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Description

BACKGROUND OF THE INVENTION

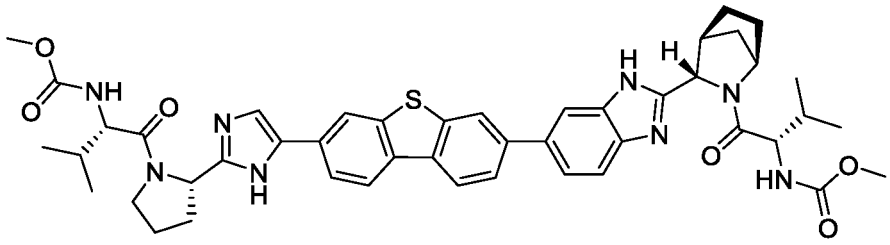
[0001] Hepatitis C is recognized as a chronic viral disease of the liver which is characterized by liver disease. Although drugs targeting the liver are in wide use and have shown effectiveness, toxicity and other side effects have limited their usefulness. Inhibitors of hepatitis C virus (HCV) are useful to limit the establishment and progression of infection by HCV as well as in diagnostic assays for HCV.

[0002] Further reference may be made to antiviral compounds disclosed in WO 2008/021927 A2, WO 2010/017401 A1, WO 2009/020828 A1, WO 2008/144380 A1, WO 2008/021928 A2 and WO 2009/102568 A1.

[0003] There is a need for new HCV therapeutic agents.

SUMMARY OF THE INVENTION

[0004] In one embodiment the invention provides a compound of the invention which is a compound of formula (I):



or a pharmaceutically acceptable salt thereof.

[0005] In another embodiment, the invention provides a pharmaceutical composition comprising the compound of formula (I), or a pharmaceutically acceptable salt; and at least one pharmaceutically acceptable carrier.

[0006] In another embodiment, the invention provides the pharmaceutical composition, further comprising at least one additional therapeutic agent. In another embodiment, the additional therapeutic agent is selected from the group consisting of ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

[0007] In another embodiment, the invention provides the pharmaceutical composition, further comprising a nucleoside analogue. In another embodiment, the nucleoside analogue is selected from ribavirin, viramidine, levovirin, an L-nucleoside, and isatoribine.

[0008] In another embodiment, the invention provides the compound of formula (I), or a pharmaceutically acceptable salt, for use in the prophylactic or therapeutic treatment of hepatitis C or a hepatitis C associated disorder. In another embodiment, the use further comprises administering at least one additional therapeutic agent. In another embodiment, the additional therapeutic agent is selected from the group consisting of ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV. In another embodiment, the NS5b polymerase inhibitor is a nucleotide inhibitor of HCV NS5b polymerase. In another embodiment, the additional therapeutic agent is a nucleoside analogue. In another embodiment, the nucleoside analogue is selected from ribavirin, viramidine, levovirin, an L-nucleoside, and isatoribine.

DETAILED DESCRIPTION OF THE INVENTION

[0009] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas.

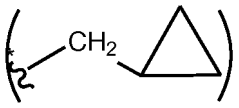
Compounds of the Invention

[0010] Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R^1" or "A^3", then it will be understood that the groups may be the same or different, i.e., each group is independently selected.

[0011] "Absent" - Some groups are defined such that they can be absent. When a group is absent it becomes a bond connector. The two groups that would otherwise be connected to that absent group are connected to each other through a bond. For example, when W is absent, M is bonded to M.

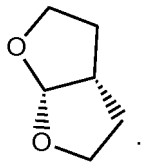
"Alkyl" is C_1-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me,

$-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl,$-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl,$-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl,$-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, and cyclopropylmethyl



[0012] "Heterocycle" as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (*e.g.* 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (*e.g.* O, N, or S).

[0013] Examples of heterocycles include by way of example and not limitation pyridyl, dihydropyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4H-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, isatinoyl, and bis-tetrahydrofuranyl:



[0014] By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

[0015] By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

[0016] "Carbocycle" refers to a saturated, unsaturated or aromatic ring having up to about 25 carbon atoms. Typically, a carbocycle has about 3 to 7 carbon atoms as a monocycle, about 7 to 12 carbon atoms as a bicycle, and up to about 25 carbon atoms as a polycycle. Monocyclic carbocycles typically have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles typically have 7 to 12 ring atoms, *e.g.,* arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. The term carbocycle includes "cycloalkyl" which is a

saturated or unsaturated carbocycle. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

[0017] The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

[0018] The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

[0019] "Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.,* melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

[0020] "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0021] The term "treatment" or "treating," to the extent it relates to a disease or condition includes preventing the disease or condition from occurring, inhibiting the disease or condition, eliminating the disease or condition, and/or relieving one or more symptoms of the disease or condition.

[0022] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, *i.e.,* they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes (D and L) or (R and S) are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and 1 or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity. The invention includes all stereoisomers of the compounds described herein.

Protecting Groups

[0023] In the context of the present invention, protecting groups include prodrug moieties and chemical protecting groups.

[0024] "Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. Chemical protecting groups and strategies for protection/deprotection are well known in the art. *See e.g.,* Protective Groups in Organic Chemistry, Theodora W. Greene, John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, *e.g.,* making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

[0025] Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, *i.e.* routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group "PG" will be dependent upon the chemistry of the reaction to be protected against (*e.g.,* acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. PGs do not need to be, and generally are not, the same if the compound is substituted with multiple PG. In general, PG will be used to protect functional groups such as carboxyl, hydroxyl, thio, or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

[0026] Various functional groups of the compounds of the invention may be protected. For example, protecting groups for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) include "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

[0027] A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Synthesis, Theodora W. Greene (John Wiley & Sons,

Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994). In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below.

[0028] Whenever a compound described herein is substituted with more than one of the same designated group, *e.g.,* "R^1" or "R^3", then it will be understood that the groups may be the same or different, *i.e.,* each group is independently selected. Wavy lines indicate the site of covalent bond attachments to the adjoining groups, moieties, or atoms.

[0029] In one embodiment of the invention, the compound is in an isolated and purified form. Generally, the term "isolated and purified" means that the compound is substantially free from biological materials (e.g. blood, tissue, cells, etc.). In one specific embodiment of the invention, the term means that the compound or conjugate of the invention is at least about 50 wt.% free from biological materials; in another specific embodiment, the term means that the compound or conjugate of the invention is at least about 75 wt.% free from biological materials; in another specific embodiment, the term means that the compound of the invention is at least about 90 wt.% free from biological materials; in another specific embodiment, the term means that the compound of the invention is at least about 98 wt.% free from biological materials; and in another embodiment, the term means that the compound of the invention is at least about 99 wt.% free from biological materials. In another specific embodiment, the invention provides a compound of the invention that has been synthetically prepared (e.g., *ex vivo*).

Stereoisomers

[0030] The compounds of the invention may have chiral centers, *e.g.,* chiral carbon atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, *e.g.,* acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

[0031] The compounds of the invention can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

Salts and Hydrates

[0032] Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth metal (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1-C_4 alkyl). Physiologically acceptable salts of a hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a C_1-C_4 alkyl group).

[0033] For therapeutic use, salts of active ingredients of the compounds of the invention will typically be physiologically acceptable, i.e. they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present invention.

[0034] Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

[0035] In addition, salts may be formed from acid addition of certain organic and inorganic acids, *e.g.,* HCl, HBr, H_2SO_4, H_3PO_4 or organic sulfonic acids, to basic centers, typically amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and

combinations with stoichiometric amounts of water as in hydrates.

[0036] Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids. Any of the natural or unnatural amino acids are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, *e.g.,* lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

Methods of Inhibition of HCV

[0037] Herein described are methods of inhibiting the activity of HCV comprising the step of treating a sample suspected of containing HCV with a compound or composition of the invention.

[0038] Compounds of the invention may act as inhibitors of HCV, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will generally bind to locations on the surface or in a cavity of the liver. Compounds binding in the liver may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method. Once labeled, the substantially irreversibly binding compounds are useful as probes for the detection of HCV. Accordingly, herein described are methods of detecting NS3 in a sample suspected of containing HCV comprising the steps of: treating a sample suspected of containing HCV with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl or amino. Within the context of the invention samples suspected of containing HCV include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing HCV. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

[0039] The treating step comprises adding the compound of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

[0040] If desired, the activity of HCV after application of the compound can be observed by any method including direct and indirect methods of detecting HCV activity. Quantitative, qualitative, and semiquantitative methods of determining HCV activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

[0041] Many organisms contain HCV. The compounds of this invention are useful in the treatment or prophylaxis of conditions associated with HCV activation in animals or in man.

[0042] However, in screening compounds capable of inhibiting HCV activity it should be kept in mind that the results of enzyme assays may not always correlate with cell culture assays. Thus, a cell based assay should typically be the primary screening tool.

Pharmaceutical Formulations

[0043] The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

[0044] While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

[0045] The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping

the product.

[0046] Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

[0047] A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

[0048] For administration to the eye or other external tissues *e.g.,* mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

[0049] If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, *i.e.* an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

[0050] The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

[0051] Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

[0052] The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

[0053] Pharmaceutical formulations according to the present invention comprise one or more compounds of the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0054] Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

[0055] Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcel-

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

[0056] Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[0057] Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0058] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

[0059] The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

[0060] The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

[0061] Formulations suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

[0062] Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0063] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0064] Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of conditions associated with HCV activity.

[0065] Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0066] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

[0067] The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

[0068] It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0069] The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

[0070] Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

[0071] Compounds of the invention can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the invention also provides compositions comprising one or more compounds of the invention formulated for sustained or controlled release.

[0072] Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses), the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies.

Routes of Administration

[0073] One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

HCV Combination Therapy

[0074] In another embodiment, non-limiting examples of suitable combinations include combinations of the compound of the present invention with one or more interferons, ribavirin or its analogs, HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV NS5B polymerase, non-nucleoside inhibitors of HCV NS5B polymerase, HCV NS5A inhibitors, TLR-7 agonists, cyclophillin inhibitors, HCV IRES inhibitors, pharmacokinetic enhancers, and other drugs for treating HCV.

[0075] More specifically, the compound of the present invention may be combined with one or more compounds selected from the group consisting of

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

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

3) HCV NS3 protease inhibitors, *e.g.,* boceprevir (SCH-503034, SCH-7), telaprevir (VX-950), TMC435350, BI-1335, BI-1230, MK-7009, VBY-376, VX-500, GS-9256, GS-9451, BMS-790052, BMS-605339, PHX-1766, AS-101, YH-5258, YH5530, YH5531, and ITMN-191,

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

5) hepatoprotectants, *e.g.,* emericasan (IDN-6556), ME-3738, GS-9450 (LB-84451), silibilin, and MitoQ,
6) nucleoside or nucleotide inhibitors of HCV NS5B polymerase, *e.g.,* R1626, R7128 (R4048), IDX184, IDX-102, BCX-4678, valopicitabine (NM-283), and MK-0608,
7) non-nucleoside inhibitors of HCV NS5B polymerase, *e.g.,* PF-868554, VCH-759, VCH-916, JTK-652, MK-3281, GS-9190, VBY-708, VCH-222, A848837, ANA-598, GL60667, GL59728, A-63890, A-48773, A-48547, BC-2329, VCH-796 (nesbuvir), GSK625433, BILN-1941, XTL-2125, and GS-9190,
8) HCV NS5A inhibitors, *e.g.,* AZD-2836 (A-831), BMS-790052, and A-689,
9) TLR-7 agonists, *e.g.,* imiquimod, 852A, GS-9524, ANA-773, ANA-975, AZD-8848 (DSP-3025), and SM-360320,
10) cyclophillin inhibitors, *e.g.,* DEBIO-025, SCY-635, and NIM811,
11) HCV IRES inhibitors, *e.g.,* MCI-067,
12) pharmacokinetic enhancers, *e.g.,* BAS-100, SPI-452, PF-4194477, TMC-41629, GS-9350, GS-9585, and roxythromycin,
13) other drugs for treating HCV, *e.g.,* thymosin alpha 1 (Zadaxin), nitazoxanide (Alinea, NTZ), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), GS-9525, KRN-7000, civacir, GI-5005, XTL-6865, BIT225, PTX-111, ITX2865, TT-033i, ANA 971, NOV-205, tarvacin, EHC-18, VGX-410C, EMZ-702, AVI 4065, BMS-650032, BMS-791325, Bavituximab, MDX-1106 (ONO-4538), Oglufanide, and VX-497 (merimepodib).

[0076] In yet another embodiment, the present application discloses pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, thereof, in combination with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or excipient.

[0077] According to the present invention, the therapeutic agent used in combination with the compound of the present invention can be any agent having a therapeutic effect when used in combination with the compound of the present invention. For example, the therapeutic agent used in combination with the compound of the present invention can be interferons, ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

[0078] In another embodiment, the present application provides pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent selected from the group consisting of pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, albuferon, rebetol, copegus, levovirin, VX-497, viramidine (taribavirin), A-831, A-689, NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, XTL-2125, SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, MX-3253 (celgosivir), UT-231B, IDN-6556, ME 3738, MitoQ, and LB-84451, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975 (isatoribine), XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811 and a pharmaceutically acceptable carrier or excipient.

[0079] In yet another embodiment, the present application provides a combination pharmaceutical agent comprising:

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

[0080] Combinations of the compounds of formula I and additional active therapeutic agents may be selected to treat patients infected with HCV and other conditions such as HIV infections. Accordingly, the compounds of formula I may be combined with one or more compounds useful in treating HIV, for example HIV protease inhibiting compounds, non-nucleoside inhibitors of HIV reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

[0081] More specifically, one or more compounds of the present invention may be combined with one or more compounds selected from the group consisting of 1) HIV protease inhibitors, e.g., amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, lopinavir + ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-

114, mozenavir (DMP-450), JE-2147 (AG1776), AG1859, DG35, L-756423, RO0334649, KNI-272, DPC-681, DPC-684, and GW640385X, DG17, PPL-100, 2) a HIV non-nucleoside inhibitor of reverse transcriptase, *e.g.,* capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirine), efavirenz, BILR 355 BS, VRX 840773, UK-453,061, RDEA806, 3) a HIV nucleoside inhibitor of reverse transcriptase, *e.g.,* zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, fosalvudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, abacavir + lamivudine, abacavir + lamivudine + zidovudine, zidovudine + lamivudine, 4) a HIV nucleotide inhibitor of reverse transcriptase, *e.g.,* tenofovir, tenofovir disoproxil fumarate + emtricitabine, tenofovir disoproxil fumarate + emtricitabine + efavirenz, and adefovir, 5) a HIV integrase inhibitor, *e.g.,* curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), BMS-707035, MK-2048, BA-011, BMS-538158, GSK364735C, 6) a gp41 inhibitor, *e.g.,* enfuvirtide, sifuvirtide, FB006M, TRI-1144, SPC3, DES6, Locus gp41, CovX, and REP 9, 7) a CXCR4 inhibitor, *e.g.,* AMD-070, 8) an entry inhibitor, *e.g.,* SP01A, TNX-355, 9) a gp120 inhibitor, *e.g.,* BMS-488043 and BlockAide/CR, 10) a G6PD and NADH-oxidase inhibitor, *e.g.,* immunitin, 10) a CCR5 inhibitor, *e.g.,* aplaviroc, vicriviroc, INCB9471, PRO-140, INCB15050, PF-232798, CCR5mAb004, and maraviroc, 11) an interferon, *e.g.,* pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, and albuferon, 12) ribavirin analogs, e.g., rebetol, copegus, levovirin, VX-497, and viramidine (taribavirin) 13) NS5a inhibitors, e.g., A-831, A-689, and BMS-790052, 14) NS5b polymerase inhibitors, e.g., NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125, 15) NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, 16) alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B, 17) hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-84451, 18) non-nucleoside inhibitors of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, 19) other drugs for treating Hepatitis C, e.g., zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975 (isatoribine), XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811, 19) pharmacokinetic enhancers, e.g., BAS-100 and SPI452, 20) RNAse H inhibitors, e.g., ODN-93 and ODN-112, 21) other anti-HIV agents, e.g., VGV-1, PA-457 (bevirimat), ampligen, HRG214, cytolin, polymun, VGX-410, KD247, AMZ 0026, CYT 99007, A-221 HIV, BAY 50-4798, MDX010 (iplimumab), PBS119, ALG889, and PA-1050040.

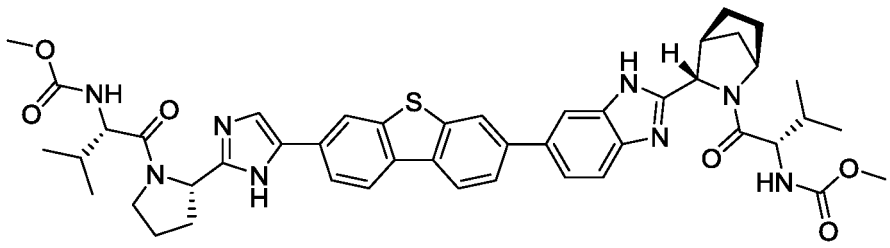
Metabolites of the Compounds of the Invention

[0082] Also herein described are the *in vivo* metabolic products of the compounds described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, herein described are compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (*e.g.,* C^{14} or H^3) compound of the invention, administering it parenterally in a detectable dose (*e.g.,* greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, *e.g.,* by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo,* are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no HCV -inhibitory activity of their own.

[0083] Methods for determining stability of compounds in surrogate gastrointestinal secretions are known.

Compound of formula (I)

[0084] In one embodiment the invention provides a compound of formula (I):



Exemplary Methods of Making the Compounds of the Invention.

[0085] Herein disclosed are also methods of making the compositions of the invention. The compositions are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in Compendium of Organic Synthetic Methods (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, Jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., Advanced Organic Chemistry, Third Edition, (John Wiley & Sons, New York, 1985), Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes, Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing). Other methods suitable for preparing compounds of the invention are described in International Patent Application Publication Number WO 2006/020276.

[0086] A number of exemplary methods for the preparation of the compositions of the invention are provided in the schemes and examples below. These methods are intended to illustrate the nature of such preparations and are not intended to limit the scope of applicable methods.

[0087] Generally, the reaction conditions such as temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

[0088] Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

[0089] Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0°C to -100°C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

[0090] Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (*e.g.,* inert gas environments) are common in the art and will be applied when applicable.

[0091] The terms "treated", "treating", "treatment", and the like, when used in connection with a chemical synthetic operation, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two. For example, treating indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis is used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

[0092] Modifications of each of the exemplary schemes and in the Examples (hereafter "exemplary schemes") leads to various analogs of the specific exemplary materials produce. The above-cited citations describing suitable methods of organic synthesis are applicable to such modifications.

[0093] In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter

separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

[0094] Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

[0095] Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

[0096] A single stereoisomer, *e.g.,* an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Stereochemistry of Carbon Compounds, (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) J. Chromatogr., 113, 3) 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

[0097] Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

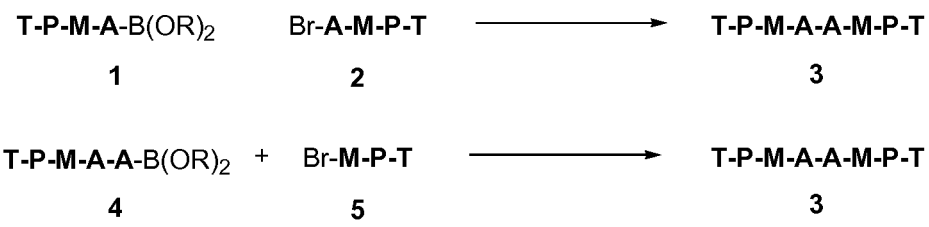
[0098] Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched substrate. A method of determining optical purity involves making chiral esters, such as a menthyl ester, *e.g.,* (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. (1982) J. Org. Chem. 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) J. of Chromatogr. 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

Schemes and Examples

[0099] General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

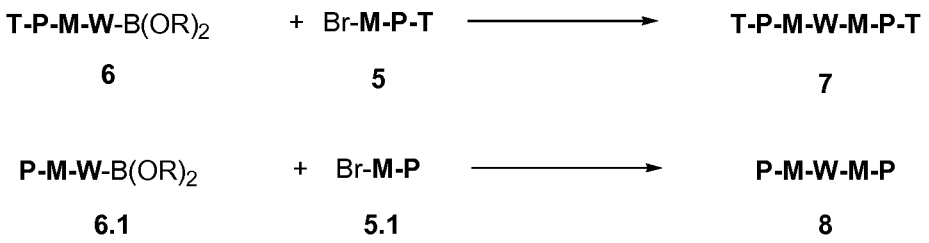
[0100] A number of exemplary methods for the preparation of compounds of the invention are provided herein, for example, in the Examples hereinbelow. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods. In the exemplary methods described herein, the fragment **E-**V- can also be written as R9-. Subsequently, the fragment **E-V-Z-** or **R9-Z-** can be written as **T-.** The fragments **E-V-Z-P, R9-Z-P-,** or **T-P-** can all be written as **J-.**

Scheme 1: Representative synthesis of T-P-M-A-A-M-P-T



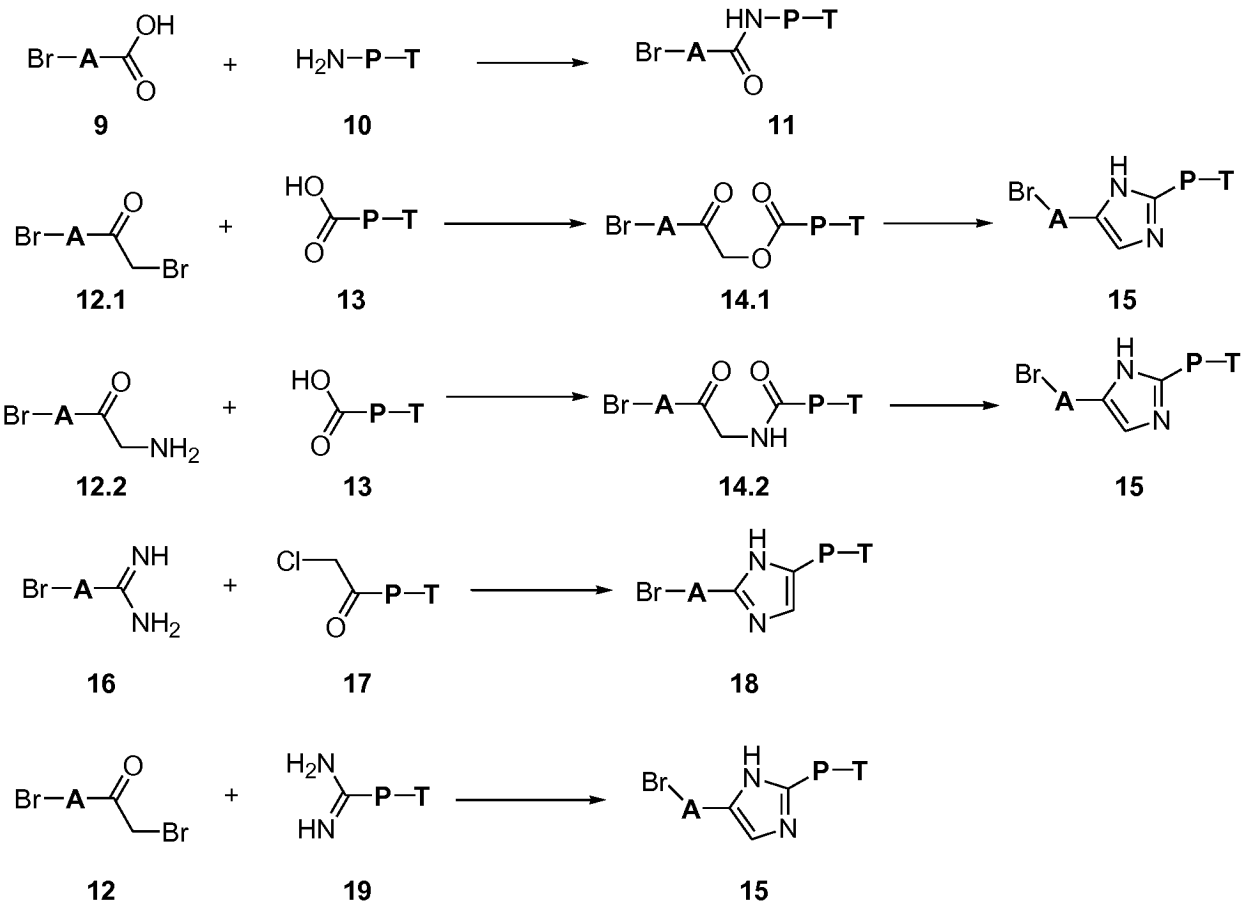
Scheme 1 shows a general synthesis of the **T-P-M-A-A-M-P-T** molecule, wherein transition metal-mediated cross-coupling reaction is utilized to construct the **A-A** bond and/or **A-M** bond. For illustrative purposes, the Suzuki reaction is employed to couple a Br-**M-P-T** and an $(RO)_2B$-**A-A-M-P-T** intermediate or a Br-**A-M-P-T** and a $(RO)_2B$-**A-M-P-T** intermediate. Boronic ester **1** (or **4**) is coupled with an appropriate coupling partner (e.g. arylbromide **2** or **5**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **3.** Palladium mediated cross-coupling reactions that enable the **A-A** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 1a: Representative synthesis of T-P-M-W-M-P-T



Scheme 1a shows a general synthesis of the **T-P-M-W-M-P-T** molecule and the **P-M-W-M-P** molecule, wherein transition metal-mediated cross-coupling reaction is utilized to construct the **W-M** bond. For illustrative purposes, the Suzuki reaction is employed to couple a Br-**M-P-T** and a $(RO)_2B$-**W-M-P-T** intermediate or a Br-**M-P**-PG to a $(RO)_2B$-**W-M-P**-PG intermediate. Boronic ester **6** (or **6.1**) is coupled with an appropriate coupling partner (e.g. arylbromide **5** or **5.1)** using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **7** and **8.** Palladium mediated cross-coupling reactions that enable the **A-A** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 2: Representative synthesis of A-M-P-T

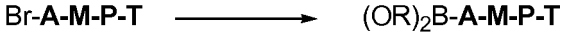


Scheme 2 shows a general synthesis of an **A-M-P-T** molecule wherein, for illustrative purposes, **M** is an amide or an imidazole. Coupling of amine **10** with acid **9** is accomplished using a peptide coupling reagent (e.g. HATU) to afford amide containing **11.**

[0101] The acid **13** is coupled with an α-haloketone, such as α-bromoketone **12.1,** under basic conditions (e.g. Et_3N) to afford **14.1.** Alternatively, the acid **13** is coupled with an α-aminoketone **12.2,** under amide formation conditions (e.g. EDC, Et_3N) to afford **14.2.** Reaction of **14.1** or **14.2** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule Br-**A-M-P-T.**

[0102] The benzamidine **16** is coupled with an α-haloketone such as α-chloroketone **17** under basic conditions such as K_2CO_3 to afford the imidazole containing molecule Br-**A-M-P-T 18. A-M-P-T 15** can be prepared analogously.

