistronic expression construct, as described by Lohmann et al. (1999) Science vol. 285 pp. 110-113 with modifications described by Krieger et al. (2001) Journal of Virology 75: 4614-4624, in a multi-target screening strategy. In essence, the method was as follows.

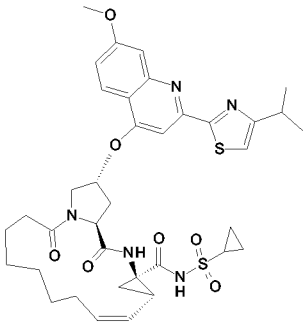
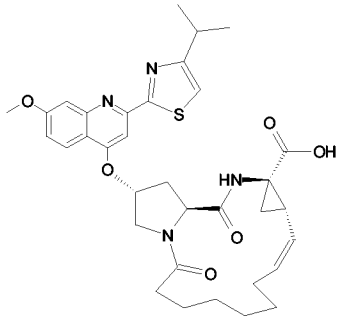
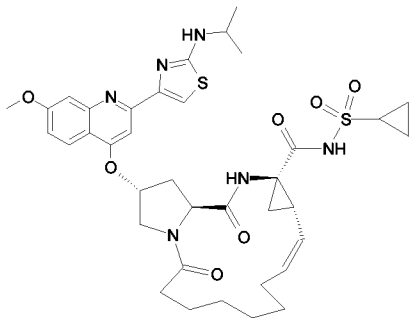
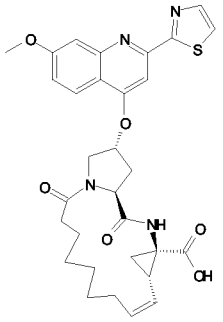
The assay utilized the stably transfected cell line Huh-7 luc/neo (hereafter referred to as Huh-Luc). This cell line harbors an RNA encoding a bicistronic expression construct comprising the wild type NS3-NS5B regions of HCV type 1b translated from an Internal Ribosome Entry Site (IRES) from encephalomyocarditis virus (EMCV), preceded by a reporter portion (FfL-luciferase), and a selectable marker portion (neo^R, neomycine phosphotransferase). The construct is bordered by 5' and 3' NTRs (non-translated regions) from HCV type 1b. Continued culture of the replicon cells in the presence of G418 (neo^R) is dependent on the replication of the HCV RNA. The stably transfected replicon cells that express HCV RNA, which replicates autonomously and to high levels, encoding *inter alia* luciferase, are used for screening the antiviral compounds.

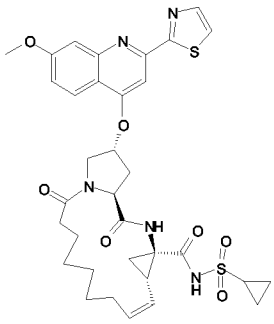
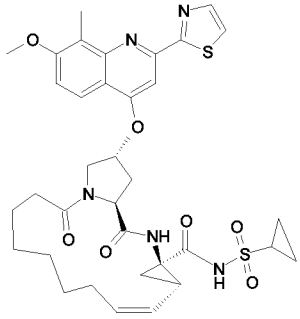
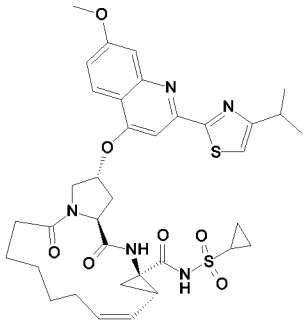
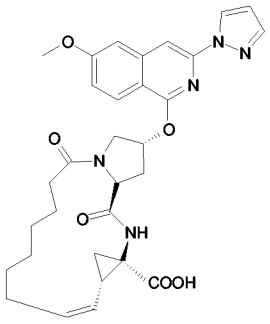
The replicon cells were plated in 384 well plates in the presence of the test and control compounds which were added in various concentrations. Following an incubation of three days, HCV replication was measured by assaying luciferase activity (using standard luciferase assay substrates and reagents and a Perkin Elmer ViewLux^{Tm} ultraHTS microplate imager). Replicon cells in the control cultures have high luciferase expression in the absence of any inhibitor. The inhibitory activity of the compound on luciferase activity was monitored on the Huh-Luc cells, enabling a dose-response curve for each test compound. EC50 values were then calculated, which value represents the amount of the compound required to decrease by 50% the level of detected luciferase activity, or more specifically, the ability of the genetically linked HCV replicon RNA to replicate.

