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(54) Title: PHOSPHONATE ANALOGS OF HIV INTEGRASE INHIBITOR COMPOUNDS

(57) Abrégé/Abstract:
Novel HIV integrase inhibitor compounds having at least one phosphonate group, protected intermediates thereof, and methods for inhibition of HIV-integrase are disclosed.

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(54) Title: PHOSPHONATE ANALOGS OF HIV INTEGRASE INHIBITOR COMPOUNDS

(57) Abstract: Novel HIV integrase inhibitor compounds having at least one phosphonate group, protected intermediates thereof, and methods for inhibition of HIV-integrase are disclosed.

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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CONTENANT LES PAGES 1 À 412

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JUMBO APPLICATIONS/PATENTS

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THIS IS VOLUME 1 OF 2
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PHOSPHONATE ANALOGS OF HIV INTEGRASE INHIBITOR COMPOUNDS

FIELD OF THE INVENTION

The invention relates generally to phosphonate compounds with antiviral activity and more specifically with anti-HIV integrase properties.

BACKGROUND OF THE INVENTION

AIDS is a major public health problem worldwide. Despite the unprecedented successes in the therapy of HIV infection, AIDS remains a major world health problem being the first cause of death in Africa and the fourth leading cause of death worldwide. Rapid emergence of drug-resistant HIV variants and severe side effects limit the efficacy of existing therapies. Although drugs targeting HIV viruses are in wide use and have shown effectiveness, toxicity and development of resistant strains have limited their usefulness. Assay methods capable of determining the presence, absence or amounts of HIV viruses are of practical utility in the search for inhibitors as well as for diagnosing the presence of HIV.

Human immunodeficiency virus (HIV) infection and related disease is a major public health problem worldwide. The retrovirus human immunodeficiency virus type 1 (HIV-1), a member of the primate lentivirus family (De Clercq E (1994) *Annals of the New York Academy of Sciences*, 724:438-456; Barre-Sinoussi F (1996) *Lancet*, 348:31-35), is generally accepted to be the causative agent of acquired immunodeficiency syndrome (AIDS) Tarrago et al *FASEB Journal* 1994, 8:497-503). AIDS is the result of repeated replication of HIV-1 and a decrease in immune capacity, most prominently a fall in the number of CD4+ lymphocytes. The mature virus has a single stranded RNA genome that encodes 15 proteins (Frankel et al (1998) *Annual Review of Biochemistry*, 67:1-25; Katz et al (1994) *Annual Review of Biochemistry*, 63:133-173), including three key enzymes: (i) protease (Prt) (von der

Helm K (1996) *Biological Chemistry*, 377:765-774); (ii) reverse transcriptase (RT) (Hottiger et al (1996) *Biological Chemistry Hoppe-Seyler*, 377:97-120), an enzyme unique to retroviruses; and (iii) integrase (Asante et al (1999) *Advances in Virus Research* 52:351-369; Wlodawer A (1999) *Advances in Virus Research* 52:335-350; Esposito et al (1999) *Advances in Virus Research* 52:319-333). Protease is responsible for processing the viral precursor polyproteins, RT is the key enzyme in the replication of the viral genome, and integrase, a viral encoded protein, is responsible for the integration of the double stranded DNA form of the viral genome into host DNA.

Until 1995, the only drugs approved in the United States were nucleoside inhibitors of RT (Smith et al (1994) *Clinical Investigator*, 17:226-243). Since then, two new classes of agents, protease inhibitors (PI) and non-nucleoside RT inhibitors (NNRTI), and more than a dozen new drugs have been approved (Johnson et al (2000) *Advances in Internal Medicine*, 45 (1-40; Porche DJ (1999) *Nursing Clinics of North America*, 34:95-112). There are now three classes of drugs available: (1) the original nucleoside RT inhibitors, (2) protease inhibitors (PI), and (3) the non-nucleoside RT inhibitors (NNRTI).

An essential step in HIV infection is the integration of the viral genome into the host cell chromosomes within the nucleus. Unlike other retroviruses, HIV can transport its genetic material, in the form of the large nucleoprotein pre-integration complex (PIC), into the nucleus through the intact nuclear envelope and infect non-dividing cells such as macrophages and microglial cells. Although several different components of the PIC have been implicated in its nuclear import, the mechanism of nuclear entry remains unclear (Piller et al (2003) *Current Drug Targets* 4:409-429; Debyser et al (2002) *Antiviral Chemistry & Chemotherapy* 13:1-15). Specifically inhibiting PIC nuclear import would likely block HIV infection in non-dividing cells, this important step of HIV replication is of great interest as a drug target. The identification of compounds unambiguously affecting HIV replication by targeting integrase supports the potential of this crucial viral enzyme as a drug target. Certain HIV integrase inhibitors have been disclosed which block integration in extracellular assays and exhibit antiviral effects against HIV-infected cells (Anthony, et al WO 02/30426; Anthony, et al WO 02/30930; Anthony, et al WO 02/30931; WO 02/055079 A2 A3; Zhuang, et al WO 02/36734; US 6395743; US 6245806; US

6271402; Fujishita, et al WO 00/039086; Uenaka et al WO 00/075122; Selnick, et al WO 99/62513; Young, et al WO 99/62520; Payne, et al WO 01/00578; Parrill, A.L. (2003) *Current Medicinal Chemistry* 10:1811-1824; Gupta et al (2003) *Current Medicinal Chemistry* 10:1779-1794; Maurin et al (2003) *Current Medicinal Chemistry* 10:1795-1810; Jing, et al *Biochemistry* (2002) 41:5397-5403; Pais, et al *Jour. Med. Chem.* (2002) 45:3184-94; Goldgur, et al *Proc. Natl. Acad. Sci. U.S.A.* (1999) 96:13040-13043; Espeseth, et al *Proc. Natl. Acad. Sci. U.S.A.* (2000) 97:11244-11249). For reviews, see: Neamati (2002) *Expert Opin. Ther. Patents* 12(5):709-724; Pommier et al (1999) *Advances in Virus Research* 52:427-458; Young (2001) *Current Opinion in Drug Discovery & Development* 4(4):402-410; Neamati et al (2001) "Human Immunodeficiency Virus type 1 Integrase Targeted Inhibitor Design", Antiretroviral Therapy, E. De Clercq, Ed., ASM Press, Washington, DC; Pani et al (2000) *Current Pharm. Design* 6:569-584; Pommier et al (2000) *Antiviral Res.* 47(3):139-148; De Clercq E. (2002) *Medicinal Research Reviews* 22(6):531-565.

HIV integrase inhibitory compounds with improved antiviral and pharmacokinetic properties are desirable, including enhanced activity against development of HIV resistance, improved oral bioavailability, greater potency and extended effective half-life *in vivo* (Nair, V. "HIV integrase as a target for antiviral chemotherapy" *Reviews in Medical Virology* (2002) 12(3):179-193). Three-dimensional quantitative structure-activity relationship studies and docking simulations (Buolamwini, et al *Jour. Med. Chem.* (2002) 45:841-852) of conformationally-restrained cinnamoyl-type integrase inhibitors (Artico, et al *Jour. Med. Chem.* (1998) 41:3948-3960) have correlated hydrogen-bonding interactions to the inhibitory activity differences among the compounds.

Phase II clinical studies candidate, S-1360 (Shionogi-GlaxoSmithKline Pharmaceuticals LLC) is the furthest advanced HIV integrase inhbitor to date. Animal toxicity studies have been reported for other candidates, L-731,988 and L-708,906, by Merck.

There is a need for anti-HIV therapeutic agents, i.e. drugs having improved antiviral and pharmacokinetic properties with enhanced activity against development of HIV resistance, improved oral bioavailability, greater potency and extended effective half-life *in vivo*. New HIV inhibitors should be active against mutant HIV

strains, have distinct resistance profiles, fewer side effects, less complicated dosing schedules, and orally active. In particular, there is a need for a less onerous dosage regimen, such as one pill, once per day. Although drugs targeting HIV protease are in wide use and have shown effectiveness, particularly when employed in combination, toxicity and development of resistant strains have limited their usefulness (Palella, et al *N. Engl. J. Med.* (1998) 338:853-860; Richman, D. D. *Nature* (2001) 410:995-1001).

Combination therapy with HIV inhibitors has proven to be highly effective in suppressing viral replication to unquantifiable levels for a sustained period of time. Also, combination therapy with RT and protease inhibitors have shown synergistic effects in suppressing HIV replication. Unfortunately, many patients currently fail combination therapy due to the development of drug resistance, non-compliance with complicated dosing regimens, pharmacokinetic interactions, toxicity, and lack of potency. Therefore, there is a need for HIV integrase inhibitors that are synergistic in combination with other HIV inhibitors, or show chemical stability in combination formulations.

Improving the delivery of drugs and other agents to target cells and tissues has been the focus of considerable research for many years. Though many attempts have been made to develop effective methods for importing biologically active molecules into cells, both *in vivo* and *in vitro*, none has proved to be entirely satisfactory. Optimizing the association of the inhibitory drug with its intracellular target, while minimizing intercellular redistribution of the drug, e.g. to neighboring cells, is often difficult or inefficient.

Most agents currently administered to a patient parenterally are not targeted, resulting in systemic delivery of the agent to cells and tissues of the body where it is unnecessary, and often undesirable. This may result in adverse drug side effects, and often limits the dose of a drug (e.g., cytotoxic agents and other anti-cancer or anti-viral drugs) that can be administered. By comparison, although oral administration of drugs is generally recognized as a convenient and economical method of administration, oral administration can result in either (a) uptake of the drug through the cellular and tissue barriers, e.g. blood/brain, epithelial, cell membrane, resulting in undesirable systemic distribution, or (b) temporary residence of the drug within the

gastrointestinal tract. Accordingly, a major goal has been to develop methods for specifically targeting agents to cells and tissues. Benefits of such treatment includes avoiding the general physiological effects of inappropriate delivery of such agents to other cells and tissues, such as uninfected cells. Intracellular targeting may be achieved by methods and compositions, including prodrugs (Krise et al (1996) *Advanced Drug Delivery Reviews* 19:287-310), which allow accumulation or retention of biologically active agents inside cells.

SUMMARY OF THE INVENTION

The present invention provides novel compounds with HIV integrase activity, i.e. novel human retroviral integrase inhibitors. Therefore, the compounds of the invention may inhibit retroviral integrases and thus inhibit the replication of the virus. They are useful for treating human patients infected with a human retrovirus, such as human immunodeficiency virus (strains of HIV-1 or HIV-2) or human T-cell leukemia viruses (HTLV-I or HTLV-II) which results in acquired immunodeficiency syndrome (AIDS) and/or related diseases. The present invention includes novel phosphonate HIV integrase inhibitor compounds and phosphonate analogs of known experimental integrase inhibitors. The compounds of the invention optionally provide cellular accumulation as set forth below.

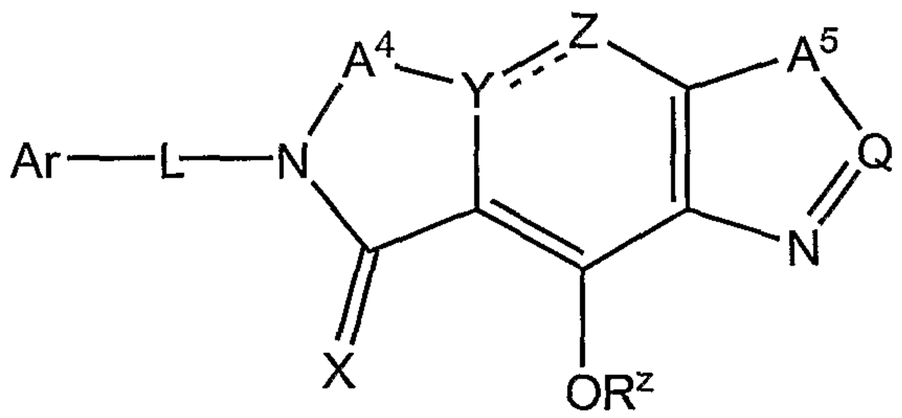
The present invention relates generally to the accumulation or retention of therapeutic compounds inside cells. The invention is more particularly related to attaining high concentrations of phosphonate-containing molecules in HIV infected cells. Intracellular targeting may be achieved by methods and compositions which allow accumulation or retention of biologically active agents inside cells. Such effective targeting may be applicable to a variety of therapeutic formulations and procedures.

Compositions of the invention include new HIV integrase inhibitor compounds having at least one phosphonate group. The compositions of the invention thus include all known approved, experimental, and proposed HIV integrase inhibitors, that do not already comprise a phosphonate group, with at least one phosphonate group covalently attached. Experimental HIV integrase inhibitors include those reviewed in: Dayam et al (2003) *Current Pharmaceutical Design* 9:1789-1802; De Clercq E. (2002) *Biochimica et Biophysica Acta* 1587(2-3):258-275;

Nair, V. (2002) *Reviews in Medical Virology* 12(3):179-193; Neamati, N. (2002) *Expert Opinion on Therapeutic Patents* 12(5):709-724; Asante-Appiah et al (1997) *Antiviral Res*. 36:139-156; Dubrovsky et al (1995) *Mol. Med*. 1:217-230; Popov et al (1998) *EMBO J*. 17:909-917; Farnet et al (1996) *AIDS* 10(Suppl. A):S3-S11; Hansen et al (1998) *Genet. Eng*. 20:41-61; Bukrinsky, M. (1997) *Drugs Future* 22:875-883; Neamati et al (2000) *Adv. Pharmacol*. 49:147-163; Pommier et al (1999) *Adv. Virus Res*. 52:427-458; Neamati et al (1997) *Drug Discovery Today* 2:487-498; Nicklaus et al (1997) *J. Med. Chem*. 40:920-929; Pommier et al (1997) *Antivir. Chem. Chemother*. 8:483-503; Robinson J. (1998) *Infect. Med*. 15:129-137; Thomas et al (1997) *Trends Biotechnol*. 15:167-172.

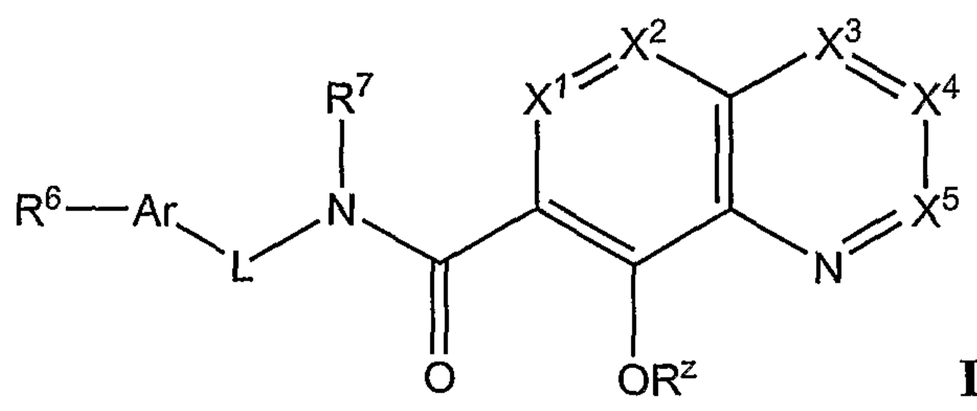
The invention includes novel phosphonate analogs of the following experimental HIV integrase inhibitors in Groups I to XXXIX.

I. In one aspect, the invention includes tricyclic phosphonate compounds represented by the following structure, Formula I:



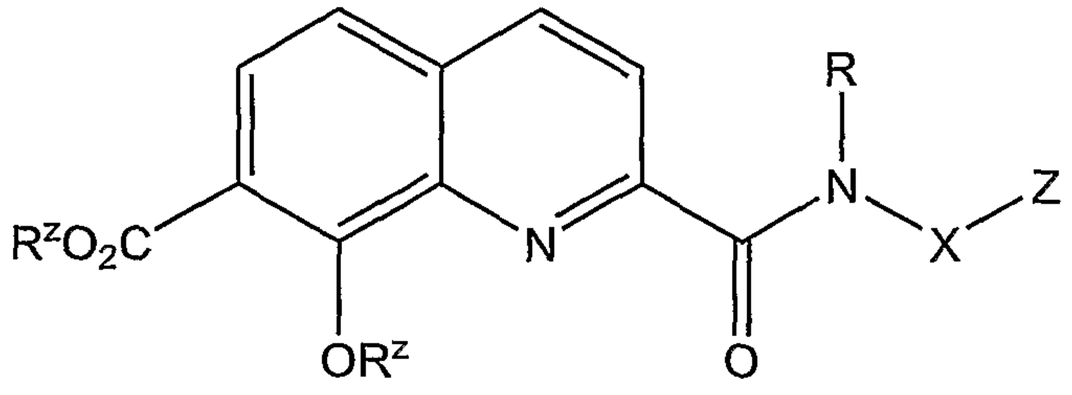
I

II. In one aspect, the invention includes phosphonate analogs of aza-quinolinol compounds represented by the Formula II:



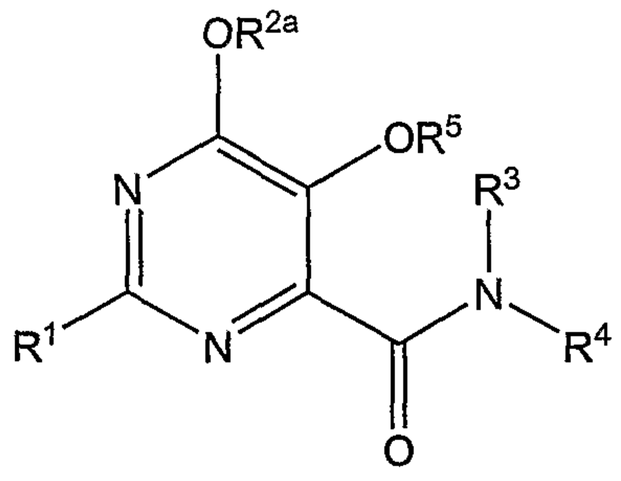
II

III. In one aspect, the invention includes phosphonate analogs of quinoline compounds represented by the Formula III:



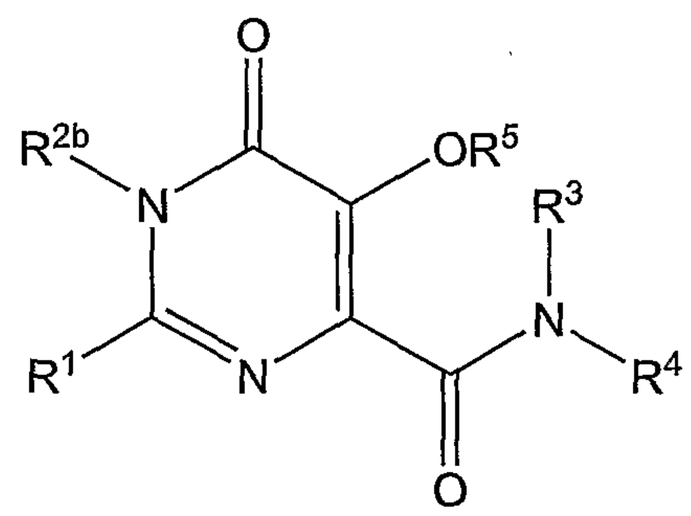
III

IV. In one aspect, the invention includes phosphonate analogs of 4,5-dihydroxypyrimidine, 6-carboxamide compounds having Formula IV:



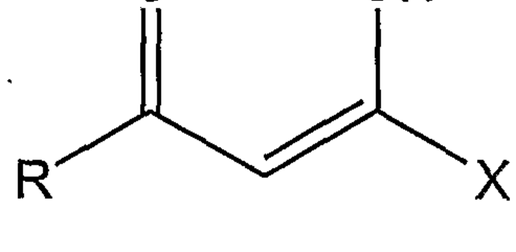
IV

V. In one aspect, the invention includes phosphonate analogs of 3-N-substituted, 5-hydroxypyrimidinone, 6-carboxamide compounds having Formula V:



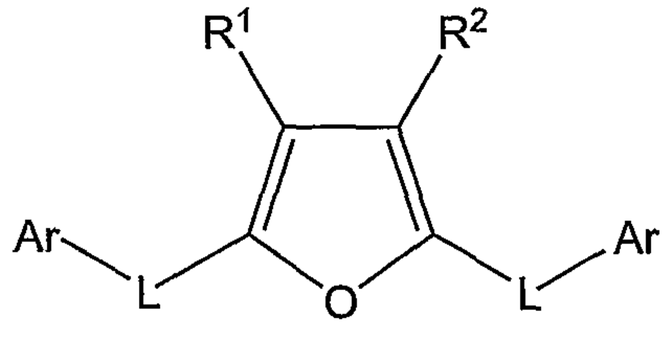
V

VI. In one aspect, the invention includes phosphonate analogs of 1,3 diketo compounds having Formula VI:



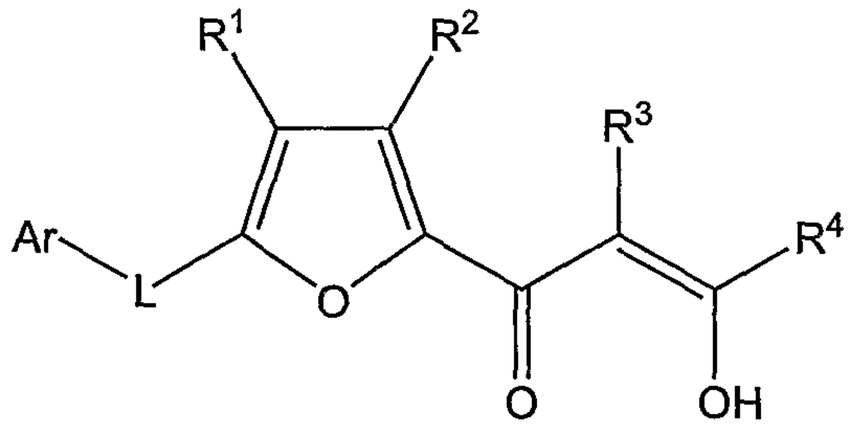
VI

VII. In one aspect, the invention includes phosphonate analogs of 2,5 diarylsubstituted, furan compounds having Formula VII:



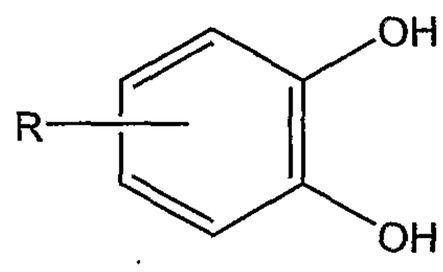
VII

VIII. In one aspect, the invention includes phosphonate analogs of 2,5 substituted, diketo-furan compounds having Formula VIII:



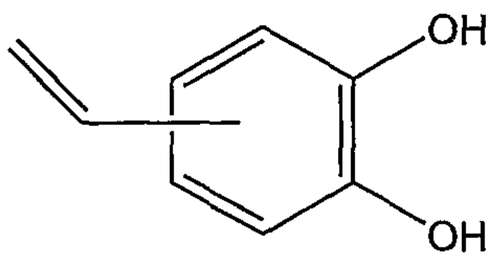
VIII

IX. In one aspect, the invention includes phosphonate analogs of catechol compounds including caffeic acid phenylethyl ester (CAPE) compounds having Formula IX:



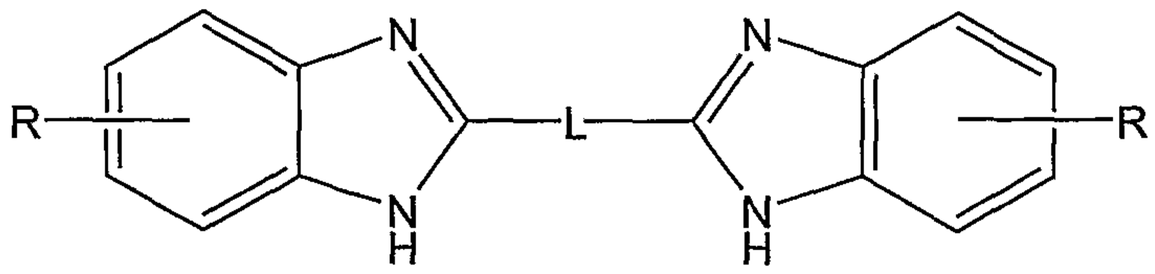
IX

X. Catechol compounds IX include phosphonate analogs of styryl catechol compounds and analogs of chicoric acid. Phosphonate analogs of styryl catechol compounds generally have Formula X:



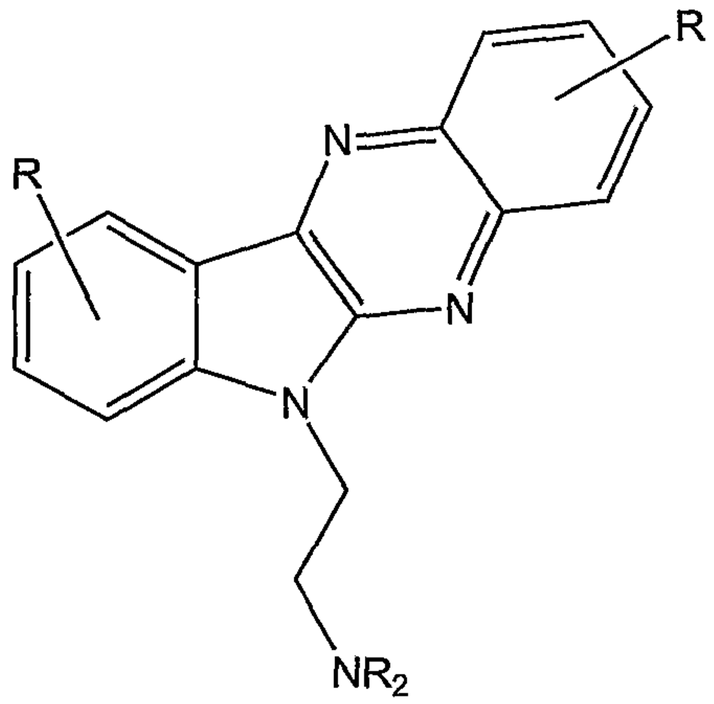
X

XI. In one aspect, the invention includes phosphonate analogs of benzimidazole compounds and bis-benzimidazole compounds having Formula XI:



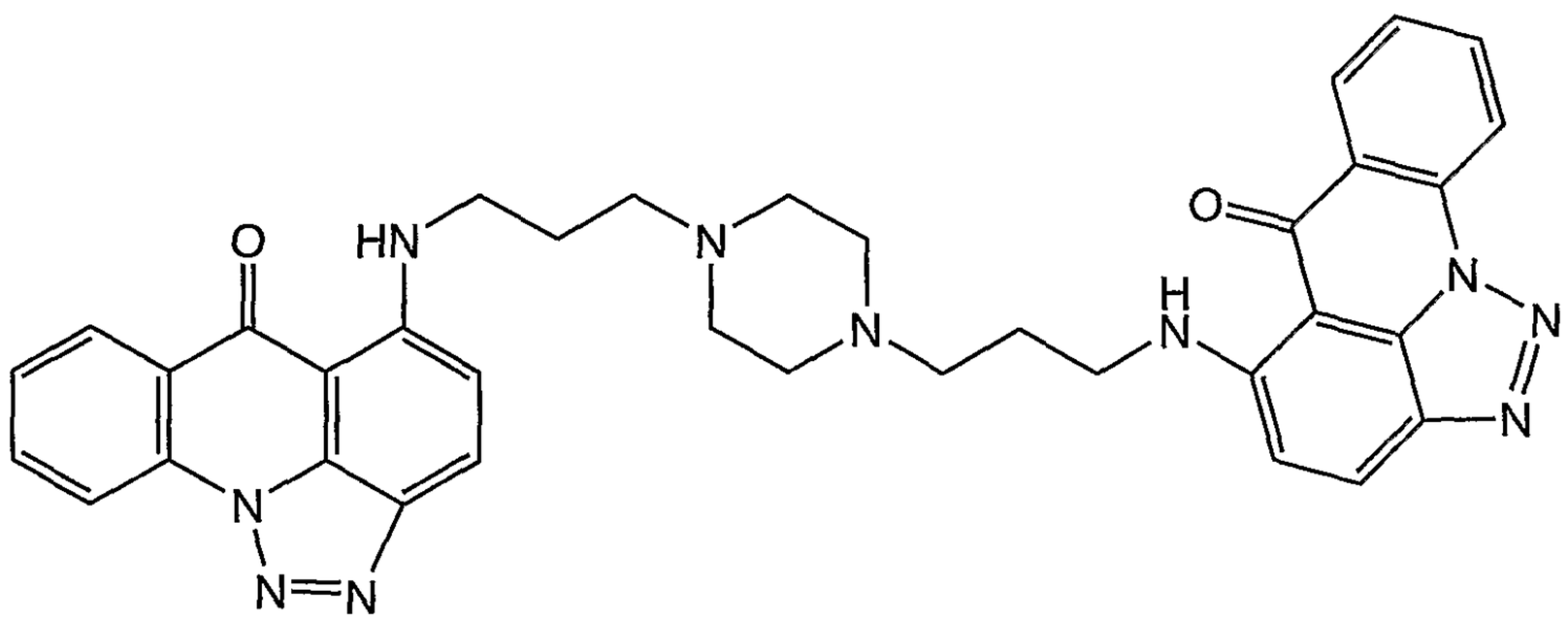
XI

XII. In one aspect, the invention includes phosphonate analogs of indoloquinoxaline compounds having Formula XII:



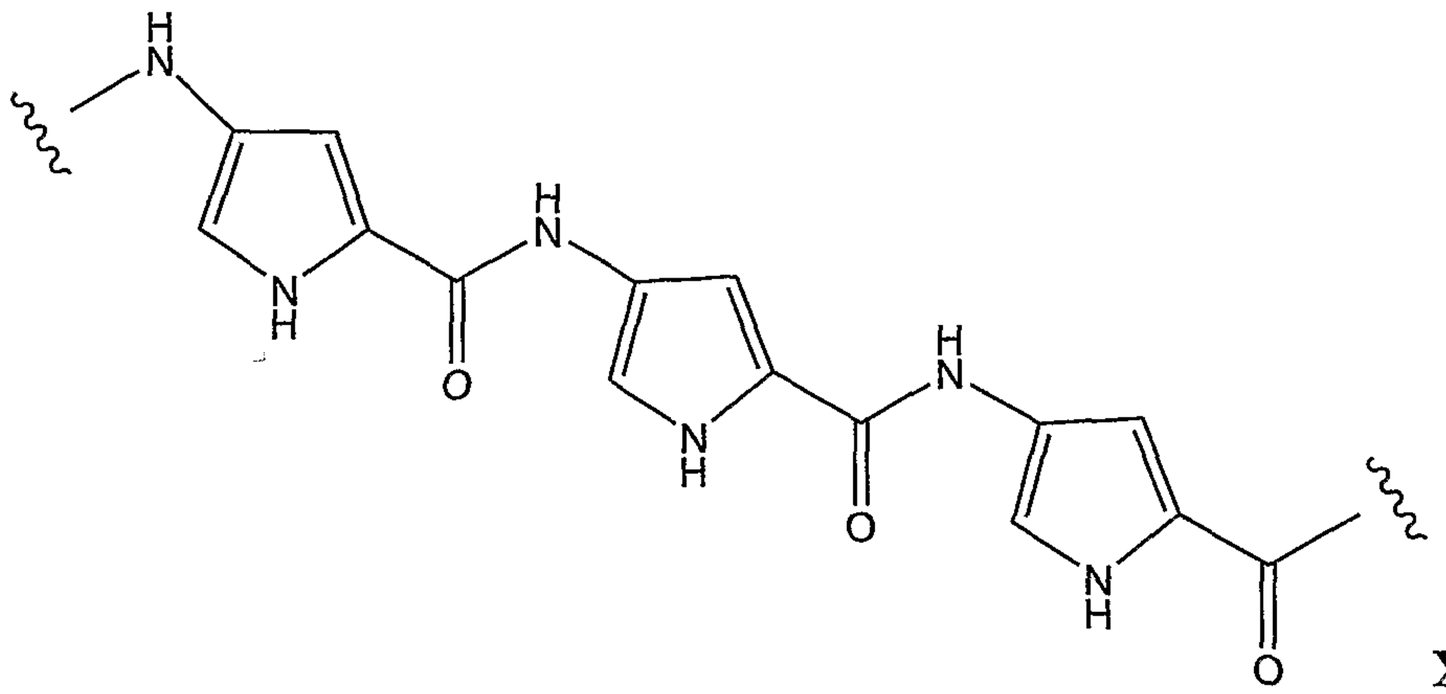
XII

XIII. In one aspect, the invention includes phosphonate analogs of acridine compounds including phosphonate analogs of bis-acridine compounds having Formula XIII:



XIII

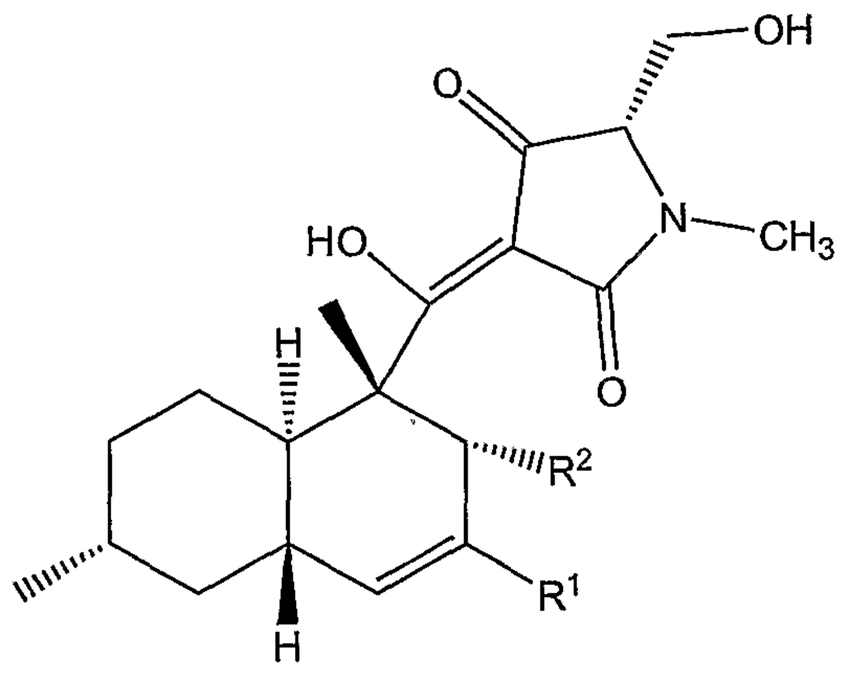
XIV. In one aspect, the invention includes phosphonate analogs of polyamide, DNA binding compounds, such as polypyrrole amide phosphonate oligomers having Formula XIV:



XIV

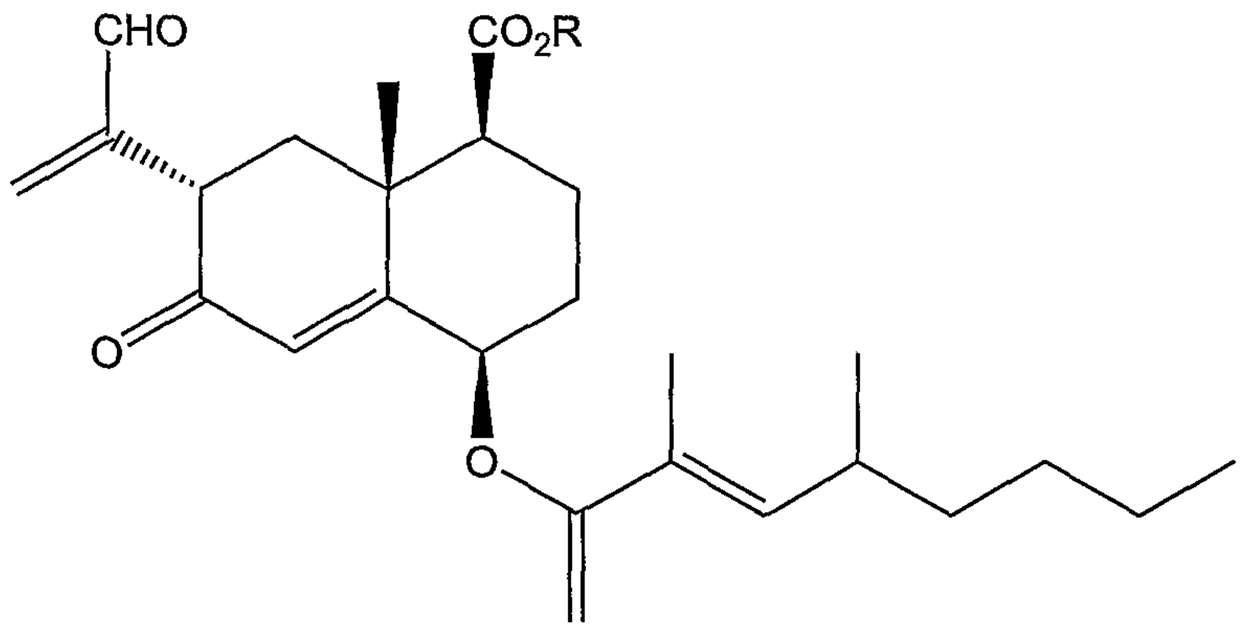
where the wavy lines indicate the depicted structure is a substructure of a repeating polymer molecule.

XV. In one aspect, the invention includes phosphonate analogs of [6,6] bicyclic compounds, including integramycins and fungal metabolites having Formula XV:



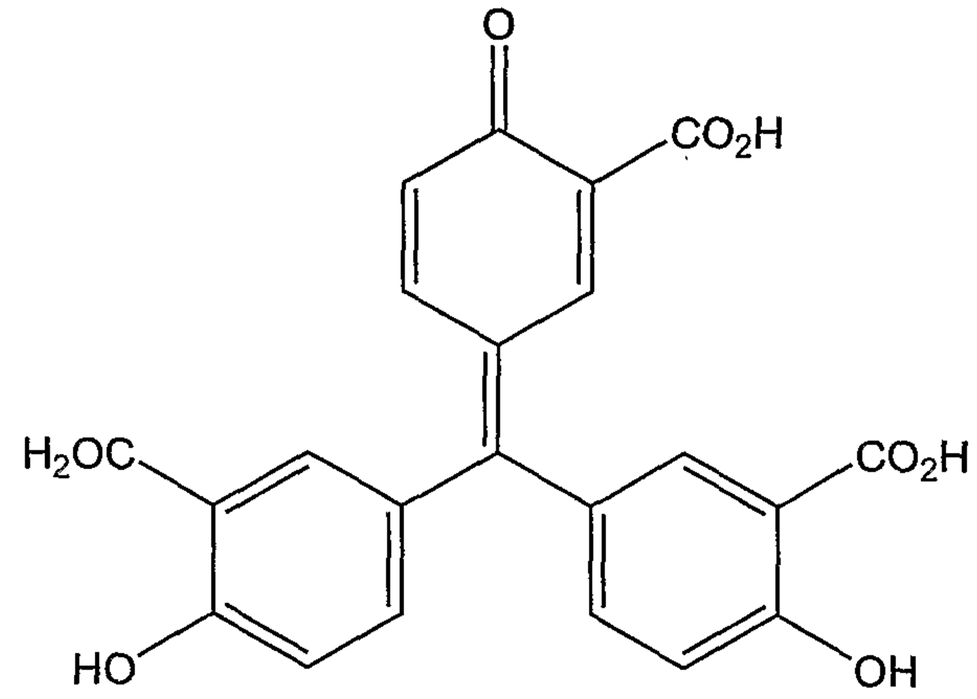
XV

XVI. In one aspect, the invention includes phosphonate analogs of [6,6] bicyclic terpenoid compounds having Formula XVI:



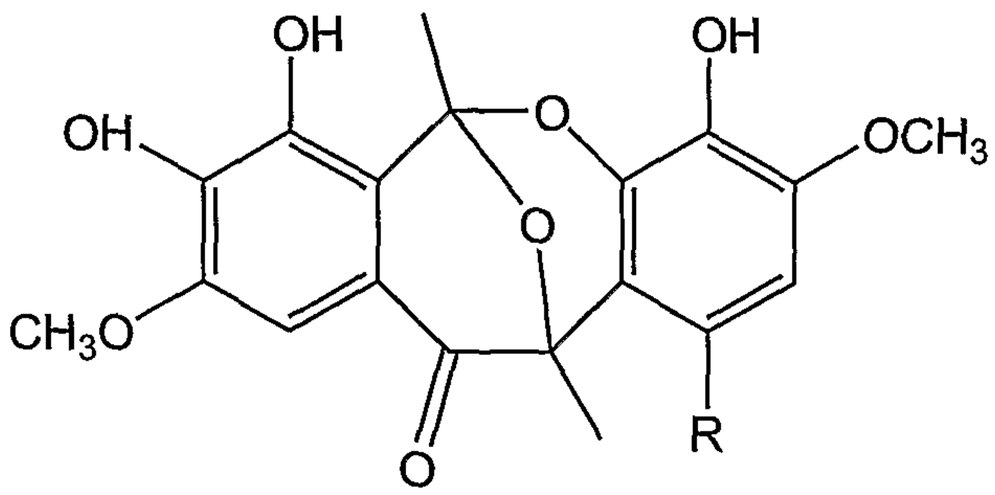
XVI

XVII. In one aspect, the invention includes phosphonate analogs of aurintricarboxylic acid compounds having Formula XVII:



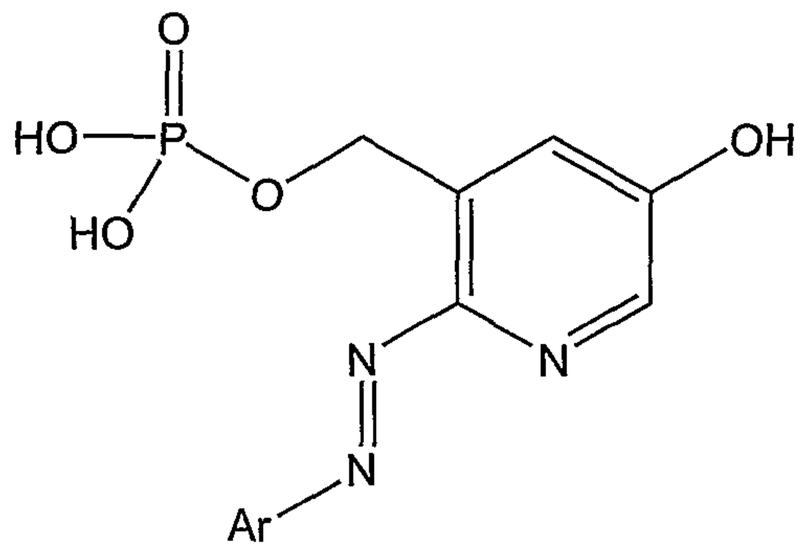
XVII

XVIII. In one aspect, the invention includes phosphonate analogs of integrastatin compounds having Formula XVIII:



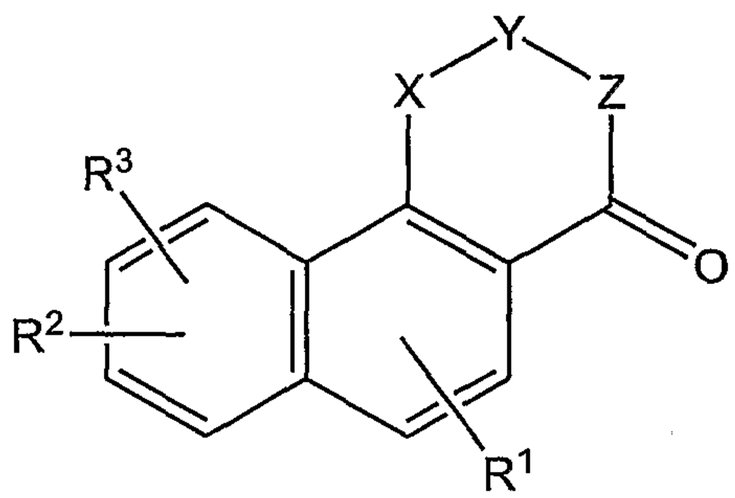
XVIII

XIX. In one aspect, the invention includes phosphonate analogs of 6-(arylazo)pyridoxal-5-phosphate compounds having Formula XIX:



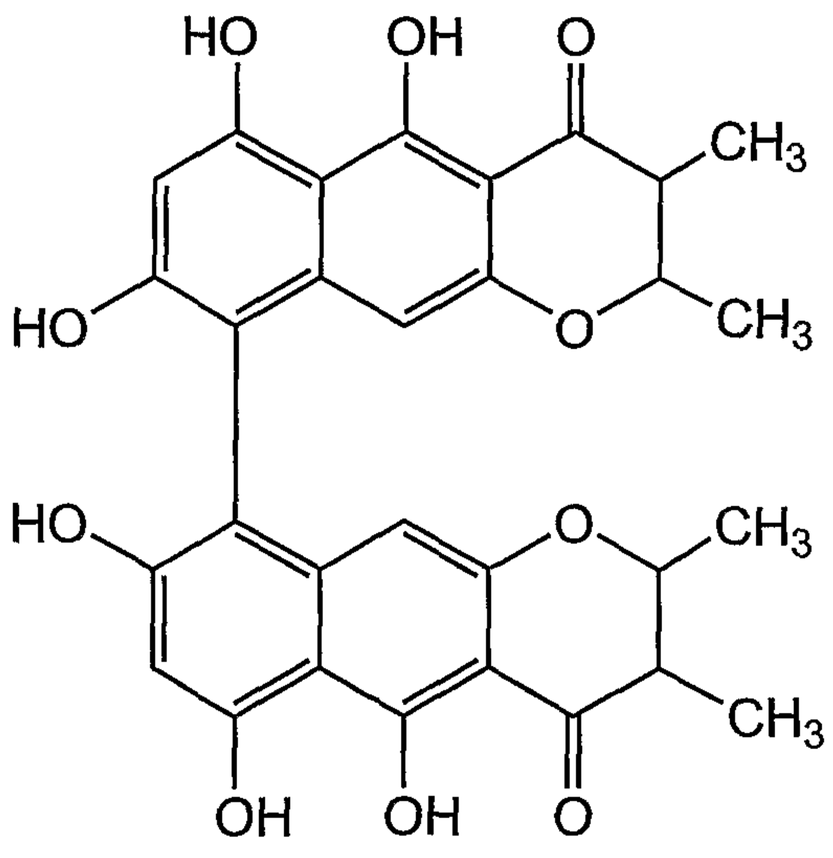
XIX

XX. In one aspect, the invention includes phosphonate analogs of 1,3-oxazine-, 1,3-thiazine-, pyran-, 1,4-oxazepine-, and 1,4-thiazepine-fused naphthalene compounds having Formula XX:



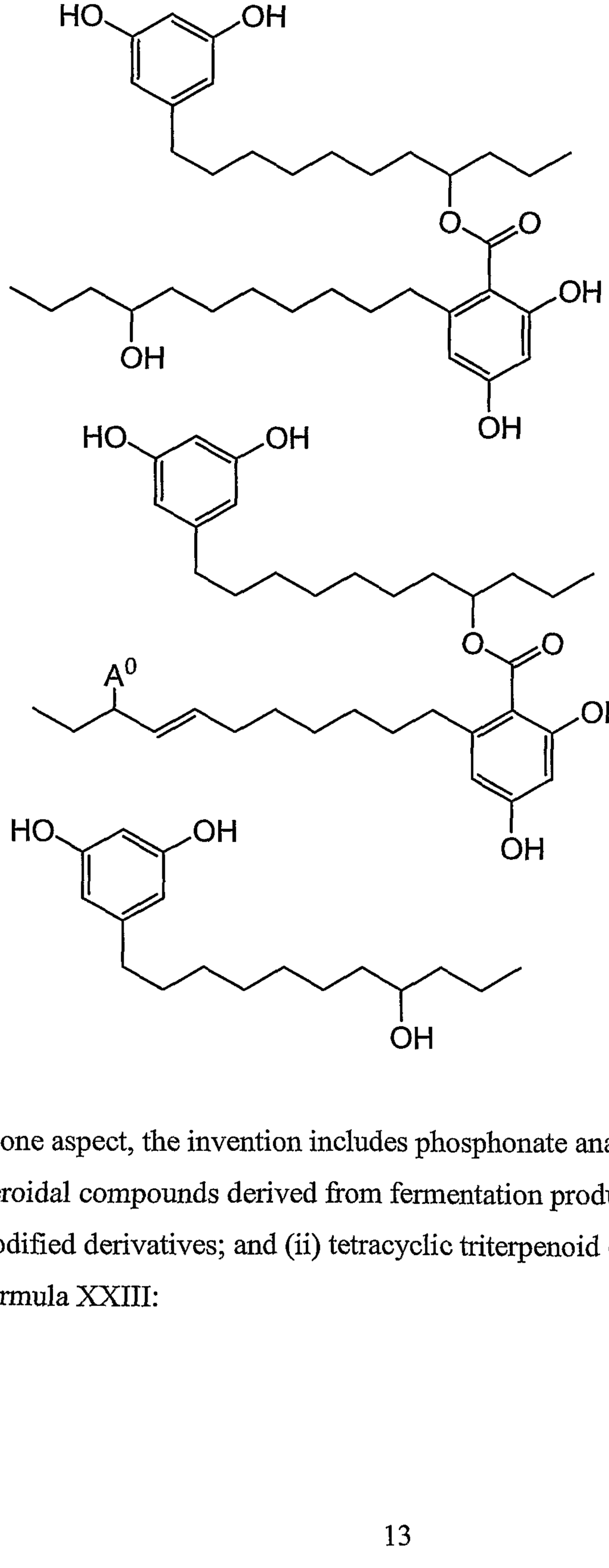
XX

XXI. In one aspect, the invention includes phosphonate analogs of chaetochromin compounds derived from chaetochromin fermentation products and their chemically modified derivatives including naphtho-γ-pyrones having Formula XXI:



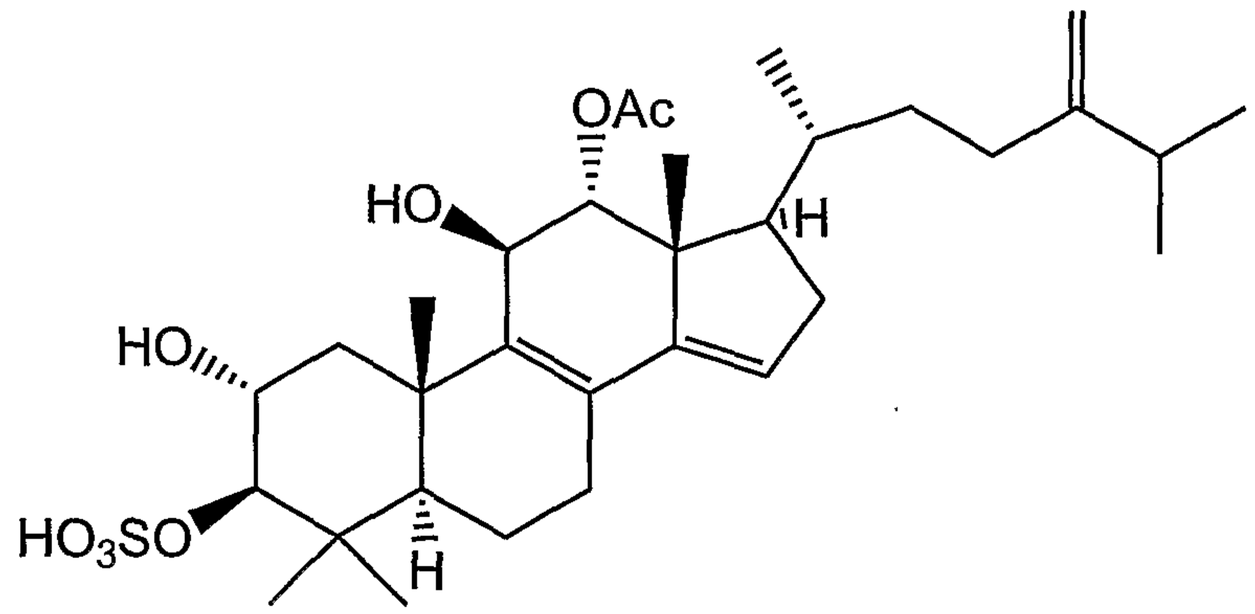
XXI

XXII. In one aspect, the invention includes phosphonate analogs of hydroxyphenylundecane compounds derived from fermentation products and their chemically modified derivatives including integracins having Formula XXII:



XXII

XXIII. In one aspect, the invention includes phosphonate analogs of: (i) tetracyclic steroidal compounds derived from fermentation products and their chemically modified derivatives; and (ii) tetracyclic triterpenoid compounds having Formula XXIII:



XXIII

XXIV. In one aspect, the invention includes phosphonate analogs of plant natural products including: (i) glycerrhenitic and betulonic acids; (ii) compounds from Coleus parvifolius Benth.; (iii) eudesmane-type sesquiterpenes and aporphine alkaloid lindechunines from Lindera chunii roots including hernandonine, laurolistine, 7-oxohernangerine and lindechunine A; and (iv) lithospermic acid.