Scheme 3: Representative synthesis of A-M-P-T



2.1 **1.1**

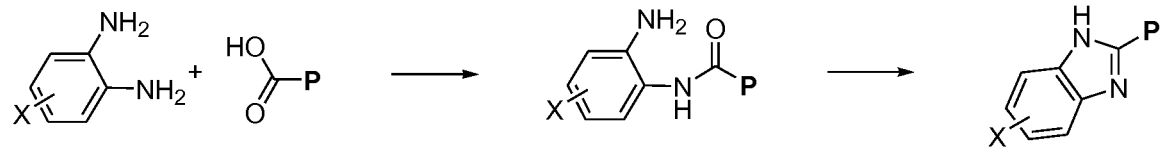
Scheme 3 shows a general synthesis of an **A-M-P-T** molecule wherein borate or boronic acid 1.1 can be synthesized from bromide **2.1.**

Scheme 4: Representative synthesis of A-M-P-Z-R9

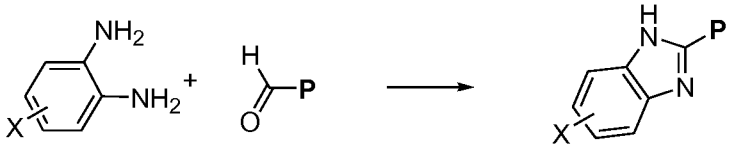
20 **21** **22**

Scheme 4 shows a general synthesis of an **A-M-P-Z-R9** fragment wherein, for illustrative purposes, **P** = pyrrolidine and **Z** = carbonyl. Coupling of amine **20** with acid **21** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **22.**

Scheme 5: Representative synthesis of L-P



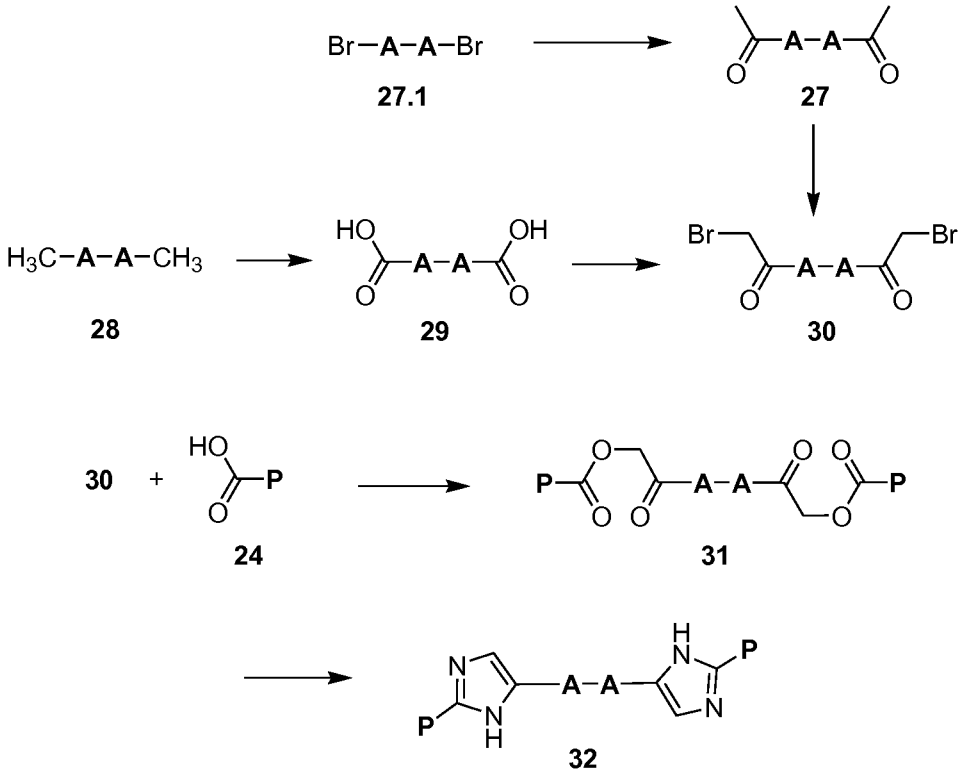
23 **24** **25** **26**



23 **27** **26**

Scheme 5 shows a general synthesis of an **L-P** molecule wherein, for illustrative purposes, **L** = benzimidazole. The acid **24** is coupled with **23** using a peptide coupling reagent such as HATU to afford **25.** Heating in solvent (such as refluxing ethanol) affords **L-P** fragment **26.** Alternatively, the **L-P** fragment **26** is obtained by reaction of diamine (such as **23**) and carbonyl compound (such as aldehyde **27**) in a solvent under heating conditions (e.g. ethanol under microwave irradiation).

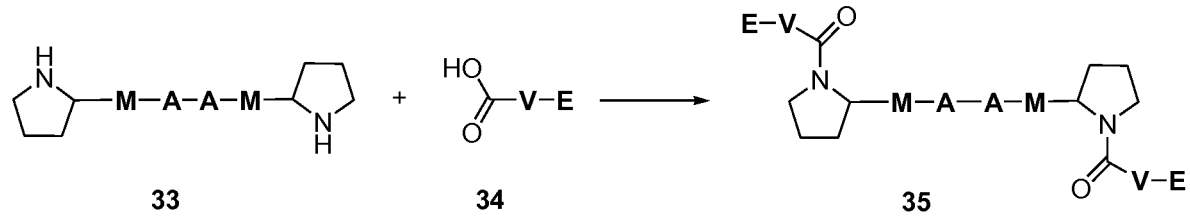
Scheme 6: Representative synthesis of P-M-A-A-M-P fragment



Scheme 6 shows a general synthesis of **P-M-A-A-M-P** molecule wherein, for illustrative purposes, **M** = imidazole. For example, the diketone **27** is converted to **30** using bromine. Compound **27** can be commercially available or can be prepared from dibromide **27.1** through coupling with a vinyltin reagent such as tributyl(ethoxyvinyl)stannane with palladium. Coupling of **30** with acid **24** under basic conditions such as diisopropylethylamine affords diester **31.** Imidazole formation is accomplished by treatment of **31** with ammonium acetate to provide the imidazole containing molecule **P-M-A-A-M-P.**

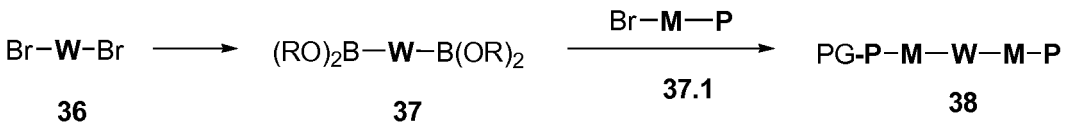
[0103] Alternatively, bromide **30** can be synthesized from **28.** The methyl compound **28** can be converted to the corresponding diacid **29** using potassium permanganate as oxidant. Conversion of **29** to **30** can be accomplished by a multi-step reaction, first treatment of **29** with oxalyl chloride, then by trimethylsilyl diazomethane, then with hydrobromic acid to afford compound **30.**

Scheme 7: Representative synthesis of E-V-P-M-A-A-M-P-V-E



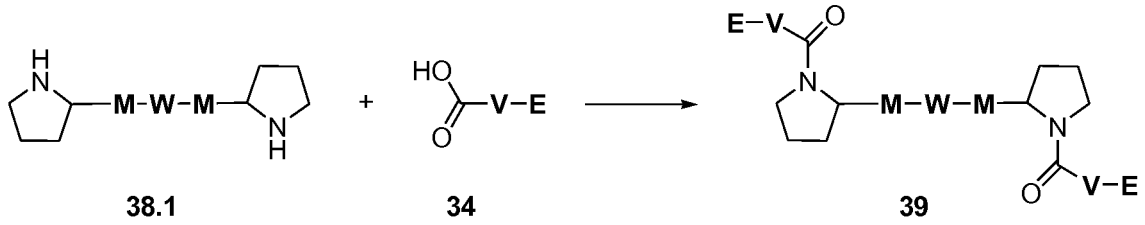
Scheme 7 shows a general synthesis of an **E-V-P-M-A-A-M-P-V-E** molecule wherein, for illustrative purposes, **P** = pyrrolidine and **Z** = carbonyl. Coupling of amine **33** with acid **34** is accomplished using a peptide coupling reagent, such as HATU, to afford **35.**

Scheme 8: Representative synthesis of P-M-W-M-P



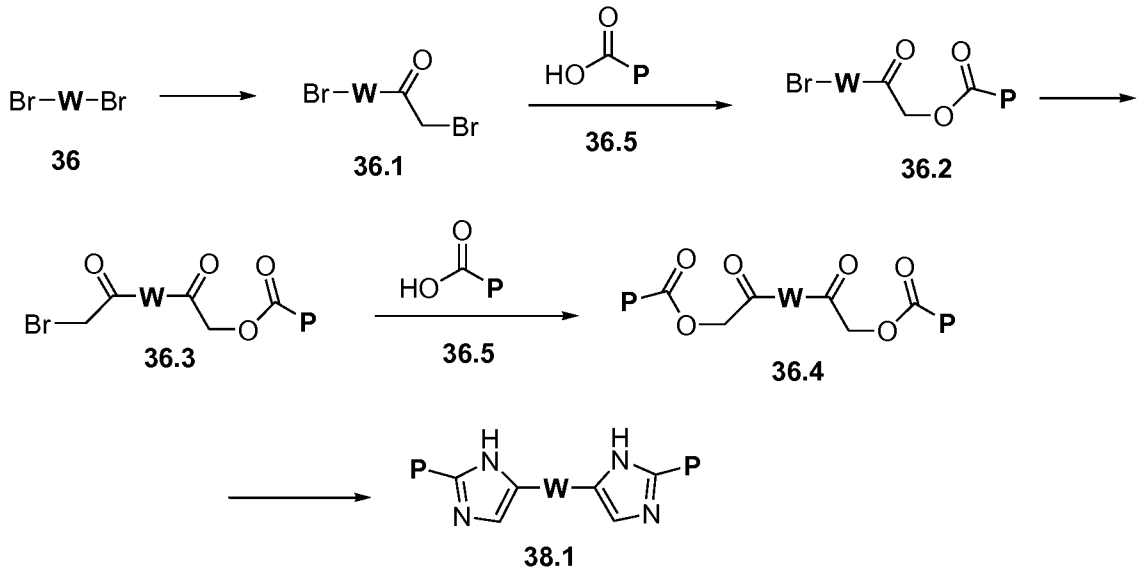
Scheme 8 shows a general synthesis of **P-M-W-M-P** molecule wherein, for illustrative purposes, **W** = polycyclic. Conversion of **36** to **37** was accomplished using transition metal-mediated reactions. Diboronic ester or acid **37** is coupled with a suitable reaction partner, such as bromide **37.1** using Suzuki coupling conditions to afford **38.**

Scheme 9: Representative synthesis of E-V-P-M-W-M-P-V-E



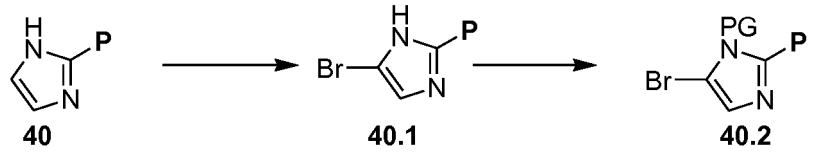
Scheme 9 shows a general synthesis of an **E-V-P-M-W-M-P-V-E** molecule wherein, for illustrative purposes, **P** = pyrrolidine and **Z** = carbonyl. Coupling of amine **38.1** with acid **34** is accomplished using a peptide coupling reagent, such as HATU, to afford **39.**

Scheme 9a: Representative synthesis of P-M-W-M-P



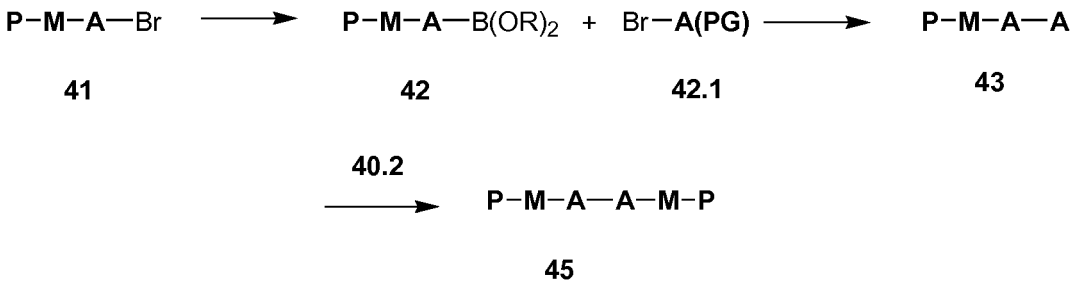
Scheme **9a** shows a general synthesis of a **P-M-W-M-P** molecule wherein, for illustrative purposes, **M** = imidazole, **W** = polycyclic. The compound **36** was coupled with a vinyltin reagent such as tributyl(ethoxyvinyl)stannane with palladium, followed by bromination and hydrolysis with NBS and water, to give bromoketone **36.1.** The reaction between bromide **36.1** and a carboxylic acid (**36.5**) under basic condition generated ester **36.2.** Following the same reaction sequence, compound **36.2** was converted to diester **36.4.** Conversion of **36.4** to **38.1** was accomplished with ammonia reagents such as ammonium acetate at elevated temperature.

Scheme 10: Representative synthesis of M-P



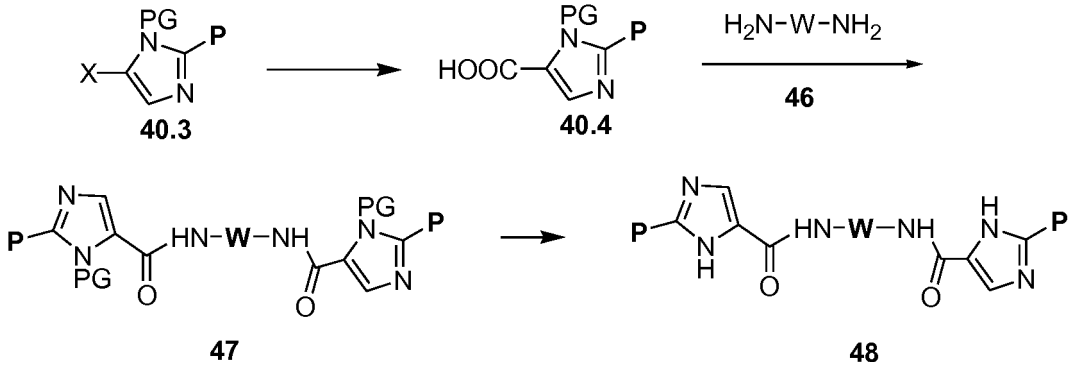
Scheme 10 shows a general synthesis of an **M-P** molecule wherein, for illustrative purposes, PG is a protecting group. Imidazole **40** can be halogenated, for example, under the action of N-bromosuccinimide to provide bromoimidazole **40.1.** Bromoimidazole **40.1** can be protected using standard conditions to give **40.2,** such as SEM-Cl and sodium hydride when PG = SEM.

Scheme 11: Representative synthesis of P-M-A-A-M-P



Scheme 11 shows a general synthesis of a **P-M-A-A-M-P** molecule wherein, for illustrative purposes, **M** = imidazole. Boronic ester **42,** which can be prepared from bromide **41,** is coupled with a suitably protected appropriate coupling partner (e.g. arylbromide **42.1,** optionally protected with PG) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **43.** Palladium mediated cross-coupling reactions that enable the **A-A** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada and Stille reactions. If optionally protected, removal of the protecting group (PG) (for example, catalytic hydrogenation of a benzyl ether) provides the deprotected compound **43.** Coupling of **43** with suitably protected imidazole **40.2** (for example, PG = SEM ether) using a metal catalyst (e.g. CuI) gives protected **P-M-A-A-M-P** (**45**). Deprotection (for example deprotection of a SEM ether using an acid such as TFA) provides the imidazole containing fragment **P-M-A-A-M-P 45.**

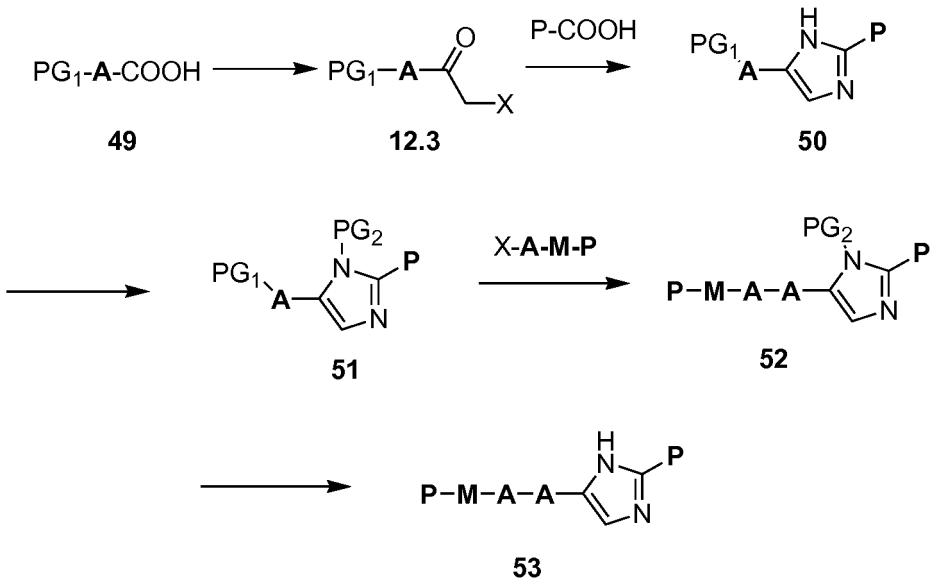
Scheme 12: Representative synthesis of P-M-W-M-P



Scheme 12 shows a general synthesis of a **P-M-W-M-P** molecule wherein, for illustrative purposes, **X** = halogen or triflate, **M** = imidazole, and **W** is **46,** PG = protecting group. Haloimdiazole **40.3,** such as a bromoimidazole, is subjected to a metal-halogen exchange reaction, such as BuLi in THF, and then treated with a CO_2 source, such as solid CO_2, to give **40.4.** Coupling of **40.4** and **46** using peptide coupling conditions, such as HATU, gives **47.** PG deprotection, such

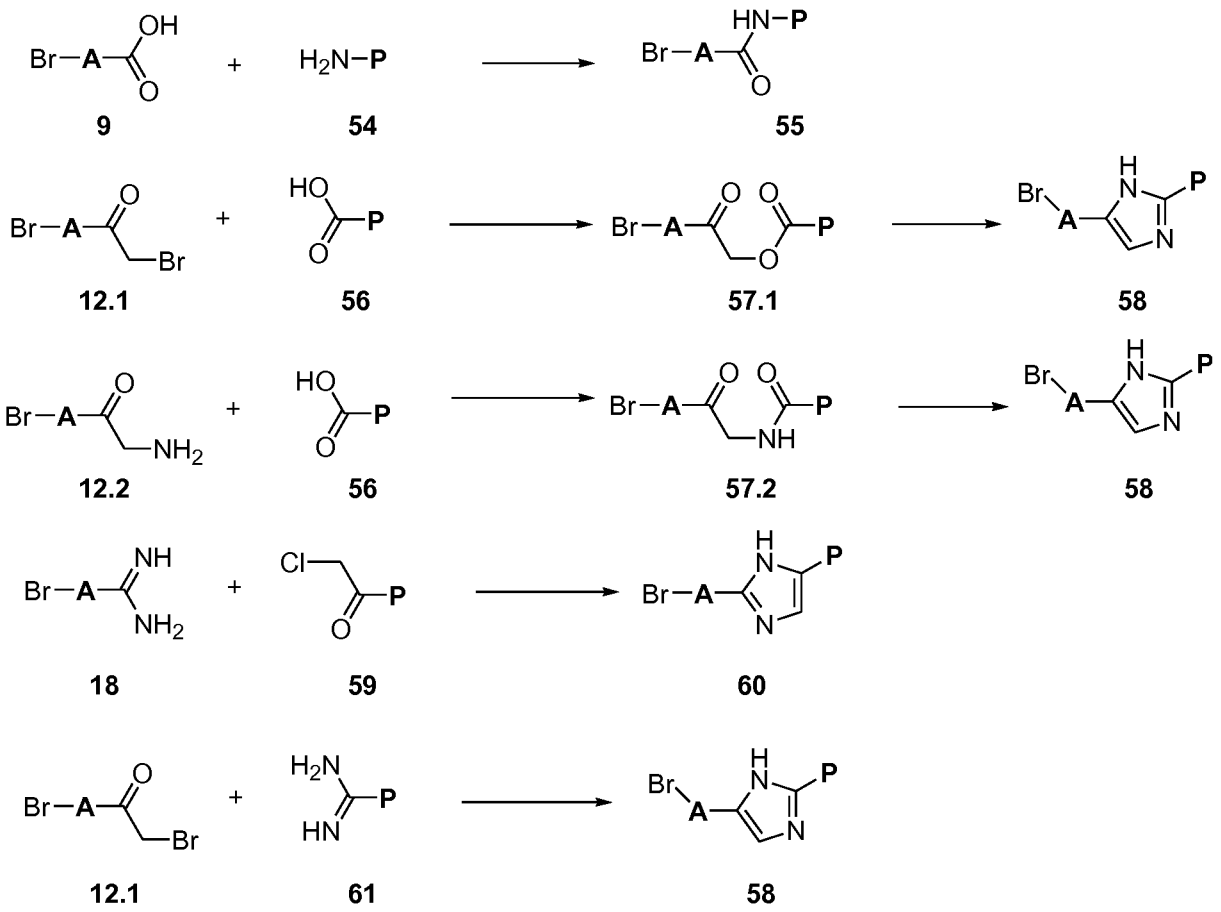
as TFA deprotection of a SEM group, gives the compound **P-M-W-M-P 48.**