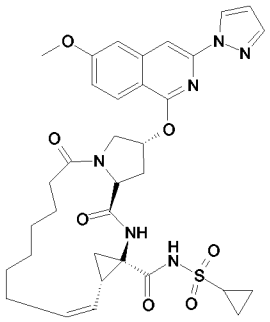
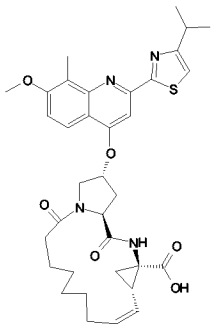
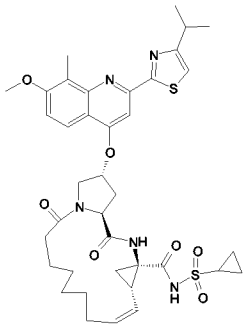
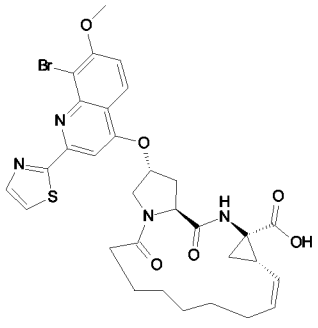
The following Table 1 lists compounds that were prepared according to any one of the above examples. The compounds are numbered with the same numbers provided in Examples 1-29. The activities of the compounds tested are also depicted.

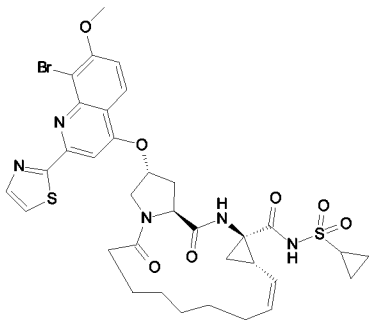
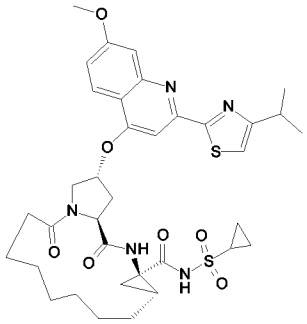
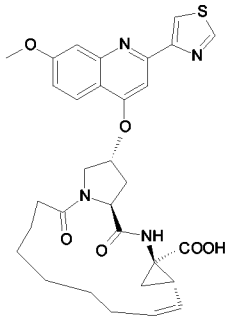
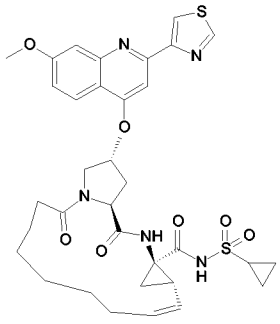
Table 1

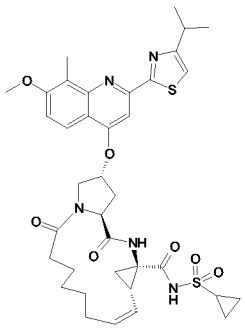
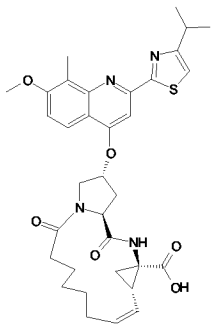
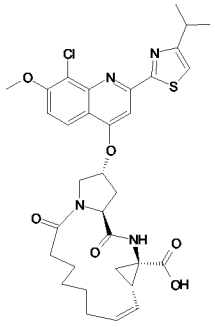
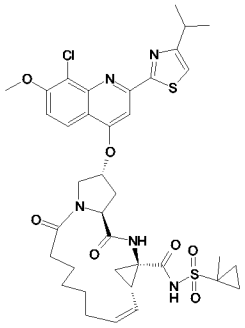
Compound No.	Structural formula	EC_{50} (μM)
57		0.012
12		1.978

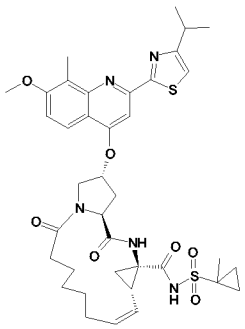
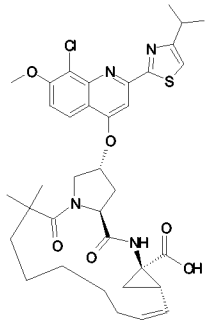
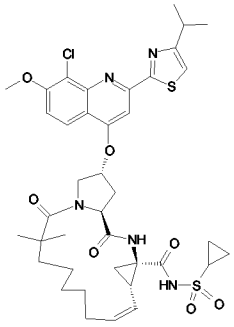
Compound No.	Structural formula	EC_{50} (μM)
11		0.017
10		5.045
13		0.020
31		4.941