XXV. In one aspect, the invention includes phosphonate analogs of tetracyclic aromatic ketone compounds and derived from fungal cultures and fungus, and their chemically modified derivatives.

XXVI. In one aspect, the invention includes phosphonate analogs of aromatic compounds derived from lichen extracts, and their chemically modified derivatives.

XXVII. In one aspect, the invention includes phosphonate analogs of salicylhydrazide and mercaptosalicylhydrazide compounds.

XXVIII. In one aspect, the invention includes phosphonate analogs of thiazolothiazepine compounds.

XXIX. In one aspect, the invention includes phosphonate analogs of benzodiazepine hydrazide compounds.

XXX. In one aspect, the invention includes phosphonate analogs of coumarin compounds, including Lamellarin-type marine natural products.

XXXI. In one aspect, the invention includes phosphonate analogs of brominated polyacetylene marine natural products from sponges such as Diplastrella sp.

XXXII. In one aspect, the invention includes phosphonate analogs of cobalamin compounds.

XXXIII. In one aspect, the invention includes phosphonate analogs of hydroxylated aromatic compounds, including: tetracycline compounds; anthraquinones and naphthoquinones; and flavones, flavanones, flavanols, and flavanoids including thalassiolins and benzopyrano-oxopyrimidotetrahydrothiazines.

XXXIV. In one aspect, the invention includes phosphonate analogs of various sulfur-containing compounds including phosphonate analogs of: polyanionic sulfonate suramin and dextran sulfate; diaryl sulfones; sulfonamides; aromatic disulfides; and 2-mercaptobenzenesulfonamides.

XXXV. In one aspect, the invention includes phosphonate analogs of symmetrical pentamidine compounds derived from serine protease inhibitors.

XXXVI. In one aspect, the invention includes phosphonate analogs of nucleic acid compounds. Nucleic acid phosphonate compounds include: (a) nucleosides and nucleotides; dinucleotides, including 5H-pyrano[2,3-d:-6,5-d']dipyrimidines; (b) oligonucleotides; and (c) analogs thereof, with one or more phosphonate groups. Nucleic acid analogs include nucleobase, sugar, and internucleotide phosphate analogs.

XXXVII. In one aspect, the invention includes phosphonate analogs of amino acids and peptides.

XXXVIII. In one aspect, the invention includes phosphonate analogs of polyketide natural products including Xanthoviridicatins isolated from a fermentation broth of an endophytic strain of Penicillium chrysogenum.

XXXIX. In one aspect, the invention includes phosphonate analogs of polyketide natural products including cytosporic acid, australifungin and australifunginol isolated from a fermentation broth of the filamentous fungus.

The compounds of the invention, including Formulas I-XXXIX, are substituted with one or more covalently attached phosphonate groups. Formulas I-XXXIX are "scaffolds", i.e. substructures which are common to the specific compounds encompassed therein.

It is to be understood that the scope of the invention includes compounds in which hydrogen atoms at any of the various positions in Formulas I-XXXIX are independently substituted with non-hydrogen substituents. In particular, the variable positions on the scaffolds of Formulas I-XXXIX and experimental HIV integrase inhibitors of Groups I-XXXIX are independently substituted with the non-hydrogen substituents described herein.

The invention includes pharmaceutically acceptable salts of Formulas I-XXXIX, and all enol and tautomeric resonance isomers thereof. Except where the stereochemistry is explicit, the compounds of the invention include all stereoisomers; i.e. each enantiomer, diastereomer, and atropisomer in purified form, or racemic and isomerically enriched mixtures.

The invention provides a pharmaceutical composition comprising an effective amount of a compound selected from Formulas I-XXXIX, or a pharmaceutically acceptable salt thereof, in a formulation, i.e. in combination with a pharmaceutically acceptable excipient, diluent or carrier.

The invention includes combination formulations including the compounds of the invention, with other active ingredients that treat or prevent HIV infections. Such combination formulations may be a fixed dose of two or more active ingredients, including at least one compound of the invention.

This invention also pertains to a method of increasing cellular accumulation and retention of drug compounds, thus improving their therapeutic and diagnostic value.

The use of the compounds of the invention in an HIV infected patient, or in a sample suspected of containing HIV, anticipates all metabolites of the compounds so administered which occur by solvolysis, hydrolysis, photolysis, or by enzymatic action which converts or degrades the administered compound into, e.g. an activated form, an incorporated form, a cleaved form, or a metabolite for excretion.

The invention also provides a method of inhibiting HIV, comprising administering to a mammal infected with HIV (HIV positive) an amount of a compound of Formulas I-XXXIX, effective to inhibit the growth of said HIV infected cells.

The invention also provides a compound selected from Formulas I-XXXIX for use in medical therapy, as well as the use of a compound of Formulas I-XXXIX for the manufacture of a medicament useful for: (1) the treatment of AIDS or ARC (AIDs related complex); or (2) the prophylaxis of infection by HIV.

The invention also provides processes and novel intermediates disclosed herein which are useful for preparing compounds of the invention. Other aspects of the invention are novel methods for synthesis, i.e. preparation, of the compounds of the invention.

Some of the compounds of Formulas I-XXXIX are useful to prepare other compounds of Formulas I-XXXIX.

One aspect of the invention is the inhibition of the activity of HIV integrase by a method comprising the step of treating a sample suspected of containing HIV virus with a compound or composition of the invention.

Other aspects of the invention are formulation compositions of the compounds of the invention, as well as methods of formulating the compositions.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those

embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims.

DEFINITIONS

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

When tradenames are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

The terms "phosphonate" and "phosphonate group" mean a functional group or moiety within a molecule that comprises at least one phosphorus-carbon bond, and at least one phosphorus-oxygen double bond. The phosphorus atom is further substituted with oxygen, sulfur, or nitrogen substituents. These substituents may be part of a prodrug moiety. As defined herein, "phosphonate" and "phosphonate group" include moieties with phosphonic acid, phosphonic monoester, phosphonic diester, phosphonamidate, and phosphonthioate functional groups.

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e. active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically-active compound. For a review of phosphorus prodrugs, see: Krise et al (1996) *Advanced Drug Delivery Reviews* 19:287-310.

"Pharmaceutically acceptable prodrug" refers to a compound that is metabolized in the host, for example hydrolyzed or oxidized, by either enzymatic action or by general acid or base solvolysis, to form an active ingredient. Typical examples of prodrugs of the compounds of the invention have biologically labile protecting groups on a functional moiety of the compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, esterified, deesterified, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated, photolyzed, hydrolyzed, or other functional group change or conversion involving forming or breaking chemical bonds on the prodrug.

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

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-CH_2OC(=O)R^9$ and acyloxymethyl carbonates $-CH_2OC(=O)OR^9$ where R^9 is C_1-C_6 alkyl, C_1-C_6 substituted alkyl, C_6-C_{20} aryl or C_6-C_{20} substituted aryl. The acyloxyalkyl ester was first used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. In certain compounds of the invention, a prodrug moiety is part of a phosphonate group. Subsequently, the acyloxyalkyl ester was used to deliver phosphonic acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-CH_2OC(=O)C(CH_3)_3$. Exemplary acyloxymethyl carbonate prodrug moieties are pivaloyloxymethylcarbonate (POC) $-CH_2OC(=O)OC(CH_3)_3$ and (pivoxil) $-CH_2OC(=O)OCH(CH_3)_2$.

The phosphonate group may be a phosphonate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a phosphonamidate-ester group.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (DeLambert et al (1994) *J. Med. Chem.* 37: 498). Phenyl

esters containing a carboxylic ester ortho to the phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate the parent phosphonic acid. In some cases, substituents at the *ortho*-or *para*-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, e.g. esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C–O bond to generate the phosphoric acid and the quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell et al (1992) *J. Chem. Soc. Perkin Trans. I* 2345; Brook et al WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier et al WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al (1993) *Antiviral Res.*, 22:155-174; Benzaria et al (1996) *J. Med. Chem.* 39:4958). Cyclic phosphonate esters have also been described as prodrugs of phosphorus-containing compounds (Erion et al, US Patent No. 6312662).

"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. The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as intermediates in the synthesis of the parental drug substance. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g. making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured

by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

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

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

For therapeutic use, salts of active ingredients of the compounds of the invention will 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.

"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 (-$CH(CH_3)C(CH_3)_3$.

"Alkenyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp^2 double bond. Examples include, but are not limited to: ethylene or vinyl (-$CH=CH_2$), allyl (-$CH_2CH=CH_2$), cyclopentenyl (-C_5H_7), and 5-hexenyl (-$CH_2CH_2CH_2CH_2CH=CH_2$)

"Alkynyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, *sp* triple bond. Examples include, but are not limited to: acetylenic (-C≡CH) and propargyl (-$CH_2C\equiv CH$),

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent

alkane. Typical alkylene radicals include, but are not limited to: methylene (-CH_2-) 1,2-ethyl (-CH_2CH_2-), 1,3-propyl (-$CH_2CH_2CH_2$-), 1,4-butyl (-$CH_2CH_2CH_2CH_2$-), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. Typical alkenylene radicals include, but are not limited to: 1,2-ethylene (-CH=CH-).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. Typical alkynylene radicals include, but are not limited to: acetylene (-C≡C-), propargyl (-CH_2C≡C-), and 4-pentynyl (-$CH_2CH_2CH_2$C≡CH-).

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

"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group comprises 6 to 20 carbon atoms, e.g. the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the arylalkyl group is 1 to 6 carbon atoms and the aryl moiety is 5 to 14 carbon atoms.

"Heteroarylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heteroaryl radical. Typical heteroarylalkyl groups include, but are not limited to, 2-benzimidazolylmethyl, 2-furylethyl, and the like. The heteroarylalkyl group comprises 6 to 20 carbon atoms, e.g. the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the heteroarylalkyl group is 1 to 6 carbon atoms and the

heteroaryl moiety is 5 to 14 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S. The heteroaryl moiety of the heteroarylalkyl group may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S), for example: a bicyclo [4,5], [5,5], [5,6], or [6,6] system.

"Substituted alkyl", "substituted aryl", and "substituted arylalkyl" mean alkyl, aryl, and arylalkyl respectively, in which one or more hydrogen atoms are each independently replaced with a substituent. Typical substituents include, but are not limited to, -X, -R, $-O^-$, -OR, -SR, $-S^-$, $-NR_2$, $-NR_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, NC(=O)R, -C(=O)R, -C(=O)NRR $-S(=O)_2O^-$, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)O_2RR$, $-P(=O)O_2RR$ $-P(=O)(O^-)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)X, -C(S)R, -C(O)OR, $-C(O)O^-$, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, -C(NR)NRR, where each X is independently a halogen: F, Cl, Br, or I; and each R is independently -H, alkyl, aryl, heterocycle, protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

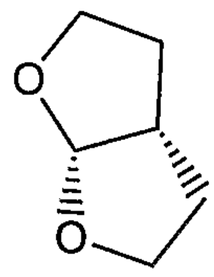
"Heteroaryl" and "Heterocycle" refer to a ring system in which one or more ring atoms is a heteroatom, e.g. nitrogen, oxygen, and sulfur. The heterocycle radical comprises 5 to 14 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S. A heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S), for example: a bicyclo [4,5], [5,5], [5,6], or [6,6] system.

Heterocycles are 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.

Examples of heterocycles include by way of example and not limitation pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl,

indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, bis-tetrahydrofuranyl, tetrahydropyranyl, bis-tetrahydropyranyl, 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, 4aH-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, and isatinoyl.

One embodiment of the bis-tetrahydrofuranyl group is:



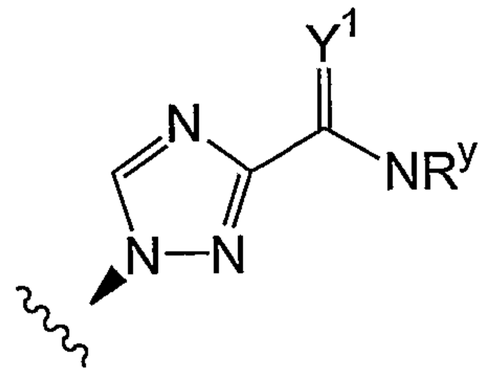
By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran,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

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-

pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Carbocycle" means a saturated, unsaturated or aromatic ring having 3 to 7 carbon atoms as a monocycle or 7 to 12 carbon atoms as a bicycle. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles 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. 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.

"Nucleobase" means any nitrogen-containing heterocyclic moiety capable of forming Watson-Crick hydrogen bonds in pairing with a complementary nucleobase or nucleobase analog, e.g. a purine, a 7-deazapurine, or a pyrimidine. Typical nucleobases are the naturally occurring nucleobases: adenine, guanine, cytosine, uracil, thymine, and analogs of the naturally occurring nucleobases, e.g. 7-deazaadenine, 7-deazaguanine, 7-deaza-8-azaguanine, 7-deaza-8-azaadenine, inosine, nebularine, nitropyrrole, nitroindole, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, pseudouridine, pseudocytosine, pseudoisocytosine, 5-propynylcytosine, isocytosine, isoguanine, 7-deazaguanine, 2-thiopyrimidine, 6-thioguanine, 4-thiothymine, 4-thiouracil, O^6-methylguanine, N^6-methyladenine, O^4-methylthymine, 5,6-dihydrothymine, 5,6-dihydrouracil, 4-methylindole, pyrazolo[3,4-D]pyrimidines (U.S. Patent Nos. 6,143,877 and 6,127,121; WO 01/38584), and ethenoadenine (Fasman (1989) in *Practical Handbook of Biochemistry and Molecular Biology*, pp. 385-394, CRC Press, Boca Raton, Fl). Nucleobases include the five-membered heterocyclic nucleobase analogs disclosed in WO 03/073989 A2 such as substituted triazoles:



Nucleobases also include any of the above nitrogen-containing heterocyclic moieties which have one or more protecting groups (PG) covalently attached to reactive functionality, such as the N-2 or N-6 exocyclic amino of purines, the N-3 or N-4 nitrogen of pyrimidines, or the O-6 oxygen of guanine type nucleobases. Suitable nucleobase protecting groups include amide-forming groups such as benzoyl or isobutyramide, acetamidine-forming groups, and formamidine-forming groups such as dimethylformamidyl (dmf). Reactive functionality of nucleobases can also be protected with transient groups such as 6-chloro of purines.

Nucleobases are typically attached in the configurations of naturally-occurring nucleic acids to the sugar moiety through a covalent bond between the 1' carbon of the sugar moiety and the N-9 of purines, e.g. adenin-9-yl and guanin-9-yl, or N-1 of pyrimidines, e.g. thymin-1-yl and cytosin-1-yl (Blackburn, G. and Gait, M. Eds. "DNA and RNA structure" in Nucleic Acids in Chemistry and Biology, 2nd Edition, (1996) Oxford University Press, pp. 15-81).

"Linker" or "link" means a chemical moiety comprising a covalent bond or a chain of atoms that covalently attaches a phosphonate group to a drug. In various embodiments, a linker is specified as L. Linkers include a divalent radical such as an alkyldiyl, an aryldiyl, or a heteroaryldiyl; or portions of substituent A^1 enumerated in Formulas I-XXXIX, which include moieties such as: $-(CR_2)_nO(CR_2)_n-$, repeating units of alkyloxy (e.g. polyethylenoxy, PEG, polymethyleneoxy) and alkylamino (e.g. polyethyleneamino, Jeffamine™); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

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

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

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

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

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

HIV Integrase Inhibitor Phosphonate Compounds

The compounds of the invention include those with HIV integrase inhibitory activity. In particular, the compounds include HIV integrase inhibitors. The compounds of the inventions bear at least one phosphonate group, selected from: phosphonic acid, phosphonate monoester, phosphonate diester, phosphonamidate, phosphonthioate, phosphondithioate, phosphonamidate-ester prodrug, or a phosphonbisamidate-ester (Jiang et al, US 2002/0173490 A1), any of which may be a prodrug moiety.

The compositions of the invention include all known approved, experimental, and proposed HIV integrase inhibitors, that do not already comprise a phosphonate group, with at least one phosphonate group covalently attached. The invention includes novel phosphonate analogs of the following experimental HIV integrase inhibitors in Groups I to XXXIX that do not already comprise a phosphonate group. Embodiments of the invention include phosphonate analogs of compounds that fall within the generic scope of the documents cited in Groups I to XXXIX.

It is to be understood that the scope of the invention includes compounds in which hydrogen atoms at any of the various positions in Formulas I-XXXIX are independently substituted with non-hydrogen substituents, including those designated with A^0, A^1, A^2, and A^3.

The invention includes pharmaceutically acceptable salts of Formulas I-XXXIX, and all enol and tautomeric resonance isomers thereof.

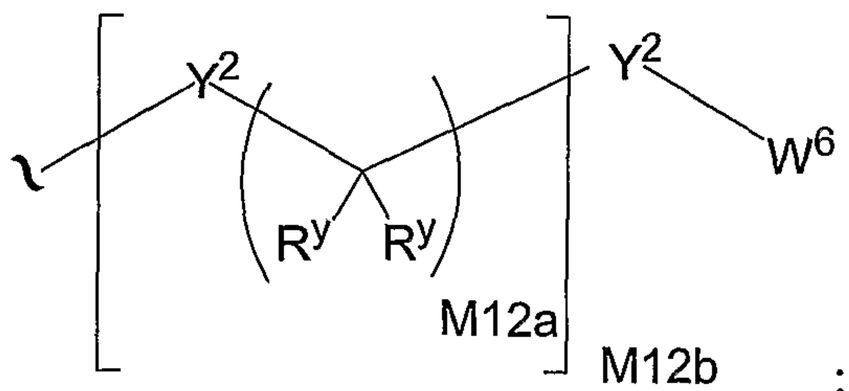
The compounds of the invention, including Formulas I-XXXIX, are substituted with one or more covalently attached groups, including at least one phosphonate group, i.e. A^1 or A^3. Formulas I-XXXIX are "scaffolds", i.e. substructures which are common to the specific compounds encompassed therein.

Formulas I-XXXIX are substituted with one or more covalently attached A^0 groups, including simultaneous substitutions at any or all A^0.

A^0 is A^1, A^2 or W^3.

Compounds of Formulas I-XXXIX include at least one A^1 and thus include at least one A^3.

A^1 is:



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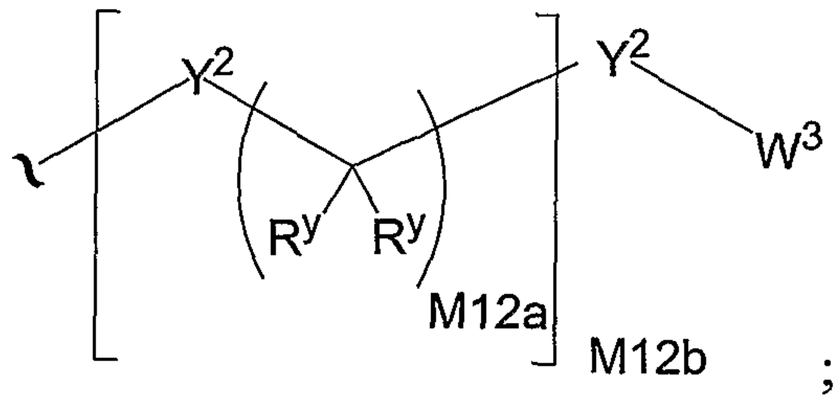
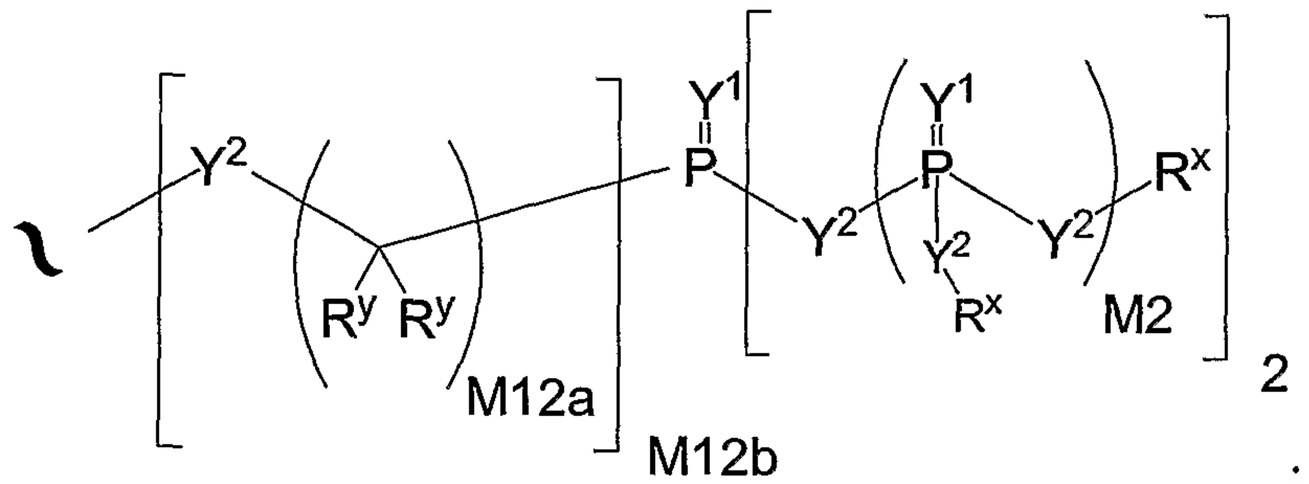
A^2 is:



;

A^3 is:



;

where:

Y^1 is independently O, S, NR^x, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)_2)$;

Y^2 is independently a bond, O, NR^x, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)_2)$, -S(O)- (sulfoxide), $-S(O)_2-$ (sulfone), -S- (sulfide), or -S-S- (disulfide);

M2 is 0, 1 or 2;

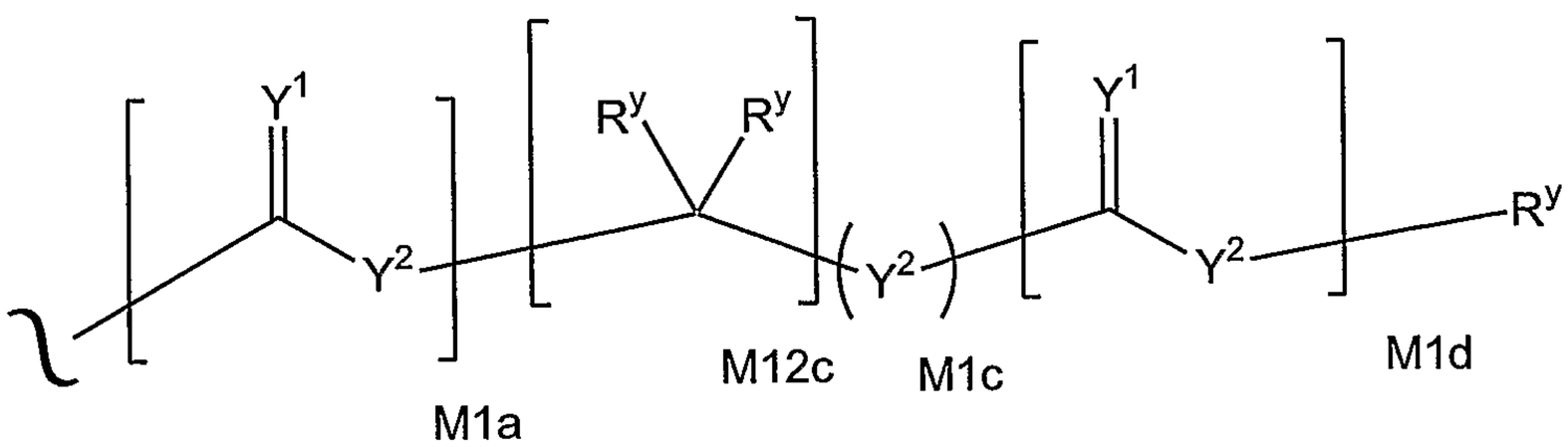
M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12; and

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

Further for the purposes of A^1, A^2 and A^3:

R^y is independently H, C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, or a protecting group, or where taken together at a carbon atom, two vicinal R^y groups form a carbocycle or a heterocycle. Alternatively, taken together at a carbon atom, two vicinal R^y groups form a ring, i.e. a spiro carbon. The ring may be all carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, or alternatively, the ring may contain one or more heteroatoms, for example, piperazinyl, piperidinyl, pyranyl, or tetrahydrofuryl;

R^x is independently H, C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, or a protecting group, or the formula:



;

where M1a, M1c, and M1d are independently 0 or 1, and M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^{3a} is W^{4a} or W^{5a};

W^{4a} is R^{5a}, $-C(Y^1)R^{5a}$, $-C(Y^1)W^{5a}$, $-SO_2R^{5a}$, or $-SO_2W^{5a}$;

W^{5a} is a multivalent substituted carbocycle or heterocycle wherein W^{5a} is independently substituted with 0 to 3 R^2 groups;

W^6 is W^{3a} independently substituted with 1, 2, or 3 A^3 groups;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups. Alternatively, taken together at a carbon atom, two R^2 groups form a ring, i.e. a spiro carbon. The ring may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. The ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)_2$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)N(R^x)_2$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)N(R^x)_2$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)N(R^x)_2$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)N(R^x)_2$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups; and

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups.