Scheme 13: Representative synthesis of P-M-A-A-M-P



Scheme 13 shows a general synthesis of a **P-M-A-A-M-P** molecule wherein, for illustrative purposes, **X** = halogen, amine or triflate, **M** = imidazole, PG_1 and PG_2 = protecting groups. The protected acid **49** (PG1 is a suitable protecting group, such as Cbz) is converted to α-halomethyl ketone **12.3.,** which is then transformed to PG_1-**A-M-P 50** using the analogous conditions for converting **12.1** and **12.2** to **15.** The imidazole is subjected to protection, with SEM for instance, to afford **51,** which is deprotected, with H_2 and Pd to remove a Cbz for example, followed by coupling with fragment X-**A-M-P,** using standard Pd coupling conditions for example, to afford **52.** PG deprotection, such as TFA deprotection of a SEM group, gives the compound **P-M-A-A-M-P 53.**

Scheme 14: Representative synthesis of A-M-P

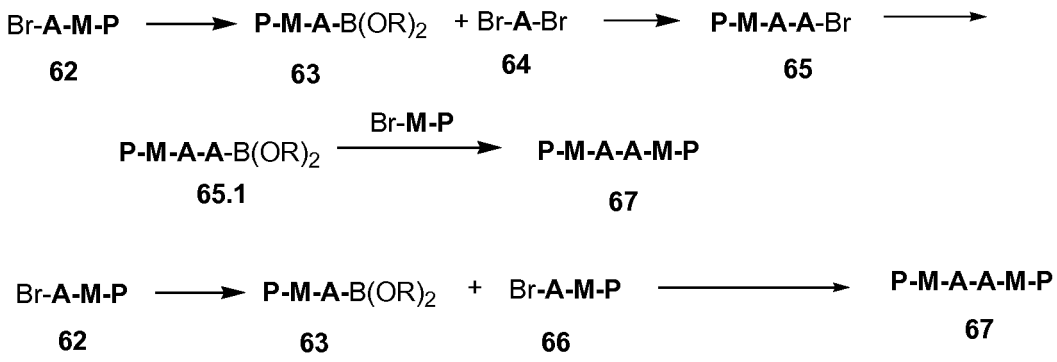


Scheme 14 shows a general synthesis of an **A-M-P** molecule wherein, for illustrative purposes, **M** is an amide bond, or an imidazole. Coupling of amine **54** with acid **9** is accomplished using a peptide coupling reagent (e.g. HATU) to afford amide containing **55.**

[0104] The acid **56** is coupled with an α-haloketone, such as α-bromoketone **12.1,** under basic conditions (e.g. Et_3N) to afford **57.1.** Alternatively, the acid **56** is coupled with an α-aminoketone **12.2,** under amide formation conditions (e.g. EDC, Et_3N) to afford **57.2.** Reaction of **57.1** and **57.2** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **A-M-P.**

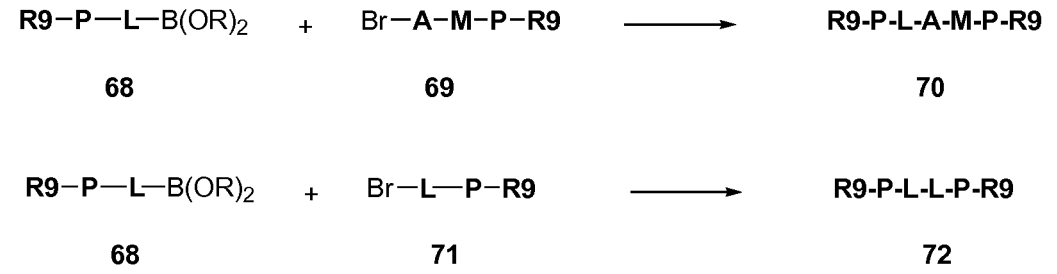
[0105] The benzamidine **18** is coupled with an α-haloketone such as α-chloroketone **59** under basic conditions such as K_2CO_3 to afford the imidazole containing molecule **A-M-P 60. A-M-P 58** can be prepared analogously.

Scheme 15: Representative synthesis of P-M-A-A-M-P



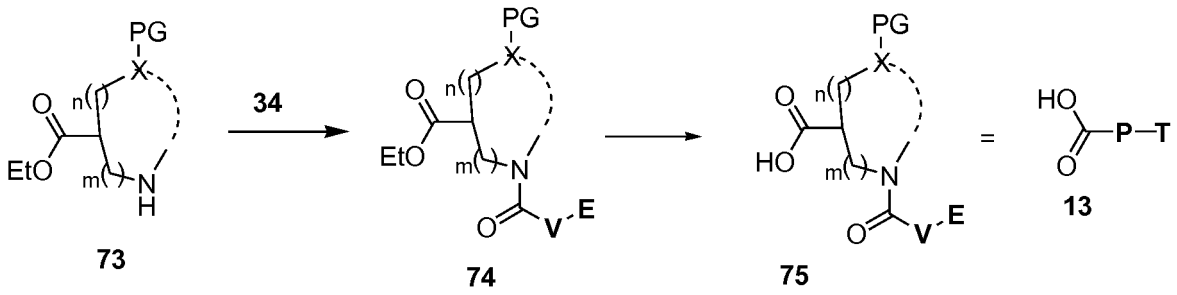
Scheme 15 shows a general synthesis of a **P-M-A-A-M-P** molecule. Boronic acid or its ester **63,** can be prepared from bromide **62** using a palladium catalyst (e.g. $Pd(PPh_3)_4$) and a boron reagent (bis(pinacolato)diboron, for example), is coupled with an excess of appropriate coupling partner (e.g. a di-halo-aromatic or di-halo-heteroaromatic moiety **64**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford bromide **65,** which then is converted to boronic acid or ester **65.1.** Palladium mediated cross-coupling reactions that enable the **A-A** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada and Stille reactions. Suzuki coupling of **65.1** with halo-imidazole such as bromo-imidazole using a palladium catalyst (such as $Pd(PPh_3)_4$) gives **P-M-A-A-M-P** fragment **67.** Alternatively, Suzuki coupling of 63 with halo-**A-M-P** fragment using a palladium catalyst (such as $Pd(PPh_3)_4$) gives **P-M-A-A-M-P** fragment **67.**

Scheme 16: Representative synthesis of R9-P-L-A-M-P-R9 and R9-P-L-L-P-R9



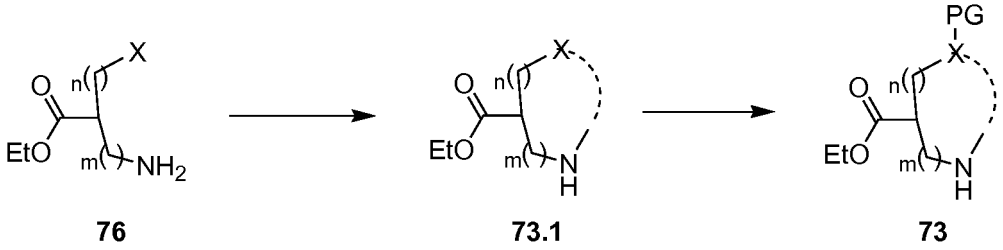
Scheme 16 shows a general synthesis of an **R9-P-L-A-M-P-R9** molecule and a **R9-P-L-L-P-R9** molecule wherein a transition metal-mediated cross-coupling reaction is utilized to construct the **A-A** bond. For illustrative purposes, the Suzuki reaction is employed to couple $(RO)_2B$-**L-P-R9** and Br-**A-M-P-R9.** Boronic ester **68** is coupled with an appropriate coupling partner (e.g. arylbromide **69**) using a palladium catalyst (such as $Pd(PPh_3)_4$) to afford **70.** Similarly, **R9-P-L-L-P-R9 72** is prepared by coupling compounds **68** and **71.**

Scheme 17: Representative synthesis of P-T



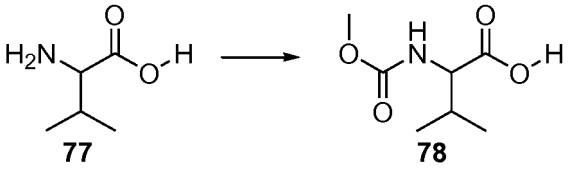
Scheme 17 shows a general synthesis of a **P-T** molecule wherein, for illustrative purposes, **P** = either an acyclic or cyclic amino ester (such as ethyl ester), optionally protected with PG if necessary, **Z** = carbonyl, **X** = carbon or heteroatom, and m and n = 0 - 5, independently. Coupling of amine **73** with acid **34** is accomplished using a peptide coupling reagent, such as HATU, to afford **75,** which after removal of ethyl group provides the **P-T** compound.

Scheme 18: Representative synthesis of P



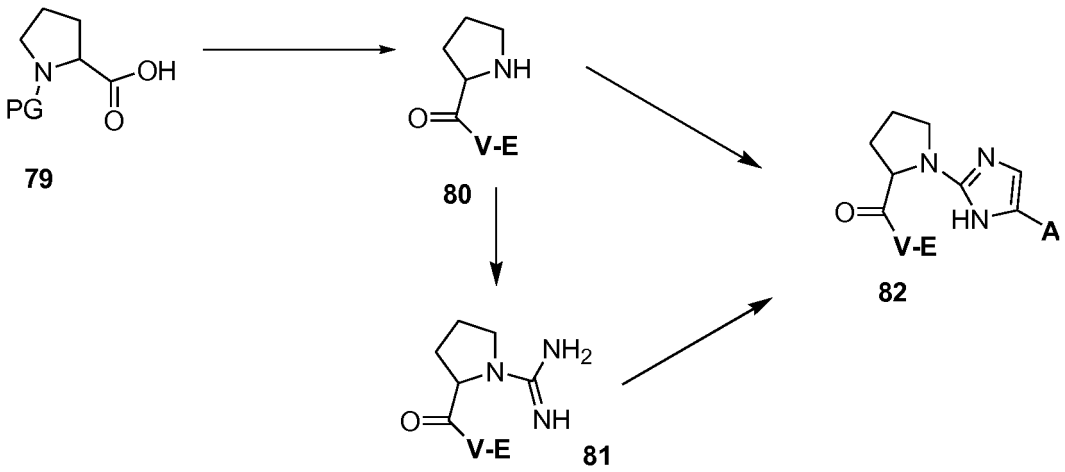
Scheme 18 shows a general synthesis of a **P** molecule wherein **X** = carbon or heteroatom and m and n = 0 - 5, independently. For illustrative purposes, **P** is substituted with an ethoxylcarbonyl group. Commercially available amino ester such an ethyl ester is converted to substituted or cyclized amino ester **73.1,** through for example, reductive amination or Mitsunobu reaction. Compound **73.1** can be protected to provide compound **73** if necessary.

Scheme 19: Representative Synthesis of E-V



Scheme 19 shows a general synthesis of an **E-V** molecule wherein, for illustrative purposes, **V** is isobutyl and **E** is methoxycarbonylamino. Amino acid **77** can be converted to the corresponding carbamate **78,** such as a methyl carbamate by reaction with methyl chloroformate under basic conditions (sodium bicarbonate).

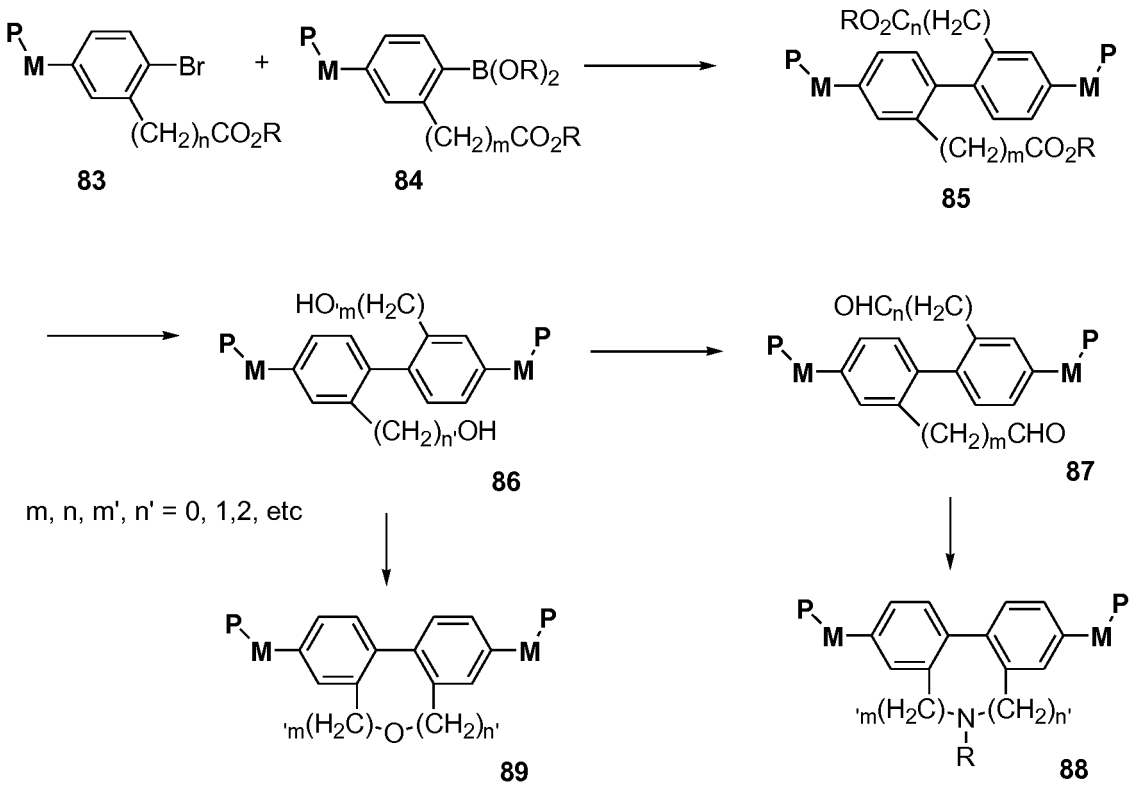
Scheme 20: Synthesis of the E-V-Z-P-M-A



Scheme 20 shows the synthesis of a **E-V-Z-P-M-A** molecule wherein, for illustrative purposes, **M** is imidazole, **P** is pyrrolidine, and **Z** is carbonyl. An amino acid derivative can be reacted with an N-protected proline derivative via reaction conditions employing a coupling reagent, such as HATU, deprotection of the resulting coupling product, for example in the case of *tert*-butoxy carbonyl, the treatment with a proton source such as HCl yielded compound **80.** The conversion of **80** to **E-V-Z-P-M-A** (**82**) can be obtained under reaction conditions of nucleophilic aromatic substitution, for example the displacement of methyl sulfonate under basic conditions and elevated temperatures.

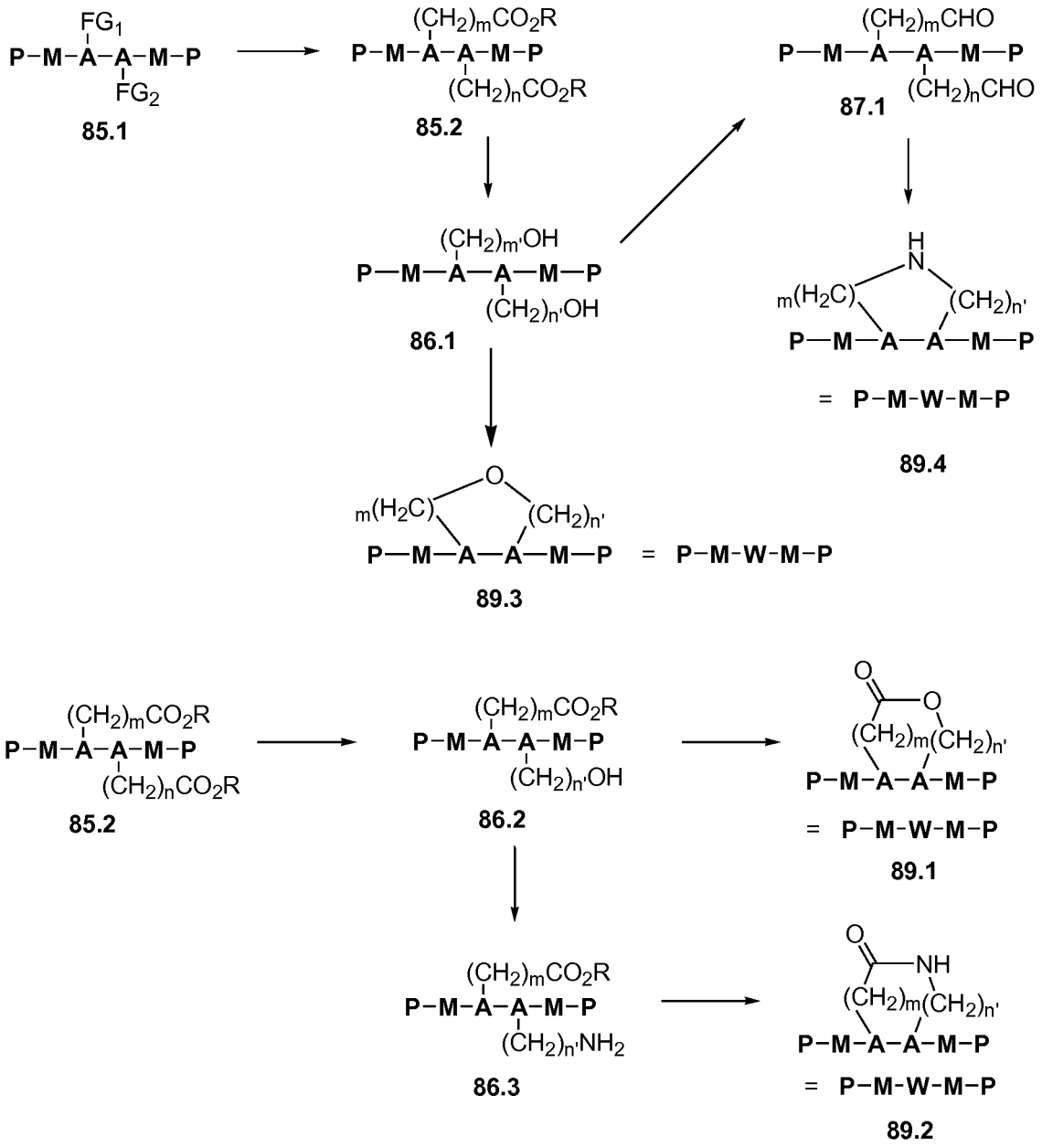
[0106] Alternatively, for illustrative purposes, the amino acid derivative **80** can be converted to a guanidinium containing compound **81,** via a reaction with a guanidylation reagent. The **E-V-Z-P-M-A** compound **82** can be obtained via reaction with a 1,2 di-electrophile such as an α-halogenated carbonyl group under basic conditions.

Scheme 21: Representative synthesis of P-M-W-M-P



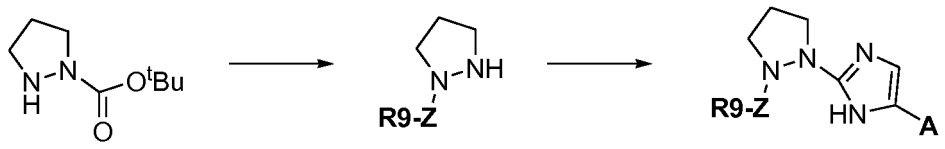
Scheme **21** shows a general synthesis of a **P-M-W-M-P** molecule wherein boronic ester **84** is coupled with an appropriate coupling partner (e.g. arylbromide **83**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **85.** Carboxylate **85** is reduced with reagents such as DIBAL-H to afford diol **86.** The treatment of diol **86** with acids such as H_3PO_4 at elevated temperature generates **P-M-W-M-P** compound **89.** Alternatively, **diol 86** can be oxidized with reagents such as pyridine-sulfur trioxide to form dialdehyde **87,** which react with amines in the presence of reducing reagents such as $NaBH(OAc)_3$ to provide **P-M-W-M-P** compound **88.**

Scheme 21a: Representative synthesis of P-M-W-M-P



Scheme **21a** shows a general synthesis of a **P-M-W-M-P** molecule. For illustrative purposes, FG_1 and FG_2 can be converted to esters attached to an **A** group. Carboxylate **85.2** is reduced with reagents, such as DIBAL-H, to afford diol **86.1.** The treatment of diol **86.1** with acids, such as H_3PO_4, at elevated temperature generates **P-M-W-M-P** compound **89.3.** Alternatively, diol **86.1** can be oxidized with reagents such as pyridine-sulfur trioxide to form dialdehyde **87.1,** which reacts with amines in the presence of reducing reagents such as $NaBH(OAc)_3$ to provide **P-M-W-M-P** compound **89.4.** The carboxylate **85.2** is selectively reduced to provide hydroxyl ester **86.2,** which can be cyclized to form **P-M-W-M-P** compound **89.1.** Compound **86.1** is converted to amine ester **86.3,** for example through azide formation and reduction with hydrogenation. Compound **86.3** can be cyclized to form **P-M-W-M-P** compound **89.2.**

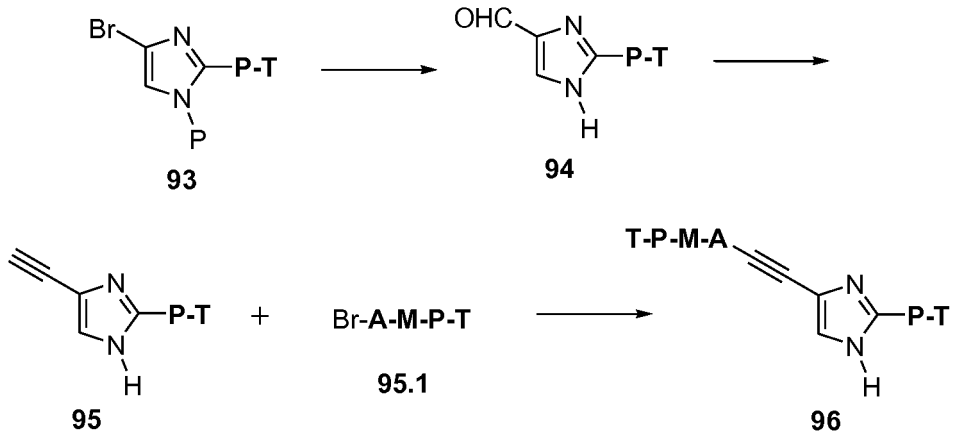
Scheme 22: Construction of a R9-Z-P-M-A



90 **91** **92**

Scheme 22 shows the general synthesis of a **R9-Z-P-M-A** molecule, for illustrative purposes starting with *tert*-butoxy carbonyl derivative **90** (J. Am. Chem. Soc. 2003, 1221). Compound **90** can be acylated with substituent **T** wherein **Z** is carbonyl, via reaction conditions employing a coupling reagent such as HATU. Removal of the protecting group, for example in the case of *tert*-butoxycarbonyl by the treatment with a proton source such as HCl, yields compound **91.** A compound like **91** can be obtained under reaction conditions of nucleophilic aromatic substitution, for example the displacement of methyl sulfonate under basic conditions and elevated temperatures to provide the **R9-Z-P-M-A** compound **92.** Alternatively, **91** can be converted into a guanidinium derivative. When suitably substituted, cyclization provides the **R9-Z-P-M-A** compound **92.**