Compound No.	Structural formula	EC_{50} (μM)
32		0.017
26		0.004
63		0.024
33		6.103

Compound No.	Structural formula	EC_{50} (μM)
34		0.040
29		1.956
30		0.006
41		0.280

Compound No.	Structural formula	EC_{50} (μM)
42		0.002
64		0.067
35		1.631
36		0.004

Compound No.	Structural formula	EC_{50} (μM)
59		0.003
58		1.595
56		0.318
61		0.001

Compound No.	Structural formula	EC_{50} (μM)
60		0.014
54		10
55		0.198

Example 31: *In vitro* metabolic blocking of HCV NS3/4a protease inhibitors by ritonavir

Compound nr 11 of Table 1 was tested in a metabolic blocking experiment using 3 μM test compound together with 10 μM ritonavir acting as booster.

The test compound and ritonavir were added to human liver microsomes (protein concentration 1 mg/ml) suspended in potassium phosphate buffer (pH = 7.4), to get final reaction mixture concentrations of 3 μM test compound and 10 μM ritonavir. In the non-boosted parallel reactions, ritonavir was not added. Boiled human liver microsomes were used for blank experiments. After addition (in a 1:3 ratio) of a cofactor mixture consisting of β-nicotinamide adenine dinucleotide phosphate (β-NADP, 0.5 mg/ml, 653.2 μM), D-Glucose-6-phosphate (2 mg/ml, 7.1 mM), Glucose-6-

phosphate dehydrogenase (1.5 U/ml) in 2% $NaHCO_3$, the reaction mixture was incubated at 37 °C for 30 or 120 minutes after which the reaction was stopped by increasing the temperature to 95 °C. Test compound concentrations were determined using HPLC-MS.

Results are summarized in the table 2 below. Values are percentages of the test compound detected after the indicated incubation times as compared to the initial test compound concentration. Each value is the mean of the results of two independent experiments.

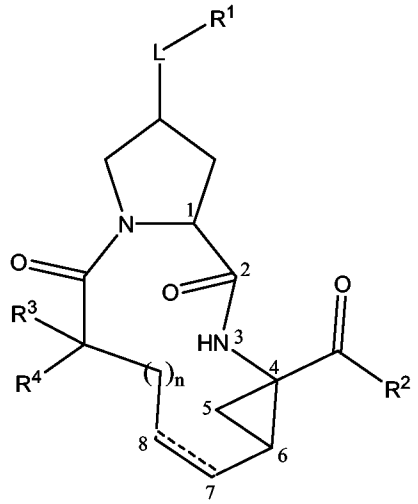
Table 2

Compound nr.	30'		120'	
	% Detected Compound		% Detected Compound	
	No Booster	ritonavir	No Booster	ritonavir
11	28	79	0	91

The experiment shows an almost complete blocking of test compound (3 μM) metabolisation by addition of 10 μM ritonavir.

Claims

1. A compound having the formula



(I)

a *N*-oxide, addition salt, quaternary amine, metal complex, and stereochemically isomeric form thereof, wherein

the dashed line represents an optional double bond between atoms C7 and C8;

$\mathbf{R^1}$ is aryl or a saturated, a partially unsaturated or completely unsaturated 5 or 6 membered monocyclic or 9 to 12 membered bicyclic heterocyclic ring system wherein said ring system contains one nitrogen, and optionally one to three additional heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, and wherein the remaining ring members are carbon atoms; wherein said ring system may be optionally substituted on any carbon or nitrogen ring atom with one, two, three, or four substituents each independently selected from C_{3-7}cycloalkyl, aryl, Het, $-C(=O)NR^{5a}R^{5b}$, $-C(=O)R^7$, $-C(=O)OR^{6a}$, and C_{1-6}alkyl optionally substituted with C_{3-7}cycloalkyl, aryl, Het, $-C(=O)NR^{5a}R^{5b}$, $-NR^{5a}R^{5b}$, $-C(=O)R^7$, $-NR^{5a}C(=O)R^7$, $-NR^{5a}SO_pR^8$, $-SO_pR^8$, $-SO_pNR^{5a}R^{5b}$, $-C(=O)OR^6$, or $-NR^{5a}C(=O)OR^{6a}$; and wherein the substituents on any carbon atom of the heterocyclic ring may also be selected from $-OR^8$, $-SR^8$, halo, polyhalo-C_{1-6}alkyl, oxo, thio, cyano, nitro, azido, $-NR^{5a}R^{5b}$, $-NR^{5a}C(=O)R^7$, $-NR^{5a}SO_pR^8$, $-SO_pR^8$, $-SO_pNR^{5a}R^{5b}$, $-C(=O)OH$, and $-NR^{5a}C(=O)OR^{6a}$;