R is independently selected from H, C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocycle, C_2–C_{20} substituted heterocycle, phosphonate, phosphate, polyethyleneoxy, a protecting group, L–A^3, and a prodrug moiety.

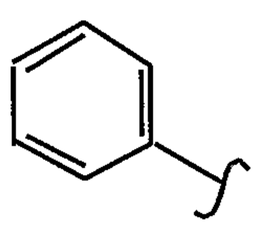
Substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, and substituted heterocycle are independently substituted with one or more substituents selected from F, Cl, Br, I, OH, amino (–NH_2), ammonium (–NH_3^+), alkylamino (–NHR), dialkylamino (–NR_2), trialkylammonium (–NR_3^+), C_1–C_8 alkyl, C_1–C_8 alkylhalide, carboxylate, thiol (–SH), sulfate (–OSO_3R), sulfamate, sulfonate (–SO_3R), 5-7 membered ring sultam, C_1–C_8 alkylsulfonate, C_1–C_8 alkylamino, 4-dialkylaminopyridinium, C_1–C_8 alkylhydroxyl, C_1–C_8 alkylthiol, alkylsulfone (–SO_2R), arylsulfone (–SO_2Ar), arylsulfoxide (–SOAr), arylthio (–SAr), sulfonamide (–SO_2NR_2), alkylsulfoxide (–SOR), ester (–COOR), amido (–C(=O)NR_2), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile (–CN), azido (–N_3), nitro (–NO_2), C_1–C_8 alkoxy (–OR), C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocycle, and C_2–C_{20} substituted heterocycle, phosphonate, phosphate, polyethyleneoxy, and a prodrug moiety.

L is a bond or any linker which covalently attaches a phosphonate group to a drug scaffold. For example, L may be a bond, O, S, S–S (disulfide), S(=O) (sulfoxide), $S(=O)_2$ (sulfone), $S(=O)_2NR$ (sulfonamide), NR, N–OR, C_1–C_{12} alkylene, C_1–C_{12} substituted alkylene, C_2–C_{12} alkenylene, C_2–C_{12} substituted alkenylene, C_2–C_{12} alkynylene, C_2–C_{12} substituted alkynylene, –$(CR_2)_nO(CR_2)_n$–, C(=O)NH, OC(=O)NH, NHC(=O)NH, C(=O), C(=O)$NH(CH_2)_n$, or $(CH_2CH_2O)_n$, where n may be 1, 2, 3, 4, 5, or 6.

Further for the purposes of A^1, A^2 and A^3 and other substituents described in the compounds of the invention:

Carbocycles and heterocycles may be independently substituted with 0 to 3 R^2 groups. Carbocycles and heterocycles may be a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. Carbocycles and heterocycles may have 3 to 10 ring atoms, e.g., 3 to 7 ring atoms. The W^5 rings are saturated when containing 3 ring atoms, saturated or mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when containing 6 ring atoms.

Carbocycles and heterocycles include, but are not limited to, examples such as: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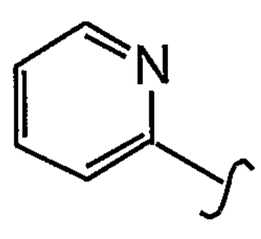
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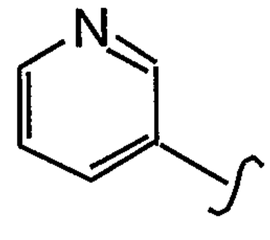
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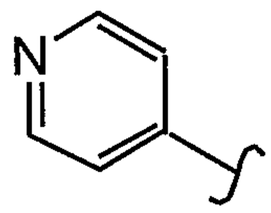
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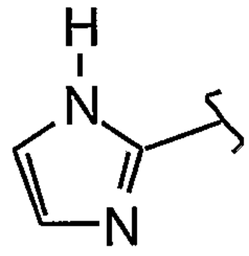
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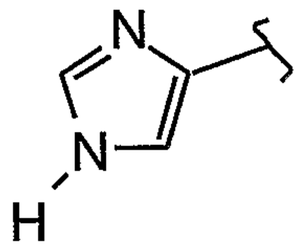
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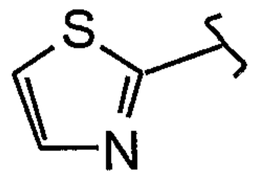
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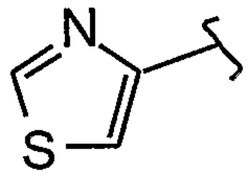
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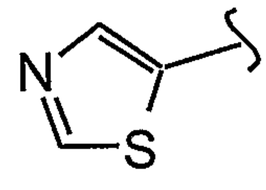
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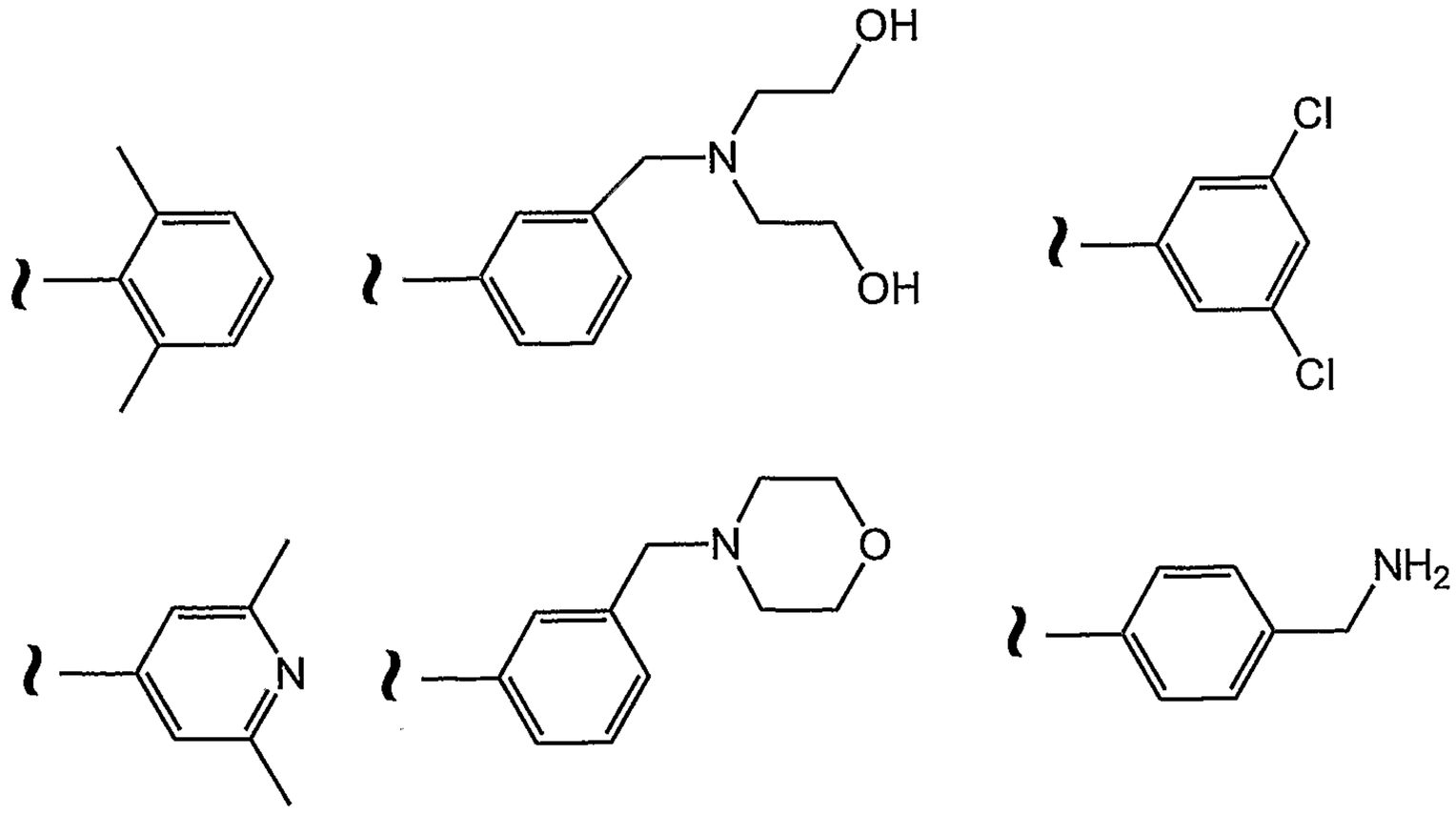
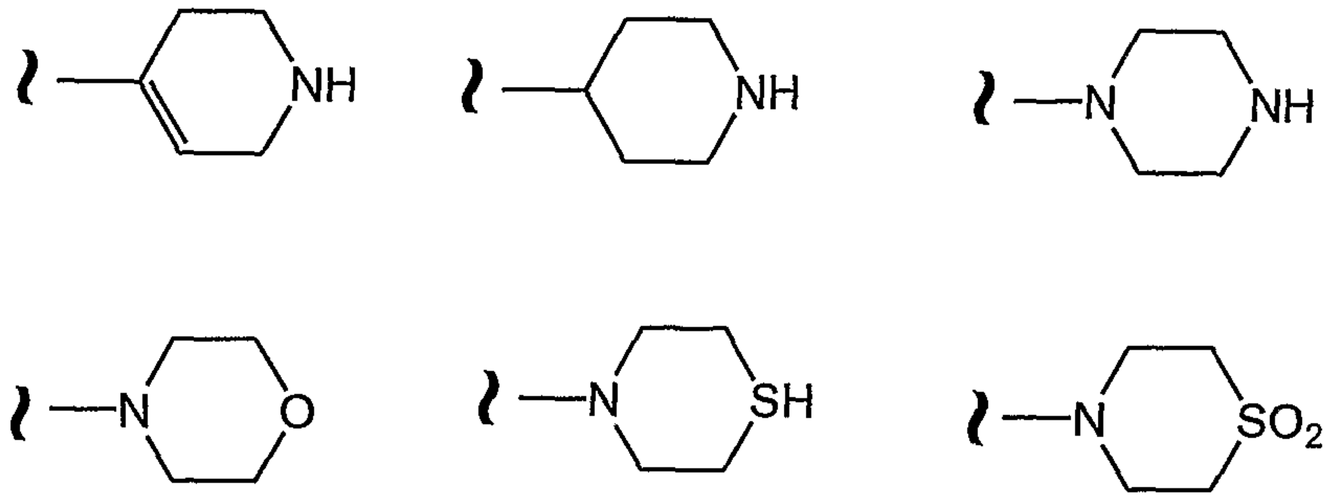
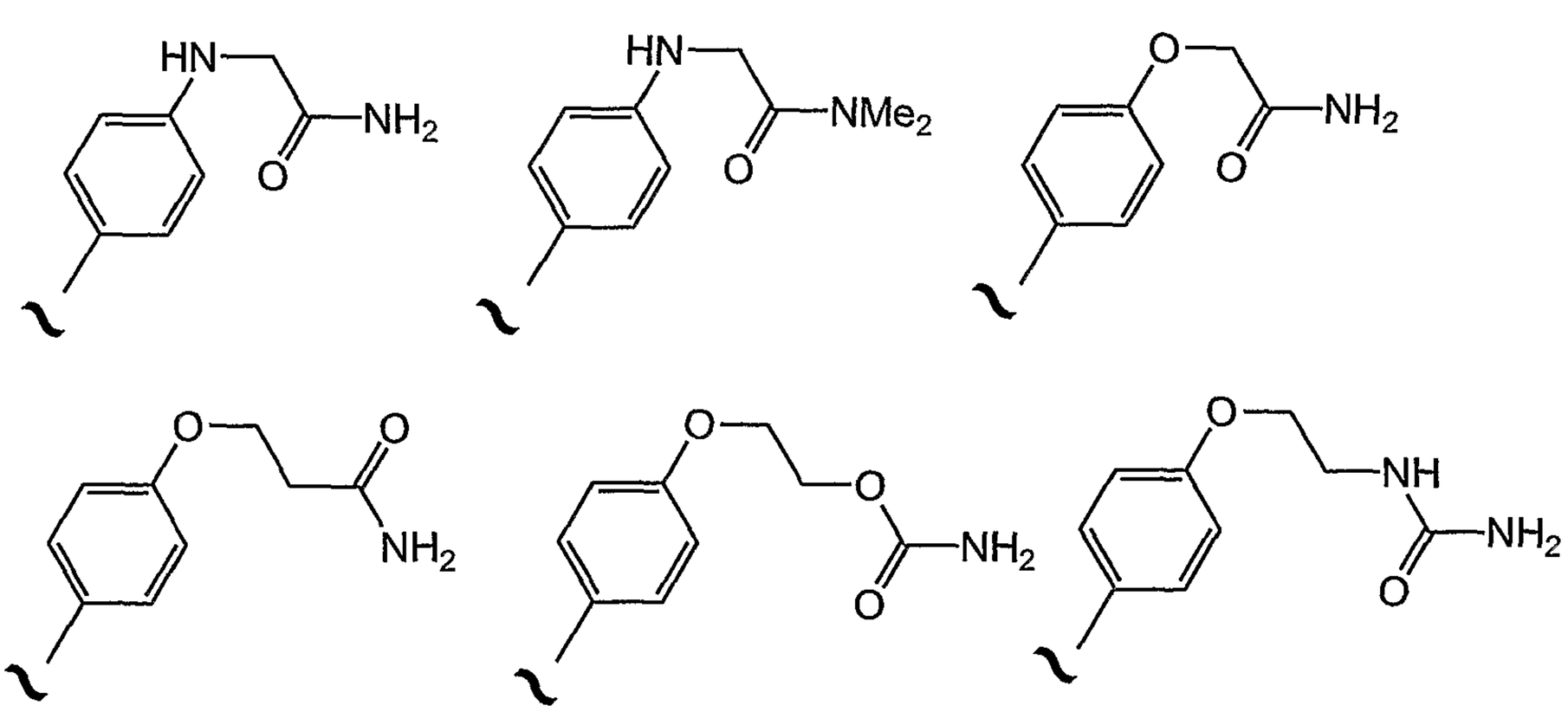
Carbocycles and heterocycles may be independently substituted with 0 to 3 groups, as defined above. For example, substituted carbocycles (Ar) include:



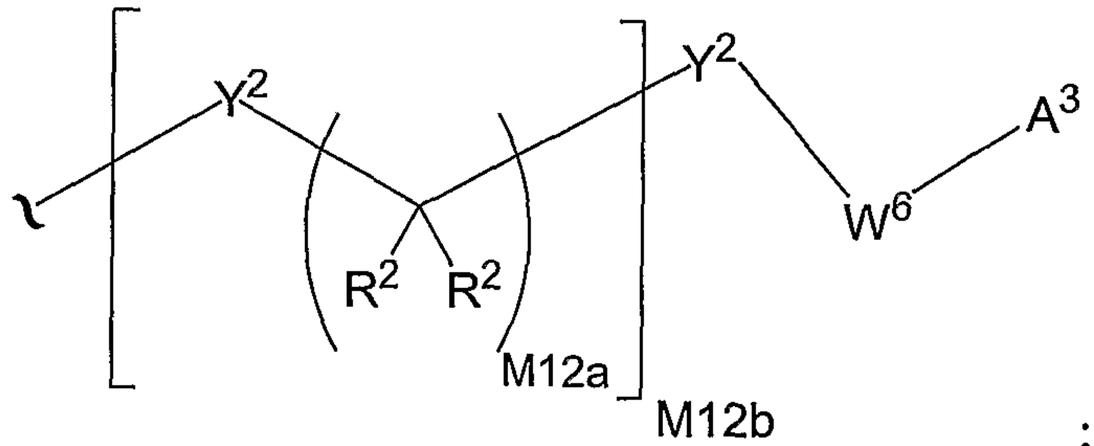


where a wavy line , in any orientation, indicates the covalent attachment site of the other structural moieties of the compound.

Exemplary embodiments of C_6–C_{20} substituted aryl groups include halo-substituted phenyl such as 4-fluorophenyl, 4-chlorophenyl, 3,5-dichlorophenyl, and 3,5-difluorophenyl. Examples of substituted phenyl carbocycles include:

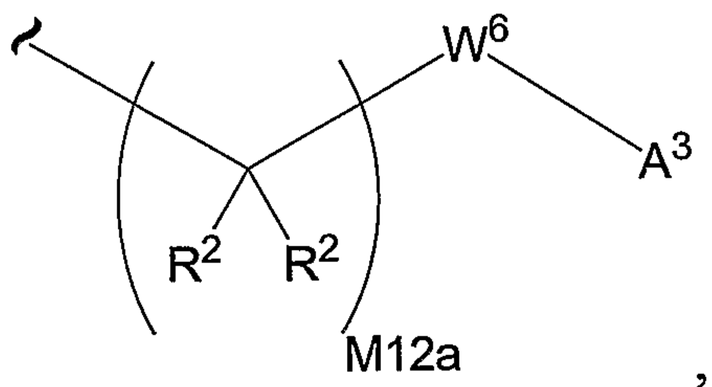


Embodiments of A^1 include:



and where one or more Y^2 are a bond, such as:

;



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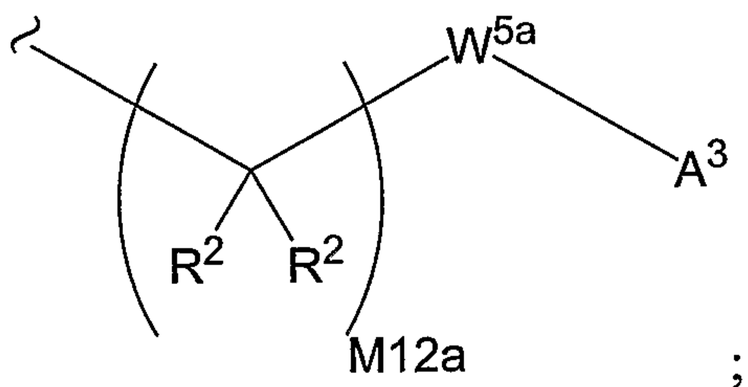

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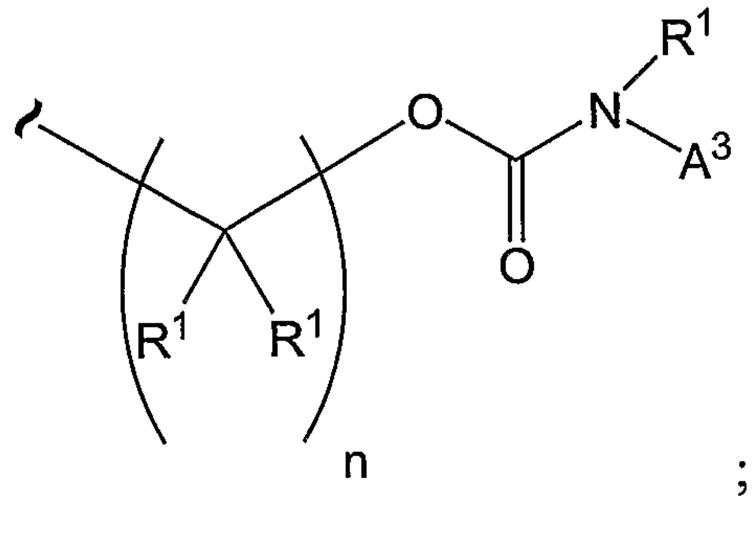
where W^{5a} is a carbocycle or a heterocycle and W^{5a} is independently substituted with 0 or 1 R^2 groups.

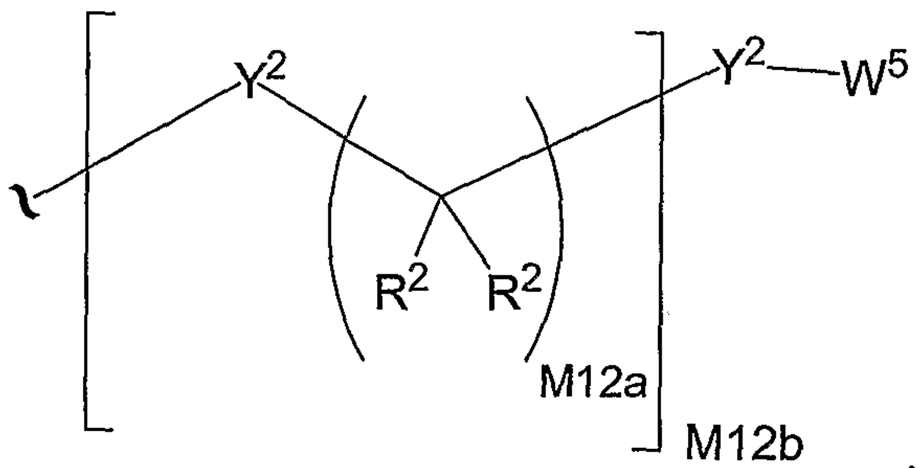
Embodiments of A^1 also include:



;

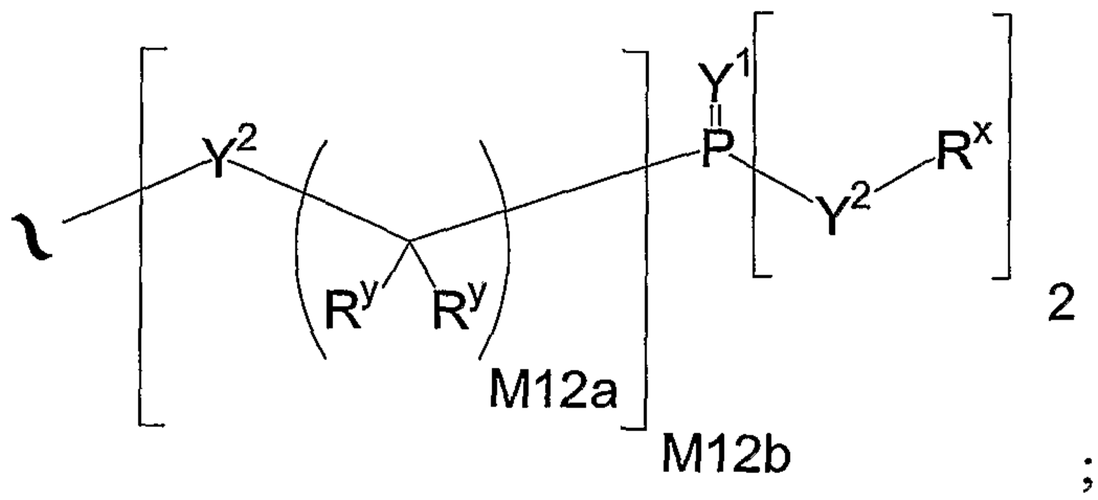
where n is an integer from 1 to 18.

Embodiments of A^2 include where W^3 is W^5, such as:



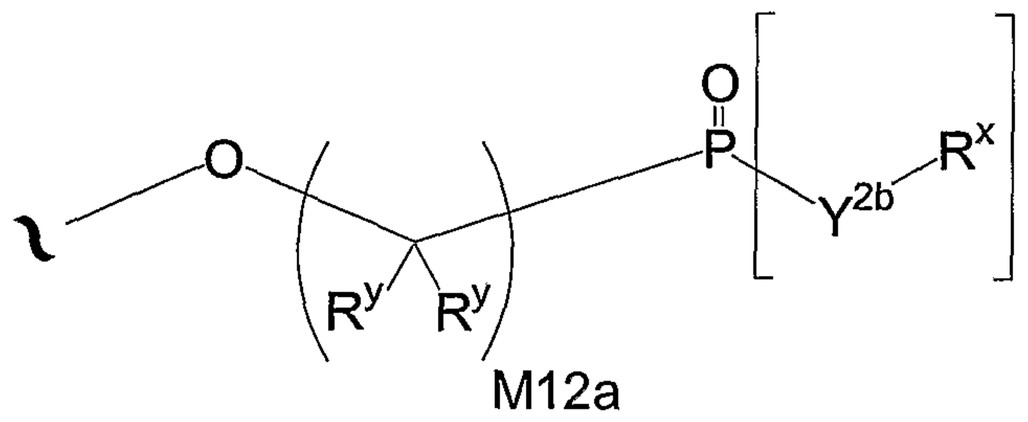
Alternatively, A^2 is phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl or substituted pyridyl.