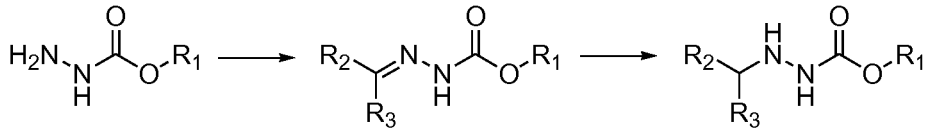
Scheme 23: Representative synthesis of T-P-M-A-A-M-P-T



93 **94** **95** **95.1** **96**

Scheme 23 shows a general synthesis of a **T-P-M-A-A-M-P-T** molecule wherein, for illustrative purposes, **M** = imidazole and **A** = alkyne. Bromoimidazole **93** is alkynylated by lithiation and trapping with a formate equivalent (e.g. DMF). The aldehyde **94** is converted to alkyne **95** using a phosphorus-based reagent (e.g. Ohira-Bestmann reagent). Compound **95** is coupled with a Br-**A-M-P-T** under Sonagashira conditions to afford the alkyne-containing compound **96.**

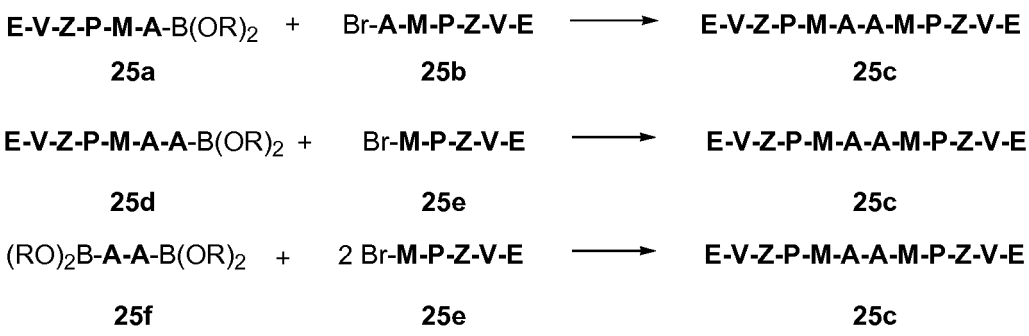
Scheme 24: Representative Synthesis of R9 Fragment



97 **98** **99**

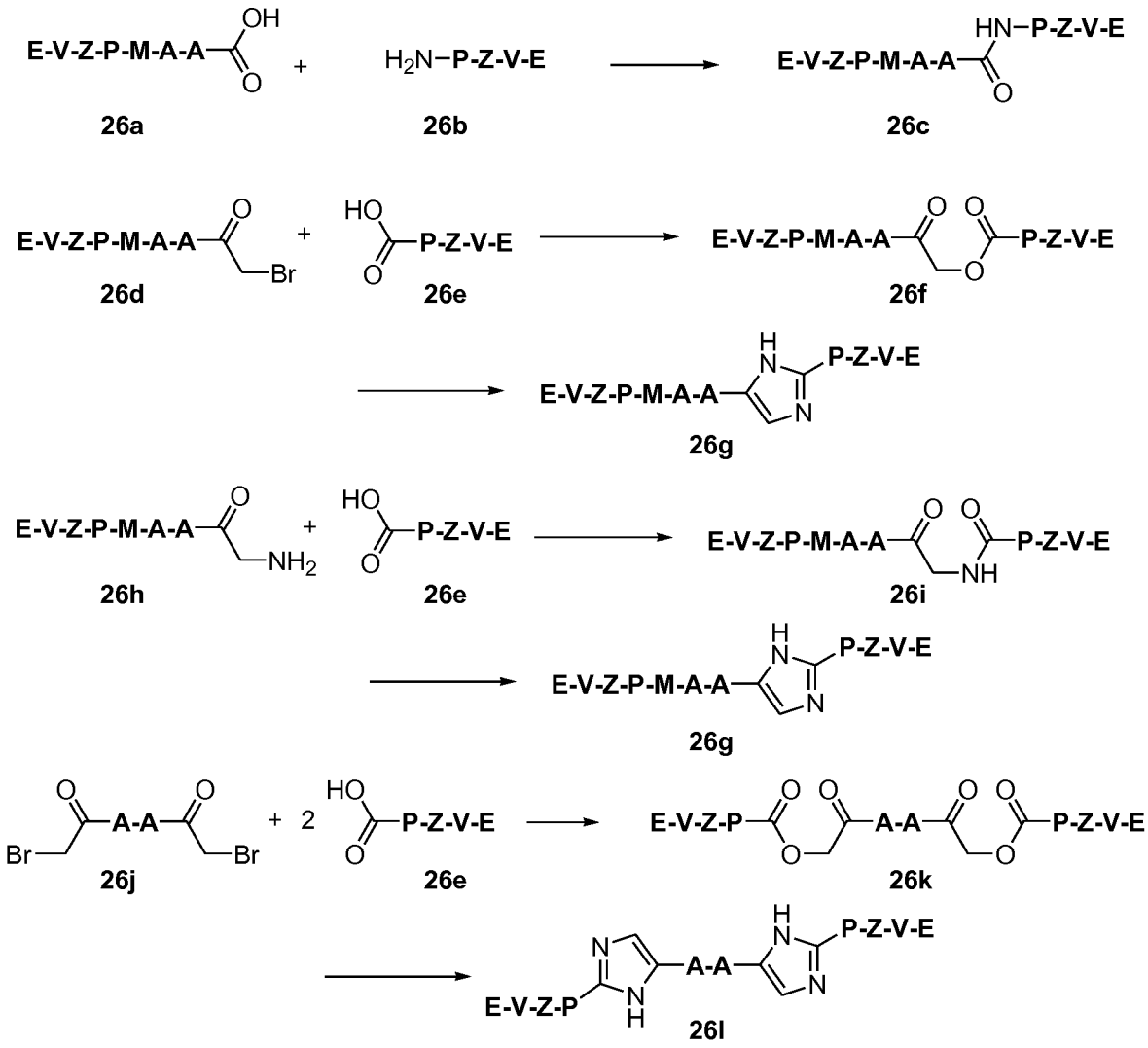
Scheme 24 shows a general synthesis of an **R9** molecule. Reaction of hydrazine carboxylate **97** with a ketone or aldehyde, such as acetone, under acidic conditions (e.g. AcOH) affords the imine **98.** Reaction of **98** under reducing conditions, such as PtO_2 and hydrogen gas, affords the substituted hydrazinecarboxylate **99.**

Scheme 25: Representative synthesis of E-V-Z-P-M-A-A-M-P-Z-V-E



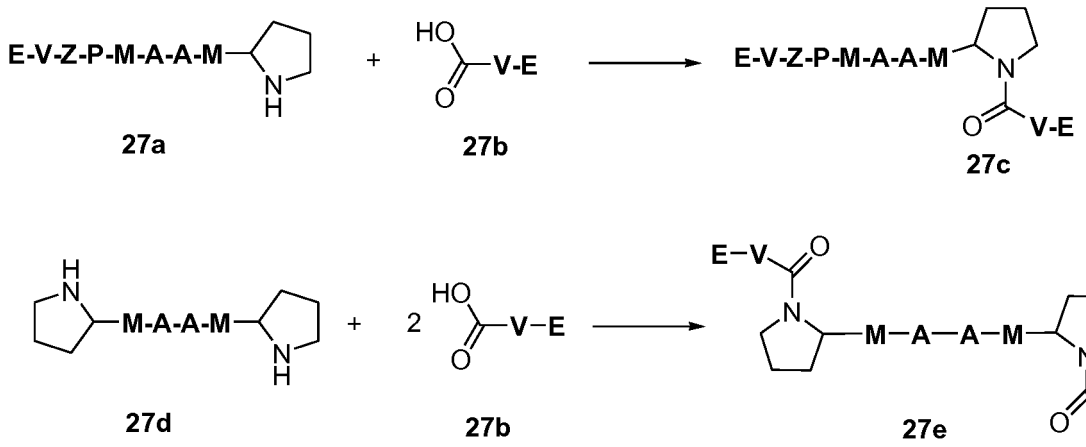
Scheme 25 shows a general synthesis of the **E-V-Z-P-M-A-A-M-P-Z-V-E** molecule, wherein a transition metal-mediated cross-coupling reaction is utilized to construct the **A-A** bond and/or **A-M** bond. For illustrative purposes, the Suzuki reaction is employed to couple **Br-M-P-Z-V-E** and $(RO)_2$B-**A-A-M-P-Z-V-E** or $(RO)_2$**B-A-M-P-Z-V-E and Br-A-M-P-Z-V-E.** Boronic ester **25a** (or **25d**) is coupled with an appropriate coupling partner (e.g. arylbromide **25b** or **25e**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **25c.** Formation of multiple A-M bonds can be conducted in a similar manner. For example, the Suzuki reaction can also be employed to couple $(RO)_2$B-**A-A**-B$(OR)_2$ (**25f**) and two equivalents of Br-**M-P-Z-V-E**. For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable the **A-A** and/or **A-M** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 26: Representative synthesis of E-V-Z-P-M-A-A-M-P-Z-V-E



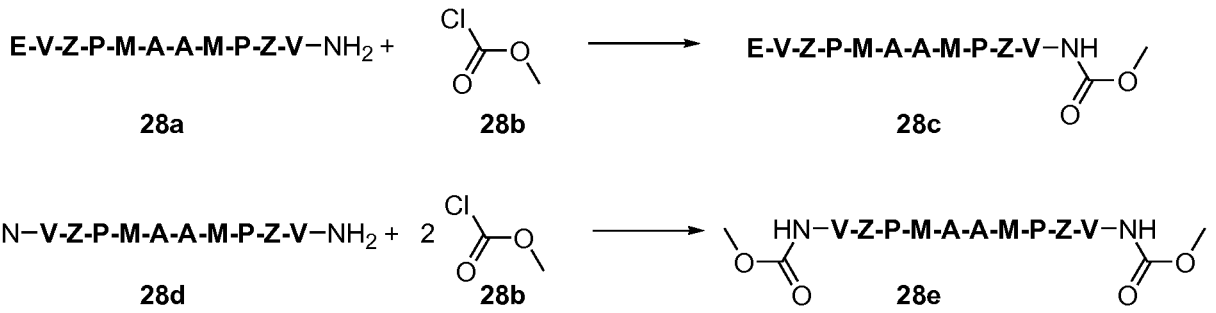
Scheme 26 shows a general synthesis of an **E-V-Z-P-M-A-A-M-P-Z-V-E** molecule wherein, for illustrative purposes, **M** is an amide, or an imidazole. Coupling of acid **26a** with amine **26b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford the amide product **26c.** The formation of an imidazole is accomplished by coupling the acid **26d** with an α-haloketone, such as α-bromoketone **26e,** under basic conditions (e.g. Et_3N) to afford **26f.** Alternatively, the acid **26d** is coupled with an α-aminoketone **26h,** under amide formation conditions (e.g. EDC, Et_3N) to afford **26i.** Reaction of **26f** or **26i** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing molecule **26g.** The formation of multiple imidazoles is performed in the same manner, starting with a bis- α-haloketone such as α-bromoketone **26j,** to provide molecule **26l.**

Scheme 27: Representative synthesis of E-V-Z-P-M-A-A-M-P-Z-V-E



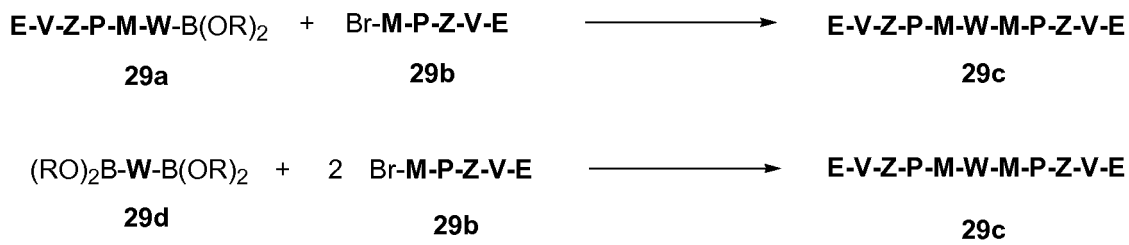
Scheme 27 shows a general synthesis of an **E-V-Z-P-M-A-A-M-P-Z-V-E** molecule wherein, for illustrative purposes, **P** is pyrrolidine and **Z** is a carbonyl. Coupling of amine **27a** with acid **27b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **27c.** Alternatively, amine **27d** is coupled with two equivalents of **27b** under similar conditions to provide **27e.**

Scheme 28: Representative synthesis of E-V-Z-P-M-A-A-M-P-Z-V-E



Scheme 28 shows a general synthesis of an **E-V-Z-P-M-A-A-M-P-Z-V-E** molecule wherein, for illustrative purposes, **E** is methoxycarbonylamino. The treatment of either **28a** or **28d** with one or two equivalents respectively of **28b** under basic conditions (e.g. sodium bicarbonate) provides the molecule **28c** or **28e.**

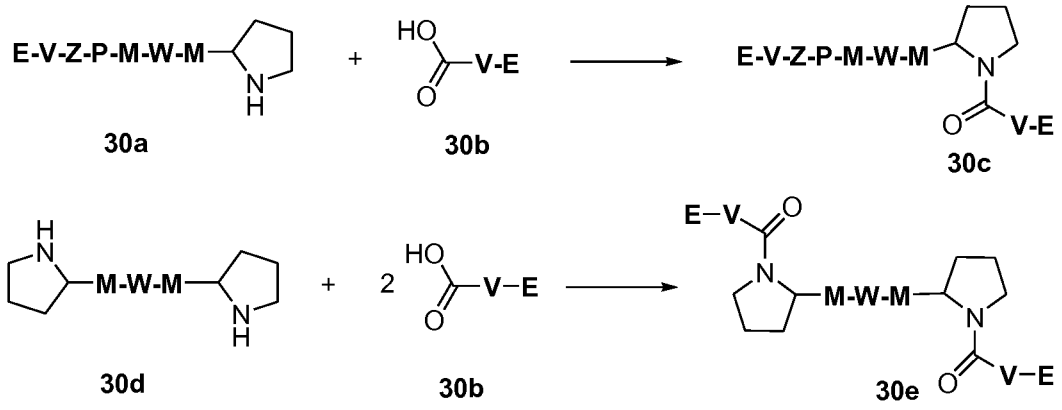
Scheme 29: Representative synthesis of E-V-Z-P-M-W-M-P-Z-V-E



Scheme 29 shows a general synthesis of the **E-V-Z-P-M-W-M-P-Z-V-E** molecule, wherein transition metal-mediated cross-coupling reaction is utilized to construct the **W-M** bond. For illustrative purposes, the Suzuki reaction is employed to couple **Br-M-P-Z-V-E** to a (RO)2B-**W-M-P-Z-V-E** or $(RO)_2$B-**W**-B$(OR)_2$ molecule. Boronic ester **29a** (or **29d**) is coupled with an appropriate coupling partner (e.g. arylbromide **29b**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **29c.** For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable the **M-W** bond

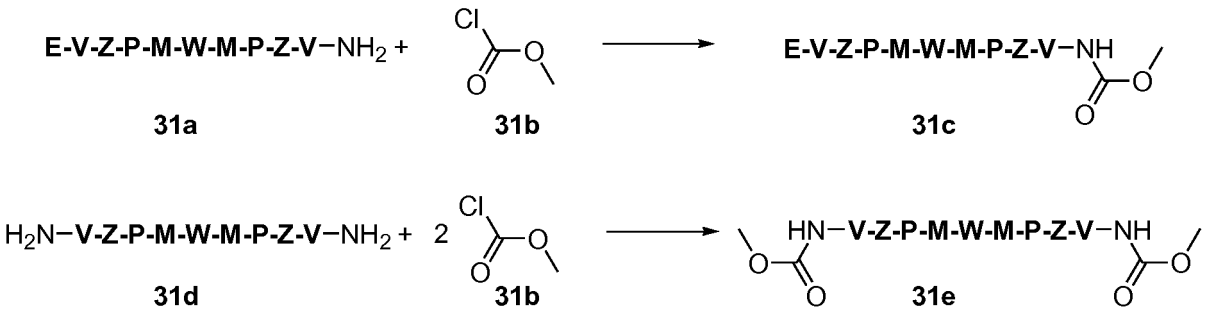
formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 30: Representative synthesis of E-V-Z-P-M-W-M-P-Z-V-E



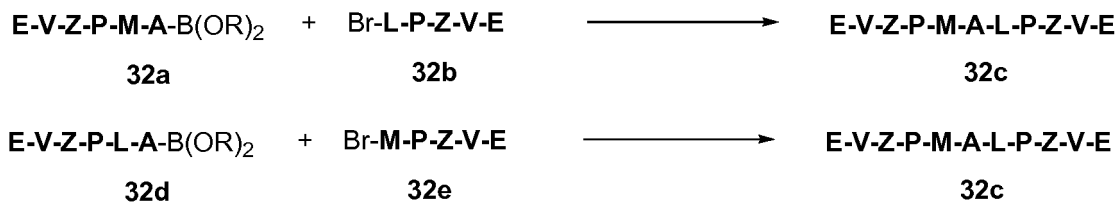
Scheme 30 shows a general synthesis of an **E-V-Z-P-M-W-M-P-Z-V-E** molecule wherein, for illustrative purposes, **P** is pyrrolidine and **Z** is a carbonyl. Coupling of amine **30a** with acid **30b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **30c.** Alternatively, amine **30d** is coupled with two equivalents of **30b** under similar conditions to provide **30e.**

Scheme 31: Representative synthesis of E-V-Z-P-M-W-M-P-Z-V-E



Scheme 31 shows a general synthesis of an **E-V-Z-P-M-W-M-P-Z-V-E** molecule wherein, for illustrative purposes, **E** is methoxycarbonylamino. The treatment of either **31a** or **31d** with one or two equivalents respectively of **31b** under basic conditions (e.g. sodium bicarbonate) provides the molecule **31c** or **31e.**

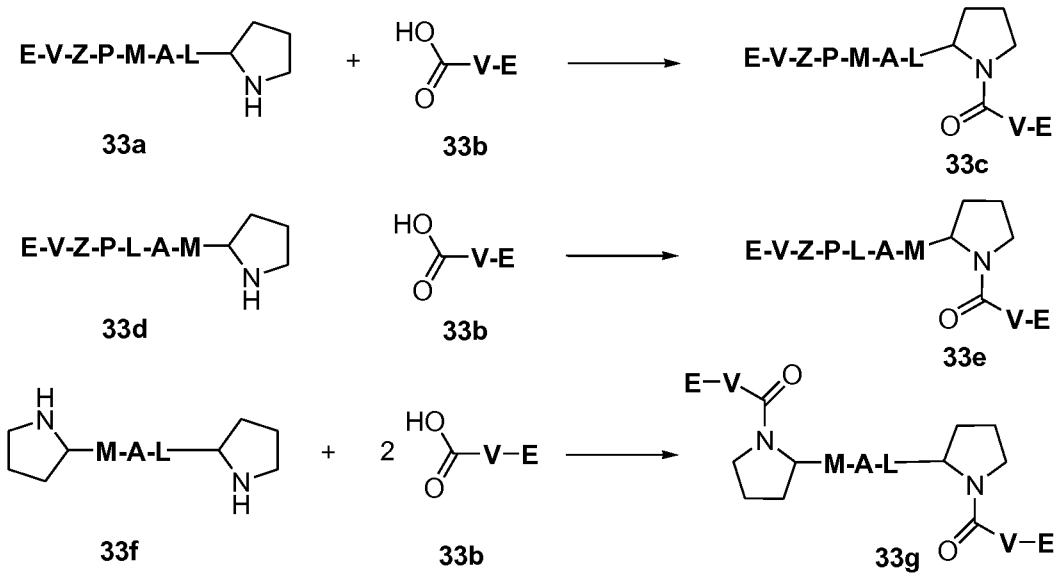
Scheme 32: Representative synthesis of E-V-Z-P-M-A-L-P-Z-V-E



Scheme 32 shows a general synthesis of the **E-V-Z-P-M-A-L-P-Z-V-E** molecule, wherein transition metal-mediated cross-coupling reaction is utilized to construct the **M-A** or **A-L** bond. For illustrative purposes, the Suzuki reaction is employed to couple a boronic ester to an arylbromide. Boronic ester **32a** (or **32d**) is coupled with an appropriate coupling

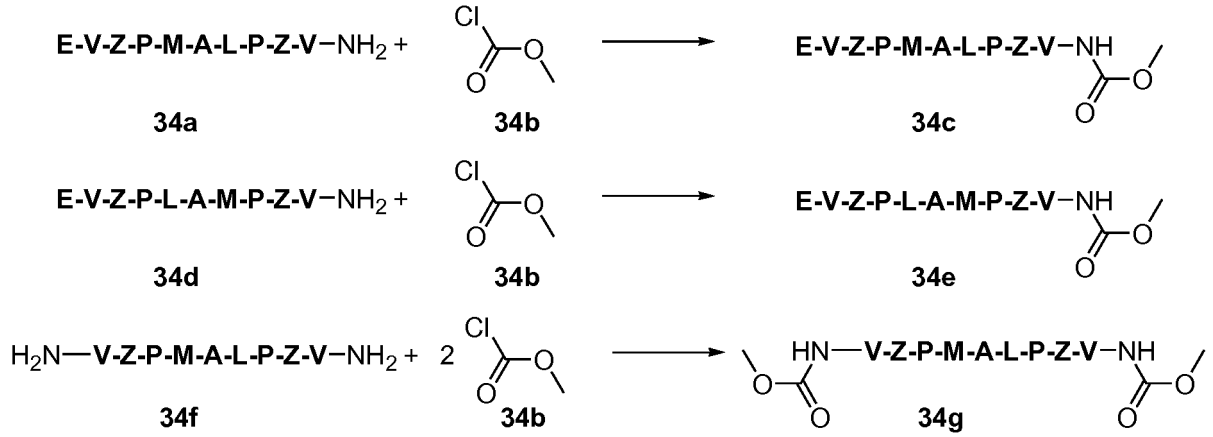
partner (e.g. arylbromide **32b** or **32e**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **32c.** For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable either the **M-A** or **A-L** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 33: Representative synthesis of E-V-Z-P-M-A-L-P-Z-V-E



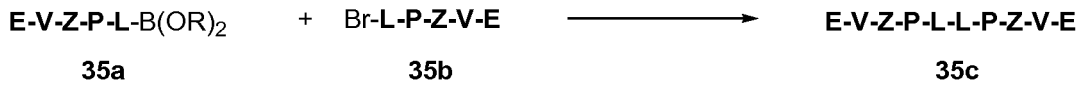
Scheme 33 shows a general synthesis of an **E-V-Z-P-M-A-L-P-Z-V-E** molecule wherein, for illustrative purposes, **P** is pyrrolidine and **Z** is a carbonyl. Coupling of amine **33a** or **33d** with acid **33b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **33c** or **33e,** respectively. Alternatively, amine **33f** is coupled with two equivalents of **33b** under similar conditions to provide **33g.**

Scheme 34: Representative synthesis of E-V-Z-P-M-A-L-P-Z-V-E



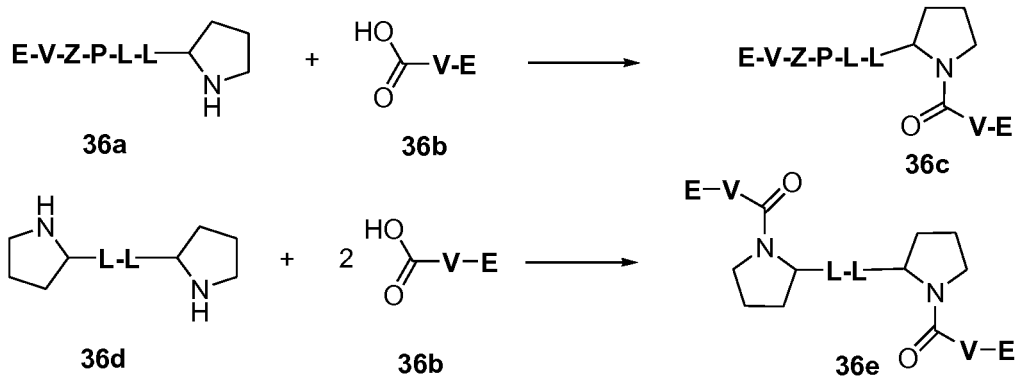
Scheme 34 shows a general synthesis of an **E-V-Z-P-M-A-L-P-Z-V-E** molecule wherein, for illustrative purposes, **E** is methoxycarbonylamino. The treatment of either **34a** or **34d** with **34b** under basic conditions (e.g. sodium bicarbonate) provides the molecule **34c** or **34e.** Correspondingly, the treatment of **34f** with two equivalents of **34b** provides **34g** under similar conditions.