L is a direct bond, –O–, -O-C_{1-4}alkanediyl-, –O-CO–, –O-C(=O)-NR^{5a}- or –O-C(=O)-NR^{5a}-C_{1-4}alkanediyl-;

$\mathbf{R^2}$ represents hydrogen, $-OR^6$, $-C(=O)OR^6$, $-C(=O)R^7$, $-C(=O)NR^{5a}R^{5b}$, $-C(=O)NHR^{5c}$, $-NR^{5a}R^{5b}$, $-NHR^{5c}$, $-NHSO_pNR^{5a}R^{5b}$, $-NR^{5a}SO_pR^8$, or $-B(OR^6)_2$;

$\mathbf{R^3}$ and $\mathbf{R^4}$ are hydrogen or C_{1-6}alkyl; or $\mathbf{R^3}$ and $\mathbf{R^4}$ taken together may form a

C_{3-7}cycloalkyl ring;

n is 3, 4, 5, or 6;

p is 1 or 2;

each $\mathbf{R^{5a}}$ and $\mathbf{R^{5b}}$ are, independently, hydrogen, C_{3-7}cycloalkyl, aryl, Het, C_{1-6}alkyl optionally substituted with halo, C_{1-6}alkoxy, cyano, polyhaloC_{1-6}alkoxy, C_{3-7}cycloalkyl, aryl, or with Het; or $\mathbf{R^{5a}}$ and $\mathbf{R^{5b}}$ taken together with the nitrogen atom to which they are attached form pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl; wherein the morpholinyl and piperidinyl groups may be optionally substituted with one or with two C_{1-6}alkyl radicals;

$\mathbf{R^{5c}}$ is C_{3-7}cycloalkyl, aryl, Het, -O-C_{3-7}cycloalkyl, -O-aryl, -O-Het, C_{1-6}alkyl, or C_{1-6}alkoxy, wherein said C_{1-6}alkyl or C_{1-6}alkoxy may be each optionally substituted with $-C(=O)OR^6$, C_{3-7}cycloalkyl, aryl, or Het;

$\mathbf{R^6}$ is hydrogen; C_{2-6}alkenyl; Het; C_{3-7}cycloalkyl optionally substituted with C_{1-6}alkyl; or C_{1-6}alkyl optionally substituted with C_{3-7}cycloalkyl, aryl or Het;

$\mathbf{R^{6a}}$ is C_{2-6}alkenyl, C_{3-7}cycloalkyl, Het, or C_{1-6}alkyl optionally substituted with C_{3-7}cycloalkyl, aryl or Het;

$\mathbf{R^7}$ is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, or aryl;

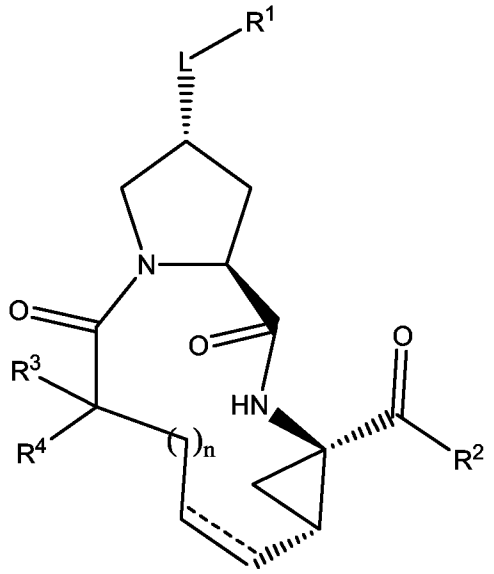
$\mathbf{R^8}$ is hydrogen, polyhaloC_{1-6}alkyl, aryl, Het, C_{3-7}cycloalkyl optionally substituted with C_{1-6}alkyl, or C_{1-6}alkyl optionally substituted with C_{3-7}cycloalkyl, aryl or Het;

aryl as a group or part of a group is phenyl, naphthyl, indanyl, or 1,2,3,4-tetrahydronaphthyl, each of which may be optionally substituted with one, two or three substituents selected from halo, C_{1-6}alkyl, polyhaloC_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkylamino, amino-carbonyl, mono- or diC_{1-6}alkylaminocarbonyl, azido, mercapto, C_{3-7}cycloalkyl, phenyl, pyridyl, thiazolyl, pyrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl; wherein the morpholinyl and piperidinyl groups may be optionally substituted with one or with two C_{1-6}alkyl radicals; and the phenyl, pyridyl, thiazolyl, pyrazolyl groups may be optionally substituted with 1, 2 or 3 substituents each independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, halo, amino, mono- or diC_{1-6}alkylamino;