Embodiments of A^3 include where M2 is 0, such as:

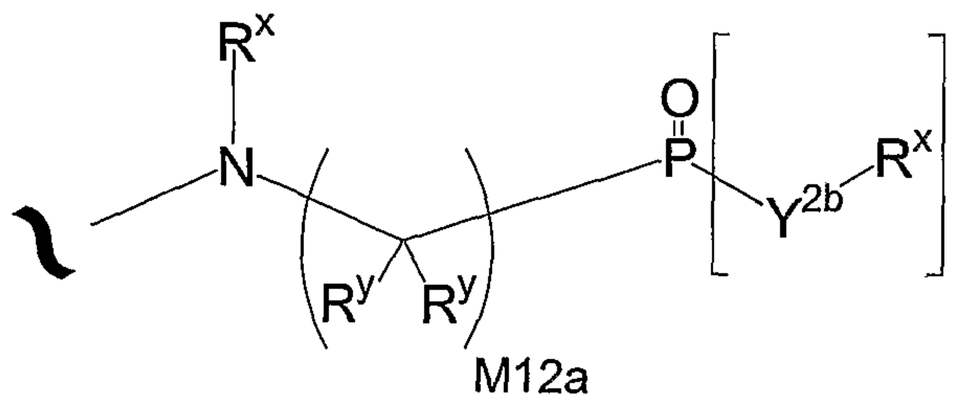


;

and where M12b is 1, Y^1 is oxygen, and Y^{2b} is independently oxygen (O) or nitrogen ($N(R^x)$) such as:

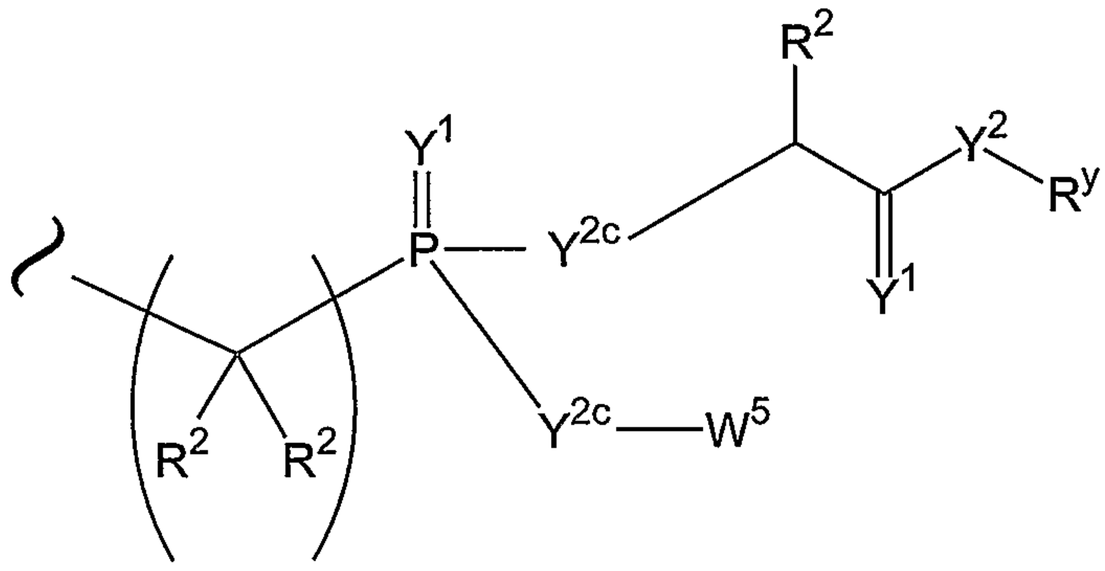


, and



.

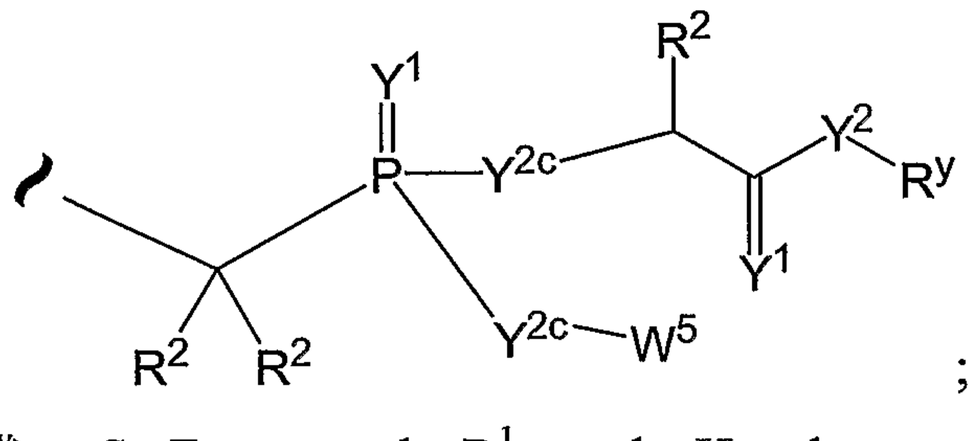
An embodiment of A^3 includes:



;

where W^5 is a carbocycle such as phenyl or substituted phenyl, and Y^{2c} is independently O, N(R^y) or S. For example, R^2 may be H and M12a may be 1.

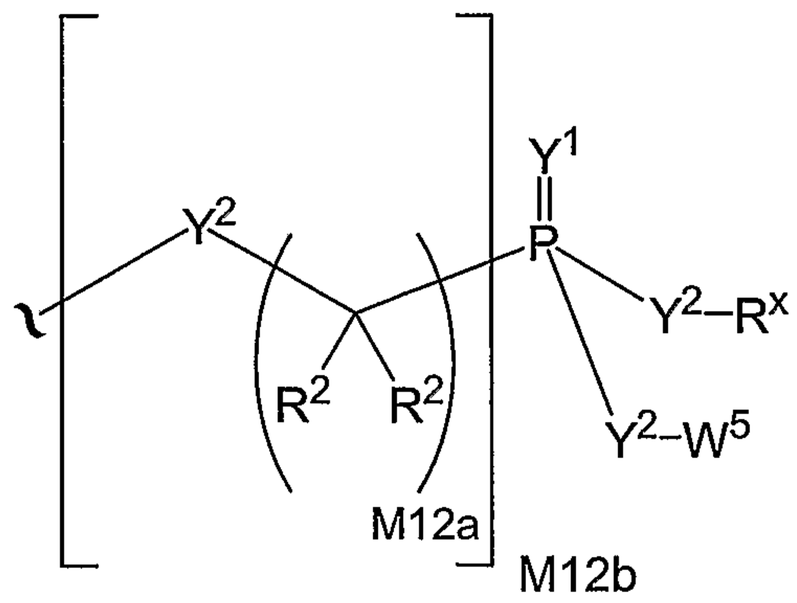
An embodiment of A^3 includes:



;

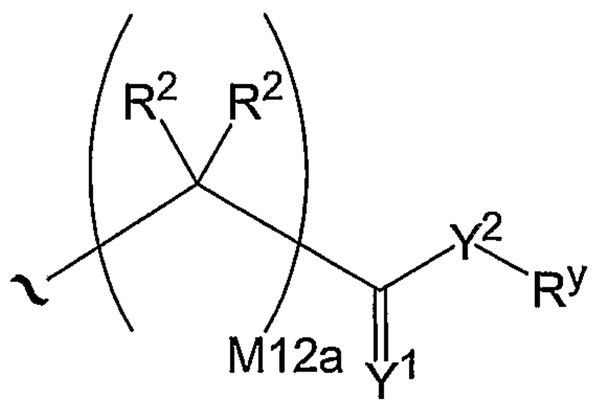
where Y^{2c} is O, N(R^y) or S. For example, R^1 may be H and n may be 1.

Another embodiment of A^3 includes:

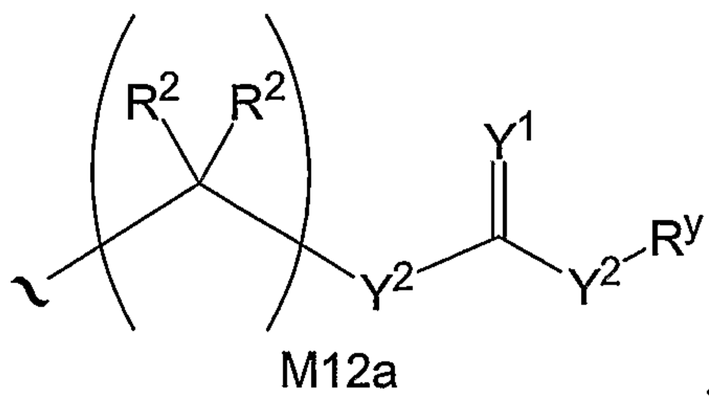


where W^5 is a carbocycle such as phenyl or substituted phenyl.

Embodiments of R^x include esters, carbamates, carbonates, thioesters, amides, thioamides, and urea groups:

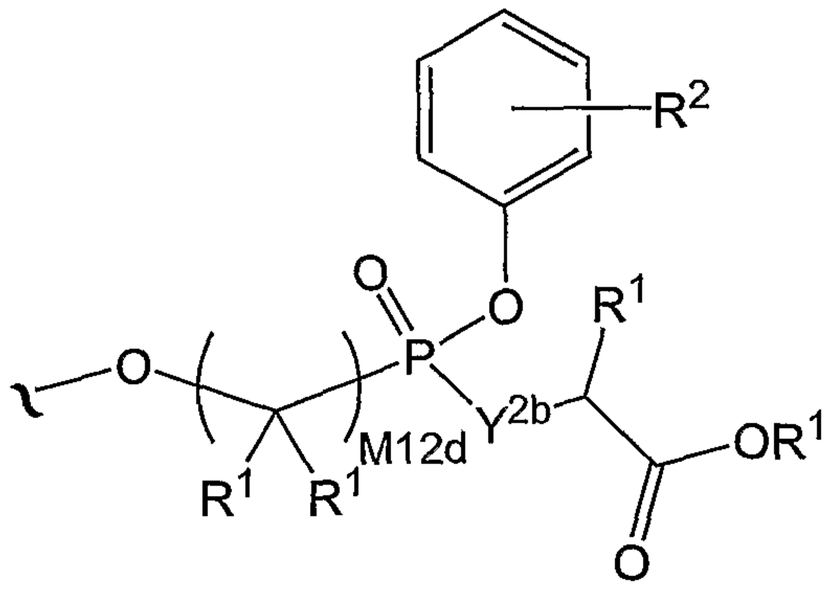


and

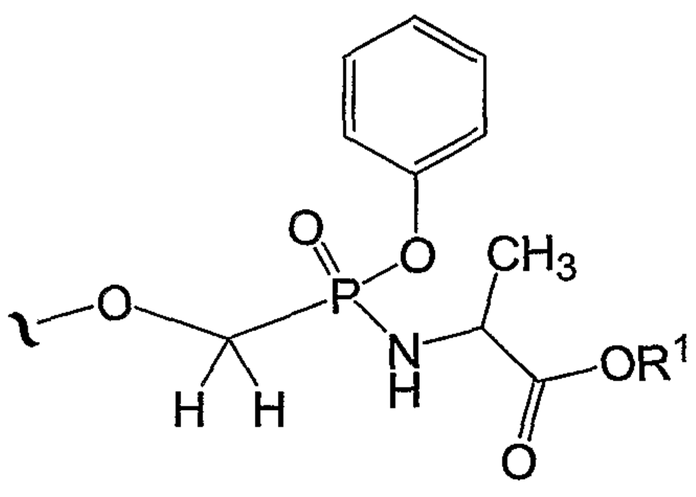


.

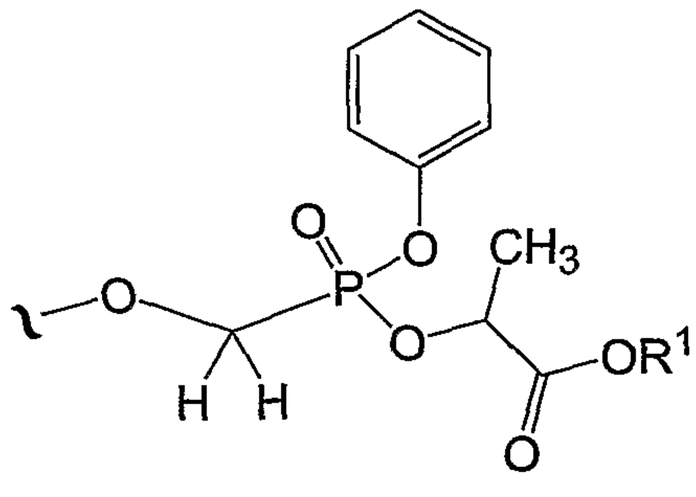
Such embodiments of A^3 include:



where Y^{2b} is O or N(R^x); M12d is 1, 2, 3, 4, 5, 6, 7 or 8; and the phenyl carbocycle is substituted with 0 to 3 R^2 groups. Such embodiments of A^3 include phenyl phosphonamidate amino acid, e.g. alanate esters and phenyl phosphonate-lactate esters:

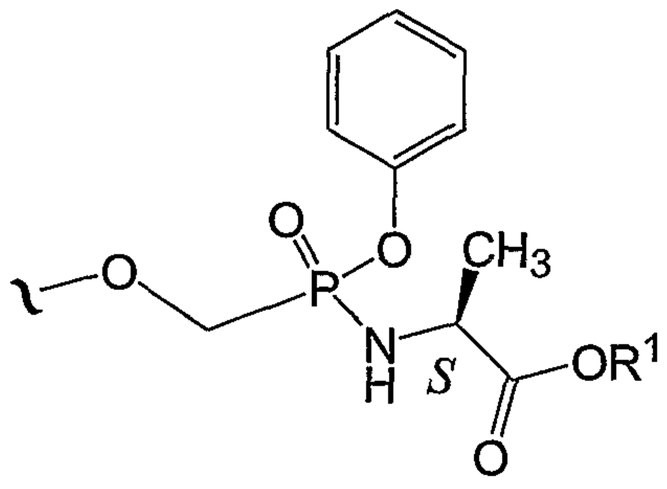


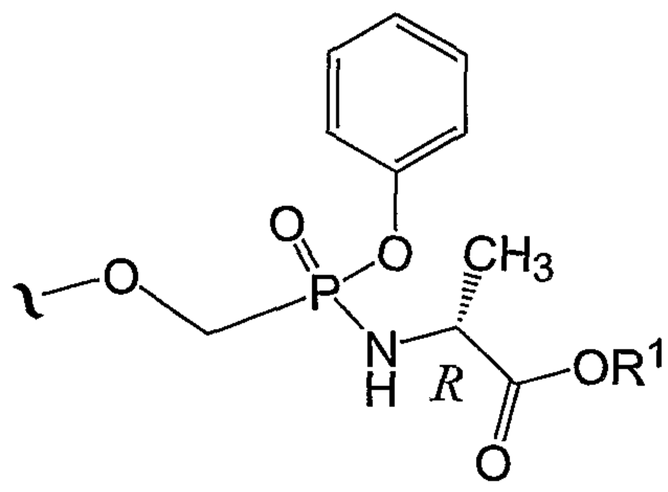
and

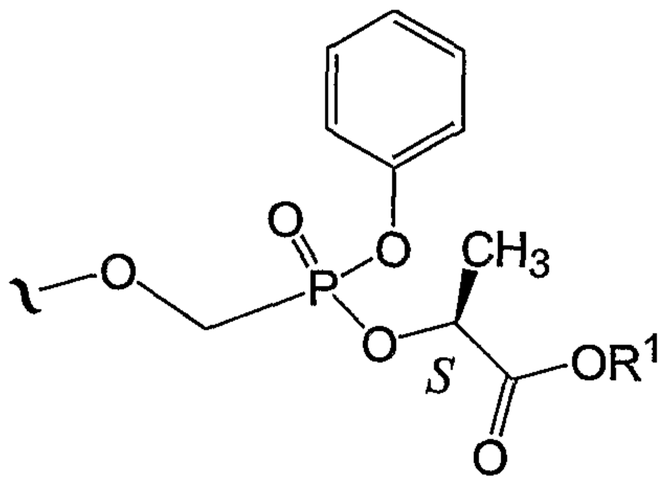


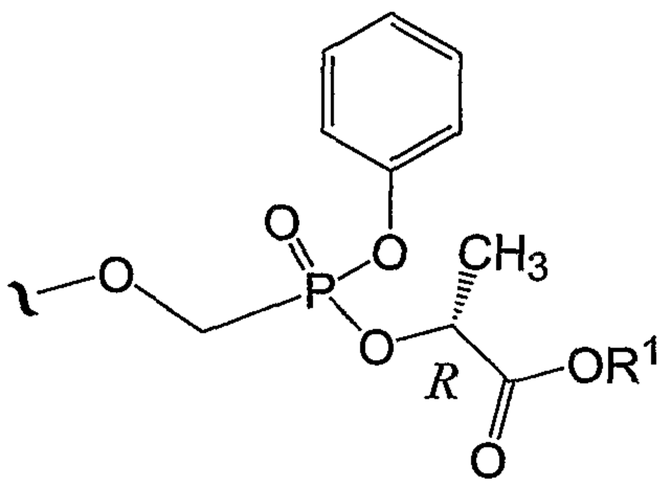
.

The chiral carbon of the amino acid and lactate moieties may be either the R or S configuration, such as:









The compounds including amino acid and lactate moieties may alternatively exist as enantiomerically-enriched mixtures or as racemic mixtures.

Formula I-XXXIX compounds include all pharmaceutically acceptable salts thereof. Formula I-XXXIX compounds also include all enol, tautomeric, and resonance isomers, enantiomers, diastereomers, and racemic mixtures thereof.

Phosphonate groups of the compounds of the invention may comprise the substituent structure A^3.

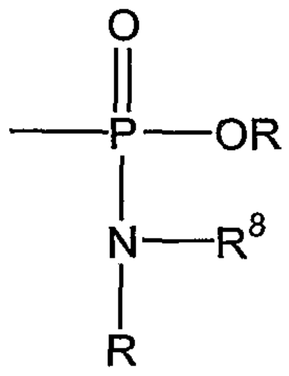
The compounds of the invention include one or more phosphonate groups located as a covalently-attached substituent at any location of Formulas I-XXXIX. Prodrug moieties of phosphorus functionality may serve to mask anionic charges and decrease polarity. The phosphonate prodrug moiety may be an ester (Oliyai etal *Pharmaceutical Res.* (1999) 16:1687-1693; Krise, J. and Stella, V. *Adv. Drug Del. Reviews* (1996) 19:287-310; Bischofberger etal, U.S. Patent No. 5,798,340; Oliyai, etal *Intl. Jour. Pharmaceutics* (1999) 179:257-265), e.g. POC and POM (pivaloyloxymethyl, Yuan, etal *Pharmaceutical Res.* (2000) 17:1098-1103), or amidate which separates from the integrase inhibitor compound *in vivo* or by exposure *in vitro* to biological conditions, e.g. cells, tissue isolates. The separation may be

mediated by general hydrolytic conditions, oxidation, enzymatic action or a combination of steps.

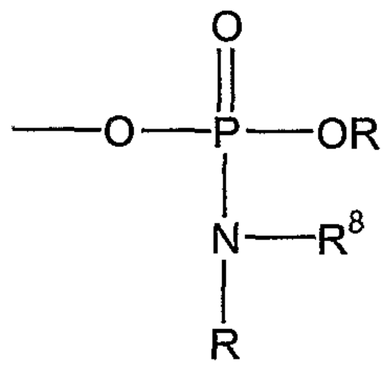
Compounds of the invention bearing one or more phosphonate groups may increase or optimize the bioavailability of the compounds as therapeutic agents. For example, bioavailability after oral administration may be preferred and depend on resistance to metabolic degradation in the gastrointestinal tract or circulatory system, and eventual uptake inside cells. Prodrug moieties are considered to confer said resistance by slowing certain hydrolytic or enzymatic metabolic processes. Lipophilic prodrug moieties may also increase active or passive transport of the compounds of the invention across cellular membranes (Darby, G. *Antiviral Chem. & Chemotherapy* (1995) Supp. 1, 6:54-63).

In one aspect, the compounds of the invention include an active form for inhibition of nuclear integration of reverse-transcribed HIV DNA.

Exemplary embodiments of the invention includes phosphonamidate and phosphoramidate (collectively "amidate") prodrug compounds. General formulas for phosphonamidate and phosphoramidate prodrug moieties include:

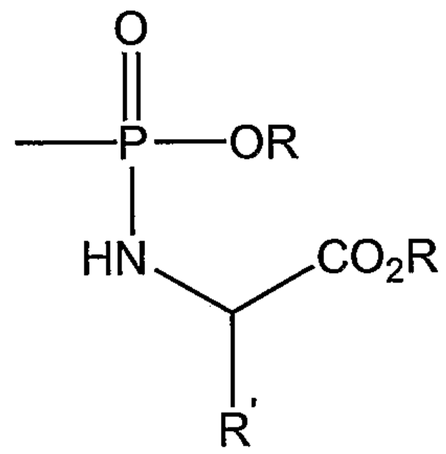


phosphonamidate



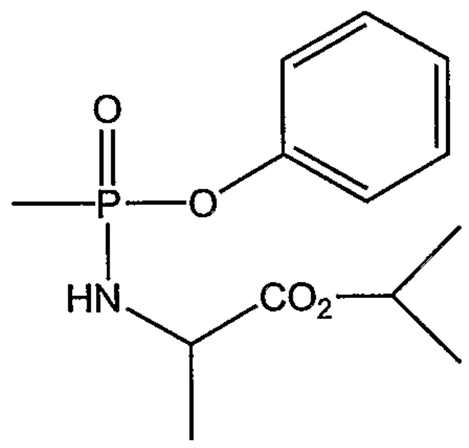
phosphoramidate

The phosphorus atom of the phosphonamidate group is bonded to a carbon atom. The nitrogen substituent R^8 may include an ester, an amide, or a carbamate functional group. For example, R^8 may be $-CR_2C(=O)OR'$ where R' is H, C_1-C_6 alkyl, C_1-C_6 substituted alkyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heterocycle, or C_2-C_{20} substituted heterocycle. The nitrogen atom may comprise an amino acid residue within the prodrug moiety, such as a glycine, alanine, or valine ester (e.g. valacyclovir, see: Beauchamp, etal *Antiviral Chem. Chemotherapy* (1992) 3:157-164), such as the general structure:



where R' is the amino acid side-chain, e.g. H, CH_3, $CH(CH_3)_2$, etc.

An exemplary embodiment of a phosphonamidate prodrug moiety is:



Those of skill in the art will also recognize that the compounds of the invention may exist in many different protonation states, depending on, among other things, the pH of their environment. While the structural formulae provided herein depict the compounds in only one of several possible protonation states, it will be understood that these structures are illustrative only, and that the invention is not limited to any particular protonation state--any and all protonated forms of the compounds are intended to fall within the scope of the invention.

Recursive Substituents

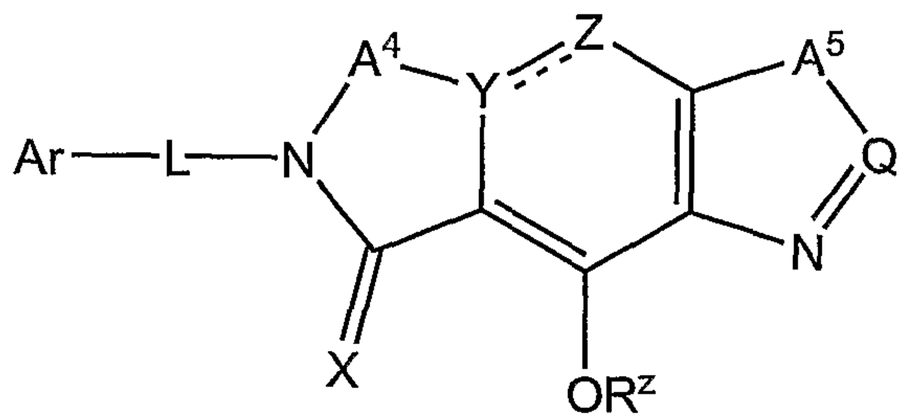
Selected substituents within the compounds of the invention are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given embodiment. For example, R^x contains a R^y substituent. R^y can be R^2, which in turn can be R^3. If R^3 is selected to be R^{3c}, then a second instance of R^x can be selected. One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

By way of example and not limitation, W^3, R^y and R^3 are all recursive substituents in certain embodiments. Typically, each of these may independently occur 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given embodiment. More typically, each of these may independently occur 12 or fewer times in a given embodiment. More typically yet, W^3 will occur 0 to 8 times, R^y will occur 0 to 6 times and R^3 will occur 0 to 10 times in a given embodiment. Even more typically, W^3 will occur 0 to 6 times, R^y will occur 0 to 4 times and R^3 will occur 0 to 8 times in a given embodiment.

Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an embodiment of the invention, the total number will be determined as set forth above.

Group I

In one aspect, the invention includes tricyclic phosphonate Group I compounds represented by the following structure, Formula I:

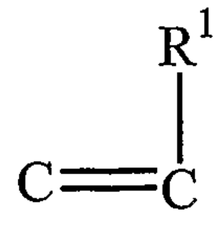
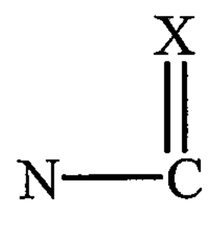
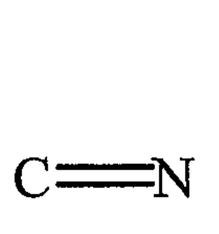


I

wherein:

A^4 and A^5 are each and independently any moiety forming a five, six, or seven membered ring. A^4 and A^5 may be independently selected from O, S, NR, $C(R^2)_2$, CR^2OR, $CR^2OC(=O)R$, C(=O), C(=S), CR^2SR, C(=NR), $C(R^2)_2$–$C(R^3)_2$, $C(R^2)$=$C(R^3)$, $C(R^2)_2$–O, NR–$C(R^3)_2$, N=$C(R^3)$, N=N, SO_2–NR, $C(=O)C(R^3)_2$, C(=O)NR, $C(R^2)_2$–$C(R^3)_2$–$C(R^3)_2$, $C(R^2)$=$C(R^3)$–$C(R^3)_2$, $C(R^2)C(=O)NR$, $C(R^2)C(=S)NR$, $C(R^2)$=N–$C(R^3)_2$, $C(R^2)$=N–NR, and N=$C(R^3)$–NR. When taken together on a single carbon, two R^2 or two R^3 may form a spiro ring.