Scheme 35: Representative synthesis of E-V-Z-P-L-L-P-Z-V-E



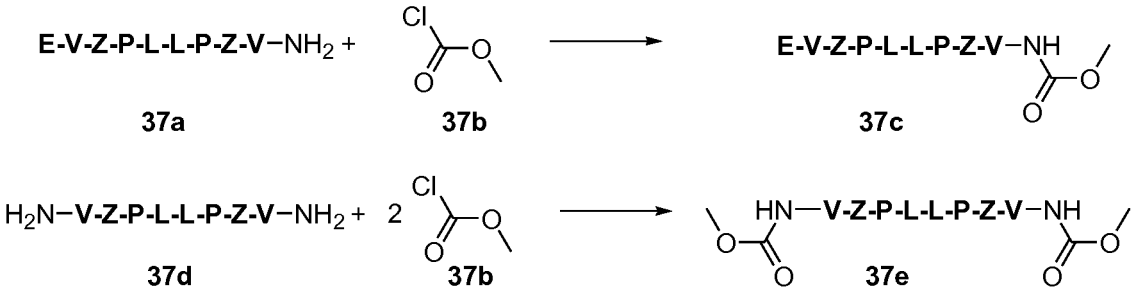
Scheme 35 shows a general synthesis of the **E-V-Z-P-L-L-P-Z-V-E** molecule, wherein transition metal-mediated cross-coupling reaction is utilized to construct the **L-L** bond. For illustrative purposes, the Suzuki reaction is employed to couple a boronic ester to an arylbromide. Boronic ester **35a** is coupled with an appropriate coupling partner (e.g. arylbromide **35b**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **35c.** For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable either the **L-L** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 36: Representative synthesis of E-V-Z-P-L-L-P-Z-V-E



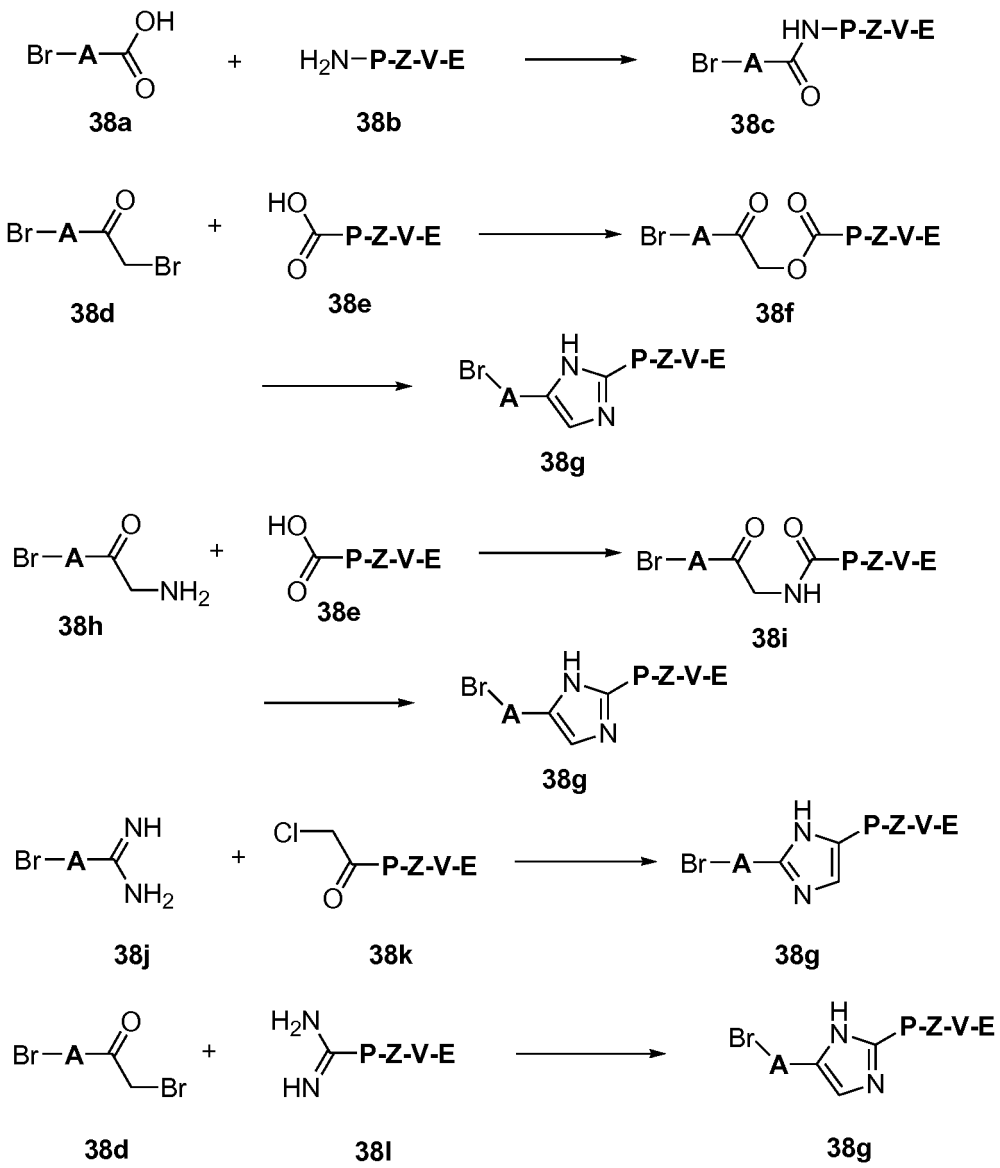
Scheme 36 shows a general synthesis of an **E-V-Z-P-L-L-P-Z-V-E** molecule wherein, for illustrative purposes, **P** is pyrrolidine and **Z** is a carbonyl. Coupling of amine **36a** with acid **36b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **36c.** Alternatively, amine **36d** is coupled with two equivalents of **36b** under similar conditions to provide **36e.**

Scheme 37: Representative synthesis of E-V-Z-P-L-L-P-Z-V-E



Scheme 37 shows a general synthesis of an **E-V-Z-P-L-L-P-Z-V-E** molecule wherein, for illustrative purposes, **E** is methoxycarbonylamino. The treatment of either **37a** or **37d** with **37b** under basic conditions (e.g. sodium bicarbonate) provides the molecule **37c** or **37e.**

Scheme 38: Representative synthesis of R-**A-M-P-**R^1

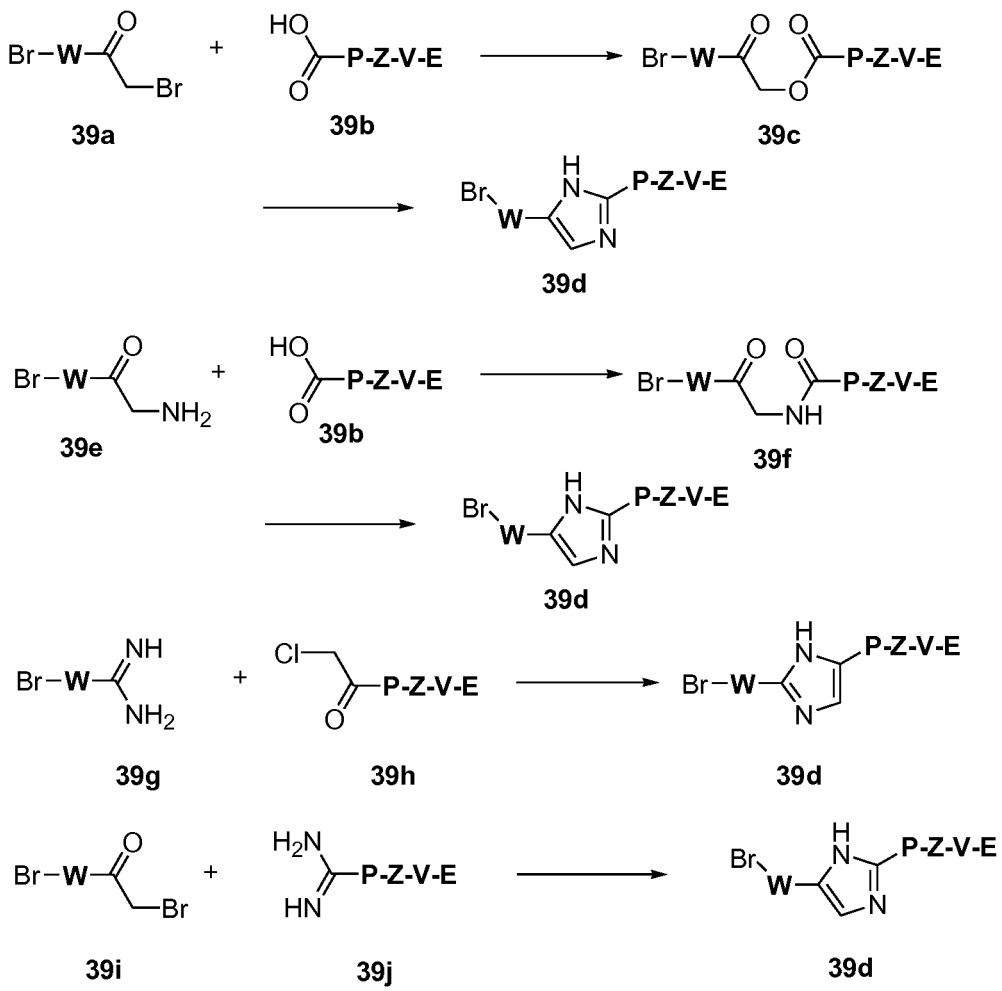


Scheme 38 shows a general synthesis of an R-**A-M-P-**R^1 intermediate wherein, for illustrative purposes, **M** is an amide or an imidazole, R is a generic group that is depicted as Br, and R^1 is a generic group that is depicted as **-Z-V-E.** Coupling of amine **38b** with acid **38a** is accomplished using a peptide coupling reagent (e.g. HATU) to afford amide containing **38c.**

[0107] The acid **38e** is coupled with an α-haloketone, such as α-bromoketone **38d,** under basic conditions (e.g. Et_3N) to afford **38f.** Alternatively, the acid **38e** is coupled with an α-aminoketone **38h,** under amide formation conditions (e.g. EDC, Et_3N) to afford **38i.** Reaction of **38f** or **38i** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing intermediate Br-**A-M-P-Z-V-E** (**38g**).

[0108] The benzamidine **38j** is coupled with an α-haloketone such as α-chloroketone **38k** under basic conditions such as K_2CO_3 to afford **38g.** The Br-**A-M-P-Z-V-E** intermediate can be prepared analogously from the coupling of **38d** and **38l.**

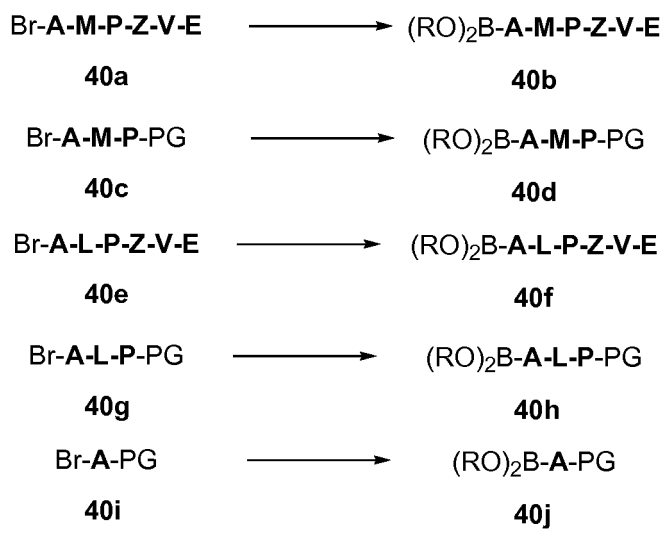
Scheme 39: Representative synthesis of R-W-M-P-R^1



Scheme 39 shows a general synthesis of an R-**W-M-P**-R^1 intermediate wherein, for illustrative purposes, **M** is an amide or an imidazole, R is a generic group that is depicted as Br, and R^1 is a generic group that is depicted as **-Z-V-E.** The acid **39b** is coupled with an α-haloketone, such as α-bromoketone **39a,** under basic conditions (e.g. Et_3N) to afford **39c.** Alternatively, the acid **39b** is coupled with an α-aminoketone **39e,** under amide formation conditions (e.g. EDC, Et_3N) to afford **39f.** Reaction of **39c** or **39f with** an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing intermediate Br-**A-M-P-Z-V-E** (**39d**).

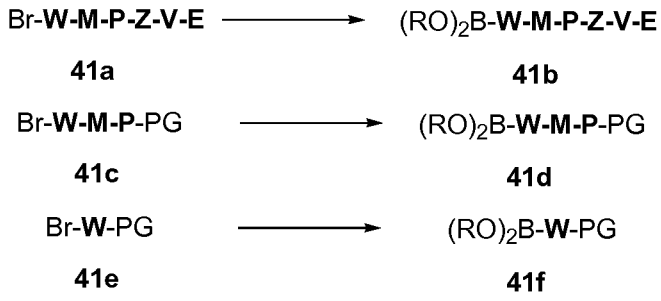
[0109] The benzamidine **39g** is coupled with an α-haloketone such as α-chloroketone **39h** under basic conditions such as K_2CO_3 to afford **39d.** The **Br-A-M-P-Z-V-E** intermediate can be prepared analogously from the coupling of **39i** and **39j.**

Scheme 40: Representative synthesis of R-A-R^1



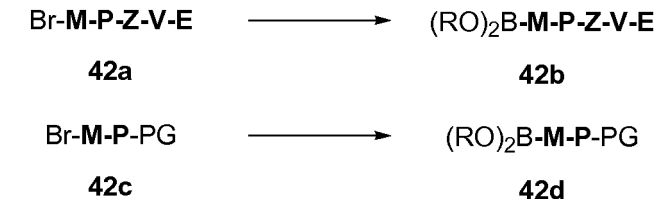
Scheme 40 shows a general synthesis of an R-A-R^1 intermediate wherein, for illustrative purposes, R is a generic group that is depicted as a boronic ester and R^1 is a generic group that is depicted as **-M-P-Z-V-E,** -M-**P**-PG, **-L-P-Z-V-E, -L-P-**PG, or a protecting group. A transition metal-mediated cross-coupling reaction is utilized to install the boronic ester on an **A** group. Treatment of the corresponding arylbromide with a palladium catalyst, such as $PdCl_2$(dppf), and a boron source such as bis(pinacolato)diborane provides the boronic ester **40b, 40d, 40f, 40h,** or **40j.**

Scheme 41: Representative synthesis of R-W-R^1



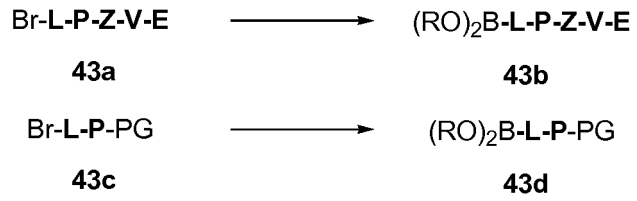
Scheme 41 shows a general synthesis of an R-**W**-R^1 intermediate wherein, for illustrative purposes, R is a generic group that is depicted as a boronic ester and R^1 is a generic group that is depicted as **-M-P-Z-V-E, -M-P-**PG, or a protecting group. A transition metal-mediated cross-coupling reaction is utilized to install the boronic ester on a **W** group. Treatment of the corresponding arylbromide with a palladium catalyst, such as $PdCl_2$(dppf), and a boron source such as bis(pinacolato)diborane provides the boronic ester **41b, 41d,** or **41f.**

Scheme 42: Representative synthesis of R-M-R^1



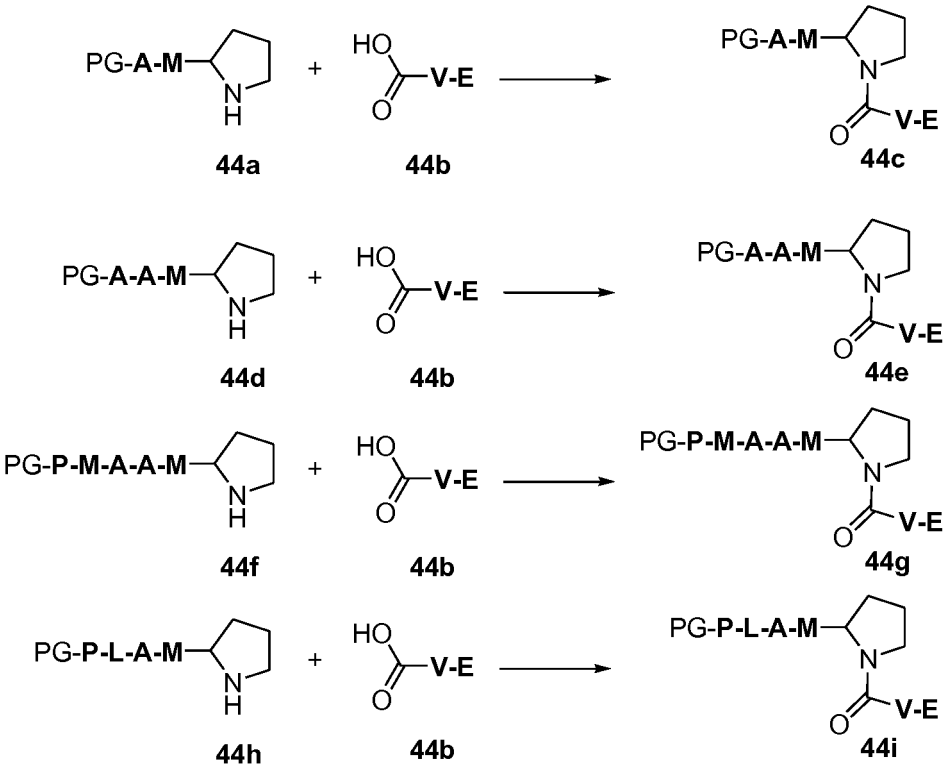
Scheme 42 shows a general synthesis of an R-**M**-R^1 intermediate wherein, for illustrative purposes, R is a generic group that is depicted as a boronic ester and R^1 is a generic group that is depicted as **-P-Z-V-E** or **-P**-PG. A transition metal-mediated cross-coupling reaction is utilized to install the boronic ester on an **M** group. Treatment of the corresponding arylbromide with a palladium catalyst, such as $PdCl_2$(dppf), and a boron source such as bis(pinacolato)diborane provides the boronic ester **42b** or **42d.**

Scheme 43: Representative synthesis of R-L-R^1



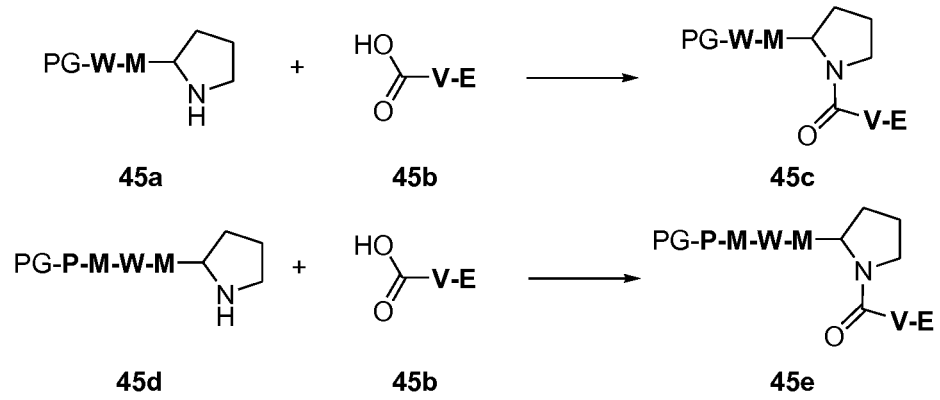
Scheme 43 shows a general synthesis of an R-**L**-R^1 intermediate wherein, for illustrative purposes, R is a generic group that is depicted as a boronic ester and R^1 is a generic group that is depicted as **-P-Z-V-E** or **-P**-PG. A transition metal-mediated cross-coupling reaction is utilized to install the boronic ester on an **L** group. Treatment of the corresponding arylbromide with a palladium catalyst, such as $PdCl_2$(dppf), and a boron source such as bis(pinacolato)diborane provides the boronic ester **43b** or **43d.**

Scheme 44: Representative synthesis of R-A-M-P-Z-V-E



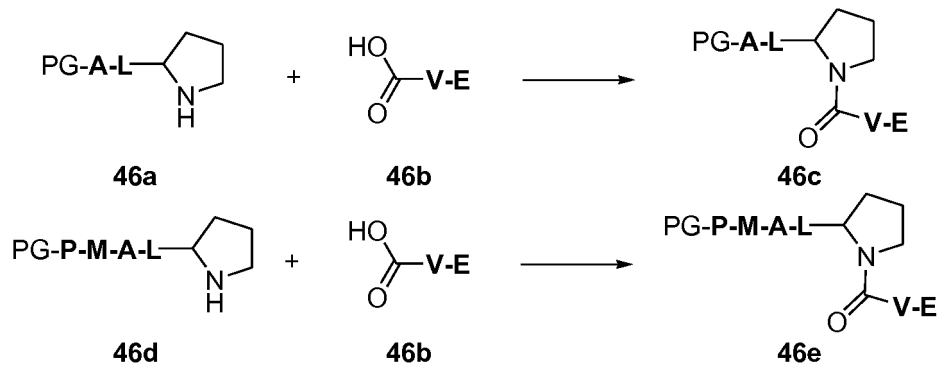
Scheme 44 shows a general synthesis of an R-**A-M-P-Z-V-E** intermediate wherein, for illustrative purposes, **P** is pyrrolidine, **Z** is carbonyl, and R is a generic group that is depicted as either **-A**-PG, **-A-M-P**-PG, **-L-P-**PG, or a protecting group. Coupling of amine **44a, 44d, 44f,** or **44h** with acid **44b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **44c, 44e, 44g,** or **44i,** respectively.