Het as a group or part of a group is a 5 or 6 membered saturated, partially unsaturated or completely unsaturated heterocyclic ring containing 1 to 4 heteroatoms each independently selected from nitrogen, oxygen and sulfur, said heterocyclic ring being optionally condensed with a benzene ring, and wherein the group Het as a whole may be optionally substituted with one, two or three substituents each independently selected from the group consisting of halo, C_{1-6}alkyl, polyhalo-

C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy, polyhaloC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl, carboxyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, cyano, nitro, amino, mono- or diC_{1-6}alkyl-amino, aminocarbonyl, mono- or diC_{1-6}alkylaminocarbonyl, C_{3-7}cycloalkyl, phenyl, pyridyl, thiazolyl, pyrazolyl, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl, 4-C_{1-6}alkylcarbonyl-piperazinyl, and morpholinyl; wherein the morpholinyl and piperidinyl groups may be optionally substituted with one or with two C_{1-6}alkyl radicals; and the phenyl, pyridyl, thiazolyl, pyrazolyl groups may be optionally substituted with 1, 2 or 3 substituents each independently selected from C_{1-6}alkyl, C_{1-6}alkoxy, halo, amino, mono- or diC_{1-6}alkylamino.

2. A compound according to claim 1 wherein the compound has the formula (I-a):



(I-a)

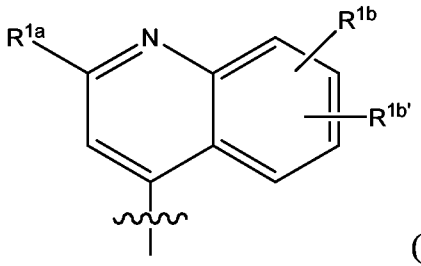
3. A compound according to any one of claims 1-2, wherein L is –O– , -O-CO- or a direct bond.

4. A compound according to any one of claims 1-2, wherein L is –O– and R^1 is quinolinyl (in particular quinolin-4-yl), isoquinolinyl (in particular isoquinolin-1-yl), quinazolinyl (in particular quinazolin-4-yl), or pyrimidinyl (in particular pyrimidin-4-yl), either of which is, independently, optionally mono, di, or tri substituted with C_{1-6}alkyl, C_{1-6}alkoxy, nitro, hydroxy, halo, trifluoromethyl, -$NR^{5a}R^{5b}$, -$C(=O)NR^{5a}R^{5b}$, C_{3-7}cycloalkyl, aryl, Het, -C(=O)OH, or –$C(=O)OR^{6a}$; wherein aryl or Het are each, independently, optionally substituted with halo, C_{1-6}alkyl, C_{1-6}alkoxy, amino, mono- or diC_{1-6}alkylamino, pyrrolidinyl, piperidinyl, piperazinyl, 4-C_{1-6}alkylpiperazinyl (e.g.4-methylpiperazinyl), or morpholinyl; and

wherein the morpholinyl and piperidinyl groups may optionally substituted with one or two C_{1-6}alkyl radicals.

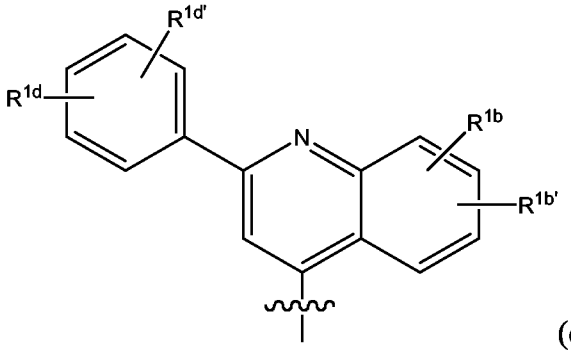
5. A compound according to claim 4 wherein L is –O– and R^1 is

(d-1) a radical of formula



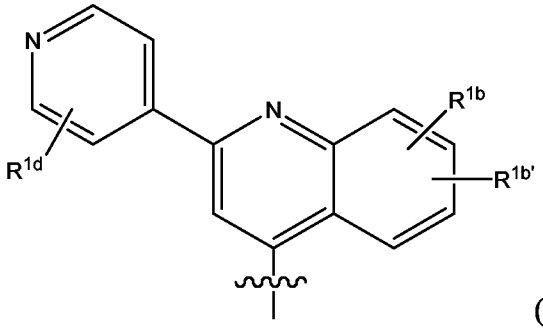
(d-1)