Q is N, $^+$NR, or CR^4.

Y---Z is  ,  , or  .

X may be O, S, NH, NR, N–OR, N–NR_2, N–CR_2OR or N–CR_2NR_2.

R^z is H; a protecting group selected from benzyhydryl ($CHPh_2$), trialkylsilyl (R_3Si), 2-trimethylsiloxyethyl, alkoxymethyl (CH_2OR), and ester (C(=O)R); or a prodrug moiety;

R^1, R^2, R^3 and R^4 are each independently selected from H, F, Cl, Br, I, OH, $–NH_2$, $–NH_3^+$, –NHR, $–NR_2$, $–NR_3^+$, $C_1–C_8$ alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, $C_1–C_8$ alkylsulfonate, $C_1–C_8$ alkylamino, 4-dialkylaminopyridinium, $C_1–C_8$ alkylhydroxyl, $C_1–C_8$ alkylthiol, $–SO_2R$, $–SO_2Ar$, –SOAr, –SAr, $–SO_2NR_2$, –SOR, $–CO_2R$, $–C(=O)NR_2$, 5-7 membered ring lactam, 5-7 membered ring lactone, –CN, $–N_3$, $–NO_2$, $C_1–C_8$ alkoxy, $C_1–C_8$ trifluoroalkyl, $C_1–C_8$ alkyl, $C_1–C_8$ substituted alkyl, $C_3–C_{12}$ carbocycle, $C_3–C_{12}$ substituted carbocycle, $C_6–C_{20}$ aryl, $C_6–C_{20}$ substituted aryl, $C_2–C_{20}$ heteroaryl, and $C_2–C_{20}$ substituted heteroaryl, polyethyleneoxy, phosphonate, phosphate, and a prodrug moiety;

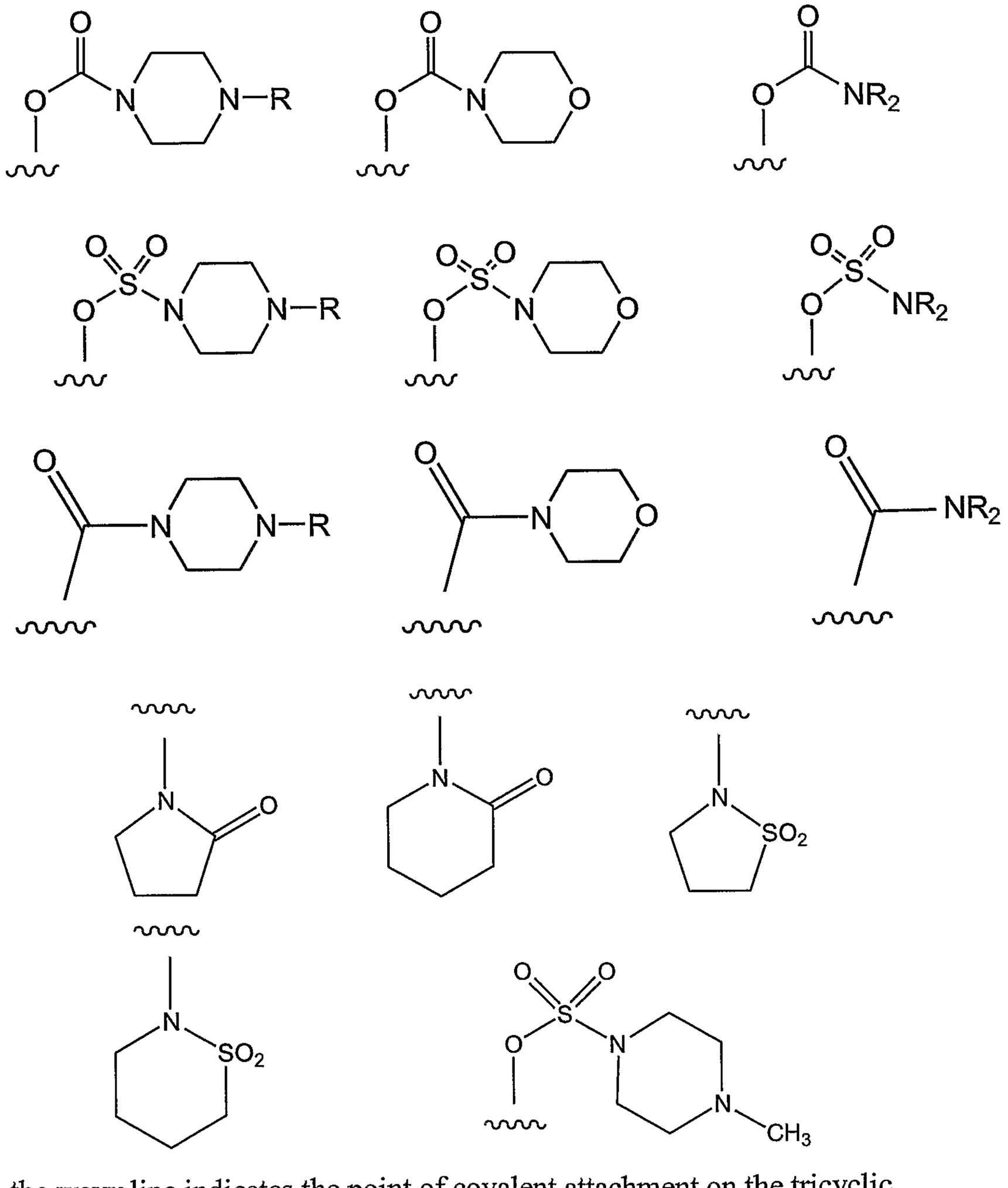
when taken together on a single carbon, two R^2 or two R^3 may form a spiro ring; and

R^1, R^2, R^3, and R^4 also include: $–OC(=O)OR$, $–OC(=O)NR_2$, $–OC(=S)NR_2$, $–OC(=O)NRNR_2$, –OC(=O)R, –C(=O)OR, $–C(=O)NR_2$, $–C(=O)NRNR_2$, –C(=O)R, $–OSO_2NR_2$ (sulfamate), $–NR_2$, $–NRSO_2R$, $–NRC(=S)NR_2$, –SR, –S(O)R, $–SO_2R$, $–SO_2NR_2$ (sulfonamide), $–OSO_2R$ (sulfonate), $–P(=O)(OR)_2$, $–P(=O)(OR)(NR_2)$, $–P(=O)(NR_2)_2$, $–P(=S)(OR)_2$, $–P(=S)(OR)(NR_2)$, $–P(=S)(NR_2)_2$, and including prodrug substituted forms thereof.

R may be independently selected from H, $C_1–C_8$ alkyl, $C_1–C_8$ substituted alkyl, $C_2–C_{18}$ alkenyl, $C_2–C_{18}$ substituted alkenyl, $C_2–C_{18}$ alkynyl, $C_2–C_{18}$ substituted alkynyl, $C_6–C_{20}$ aryl, $C_6–C_{20}$ substituted aryl, $C_2–C_{20}$ heteroaryl, $C_2–C_{20}$ substituted heteroaryl, polyethyleneoxy, phosphonate, phosphate, and a prodrug moiety. Two R groups may form a ring, such as when the two R groups are bonded to a nitrogen atom

and form a ring such as aziridinyl, azetidinyl, pyrrolidinyl, pyrazinyl, imidazolyl, piperidyl, piperazinyl, pyridinium, or morpholino.

Exemplary embodiments of R^1, R^2, R^3, and R^4 include the structures:



where the wavy line indicates the point of covalent attachment on the tricyclic structure.

Alternatively, R, R^1, R^2, R^3, or R^4 may independently comprise A^1, A^3 or $L–A^3$.

L is a bond or any linker which covalently attaches the Ar group to the tricyclic scaffold. For example, L may be a bond, O, S, S–S (disulfide), S(=O) (sulfoxide), $S(=O)_2$ (sulfone), $S(=O)_2NR$ (sulfonamide), NR, N–OR, $C_1–C_{12}$ alkylene,

C_1–C_{12} substituted alkylene, C_2–C_{12} alkenylene, C_2–C_{12} substituted alkenylene, C_2–C_{12} alkynylene, C_2–C_{12} substituted alkynylene, $-(CR_2)_nO(CR_2)_n-$, C(=O)NH, OC(=O)NH, NHC(=O)NH, C(=O), C(=O)NH$(CH_2)_n$, or $(CH_2CH_2O)_n$, where n may be 1, 2, 3, 4, 5, or 6.

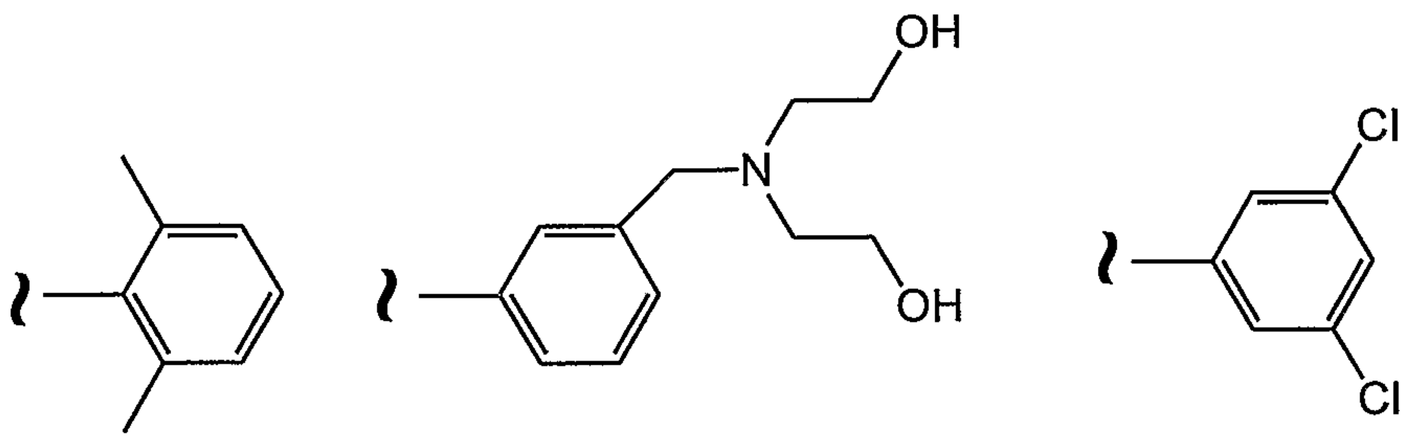
Substituted alkylene, substituted alkyenylene, substituted alkynylene, substituted aryl, and substituted heteroaryl are independently substituted with one or more substituents selected from F, Cl, Br, I, OH, amino ($-NH_2$), ammonium ($-NH_3^+$), alkylamino, dialkylamino, trialkylammonium, C_1–C_8 alkyl, C_1–C_8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, C_1–C_8 alkylsulfonate, C_1–C_8 alkylamino, 4-dialkylaminopyridinium, C_1–C_8 alkylhydroxyl, C_1–C_8 alkylthiol, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide (–SOAr), arylthio (–SAr), sulfonamide ($-SO_2NR_2$), alkylsulfoxide (–SOR), ester ($-CO_2R$), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile (–CN), azido ($-N_3$), nitro ($-NO_2$), C_1–C_8 alkoxy (–OR), C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl, phosphonate, phosphate, polyethyleneoxy, and a prodrug moiety.

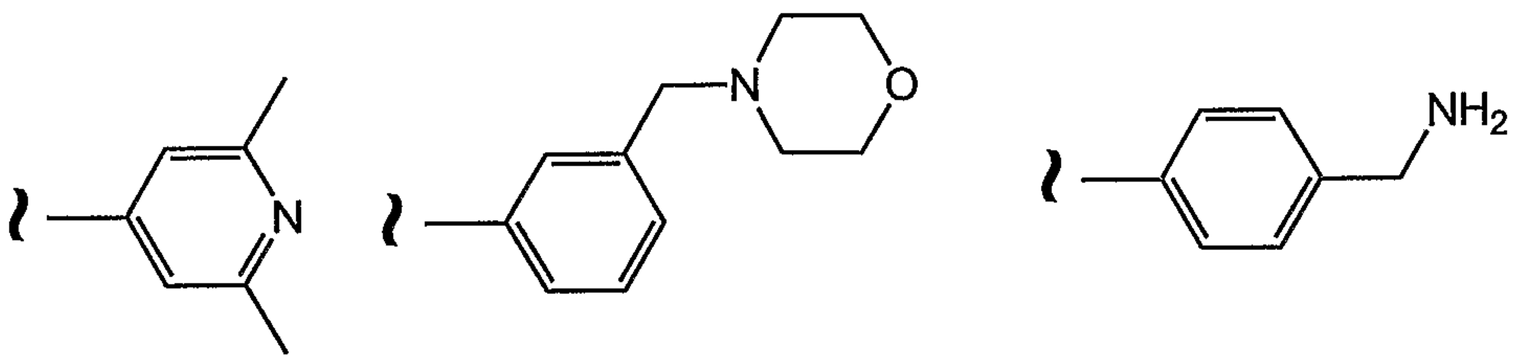
Ar groups may be any saturated, unsaturated or aromatic ring or ring system comprising a mono- or bicyclic carbocycle or heterocycle, e.g. 3 to 12 ring atoms. The rings are saturated when containing 3 ring atoms, saturated or mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when containing 6 ring atoms.

For example, Ar may be C_3–C_{12} carbocycle, C_3–C_{12} substituted carbocycle, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, or C_2–C_{20} substituted heteroaryl.

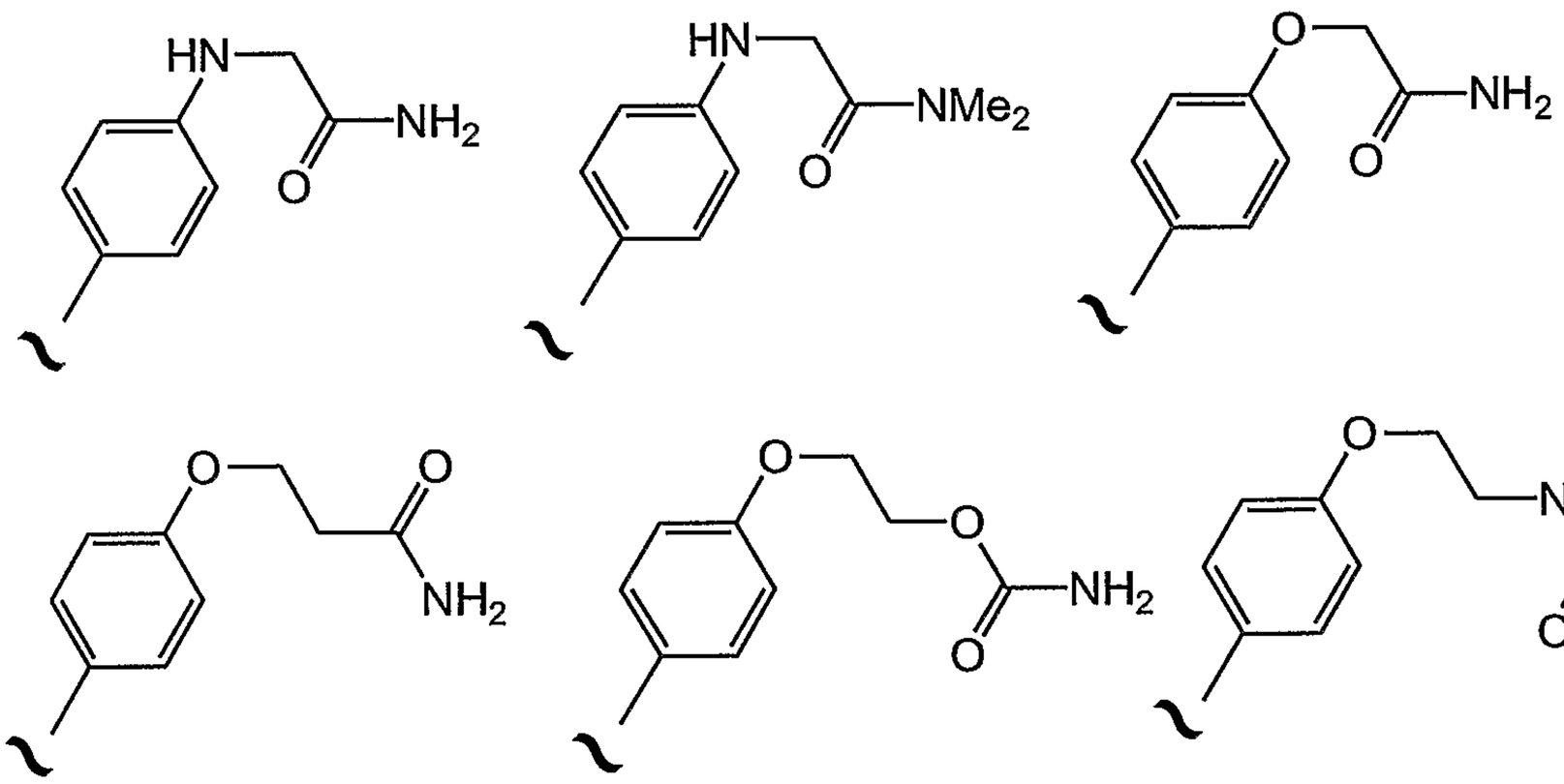
Exemplary embodiments of C_6–C_{20} substituted aryl groups include halo-substituted phenyl such as 4-fluorophenyl, 4-chlorophenyl, 4-trifluoromethyl, 2-amide phenyl, 3,5-dichlorophenyl, and 3,5-difluorophenyl.

Ar groups include substituted phenyl groups such as, but not limited to:



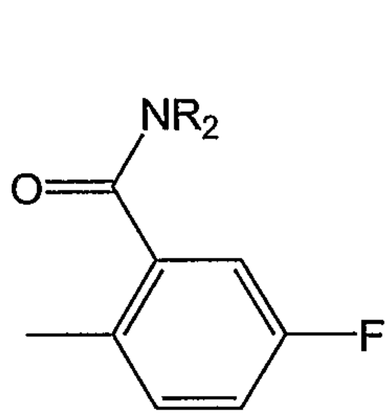
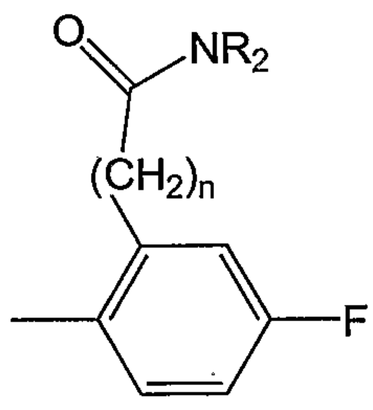
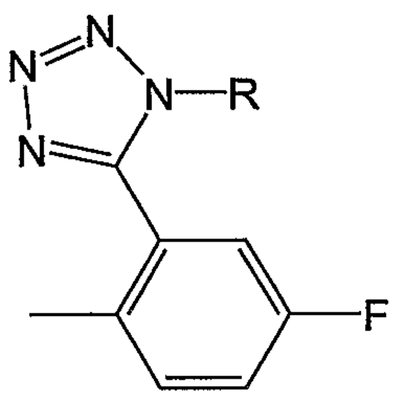
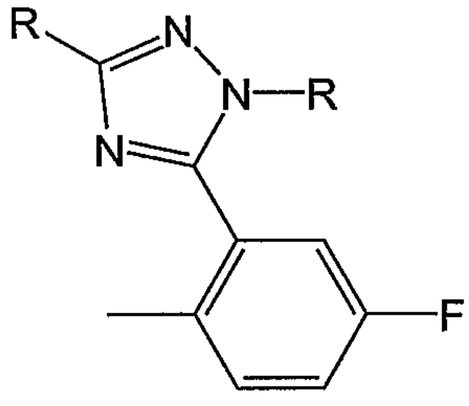


Other examples of substituted phenyl groups include:



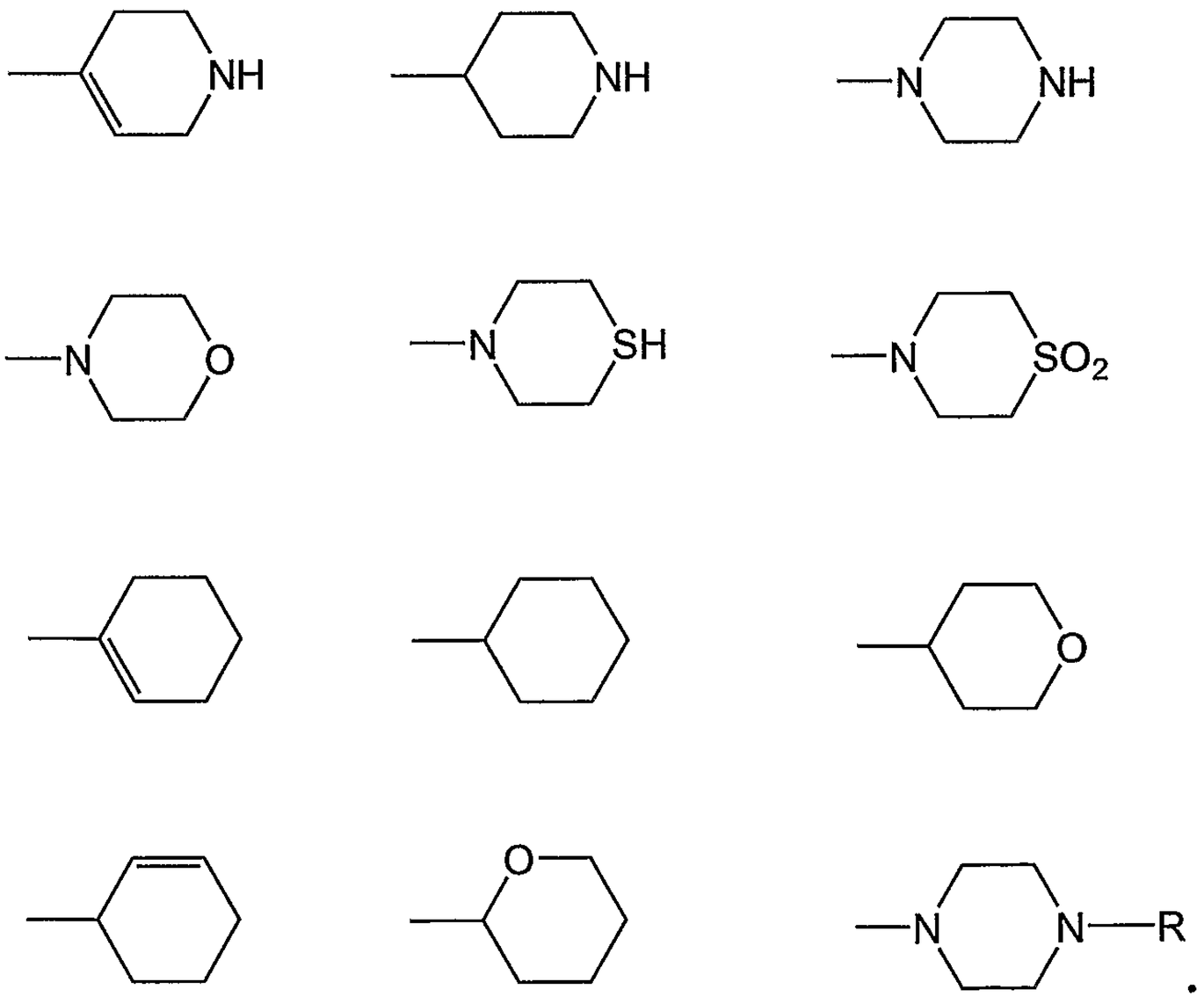
where a wavy line ~, in any orientation, indicates the covalent attachment site to L.

Ar groups also include disubstituted phenyl groups such as, but not limited to:

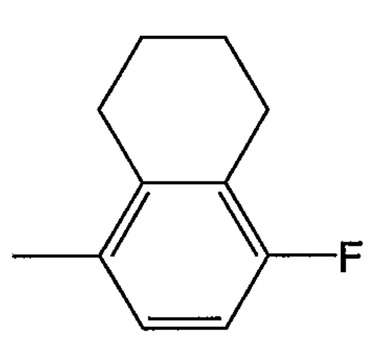





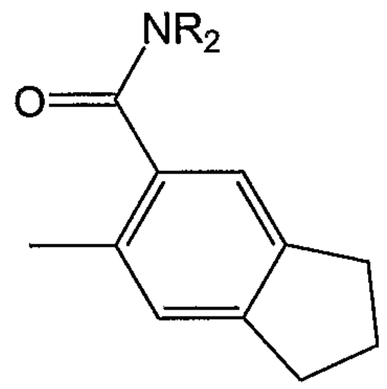
where n is 1 to 6.