Scheme 45: Representative synthesis of R-W-M-P-Z-V-E



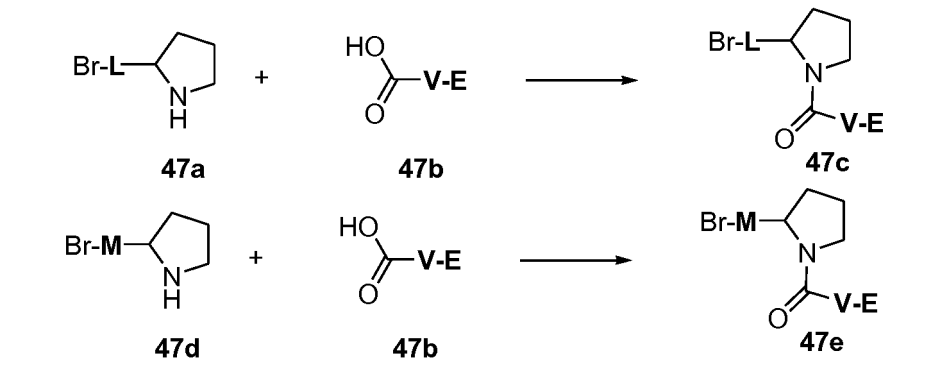
Scheme 45 shows a general synthesis of an R-**W-M-P-Z-V-E** intermediate wherein, for illustrative purposes, **P** is pyrrolidine, **Z** is carbonyl, and R is a generic group that is depicted as either **-M-P-**PG or a protecting group. Coupling of amine **45a** or **45d** with acid **45b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **45c** or **45e,** respectively.

Scheme 46: Representative synthesis of R-A-L-P-Z-V-E



Scheme 46 shows a general synthesis of an R-**A-L-P-Z-V-E** intermediate wherein, for illustrative purposes, **P** is pyrrolidine, **Z** is carbonyl, and R is a generic group that is depicted as either **-M-P**-PG or a protecting group. Coupling of amine **46a** or **46d** with acid **46b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **46c** or **46e**, respectively.

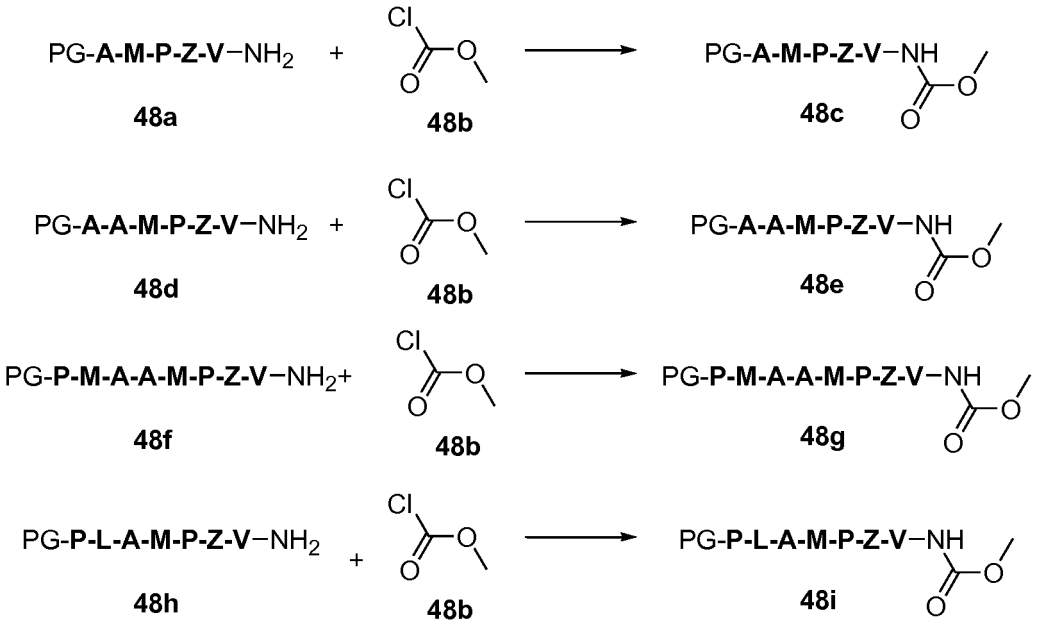
Scheme 47: Representative synthesis of R-L-P-Z-V-E and R-M-P-Z-V-E



Scheme 47 shows a general synthesis of an R-**L-P-Z-V-E** or R-**M-P-Z-V-E** intermediate wherein, for illustrative purposes,

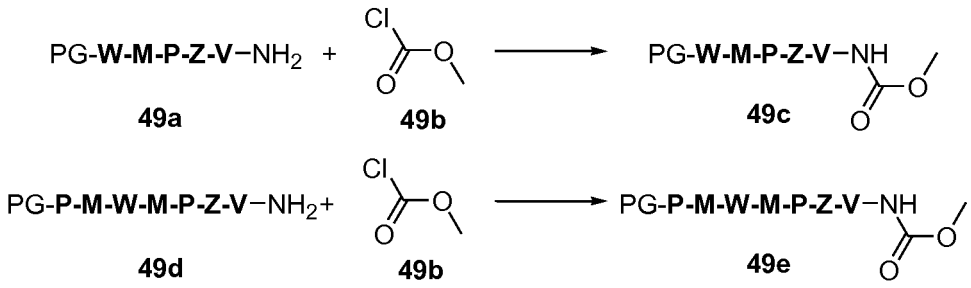
P is pyrrolidine, **Z** is carbonyl, and R is a generic group that is depicted as Br. Coupling of amine **47a** or **47d** with acid **47b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **47c** or **47e,** respectively.

Scheme 48: Representative synthesis of R-A-M-P-Z-V-E



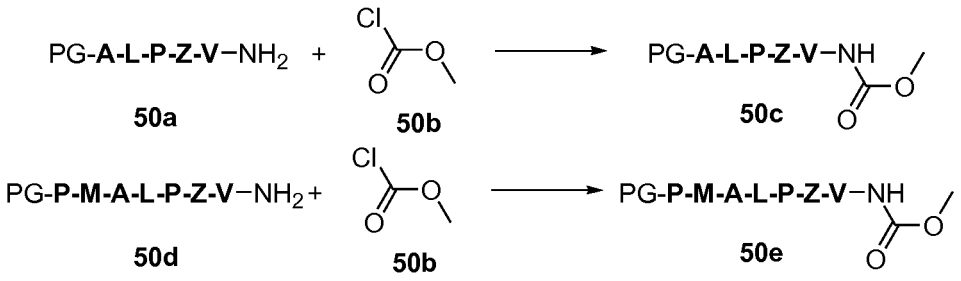
Scheme 48 shows a general synthesis of an R**-A-M-P-Z-V-E** intermediate wherein, for illustrative purposes, **E** is methoxycarbonylamino and R is a generic group that is depicted as a either **-A-**PG, **-A-M-P-**PG, **-L-P-**PG, or a protecting group. Treatment of **48a**, **48d, 48f,** or **48h** with **48b** under basic conditions (e.g. sodium bicarbonate) provides the intermediate **48c, 48e, 48g,** or **48i,** respectively.

Scheme 49: Representative synthesis of R-W-M-P-Z-V-E



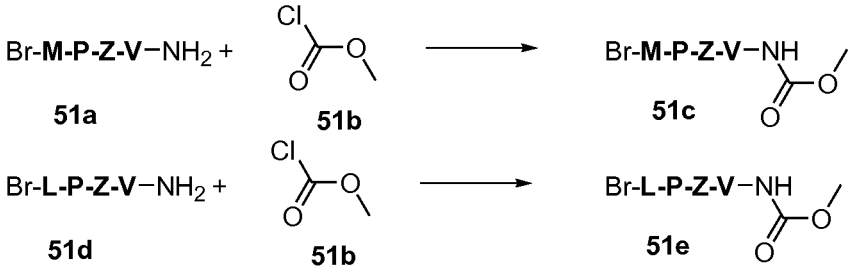
Scheme 49 shows a general synthesis of an R**-W-M-P-Z-V-E** intermediate wherein, for illustrative purposes, **E** is methoxycarbonylamino and R is a generic group that is depicted as either **-M-P-**PG or a protecting group. Treatment of **49a** or **49d** with **49b** under basic conditions (e.g. sodium bicarbonate) provides the intermediate **49c** or **49e,** respectively.

Scheme 50: Representative synthesis of R-A-L-P-Z-V-E



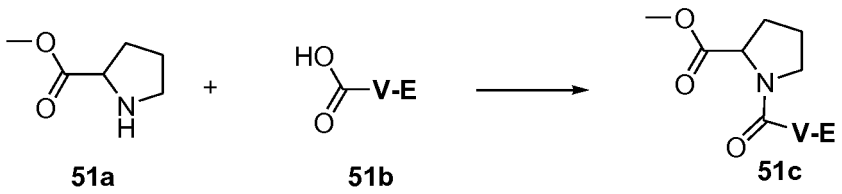
Scheme 50 shows a general synthesis of an R-**A-L-P-Z-V-E** intermediate wherein, for illustrative purposes, **E** is methoxycarbonylamino and R is a generic group that is depicted as a either **-M-P**-PG or a protecting group. Treatment of **50a** or **50d** with **50b** under basic conditions (e.g. sodium bicarbonate) provides the intermediate **50c** or **50e**, respectively.

Scheme 51: Representative synthesis of R-A-L-P-Z-V-E



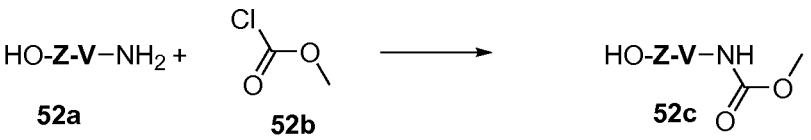
Scheme 51 shows a general synthesis of an R-**L-P-Z-V-E** or R-**M-P-Z-V-E** intermediate wherein, for illustrative purposes, **E** is methoxycarbonylamino and R is a generic group that is depicted as a Br. Treatment of **51a** or **51d** with **51b** under basic conditions (e.g. sodium bicarbonate) provides the intermediate **51c** or **51e**, respectively.

Scheme 51a: Representative synthesis of R-P-Z-V-E



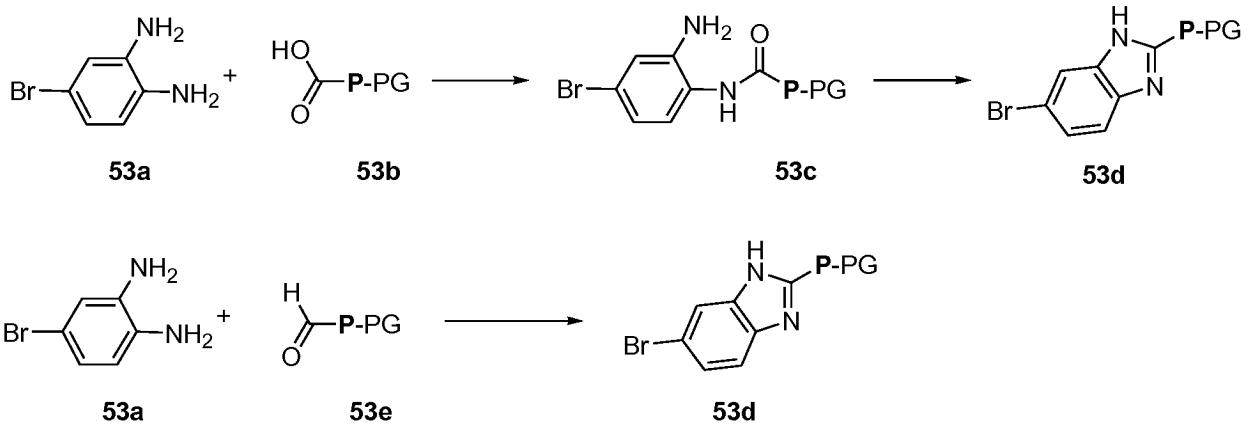
Scheme 51a shows a general synthesis of an R-**P-Z-V-E** intermediate wherein, for illustrative purposes, **P** is pyrrolidine, **Z** is carbonyl, and R is a generic group that is depicted as a methoxycarbonyl. Coupling of amine **51a** with acid **51b** is accomplished using a peptide coupling reagent (e.g. HATU) to afford **51c.**

Scheme 52: Representative synthesis of R-Z-V-E



Scheme 52 shows a general synthesis of an R-**Z-V-E** intermediate wherein, for illustrative purposes, **E** is methoxycarbonylamino and R is a generic group that is depicted as a hydroxyl. Treatment of **52a** under basic conditions (e.g. sodium bicarbonate) with **52b** provides the intermediate **52c.**

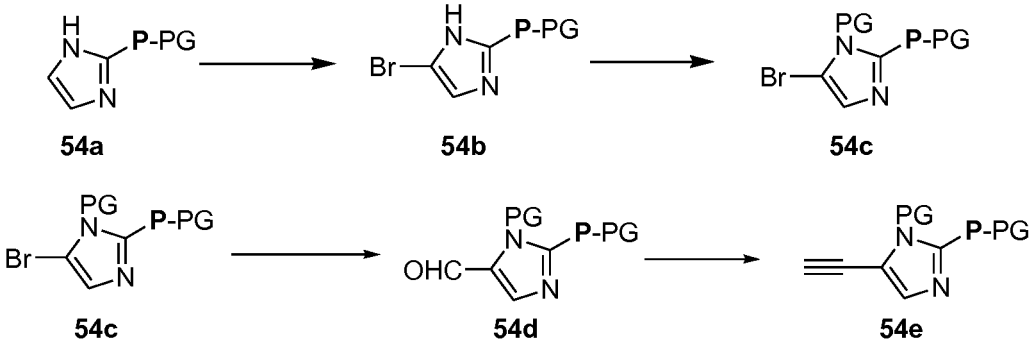
Scheme 53: Representative synthesis of R-L-P-R^1



Scheme 53 shows a general synthesis of an R-**L-P**-R^1 intermediate wherein, for illustrative purposes, **L** is benzimidazole, R is a generic group that is depicted as a bromide, and R^1 is a protecting group. The acid **53b** is coupled with **53a** using a peptide coupling reagent such as HATU to afford **53c.** Heating in solvent (such as refluxing ethanol) affords the R-**L-P-**R^1 intermediate **53d.**

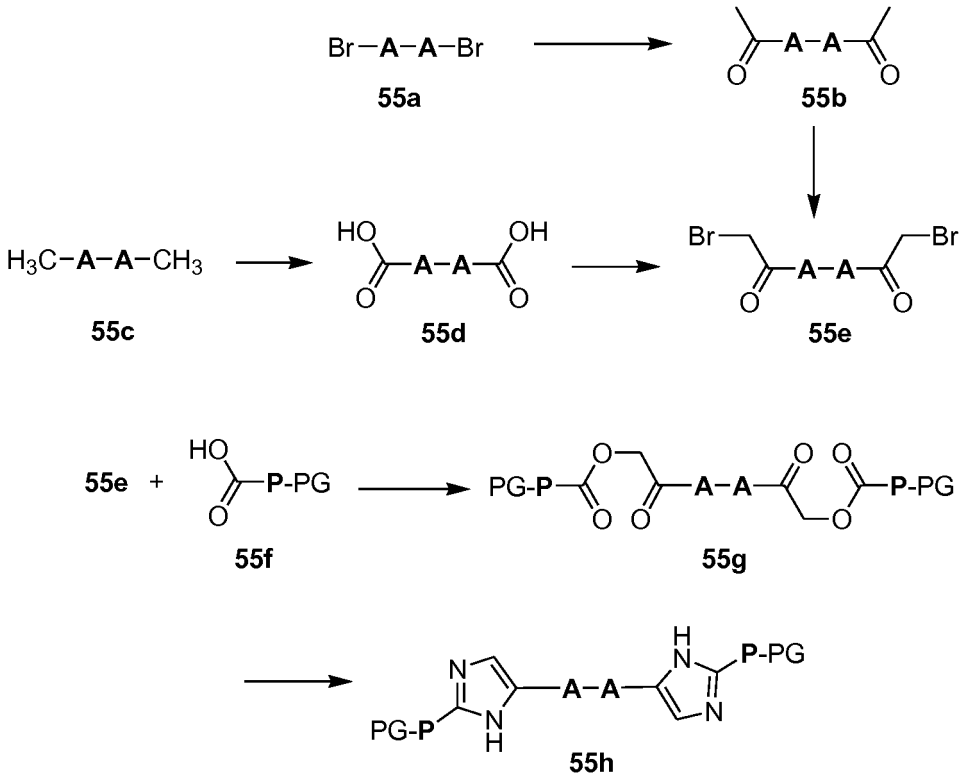
[0110] Alternatively, the R-**L-P**-R^1 intermediate **53d** is obtained by reaction of a diamine (such as **53a**) and carbonyl compound (such as aldehyde **53e**) in a solvent under heating conditions (e.g. ethanol under microwave irradiation).

Scheme 54: Representative synthesis of R-M-P-R^1



Scheme 54 shows a general synthesis of an R-**M-P**-R^1 intermediate wherein, for illustrative purposes, **M** is imidazole, R is a generic group that is depicted as a bromide, aldehyde, or alkyne and R^1 is a protecting group. Imidazole **54a** can be halogenated, for example, under the action of N-bromosuccinimide to provide bromoimidazole **54b.** Bromoimidazole 54b can be protected using standard conditions to give **54c**, such as SEM-Cl and sodium hydride when PG = SEM. The bromoimidazole **54b** can be further elaborated, for example, to the corresponding aldehyde or alkyne. Lithiation of **54c** and condensation with a formate equivalent (e.g. DMF) provides the aldehyde **54d.** The aldehyde **54d** is converted to alkyne **54e** using a phosphorus-based reagent (e.g. Ohira-Bestmann reagent).

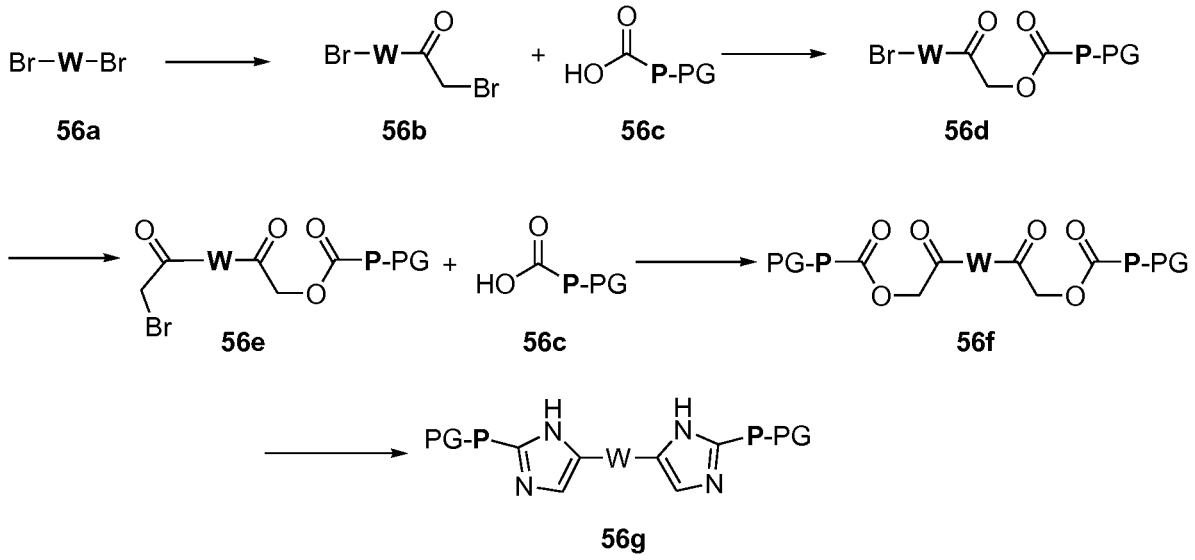
Scheme 55: Representative synthesis of R-P-M-A-A-M-P-R



Scheme 55 shows a general synthesis of an R-**P-M-A-A-M-P-**R intermediate wherein, for illustrative purposes, **M** is imidazole and R is a generic group that is depicted as a protecting group. For example, the diketone **55b** is converted to **55e** using bromine. Compound **55b** can be commercially available or can be prepared from the corresponding dibromide **55a** through coupling with a vinyltin reagent such as tributyl(ethoxyvinyl)stannane in the presence of a palladium catalyst. Coupling of **55e** with acid **55f** under basic conditions such as diisopropylethylamine affords diester **55g.** Imidazole formation is accomplished by treatment of **55g** with ammonium acetate to provide the imidazole containing intermediate R-P-M-A-A-M-**P**-R (**55h**).

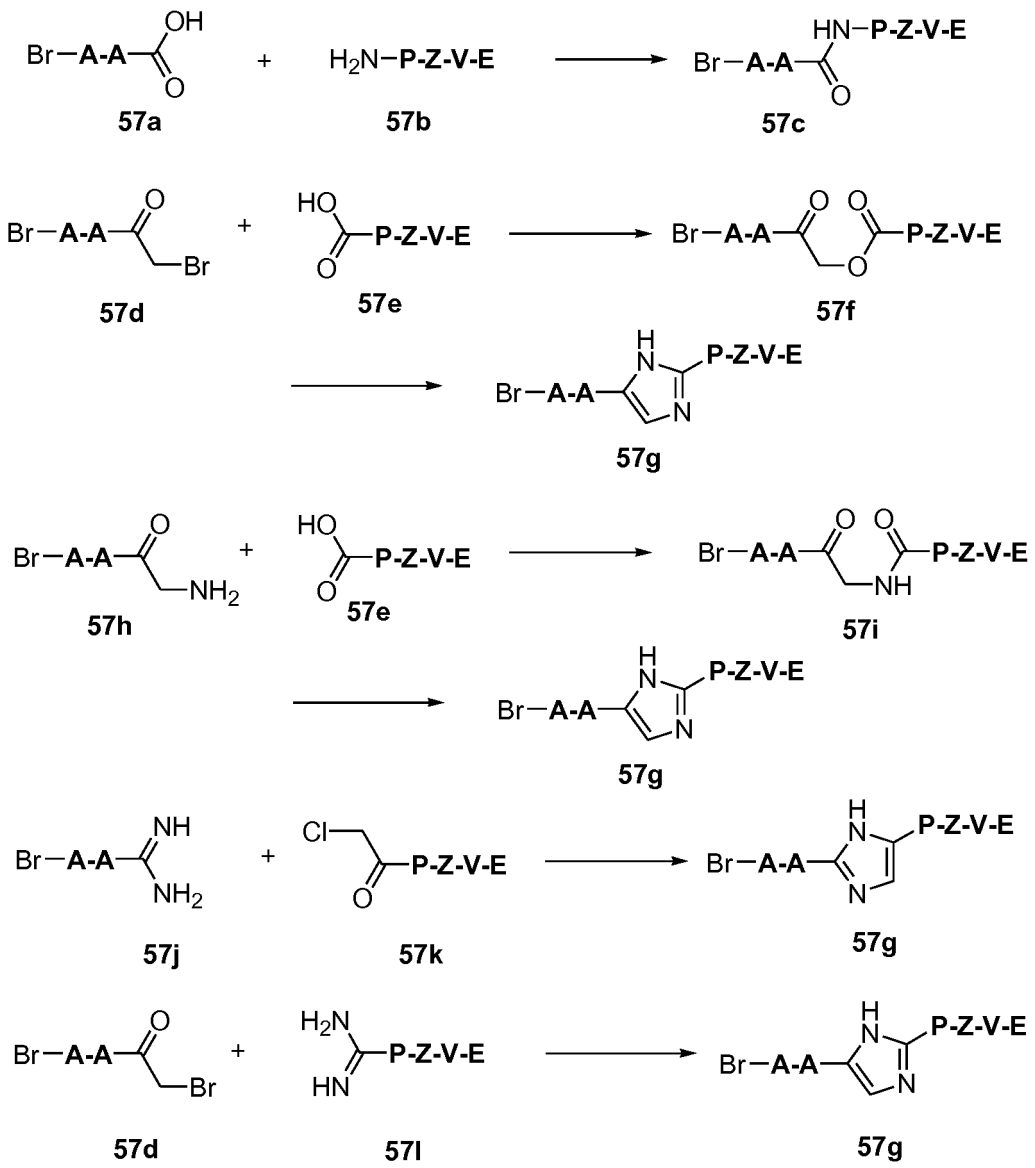
[0111] Alternatively, bromide **55e** can be synthesized from **55c.** The dimethyl compound **55c** can be converted to the corresponding diacid **55d** using potassium permanganate as oxidant. Conversion of **55d** to **55e** can be accomplished by a multi-step homologation. For example, the treatment of **55d** with oxalyl chloride, followed by trimethylsilyl diazomethane and then hydrobromic acid can afford compound **55e.**

Scheme 56: Representative synthesis of R-P-M-W-M-P-R



Scheme **56** shows a general synthesis of an R-**P-M-W-M-P**-R intermediate wherein, for illustrative purposes, **M** is imidazole and R is a generic group that is depicted as a protecting group. The compound **56a** is coupled with vinyltin reagent such as tributyl(ethoxyvinyl)stannane in the presence of a palladium catalyst, followed by bromination and hydrolysis with NBS and water, to give the bromoketone **56b.** The reaction between bromide **56b** and a carboxylic acid under basic condition generates the ester **56d.** Following the same reaction sequence, compound **56d** can be elaborated to the diester **56f.** Conversion of **56f** to **56g** is accomplished with ammonia reagents such as ammonium acetate at elevated temperature.