(d-2) a radical of formula



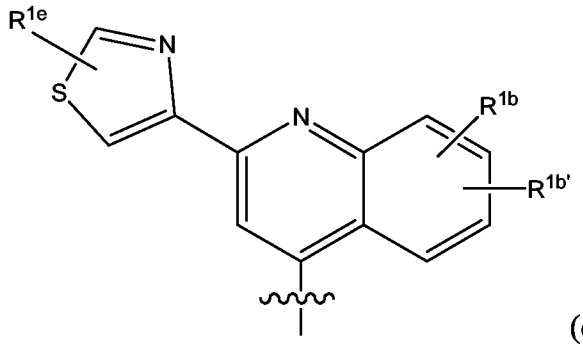
(d-2)

(d-3) a radical of formula



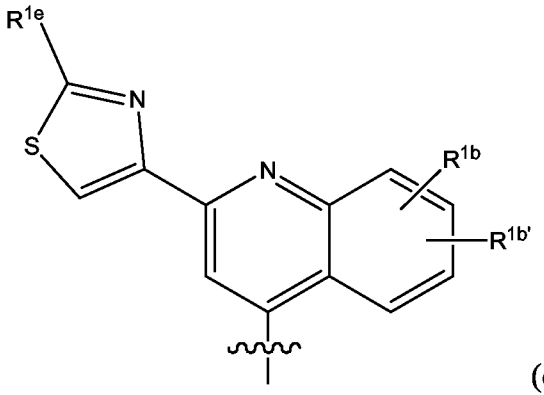
(d-3)

(d-4) a radical of formula



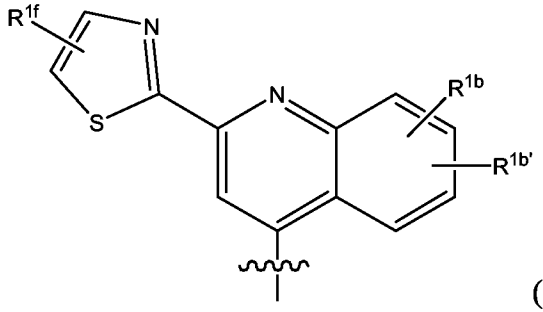
(d-4)

or in particular, (d-4-a) a radical of formula



(d-4-a)

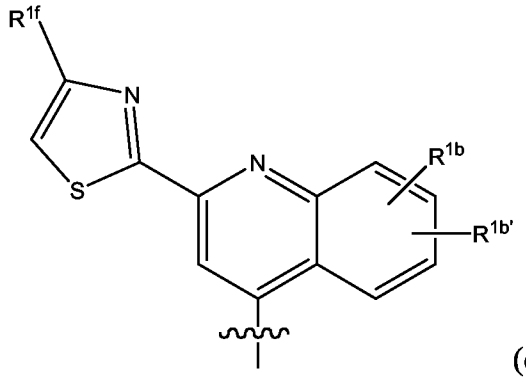
(d-5) a radical of formula



(d-5)

wherein in radicals (d-1) – (d-5), as well as in (d-4-a) and (d-5-a):
each R^{1a}, R^{1b}, $R^{1b'}$, R^{1d}, $R^{1d'}$, R^{1e}, R^{1f} are independently any of the substituents selected from those mentioned as possible substituents on the monocyclic or bicyclic ring systems of R^1, as specified in claim 1.

6. A compound according to claim 4 wherein L is –O– and R^1 is a radical of formula



(d-5-a)

wherein R^{1f} is hydrogen, C_{1-6}alkyl, amino, mono- or diC_{1-6}alkylamino, pyrrolidinyl, piperidinyl, piperazinyl, 4- C_{1-6}alkylpiperazinyl (in particular 4-methylpiperazinyl), or morpholinyl.

7. A compound according to any one of claims 1-6, wherein
(f) R^2 is $-NHR^{5c}$, where R^{5c} is C_{1-6}alkyl, aryl, Het, C_{1-6}alkoxy, -O-aryl, or –O-Het; or
(g) R^2 is $-OR^6$, wherein R^6 is hydrogen, methyl, ethyl, or *tert*-butyl; or
(h) R^2 is $-NHS(=O)_2R^8$, where R^8 is methyl, cyclopropyl, methylcyclopropyl, or phenyl; or
(i) R^2 is $-C(=O)OR^6$, $-C(=O)R^7$, $-C(=O)NR^{5a}R^{5b}$, or $-C(=O)NHR^{5c}$, wherein R^{5a}, R^{5b}, R^{5c}, R^6, or R^7 are as defined in claim 1, and where R^{5c} is cyclopropyl; or
(j) R^2 is $-NHS(=O)_2NR^{5a}R^{5b}$ where R^{5a} and R^{5b} are, each independently, hydrogen, C_{3-7}cycloalkyl or C_{1-6}alkyl.