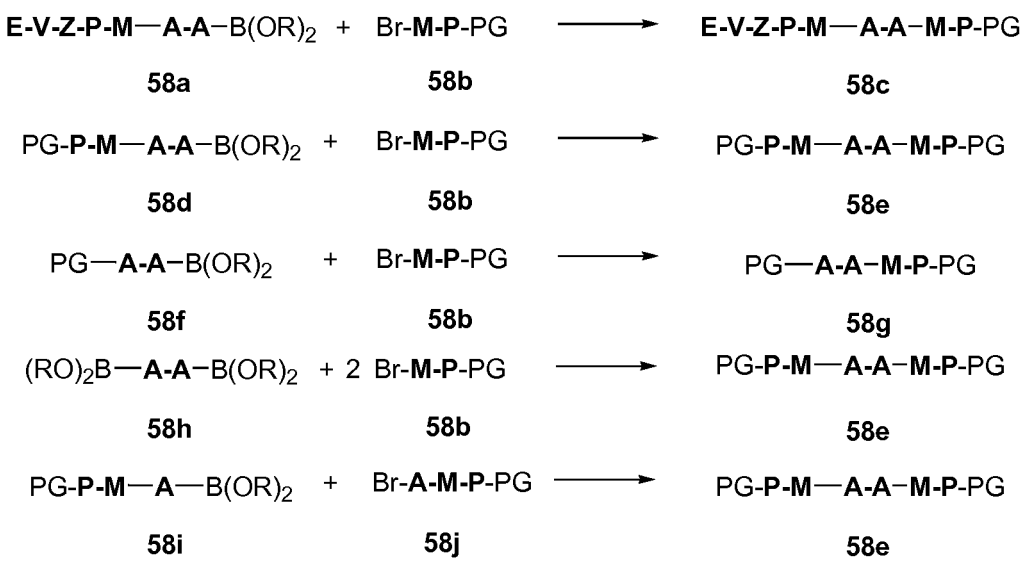
Scheme 57: Representative synthesis of R-A-A-M-P-R^1



Scheme 57 shows a general synthesis of an R-**A-A-M-P**-R^1 intermediate wherein, for illustrative purposes, **M** is an amide or an imidazole, R is a generic group that is depicted as Br, and R^1 is a generic group that is depicted as **-Z-V-E.** Coupling of amine **57b** with acid **57a** is accomplished using a peptide coupling reagent (e.g. HATU) to afford amide containing **57c.**

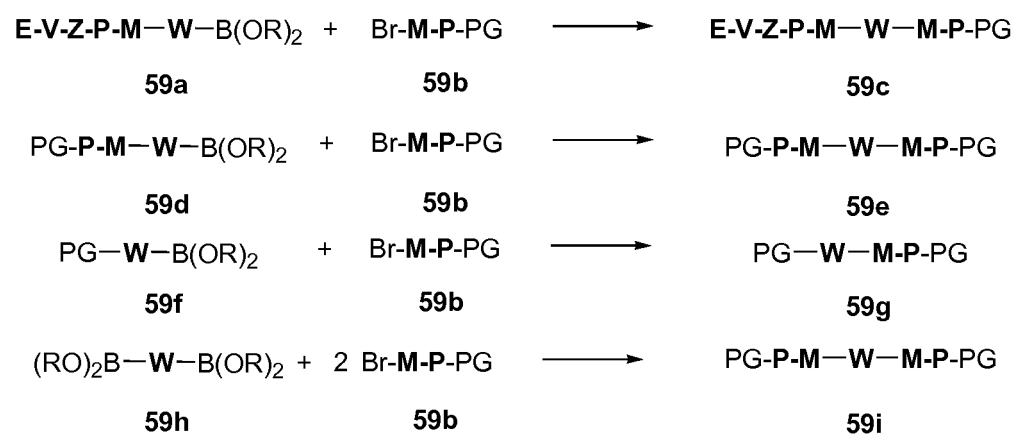
[0112] The acid **57e** is coupled with an α-haloketone, such as α-bromoketone **57d,** under basic conditions (e.g. Et_3N) to afford **57f.** Alternatively, the acid **57e** is coupled with an α-aminoketone **57h**, under amide formation conditions (e.g. EDC, Et_3N) to afford **57i.** Reaction of **57f** or **57i** with an amine or amine salt (e.g. ammonium acetate) affords the imidazole containing intermediate Br-A-M-P-Z-V-E (**57g**). Coupling of 57j and 57k and, in the alternative, coupling of 57d and 571 under appropriate conditions can also be used in preparation of intermediate Br-**A-M-P-Z-V-E** (**57g**).

Scheme 58: Representative synthesis of R-A-A-M-P-R^1



Scheme 58 shows a general synthesis of the R-**A-A-M-P**-R^1 molecule, wherein a transition metal-mediated cross-coupling reaction is utilized to construct the **A-A** bond or **A-M** bond. For illustrative purposes, the Suzuki reaction is employed to couple two corresponding intermediates, R is a generic group that is depicted as **-M-P-Z-V-E, -M-P-**PG, or a protecting group, and R^1 is a generic group that is depicted as a protecting group. Boronic ester **58a, 58d, 58f** or **58i** is coupled with an appropriate coupling partner (e.g. arylbromide **58b** or **58j**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **58c, 58e,** or **58g.** Formation of multiple **A-M** bonds can be conducted in a similar manner. For example, the Suzuki reaction can also be employed to couple $(RO)_2B$-**A-A**-$B(OR)_2$ (**58h**) and two equivalents of Br-**M-P-**PG. For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable the **A-A** and/or **A-M** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

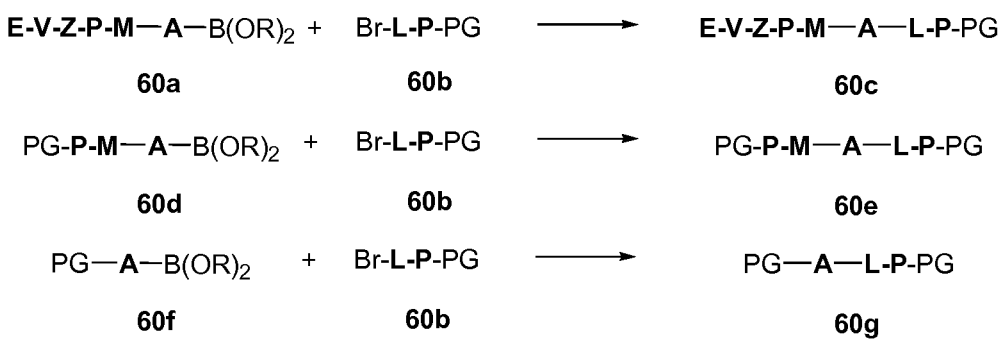
Scheme 59: Representative synthesis of R-W-M-P-R^1



Scheme 59 shows a general synthesis of the R-**W-M-P**-R^1 molecule, wherein a transition metal-mediated cross-coupling reaction is utilized to construct the **W-M** bond. For illustrative purposes, the Suzuki reaction is employed to couple two corresponding intermediates, R is a generic group that is depicted as **-M-P-Z-V-E, -M-P-**PG, or a protecting group, and R^1 is a generic group that is depicted as a protecting group. Boronic ester **59a, 59d,** or **59f** is coupled with an appropriate

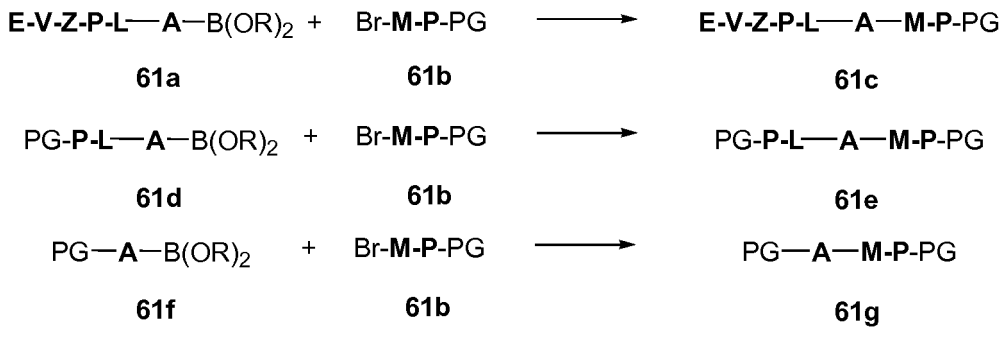
coupling partner (e.g. arylbromide **59b**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **59c, 59e,** or **59g.** Formation of multiple **W-M** bonds can be conducted in a similar manner. For example, the Suzuki reaction can also be employed to couple (RO)2B-**W-**$B(OR)_2$ (**59h**) and two equivalents of Br**-M-P-**PG. For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable the **W-M** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 60: Representative synthesis of R-A-L-P-R^1



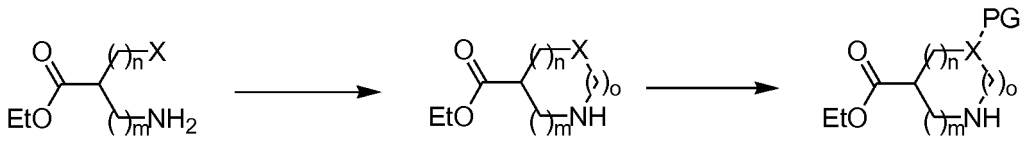
Scheme 60 shows a general synthesis of the R-**A-L-P**-R^1 molecule, wherein a transition metal-mediated cross-coupling reaction is utilized to construct the **A-L** bond. For illustrative purposes, the Suzuki reaction is employed to couple two corresponding intermediates, R is a generic group that is depicted as **-M-P-Z-V-E, -M-P-**PG, or a protecting group, and R^1 is a generic group that is depicted as a protecting group. Boronic ester **60a, 60d,** or **60f** is coupled with an appropriate coupling partner (e.g. arylbromide **60b**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **60c, 60e,** or **60g.** For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable the **A-L** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

Scheme 61: Representative synthesis of R-A-M-P-R^1



Scheme 61 shows a general synthesis of the R-**A-M-P**-R^1 molecule, wherein a transition metal-mediated cross-coupling reaction is utilized to construct the **A-M** bond. For illustrative purposes, the Suzuki reaction is employed to couple two corresponding intermediates, R is a generic group that is depicted as **-L-P-Z-V-E, -L-P-**PG, or a protecting group, and R^1 is a generic group that is depicted as a protecting group. Boronic ester **61a, 61d,** or **61f** is coupled with an appropriate coupling partner (e.g. arylbromide **61b**) using a palladium catalyst, such as $Pd(PPh_3)_4$, to afford **61c, 61e,** or **61g.** For each transition metal-mediated cross-coupling reaction the roles of the nucleophile and electrophile can be reversed to provide the same coupling product. Palladium mediated cross-coupling reactions that enable the **A-M** bond formation, but employ alternative coupling partners and reagents, include for example the Negishi, Kumada, Sonagashira and Stille reactions.

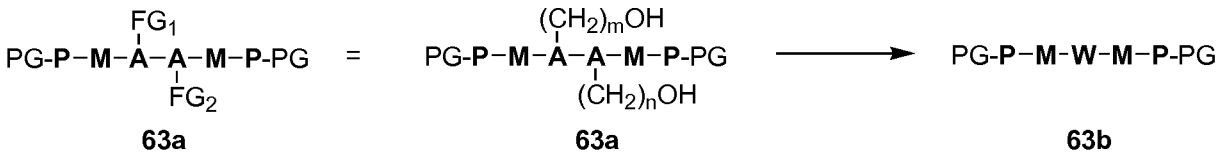
Scheme 62: Representative synthesis of R-**P**-H



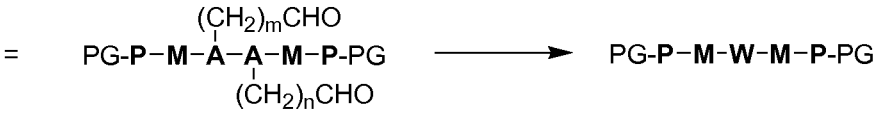
62a **62b** **62c**

Scheme 62 shows a general synthesis of a R-**P**-H molecule wherein, for illustrative purposes, R is a generic group that is depicted as ethoxycarbonyl and P is a carbocyclic or heterocyclic ring (e.g. X is carbon or heteroatom) and m, n, and o are 0 - 3, independently. The amino ester **62a** is converted to the substituted or cyclized amino ester **62b** through for example a reductive amination or Mitsunobu reaction. Compound **62b** can be protected to provide compound **62c** if necessary.

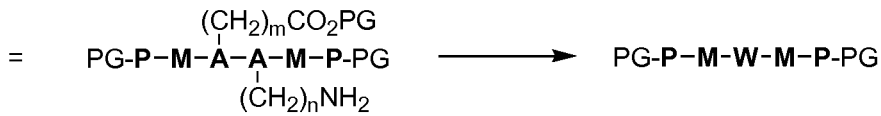
Scheme 63: Representative synthesis of R-**P-M-W-M-P**-R



63a **63a** **63b**



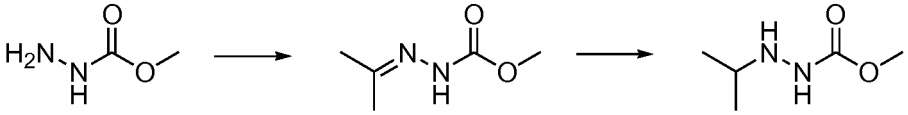
63c **63b**



63d **63b**

Scheme **63** shows a general synthesis of a R**-P-M-W-M-P**-R intermediate wherein, for illustrative purposes, R is a generic group that is depicted as a protecting group and **A** is functionalized with a group depicted as either hydroxyalkyl, aminoalkyl, carbonylalkyl, or alkoxycarbonylalkyl. The cyclization of **63a, 63c,** and **63d** can be performed through several functional group transformations which include, but are not limited to, Mitsunobu reaction, reductive amination, and lactamization.

Scheme 64: Representative Synthesis of H-**V-E**



64a **64b** **64c**

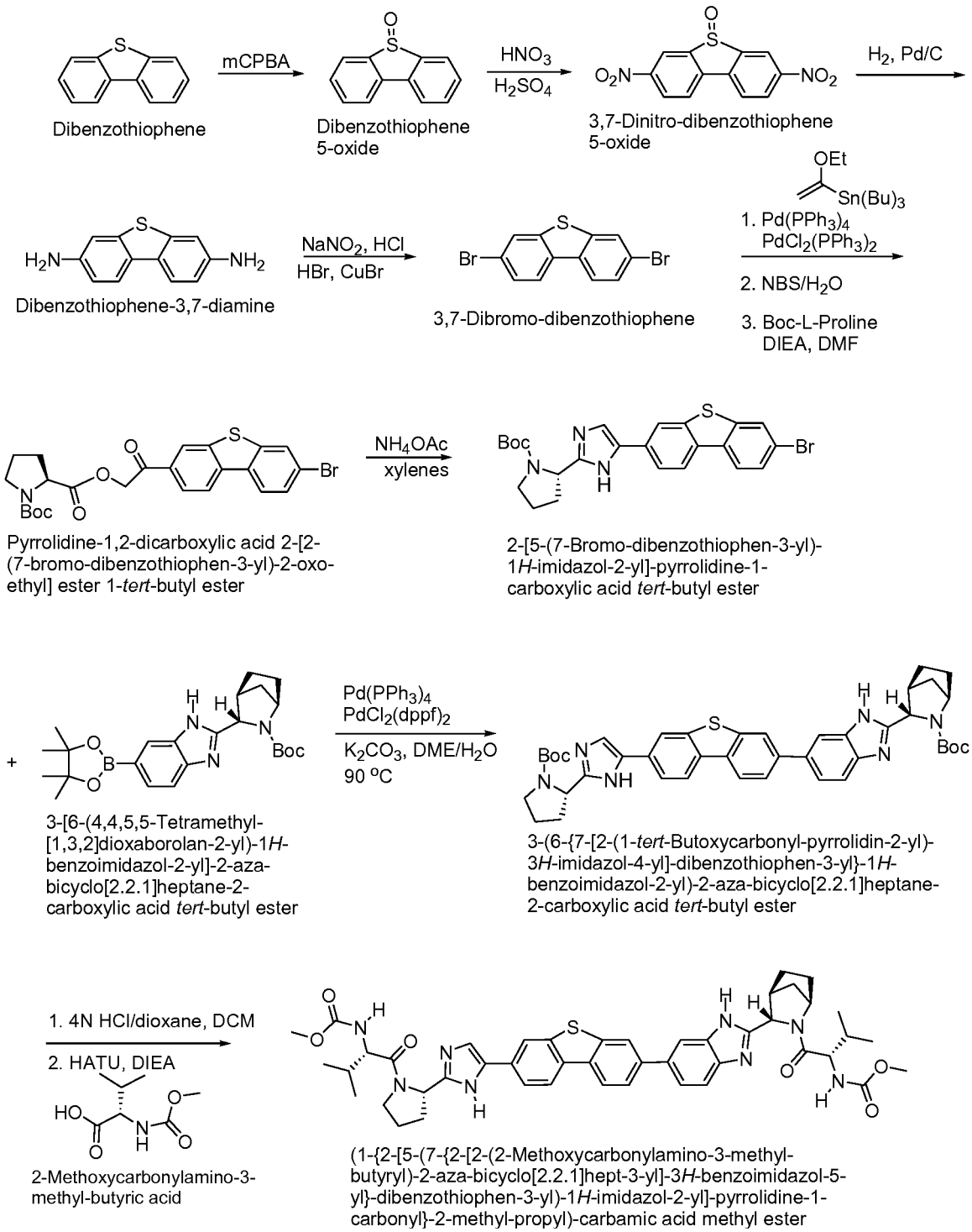
Scheme 64 shows a general synthesis of a H**-V-E** intermediate wherein, for illustrative purposes **E** is methoxycarbonylamino and **V** is isopropylamino. The reaction of hydrazine carboxylate **64a** with a ketone or aldehyde, such as acetone, under acidic conditions (e.g. AcOH) affords the imine **64b.** Reaction **of 64b** under reducing conditions, such as PtO_2 and hydrogen gas, affords the substituted hydrazinecarboxylate **64c.**

[0113] The invention will now be illustrated by the following non-limiting Example.

EXAMPLE

Example DE

[0114]



[0115] **Dibenzothiophene 5-oxide:** A solution of mCPBA (8.27 g, 36.9 mmol) in 71 mL chloroform was added dropwise over 30 minutes to a solution of dibenzothiophene in 89 mL chloroform at - 35°C. The reaction mixture was stirred at -35°C for 1 hour and then warmed up to room. The reaction was quenched with saturated sodium bicarbonate aqueous solution. The organic layer was washed with saturated sodium bicarbonate solution twice and dried over MgSO4, con-

centrated down to give an off-white solid. The solid was dissolved in refluxing ethanol and slowly cooled to room temperature to give a white crystalline solid Dibenzothiophene 5-oxide (5.65g, 76%). LCMS-ESI$^-$: calc'd for $C_{12}H_8OS$: 200.26; Found: 200.9 ($M+H^+$).

[0116] 3,7-Dinitro-dibenzothiophene 5-oxide: A solution of Dibenzothiophene 5-oxide (5.34g, 26.7 mmol) in concentrated sulfuric acid (120 mL) was cooled to 6°C. Nitric acid (108 mL) was added slowly so that the internal temperature stayed at 10°C. The reaction was stirred at 10°C for 30 minutes then warmed up to room temperature over 30 minutes. The reaction mixture was poured into ice and formed precipitate. The precipitate was washed with water and dried to give a yellow solid 3,7-Dinitro-dibenzothiophene 5-oxide (7.8 g, still containing some water and inorganic material).

[0117] Dibenzothiophene-3,7-diamine: Two batches of the above solid 3,7-dinitro-dibenzothiophene 5-oxide was hydrogenated at 45 psi in ethanol (250 mL for each batch) with 10% Pd on carbon (0.46 g each batch) for 2 hours. Two batches were combined and filtered through CELITE to give an orange solution. Hydrogen chloride gas was bubbled into the solution to form precipitate (at pH 1). The precipitate was filtered and washed with small amount of ethanol and dried on vacuum to give an orange solid Dibenzothiophene-3,7-diamine (2.46 g). LCMS-ESI$^-$: calc'd for $C_{12}H_{10}N_2S$: 214.29; Found: 215.0 ($M+H^+$).

[0118] 3,7-Dibromo-dibenzothiophene: A suspension of Dibenzothiophene-3,7-diamine (2.46 g, 8.57 mmol) in water (16 mL) and concentrated HCl (4.3 mL) was cooled to 5°C (internal temperature). A solution of sodium nitrite (1.54 g, 25.67 mmol) in water (5 mL) was added dropwise so that the internal temperature didn't exceed to 10°C. After 1 hour the reaction mixture was poured into a solution of CuBr (1.8 g, 12.55 mmol) in 48% HBr (18 mL). The mixture was transferred into a 1 L 3 neck flask using water (100 mL) and refluxed for 2 hours. The reaction mixture was cooled down and poured into ice water mixture. Precipitate formed and collected by filtration, dried and purified by flash column chromatography (silica gel, 0 to 10% MeOH/ethyl acetate) to give a white solid 3,7-Dibromo-dibenzothiophene (1.6 g, 55%).

Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-dibenzothiophen-3-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester:

[0119] [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)(3%, 69 mg, 0.098 mmol) and tetrakis(triphenylphosphine)palladium (3%, 113 mg, 0.098 mmol) were added to the mixture of 3,7-Dibromo-dibenzothiophene (1.12 g, 3.27 mmol) and tributyl(1-ethoxyvinyl)tin (1.2 eq., 1.33 mL) in 25 mL dioxane. The reaction was heated to 80°C under Ar overnight. The reaction was cooled to room temprature. 8 mL water was added and followed by NBS (1eq., 699 mg). The reaction was stirred at room for 1 hour. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated down and dried on vacuum to give a residue which was used in next step.

[0120] The residue was dissolved in 20 mL anhydrous DMF. Boc-L-Pro-OH (4 eq., 2.815 g) was added, followed by DIEA (3.5 eq., 1.60 mL) in 20 mL MeCN and 15 mL DMF dropwise. The reaction was stirred at room temperature overnight. The reaction crude was diluted with EtOAc and washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 0 to 50% ethyl acetate/hexane) to give Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-dibenzothiophen-3-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (593 mg, yield 33%) and bis product. LCMS-ESI$^-$: calc'd for $C_{24}H_{24}BrNO_5S$: 518.42; Found: 541.9($M+Na^+$).

[0121] 2-[5-(7-Bromo-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester: 10 mL Xylenes was added to the mixture of Pyrrolidine-1,2-dicarboxylic acid 2-[2-(7-bromo-dibenzothiophen-3-yl)-2-oxo-ethyl] ester 1-*tert*-butyl ester (514 mg, 0.99 mmol) and ammonia acetate (20eq., 1.53 g). The mixture was heated in microwave at 140°C for 60 minutes. The mixture was diluted with EtOAc and washed with sat.NaHCO3 aqueous solution. The organic layer was concentrated down and purified by flash column chromatography (silica gel, 20 to 80% ethyl acetate/hexane) to give 2-[5-(7-Bromo-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (391 mg, yield 79%). LCMS-ESI$^-$: calc'd for $C_{24}H_{24}BrN_3O_2S$: 498.44; Found: 499.9($M+Na^+$).

3-(6-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzothiophen-3-yl}-1H-benzoimidazol-2-yl)-2-aza-bicydo[2.2.1]heptane-2-carboxylic acid *tert*-butyl ester:

[0122] A mixture of 2-[5-(7-Bromo-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester (300 mg, 0.48 mmol, 1 eq.), 3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-benzoimidazol-2-yl]-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester (1.1 eq., 530 mg), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)(3%, 12 mg), tetrakis(triphenylphosphine)palladium (3%, 17 mg) and 2N potassium carbonate aqueous solution (3.3 eq., 0.8 mL) in 2 mL DME was heated to 80°C under Argon for 5 hours. The reaction mixture was cooled and diluted in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 20 to 100% ethyl acetate/hexane) to give a yellow foam 3-(6-{7-[2-(1-*tert*- Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzothiophen-3-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester (245 mg, yield 70%). LCMS-ESI$^-$: calc'd for

$C_{42}H_{46}N_6O_4S$: 730.92; Found: 731.2($M+H^+$).

[0123] (1-{2-[5-(7-{2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo [2.2.1] hept-3-yl]-3H-benzoimidazol-5-yl}-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DE**): 4N HCl in dioxane (3 mL) was added to 3-(6-{7-[2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-3H-imidazol-4-yl]-dibenzothiophen-3-yl}-1H-benzoimidazol-2-yl)-2-aza-bicyclo[2.2.1]heptane-2-carboxylic acid tert-butyl ester (141 mg, 0.194 mmol) in 3 mL DCM. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated and dried overnight under vacuum. The residue was dissolved in DMF (4 mL) and to this solution was added 2-Methoxycarbonylamino-3-methyl-butyric acid (2.08 eq., 71 mg), 4-methylmorpholine (6 eq., 0.12 mL), followed by HATU (2.04 eq., 150 mg). Reaction mixture was stirred at 0°C for 30 minutes. The reaction mixture was diluted in ethyl acetate and washed with saturated sodium bicarbonate solution. The organic layer was dried (MgSO4), concentrated and purified by flash column chromatography (silica gel, 0 to 20% MeOH/ethyl acetate), followed by preparative reverse phase HPLC (GEMINI, 5 to 100% ACN/H_2O + 0.1% TFA). Product was lyophilized to give (1-{2-[5-(7- {2-[2-(2-Methoxycarbonylamino-3-methyl-butyryl)-2-aza-bicyclo[2.2.1]hept-3-yl]-3H-benzoimidazol-5-yl}-dibenzothiophen-3-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (Example **DE**) (121 mg, 59%). ^{1}H-NMR: 300 MHz, (DMSO-d_6) δ: 8.60-8.40 (m, 4H), 8.16(m, 1H), 8.01 (m, 1H), 7.90(m, 2H), 7.76(m, 1H), 7.33 (m, 2H), 5.15(m, 1H), 4.76(m,1H), 4.56(d, 1H), 4.22-4.08(m, 3H), 3.85(m, 2H), 3.55 (d, 6H), 2.76(m,1H), 2.30-1.50 (m, 9H), 0.96-0.75 (m, 12 H). ^{19}F-NMR: 300 MHz, (CD_3OD-d_4) 8: -112.88. LCMS-ESI$^+$: calc'd for $C_{46}H_{52}N_8O_6S$: 845.02; Found: 845.4 ($M+H^+$).

BIOLOGICAL ASSAYS

Effect of serum proteins on replicon potency

[0124] Replicon assays are conducted in normal cell culture medium (DMEM + 10%FBS) supplemented with physiologic concentrations of human serum albumin (40 mg/mL) or α-acid glycoprotein (1 mg/mL). EC_{50}s in the presence of human serum proteins are compared to the EC_{50} in normal medium to determine the fold shift in potency.

[0125] Enyzmatic Selectivity: The inhibition of mammalian proteases including Porcine Pancreatic Elastase, Human Leukocyte Elastase, Protease 3, and Cathepsin D are measured at K_m for the respective substrates for each enzyme. IC_{50} for each enzyme is compared to the IC_{50} obtained with NS3 1b protease to calculate selectivity. Representative compounds of the invention have shown activity.

[0126] MT-4 Cell Cytotoxicity: MT4 cells are treated with serial dilutions of compounds for a five day period. Cell viability is measured at the end of the treatment period using the Promega CellTiter-Glo assay and non-linear regression is performed to calculate CC_{50}.

[0127] Compound Concentration Associated with Cells at EC_{50}: Huh-luc cultures are incubated with compound at concentrations equal to EC_{50}. At multiple time points (0 - 72 hours), cells are washed 2X with cold medium and extracted with 85% acetonitrile; a sample of the media at each time-point will also be extracted. Cell and media extracts are analyzed by LC/MS/MS to determine the Molar concentration of compounds in each fraction. Representative compounds of the invention have shown activity.

[0128] Solubility and Stability: Solubility is determined by taking an aliquot of 10 mM DMSO stock solution and preparing the compound at a final concentration of 100 μM in the test media solutions (PBS, pH 7.4 and 0.1 N HCl, pH 1.5) with a total DMSO concentration of 1%. The test media solutions are incubated at room temperature with shaking for 1 hr. The solutions will then be centrifuged and the recovered supernatants are assayed on the HPLC/UV. Solubility will be calculated by comparing the amount of compound detected in the defined test solution compared to the amount detected in DMSO at the same concentration. Stability of compounds after an 1 hour incubation with PBS at 37°C will also be determined.

[0129] Stability in Cryopreserved Human, Dog, and Rat Hepatocytes: Each compound is incubated for up to 1 hour in hepatocyte suspensions (100 μl, 80,000°Cells per well) at 37°C. Cryopreserved hepatocytes are reconstituted in the serum-free incubation medium. The suspension is transferred into 96-well plates (50 μL/well). The compounds are diluted to 2 μM in incubation medium and then are added to hepatocyte suspensions to start the incubation. Samples are taken at 0, 10, 30 and 60 minutes after the start of incubation and reaction will be quenched with a mixture consisting of 0.3% formic acid in 90% acetonitrile/10% water. The concentration of the compound in each sample is analyzed using LC/MS/MS. The disappearance half-life of the compound in hepatocyte suspension is determined by fitting the concentration-time data with a monophasic exponential equation. The data will also be scaled up to represent intrinsic hepatic clearance and/or total hepatic clearance.

[0130] Stability in Hepatic S9 Fraction from Human, Dog, and Rat: Each compound is incubated for up to 1 hour in S9 suspension (500 μl, 3 mg protein/mL) at 37°C (n = 3). The compounds are added to the S9 suspension to start the incubation. Samples are taken at 0, 10, 30, and 60 minutes after the start of incubation. The concentration of the compound in each sample is analyzed using LC/MS/MS. The disappearance half-life of the compound in S9 suspension

is determined by fitting the concentration-time data with a monophasic exponential equation.

[0131] Caco-2 Permeability: Compounds are assayed via a contract service (Absorption Systems, Exton, PA). Compounds are provided to the contractor in a blinded manner. Both forward (A-to-B) and reverse (B-to-A) permeability will be measured. Caco-2 monolayers are grown to confluence on collagen-coated, microporous, polycarbonate membranes in 12-well Costar TRANSWELL® plates. The compounds are dosed on the apical side for forward permeability (A-to-B), and are dosed on the basolateral side for reverse permeability (B-to-A). The cells are incubated at 37°C with 5% CO_2 in a humidified incubator. At the beginning of incubation and at 1 hr and 2 hr after incubation, a 200-μL aliquot is taken from the receiver chamber and replaced with fresh assay buffer. The concentration of the compound in each sample is determined with LC/MS/MS. The apparent permeability, Papp, is calculated.

Plasma Protein Binding:

[0132] Plasma protein binding is measured by equilibrium dialysis. Each compound is spiked into blank plasma at a final concentration of 2 μM. The spiked plasma and phosphate buffer is placed into opposite sides of the assembled dialysis cells, which will then be rotated slowly in a 37°C water bath. At the end of the incubation, the concentration of the compound in plasma and phosphate buffer is determined. The percent unbound is calculated using the following equation:

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

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

CYP450 Profiling:

[0133] Each compound is incubated with each of 5 recombinant human CYP450 enzymes, including CYP1A2, CYP2C9, CYP3A4, CYP2D6 and CYP2C19 in the presence and absence of NADPH. Serial samples will be taken from the incubation mixture at the beginning of the incubation and at 5, 15, 30, 45 and 60 minutes after the start of the incubation. The concentration of the compound in the incubation mixture is determined by LC/MS/MS. The percentage of the compound remaining after incubation at each time point is calculated by comparing with the sampling at the start of incubation.

Stability in Rat, Dog, Monkey and Human Plasma:

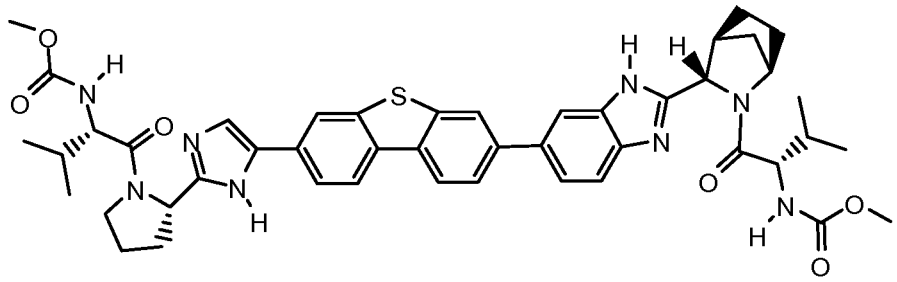
[0134] Compounds will be incubated for up to 2 hours in plasma (rat, dog, monkey, or human) at 37 °C. Compounds are added to the plasma at final concentrations of 1 and 10 μg/mL. Aliquots are taken at 0, 5, 15, 30, 60, and 120 minutes after adding the compound. Concentration of compounds and major metabolites at each timepoint are measured by LC/MS/MS.

Evaluation of cell-based anti-HCV activity:

[0135] Antiviral potency (EC_{50}) was determined using a *Renilla* luciferase (RLuc)-based HCV replicon reporter assay. To perform the assay, HCV 1b RLuc cells (harboring a dicistronic genotype 1b Con1 replicon that encodes a RLuc reporter), or HCV 1a RLuc cells (harboring a dicistronic genotype 1a H77 replicon that encodes a RLuc reporter), were dispensed into 384-well plates. Compounds were re-suspended in DMSO at a concentration of 10 mM and serially diluted in DMSO using an automated pipeting instrument. Serially diluted compounds were mixed with cell culture media and added to the seeded cells. DMSO was used as a negative (solvent) control, and the protease inhibitor ITMN-191 was included at a concentration > 100 x EC_{50} as a positive control. 72 hours later, cells were lysed and *Renilla* luciferase activity quantified as recommended by the manufacturer (Promega-Madison, WI). Non-linear regression was performed to calculate EC_{50} values.

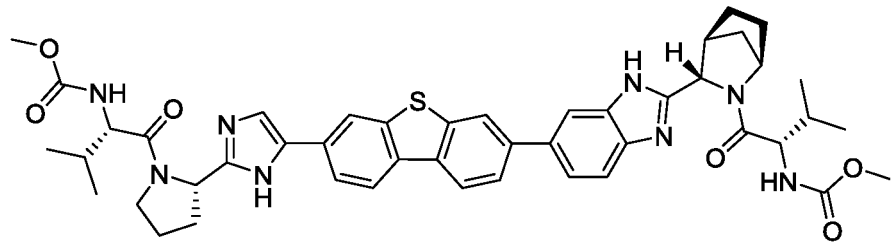
[0136] Typically the compounds of the invention can inhibit multiple genotypes of HCV. For example, compounds of the present invention are active against multiple HCV genotypes selected from 1a, 1b, 2a, 2b, 3a, 4a, and 5a.

[0137] Biological data (antiviral potency [EC_{50}] was determined using a *Renilla* luciferase (RLuc)-based HCV replicon reporter assay - HCV 1b RLuc) for representative compounds of the invention is provided in the following table. These compounds can be prepared using procedures similar to those described above.

Representative Compound of the Invention	Activity (nM)
	0.0037

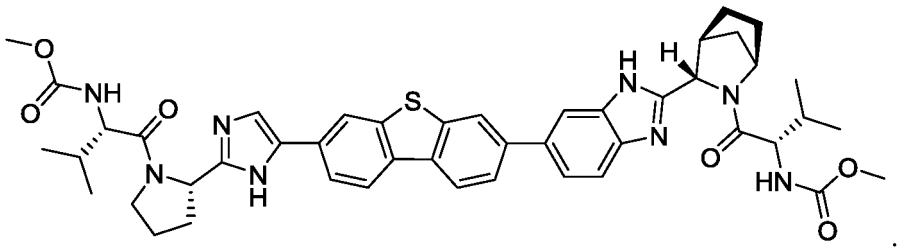
Claims

1. A compound of formula:



or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 of formula:



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

4. The pharmaceutical composition of claim 3, further comprising at least one additional therapeutic agent.

5. The pharmaceutical composition of claim 4, wherein said additional therapeutic agent is selected from the group consisting of ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

6. The pharmaceutical composition according to claim 3, further comprising a nucleoside analogue.

7. The pharmaceutical composition according to claim 6, wherein said nucleoside analogue is selected from ribavirin, viramidine, levovirin, an L-nucleoside, and isatoribine.

8. The compound of claim 1, or a pharmaceutically acceptable salt thereof for use in the prophylactic or therapeutic treatment of hepatitis C or a hepatitis C associated disorder.

9. The compound for the use of claim 8, further comprising administering at least one additional therapeutic agent.

10. The compound for the use of claim 9, wherein said additional therapeutic agent is selected from the group consisting of ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

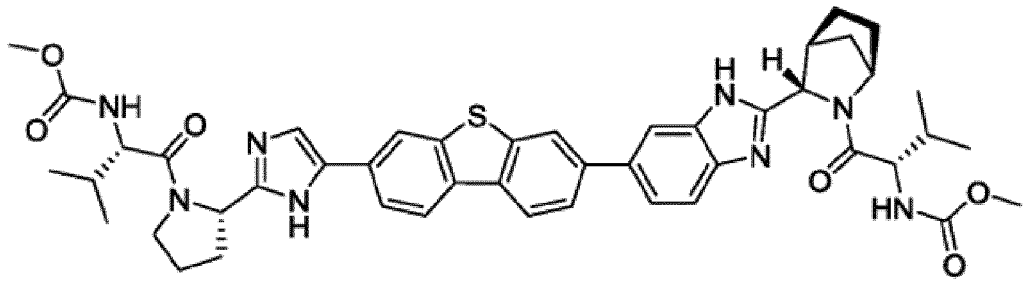
11. The compound for the use of claim 10, wherein the NS5b polymerase inhibitor is a nucleotide inhibitor of HCV NS5b polymerase.

12. The compound for the use of claim 9, wherein said additional therapeutic agent is a nucleoside analogue.

13. The compound for the use of claim 12, wherein said nucleoside analogue is selected from ribavirin, viramidine, levovirin, an L-nucleoside, and isatoribine.

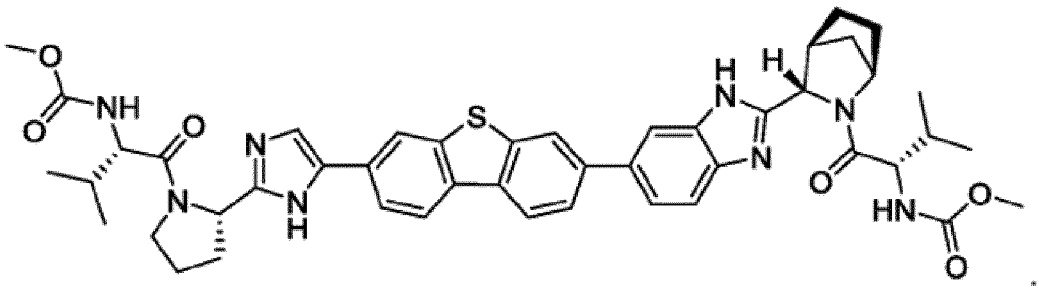
Patentansprüche

1. Verbindung der Formel:



oder ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1 der Formel:



3. Pharmazeutische Zusammensetzung umfassend die Verbindung nach Anspruch 1, oder ein pharmazeutisch verträgliches Salz davon; und mindestens einen pharmazeutisch verträglichen Träger.

4. Pharmazeutische Zusammensetzung nach Anspruch 3, ferner umfassend mindestens ein zusätzliches therapeutisches Mittel.

5. Pharmazeutische Zusammensetzung nach Anspruch 4, wobei das zusätzliche therapeutische Mittel aus der Gruppe ausgewählt ist bestehend aus Ribavirinanalogen, NS3-Proteasehemmern, NS5b- Pol ymerasehemmern, alpha-Glucosidase-1-Hemmern, Leberschutzmitteln, Nicht-Nukleosid-HCV-Hemmern und sonstigen Pharmaka zur Behandlung des HCV.

6. Pharmazeutische Zusammensetzung nach Anspruch 3, ferner umfassend ein Nukleosidanalogon.

7. Pharmazeutische Zusammensetzung nach Anspruch 6, wobei der Nukleosidanalogon ausgewählt ist aus Ribavirin, Viramidin, Levovirin, einem L-Nukleosid und Isatoribin.

8. Verbindung nach Anspruch 1, oder ein pharmazeutisch verträgliches Salz davon zur Verwendung in der prophylaktischen oder therapeutischen Behandlung von Hepatitis C oder einer Hepatitis-C-assoziierten Störung.

9. Verbindung zur Verwendung nach Anspruch 8, ferner umfassend Verabreichen von wenigstens einem zusätzlichen therapeutischen Mittel.

10. Verbindung zur Verwendung nach Anspruch 9, wobei das zusätzliche therapeutische Mittel ausgewählt ist aus der Gruppe bestehend aus Ribavirinanalogen, NS3-Proteasehemmern, NS5b- Polymerasehemmern, alpha-Glucosidase-1-Hemmern, Leberschutzmitteln, Nicht-Nukleosid-HCV-Hemmern und sonstigen Pharmaka zur Behandlung des HCV.

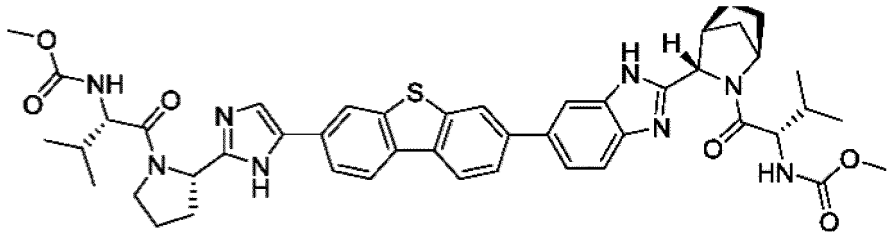
11. Verbindung zur Verwendung nach Anspruch 10, wobei der NS5b-Polymerasehemmer ein Nukleotidhemmer von HCV-NS5b-Polymerase ist.

12. Verbindung zur Verwendung nach Anspruch 9, wobei das zusätzliche therapeutische Mittel ein Nukleosidanalogon ist.

13. Verbindung zur Verwendung nach Anspruch 12, wobei das Nukleotidanalogon ausgewählt ist aus Ribavirin, Viramidin, Levovirin, einem L-Nukleosid und Isatoribin.

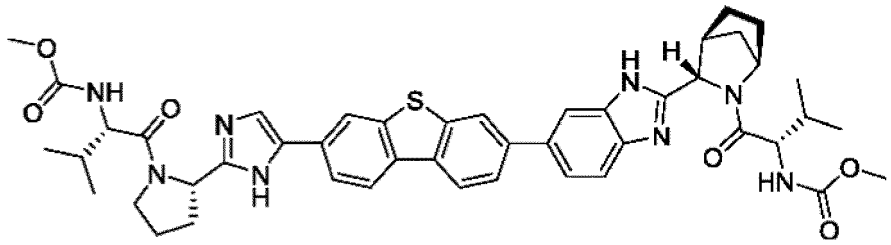
Revendications

1. Composé de formule:



ou un sel pharmaceutiquement acceptable de celui-ci.

2. Composé selon la revendication 1 de formule:



3. Composition pharmaceutique comprenant le composé de la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci; et au moins un support pharmaceutiquement acceptable.

4. Composition pharmaceutique selon la revendication 3, comprenant en outre au moins un agent thérapeutique supplémentaire.

5. Composition pharmaceutique selon la revendication 4, dans laquelle ledit agent thérapeutique supplémentaire est choisi dans le groupe constitué des analogues de la ribavirine, des inhibiteurs de la protéase NS3, des inhibiteurs de la polymérase NS5b, des inhibiteurs de l'alpha-glucosidase 1, des hépatoprotecteurs, des inhibiteurs non nucléosidiques du VHC et d'autres médicaments pour traiter le VHC.

6. Composition pharmaceutique selon la revendication 3, comprenant en outre un analogue de nucléoside.

7. Composition pharmaceutique selon la revendication 6, dans laquelle ledit analogue de nucléoside est choisi parmi la ribavirine, la viramidine, la lévovirine, un L-nucléoside et l'isatoribine.

8. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, destiné à être utilisé dans le traitement prophylactique ou thérapeutique de l'hépatite C ou d'un trouble associé à l'hépatite C.

9. Composé pour l'utilisation selon la revendication 8, comprenant en outre l'administration d'au moins un agent thérapeutique supplémentaire.

10. Composé à utiliser selon la revendication 9, dans lequel ledit agent thérapeutique supplémentaire est choisi dans le groupe comprenant les analogues de la ribavirine, les inhibiteurs de la protéase NS3, les inhibiteurs de la polymérase NS5b, les inhibiteurs de l'alpha-glucosidase 1, les hépatoprotecteurs, les inhibiteurs non nucléosidiques du VHC et autres médicaments pour traiter le VHC.

11. Composé pour l'utilisation selon la revendication 10, dans lequel l'inhibiteur de la polymérase NS5b est un inhibiteur nucléotidique de la polymérase NS5b du VHC.

12. Composé pour l'utilisation selon la revendication 9, dans lequel ledit agent thérapeutique supplémentaire est un analogue de nucléoside.

13. Composé pour l'utilisation selon la revendication 12, dans lequel ledit analogue de nucléoside est choisi parmi la ribavirine, la viramidine, la lévovirine, un L-nucléoside et l'isatoribine.

REFERENCES CITED IN THE DESCRIPTION

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