8. A compound according to any one of claims 1-7, wherein R^3 and R^4 are both hydrogen.

9. A compound according to any one of claims 1-8 wherein n is 4 or 5.

10. A compound according to any of claims 1-9 other than an N-oxide, or salt.

11. A combination comprising
(a) a compound as defined in any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof; and
(b) ritonavir, or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a carrier, and as active ingredient an anti-virally effective amount of a compound as claimed in any one of claims 1-10 or a combination according to claim 11

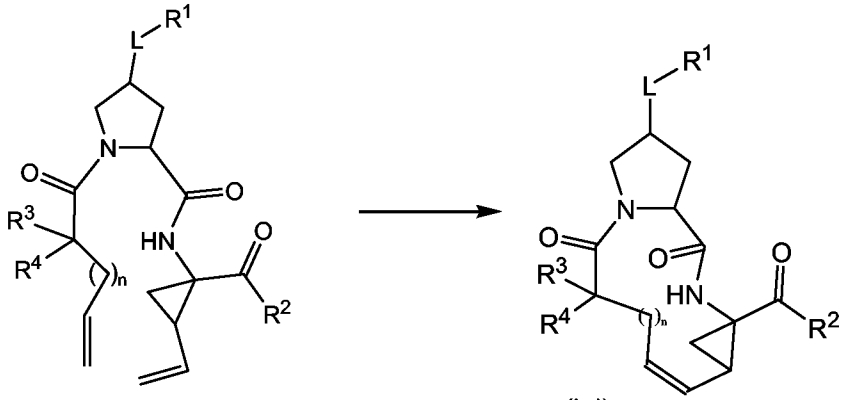
13. A compound according to any of claims 1-10 or a combination according to claim 11, for use as a medicament.

14. Use of a compound according to any of claims 1-10 or a combination according to claim 11, for the manufacture of a medicament for inhibiting HCV replication.

15. A method of inhibiting HCV replication in a warm-blooded animal said method comprising the administration of an effective amount of a compound according to any of claims 1-10 or an effective amount of each component of the combination according to claim 11.

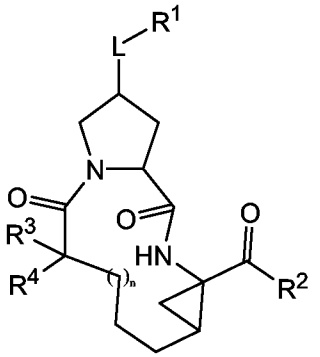
16. A process for preparing a compound as claimed in any of claims 1 - 10, wherein said process comprises:

(a) preparing a compound of formula (I) wherein the bond between C_7 and C_8 is a double bond, which is a compound of formula (I-d), by forming a double bond between C_7 and C_8, in particular via an olefin metathesis reaction, with concomitant cyclization to the macrocycle as outlined in the following reaction scheme:



;

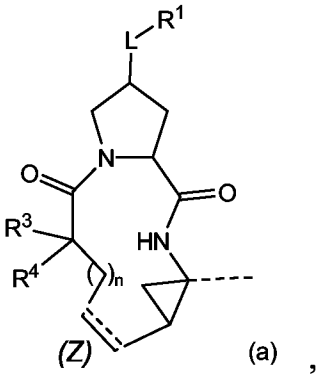
(b) converting a compound of formula (I-d) to a compound of formula (I) wherein the link between C7 and C8 in the macrocycle is a single bond, i.e. compounds of formula (I-e):



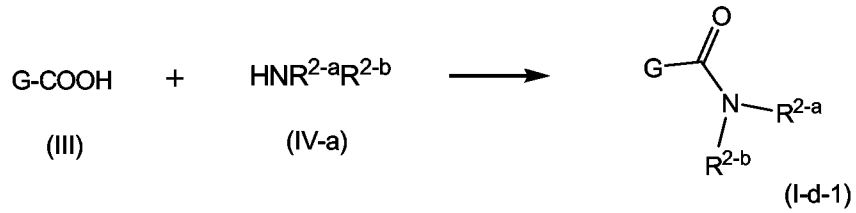
(I-e) ,

by a reduction of the C7-C8 double bond in the compounds of formula (I-d);

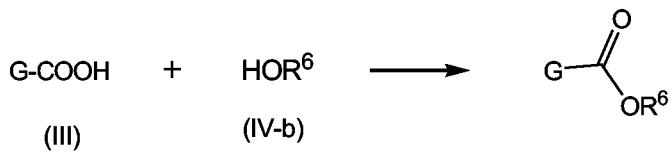
(c) preparing a compound of formula (I) wherein R^2 represents $-NR^{5a}R^{5b}$, $-NHR^{5c}$, $-NHSO_pNR^{5a}R^{5b}$, $-NR^{5a}SO_pR^8$, these groups being collectively represented by $-NR^{2-a}R^{2-b}$, said compound being represented by formula (I-d-1), by forming an amide bond between a intermediate (III) and an $H-NR^{2-a}R^{2-b}$ (IV-a), or preparing a compound of formula (I) wherein R^2 represents $-OR^6$, i.e. a compound (I-d-2), by forming an ester bond between an intermediate (III) and an alcohol (IV-b) as outlined in the following scheme wherein G represents a group:



(Z) (a) ,

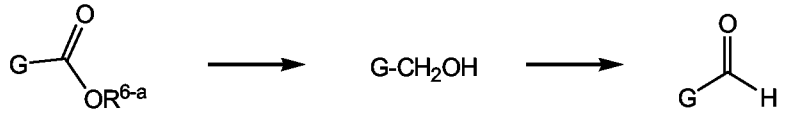


(III) (IV-a) (I-d-1)



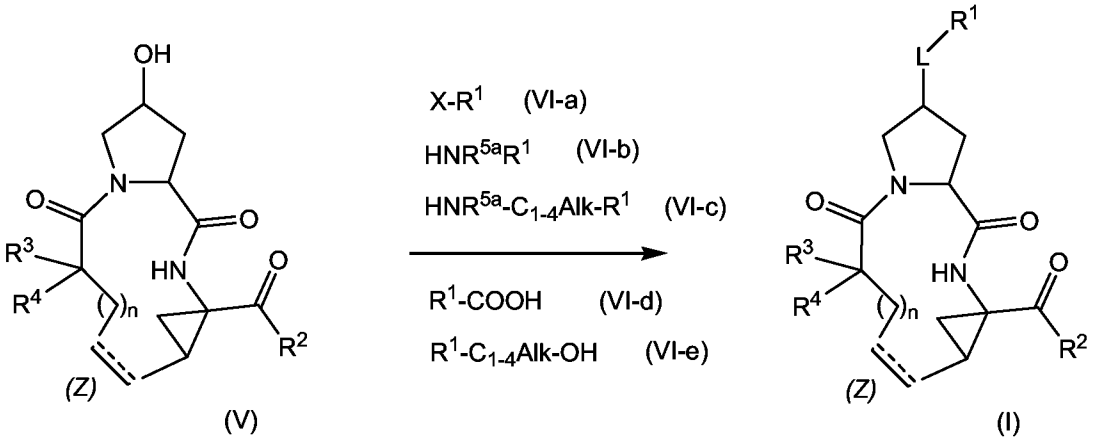
(III) (IV-b) (I-d-2) ;

(d) preparing a compounds of formula (I) wherein R^2 represents hydrogen, i.e. a compound (I-d-4), from an ester (I-d-2-a), which is an intermediate of formula (I-d-2) wherein R^6 is C_{1-4}alkyl, by a reduction reaction to the corresponding alcohol (I-d-3), followed by an oxidation reaction with a mild oxidant:



(I-d-2-a) (I-d-3) (I-d-4) ;

(e) reacting an intermediate (V) with intermediates (VI-a), (VI-b), (VI-c), (VI-d) or (VI-e) as outlined in the following reaction scheme wherein the various radicals have the meanings specified above and C_{1-4}Alk represents C_{1-4}alkanediyl:



(V) (I)

and wherein X in (VI-a) represents hydroxy or a leaving group; which reaction in particular is an O-arylation reaction wherein X represents a leaving group, or a Mitsunobu reaction, wherein X is hydroxy;

(f) preparing a compound of formula (I) wherein L is a urethane group (L is –O-C(=O)-NR^{5a}-) by reacting an intermediate (V) with an amine (VI-b) or (VI-c) in the presence of a carbonyl introducing agent, the latter in particular comprising phosgene or a phosgene derivative;

(g) preparing a compound of formula (I) wherein L is –O-C(=O)- by reacting an alcohol (V) with an acid (VI-d) or active derivative thereof, such as a corresponding acylating agent, in particular an acid anhydride or acid halide;

(h) preparing a compound of formula (I) wherein L is –O-C_{1-4}alkanediyl– by an ether forming reaction between (V) and (VI-e);

(i) converting compounds of formula (I) into each other by a functional group transformation reaction; or

(j) preparing a salt form by reacting the free form of a compound of formula (I) with an acid or a base.