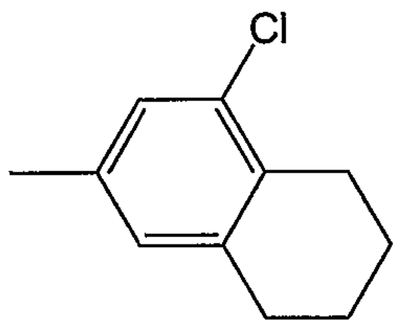
Ar groups also include carbocycles such as, but not limited to:

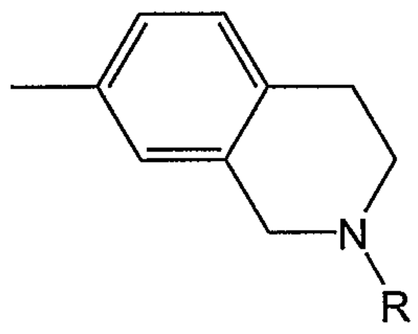


Ar groups also include phenyl and substituted phenyl fused to a carbocycle to form groups including:



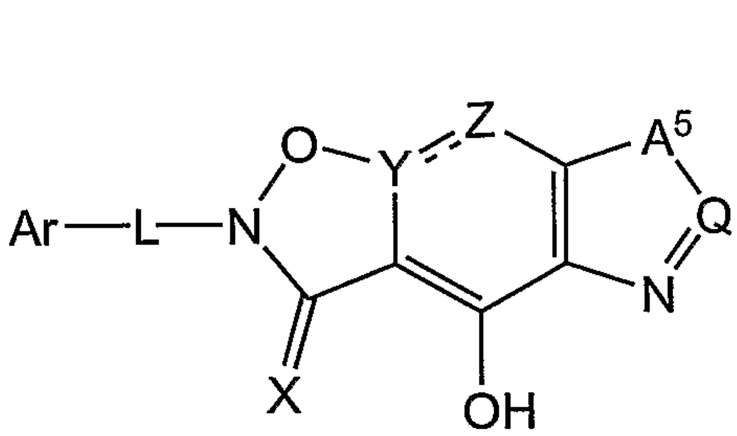


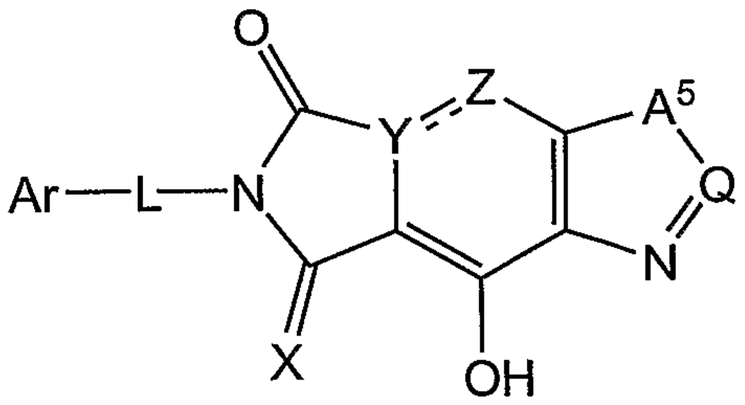


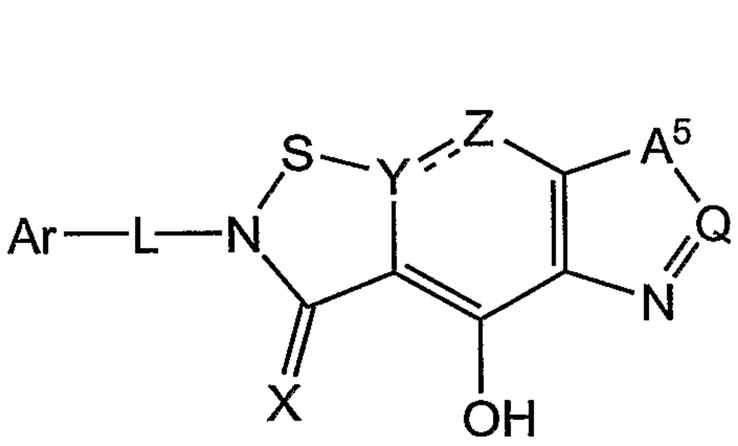


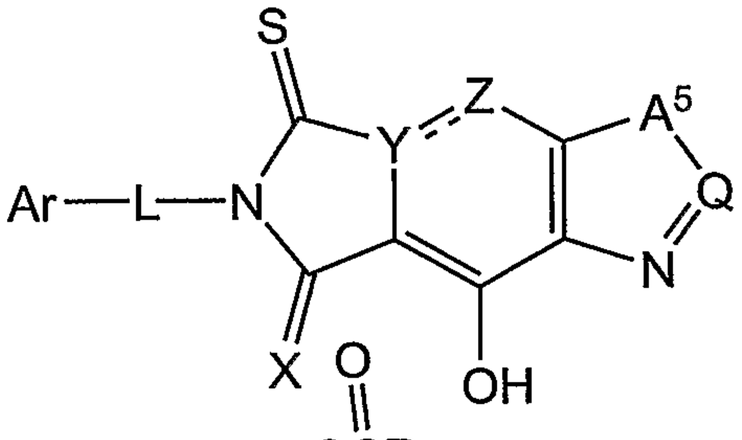
Substituents of Ar, may independently be H, F, Cl, Br, I, OH, amino ($-NH_2$), ammonium ($-NH_3^+$), alkylamino, dialkylamino, trialkylammonium, C_1-C_8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, C_1-C_8 alkylsulfonate, C_1-C_8 alkylamino, 4-dialkylaminopyridinium, C_1-C_8 alkylhydroxyl, C_1-C_8 alkylthiol, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide ($-SOAr$), arylthio ($-SAr$), sulfonamide ($-SO_2NR_2$), alkylsulfoxide ($-SOR$), ester ($-CO_2R$), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile ($-CN$), azido ($-N_3$), nitro ($-NO_2$), C_1-C_8 alkoxy ($-OR$), C_1-C_8 trifluoroalkyl, C_1-C_8 alkyl, C_1-C_8 substituted alkyl, C_3-C_{12} carbocycle, C_3-C_{12} substituted carbocycle, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heteroaryl, and C_2-C_{20} substituted heteroaryl, phosphonate, phosphate, polyethyleneoxy, and a prodrug moiety.

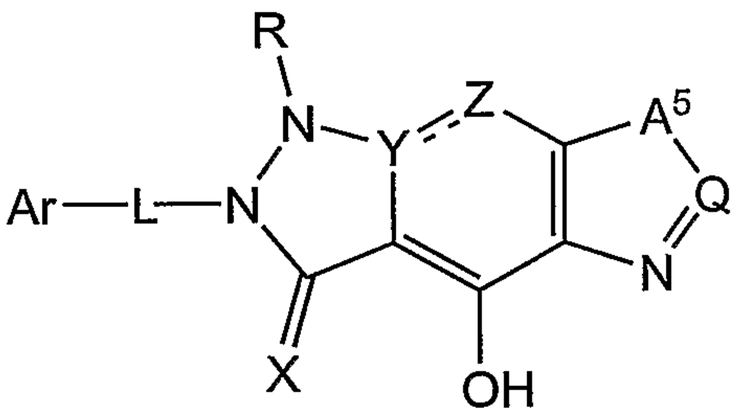
The following embodiments of A^4 and A^5 in Formula I compounds include but are not limited to the following structures. Various embodiments of A^4 form 5-membered rings in the exemplary structures:

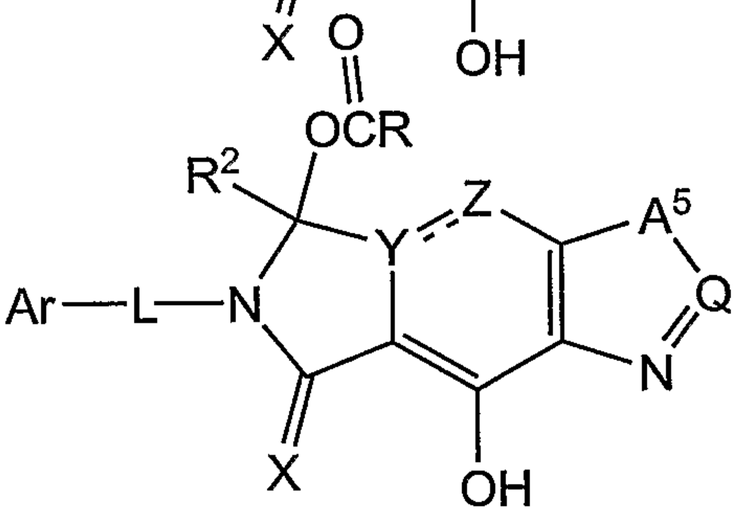


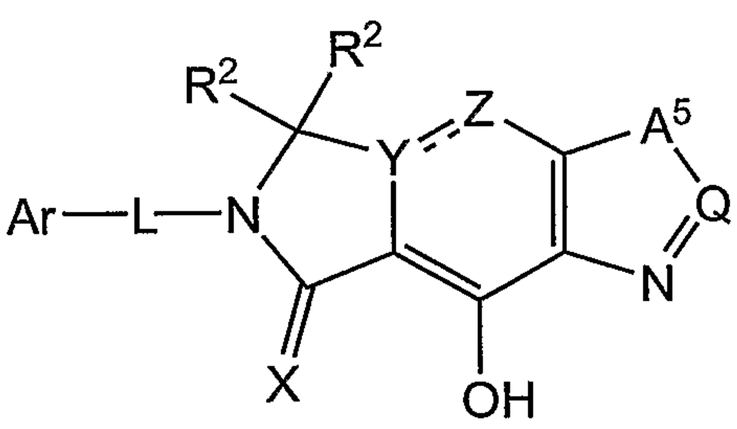


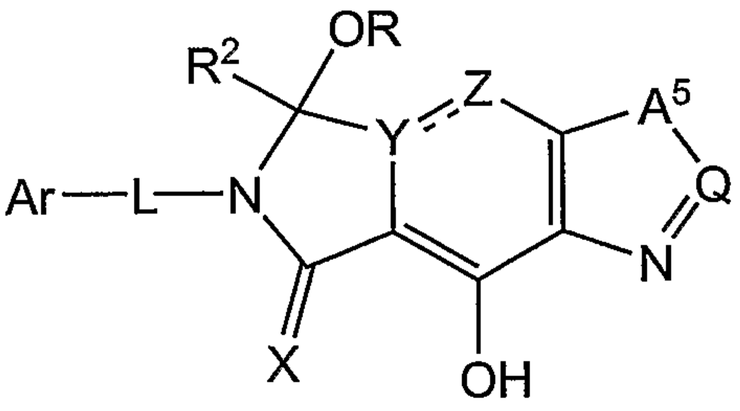


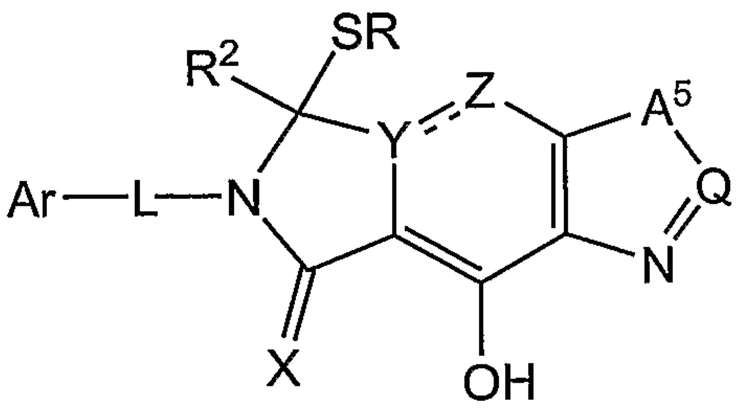


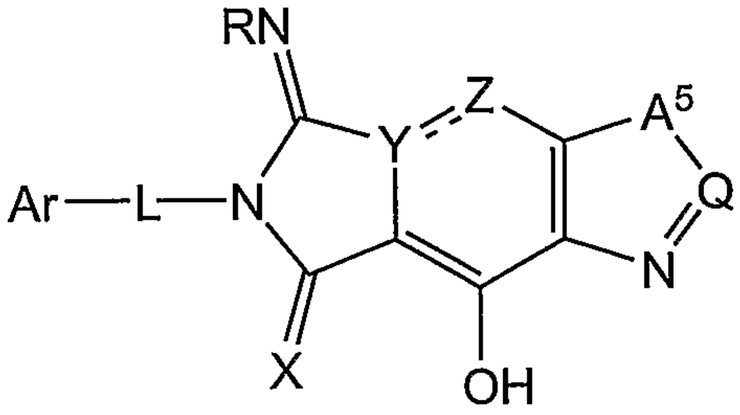






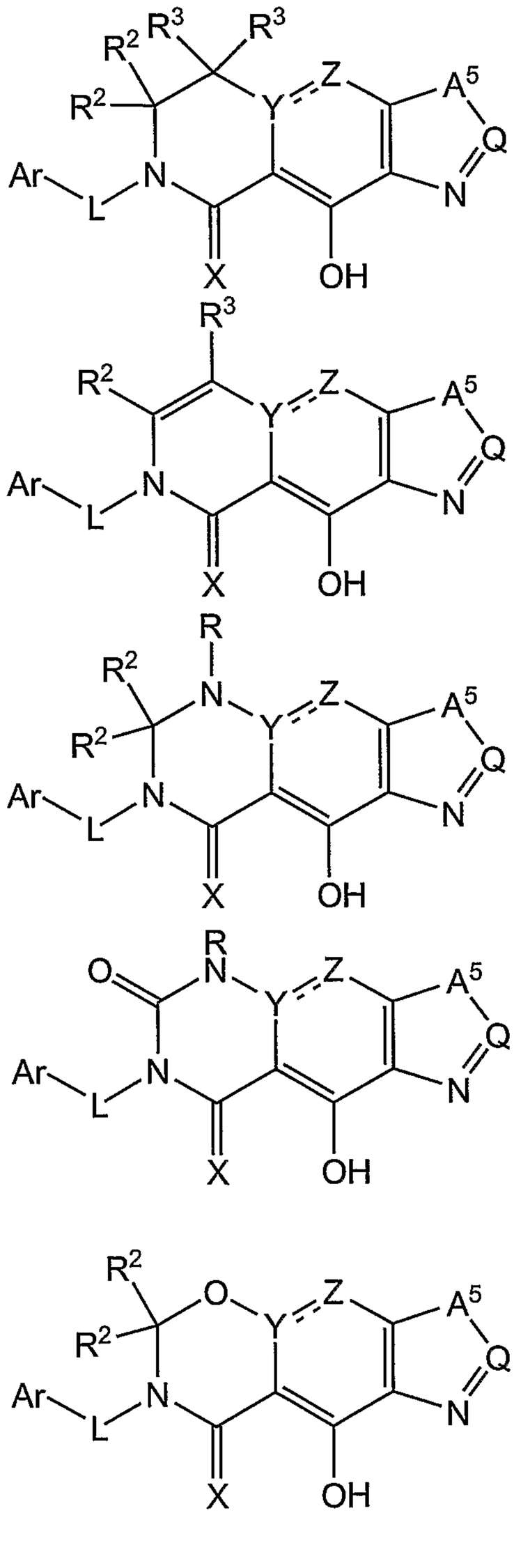


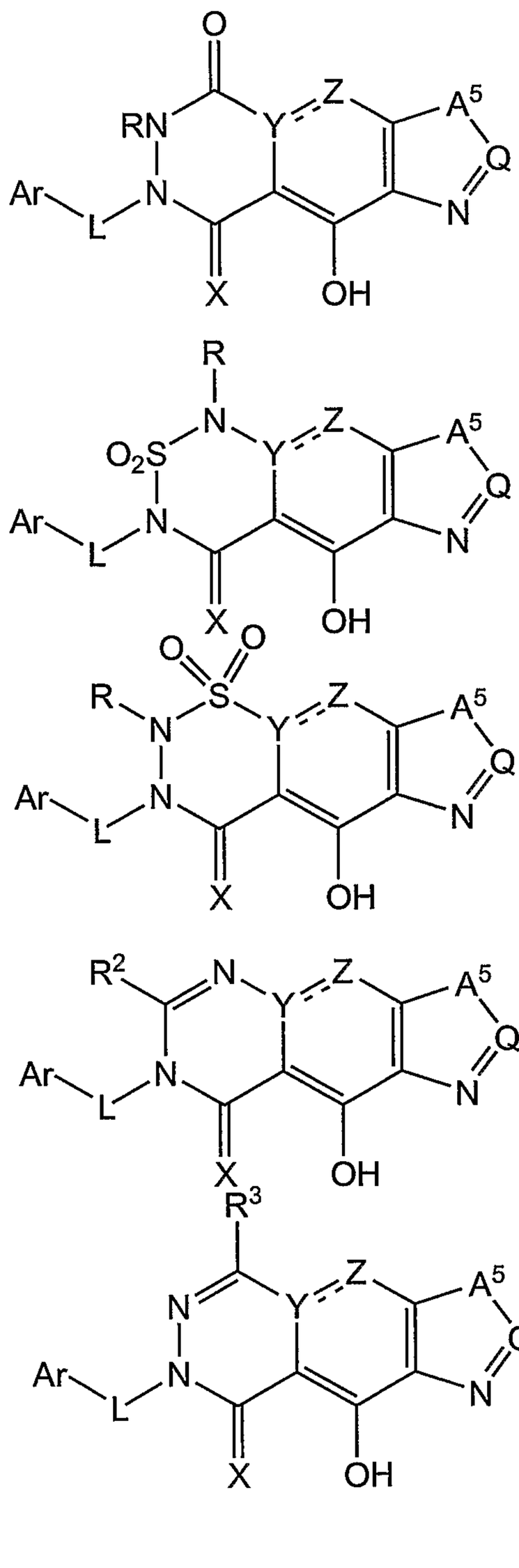




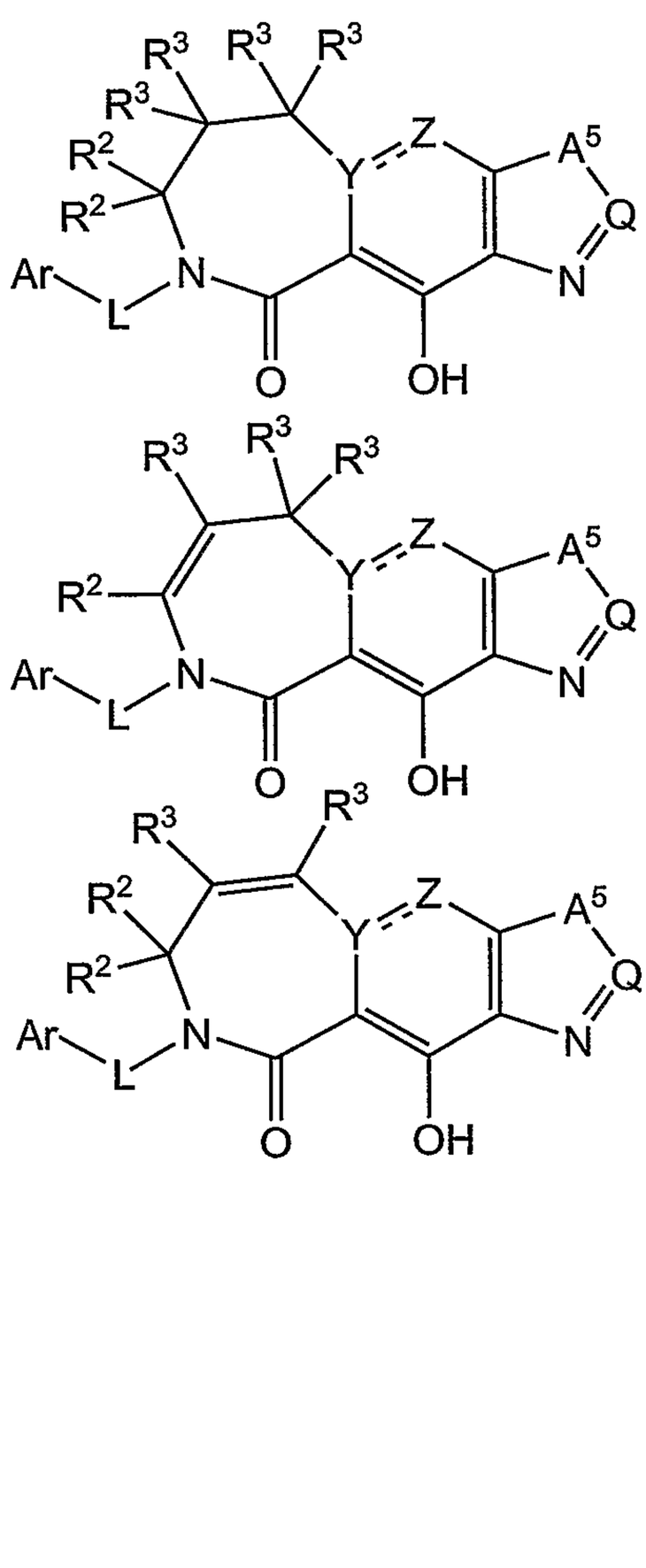
5

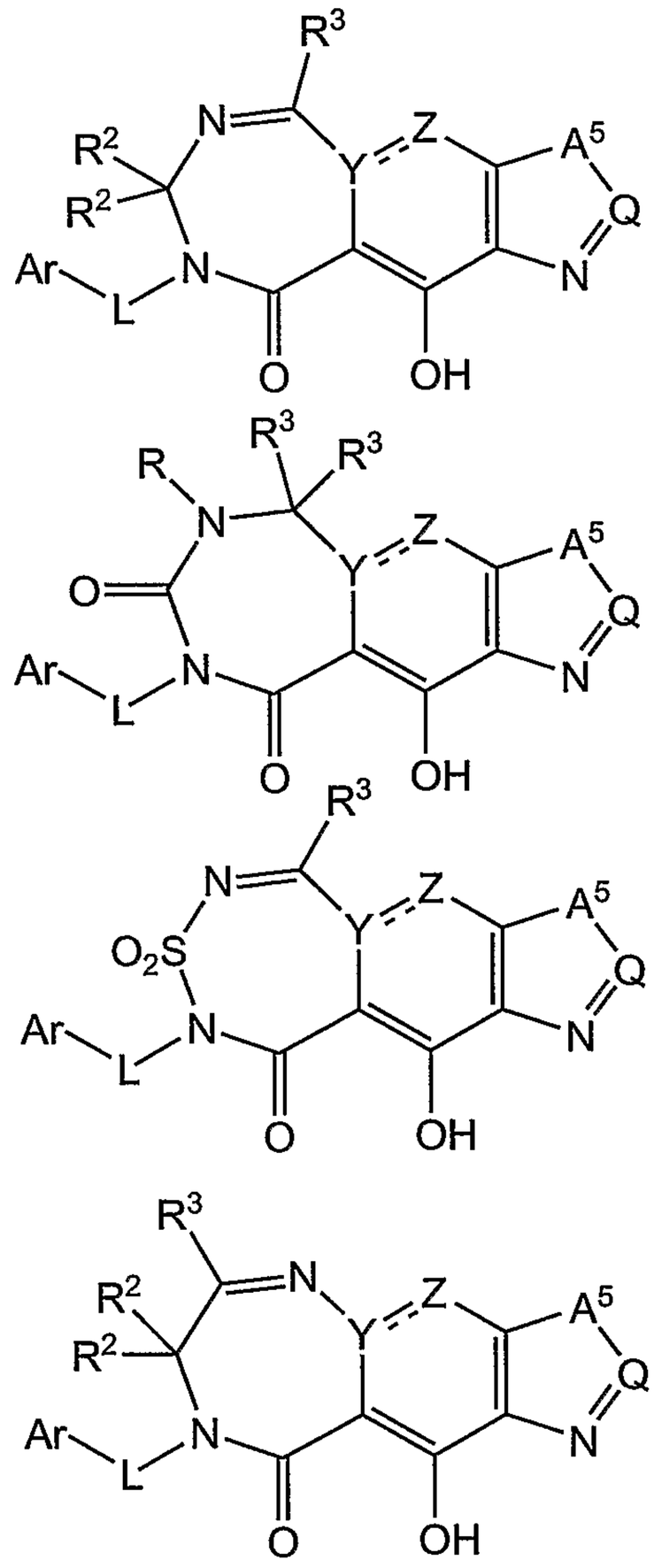
Various embodiments of A^4 form 6-membered rings in the exemplary structures:



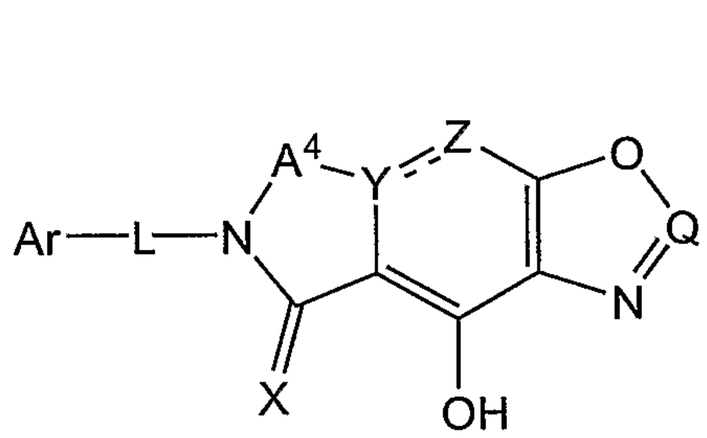


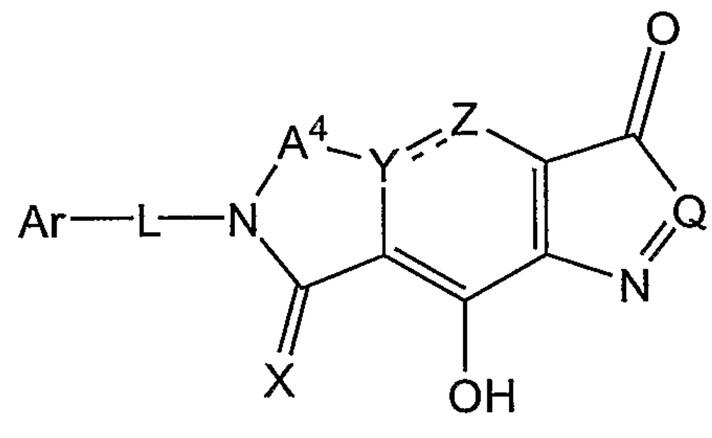
Various embodiments of A^4 form 7-membered rings in the exemplary structures:

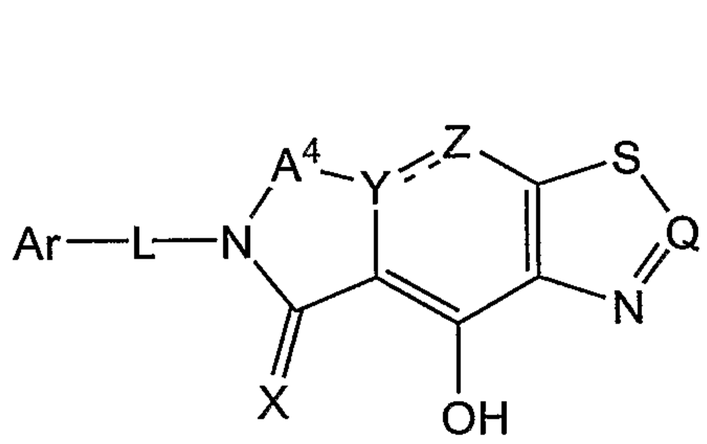


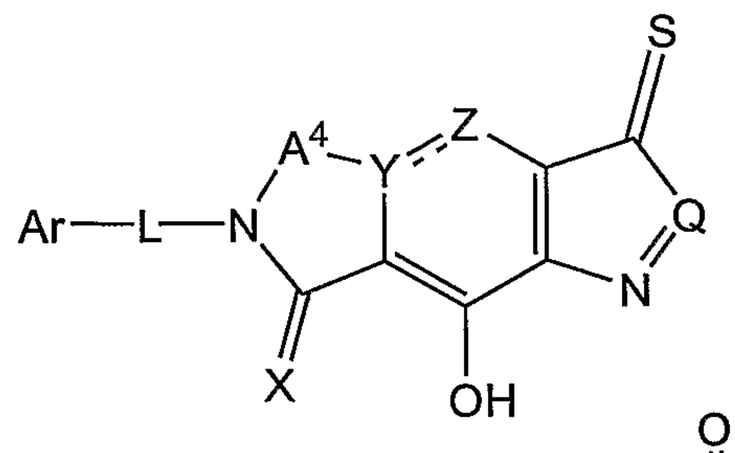


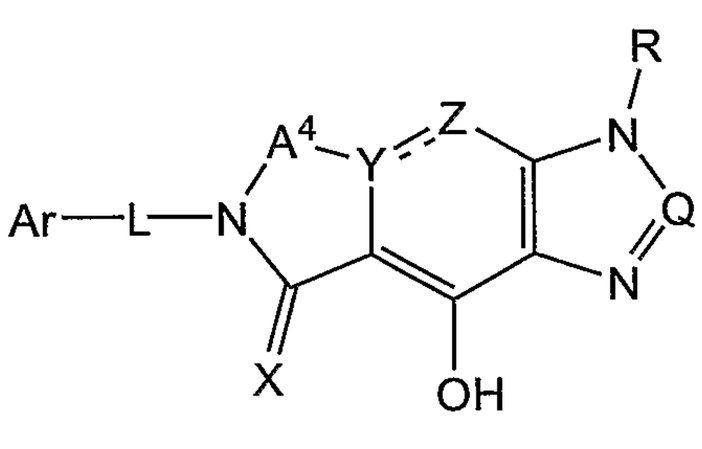
Various embodiments of A^5 form 5-membered rings in the exemplary structures:

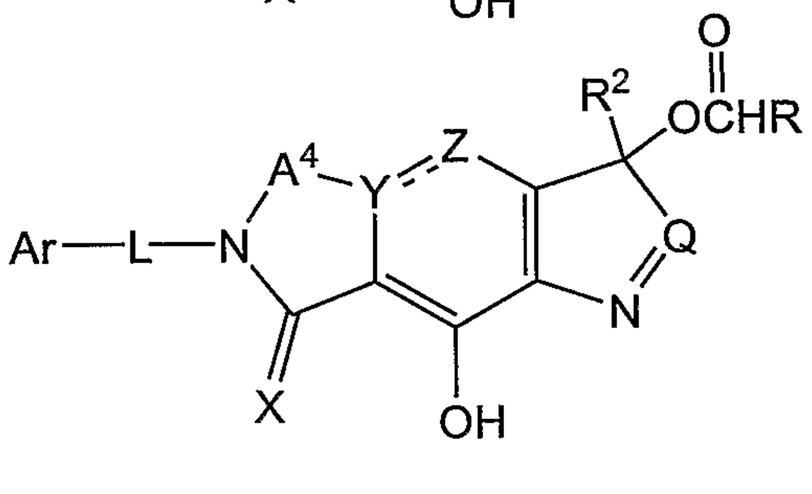


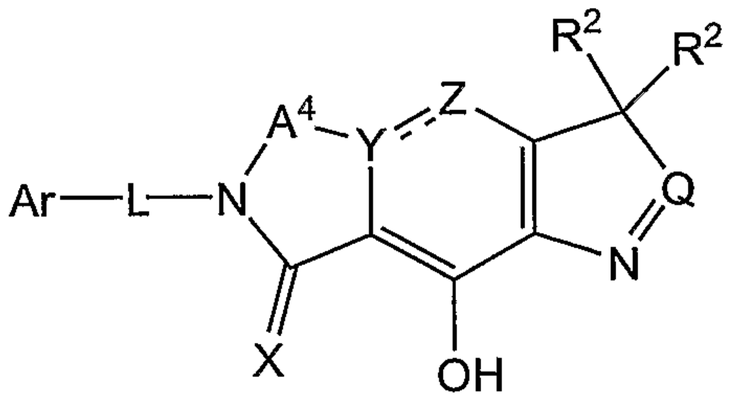


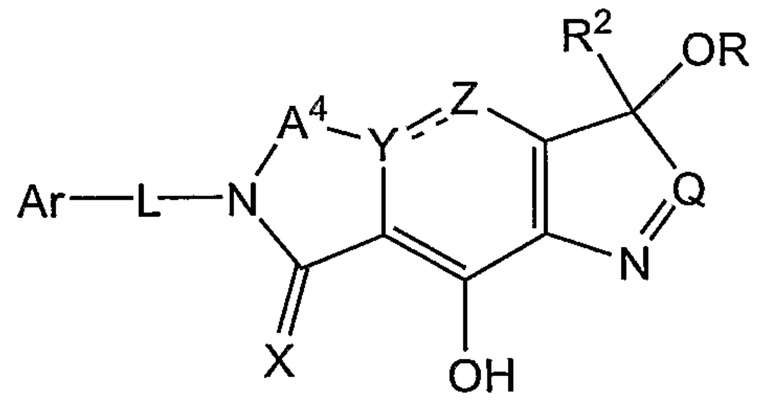


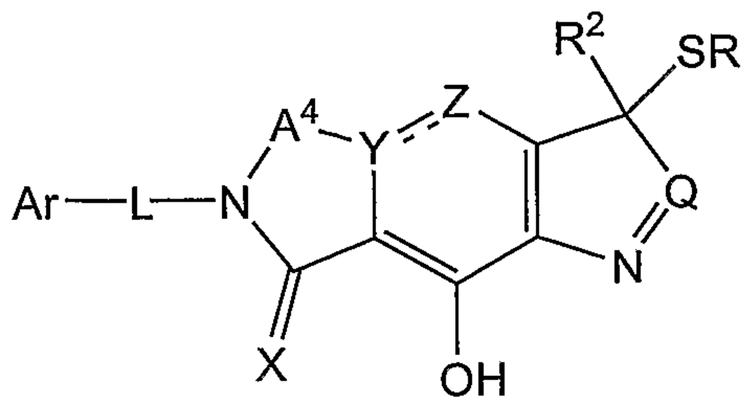












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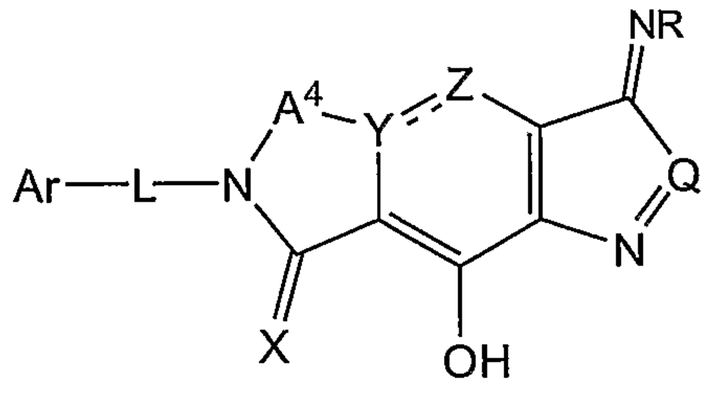
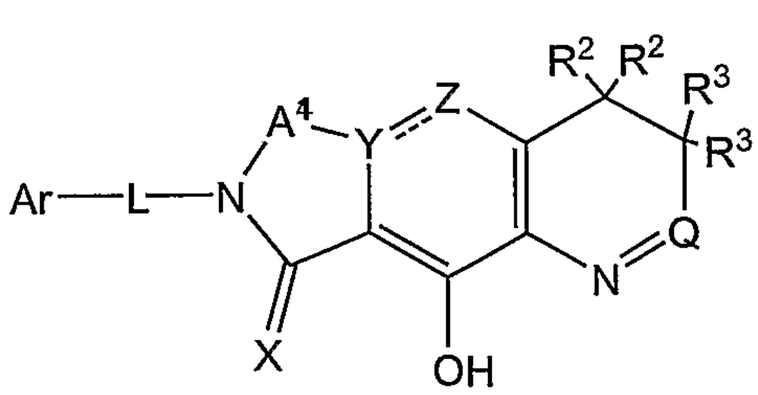
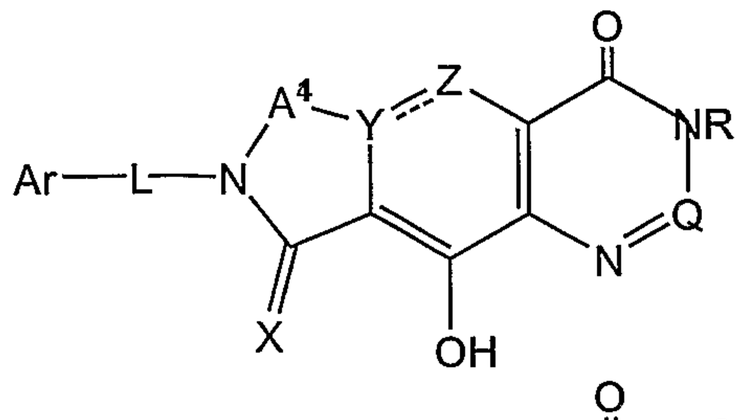
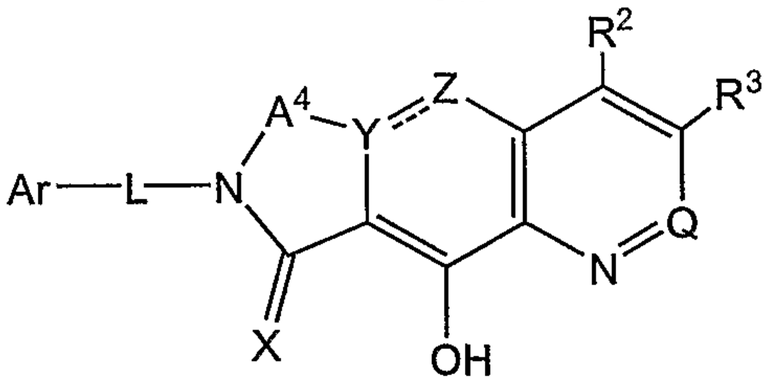
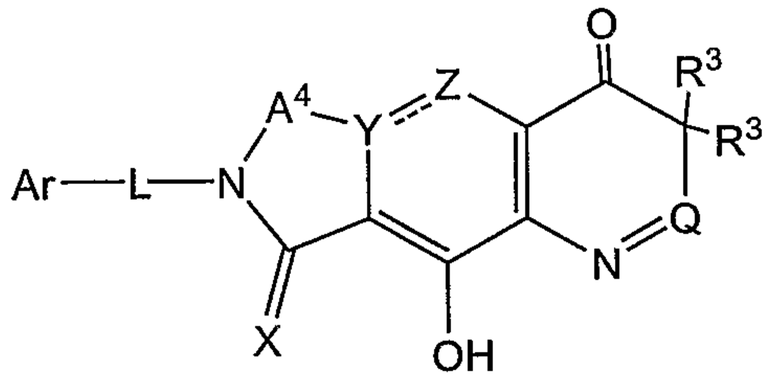


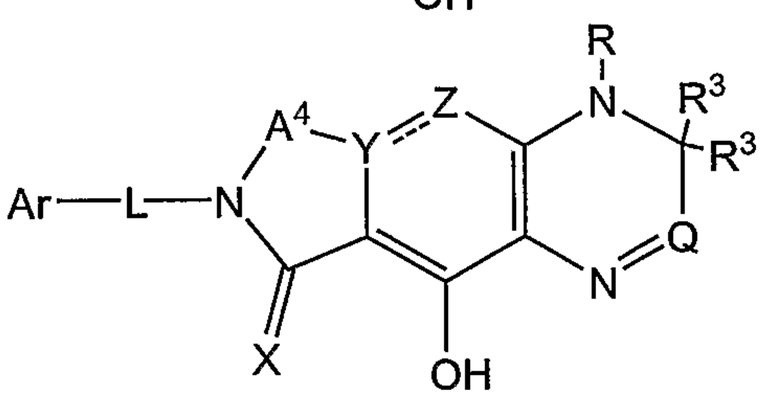
Other various embodiments of A^5 form 6-membered rings in the exemplary structures:

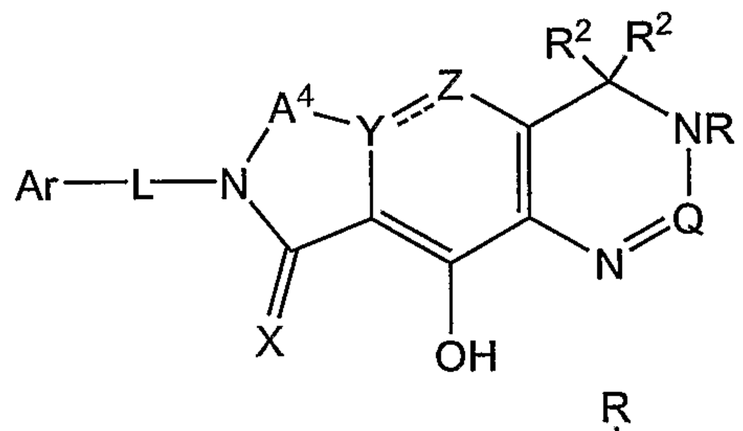


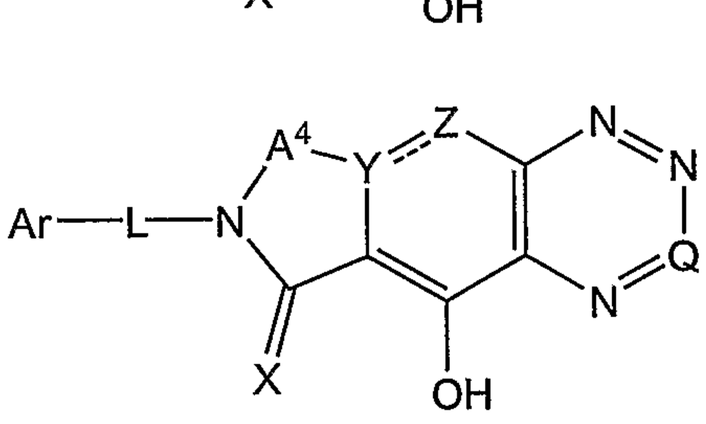


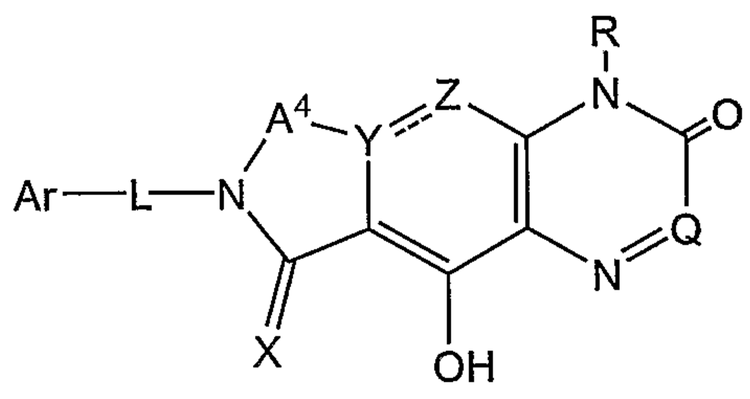












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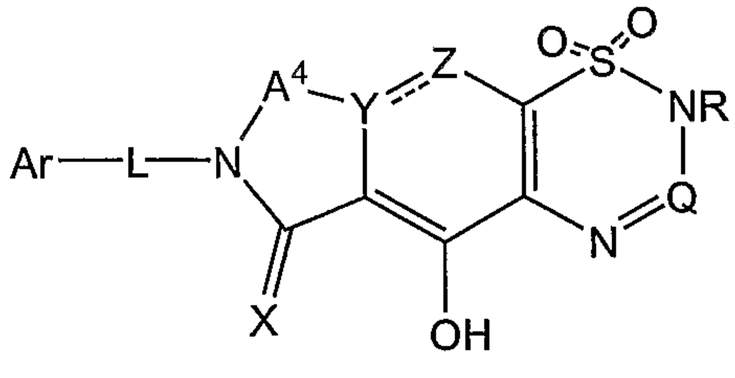
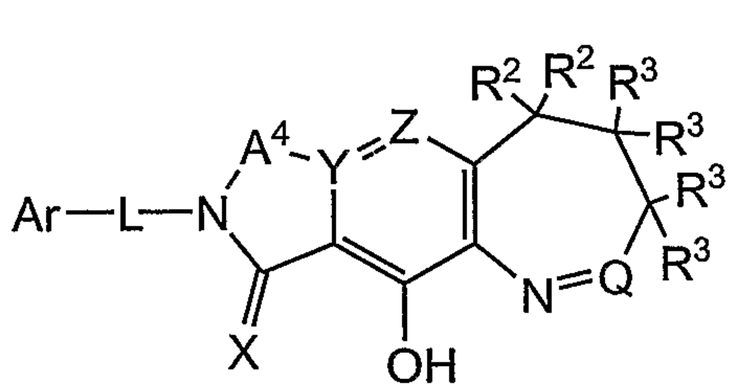
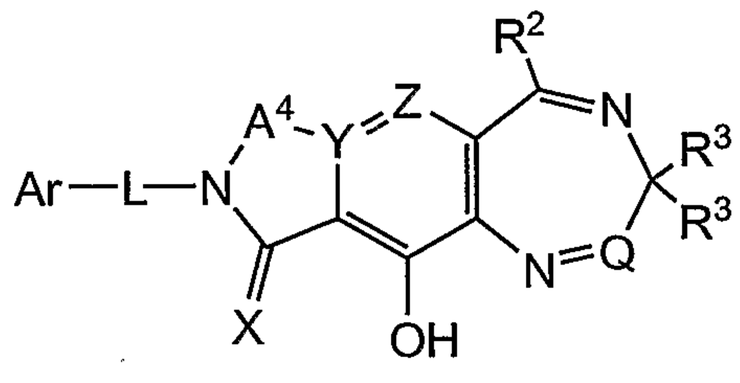
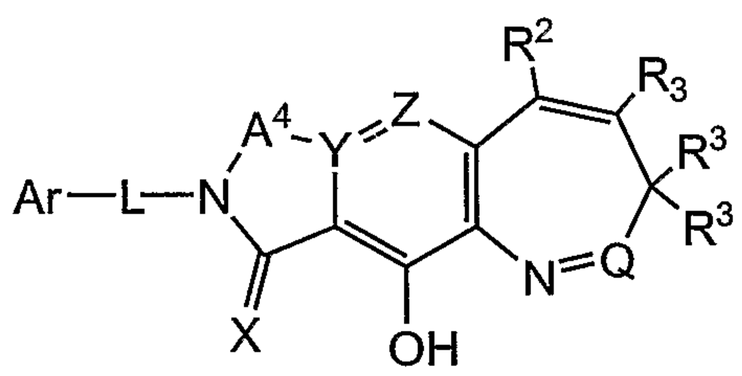
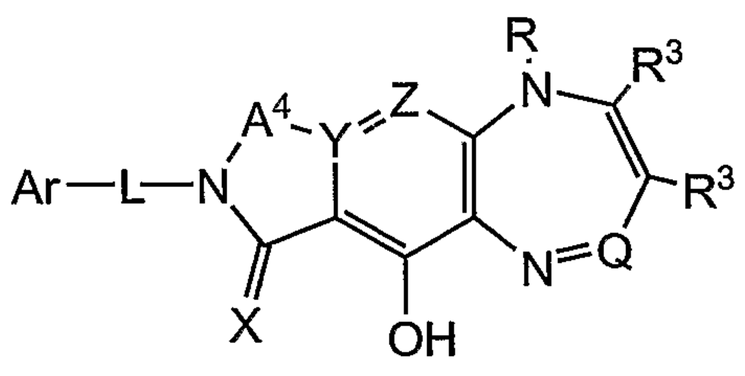


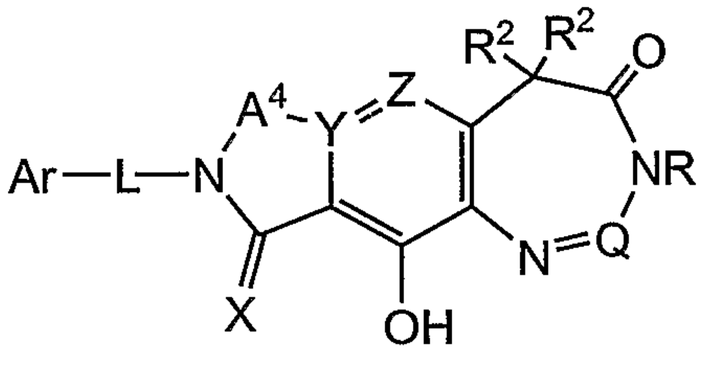
Other various embodiments of A^5 form 7-membered rings in the exemplary structures:

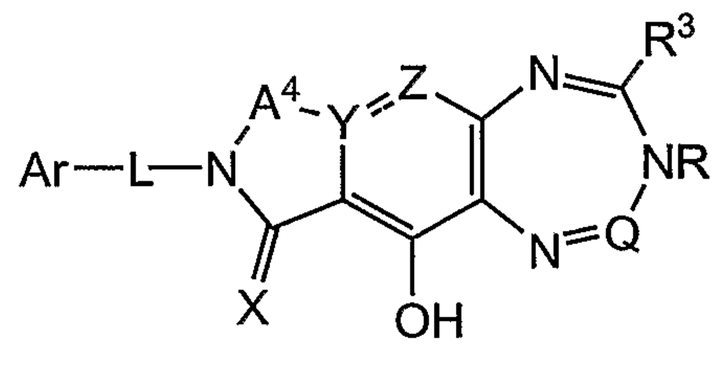












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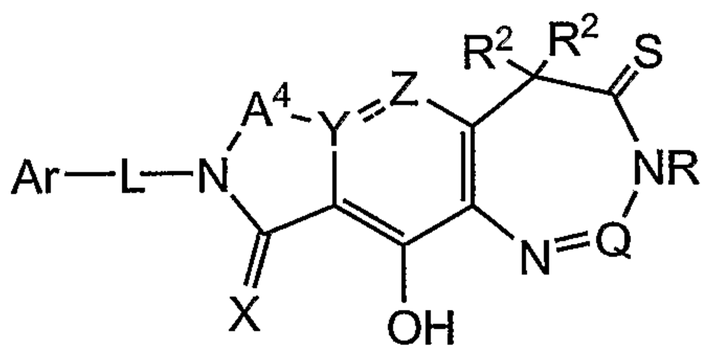
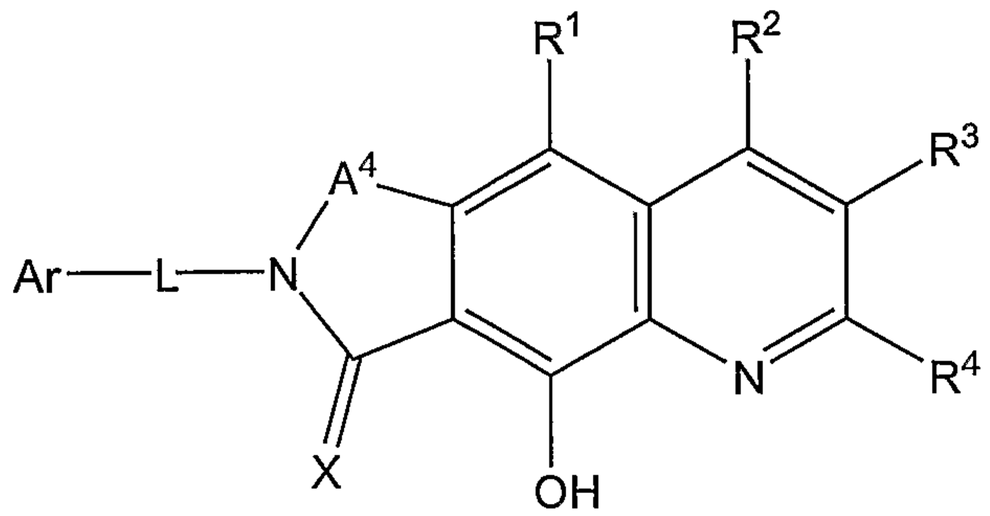
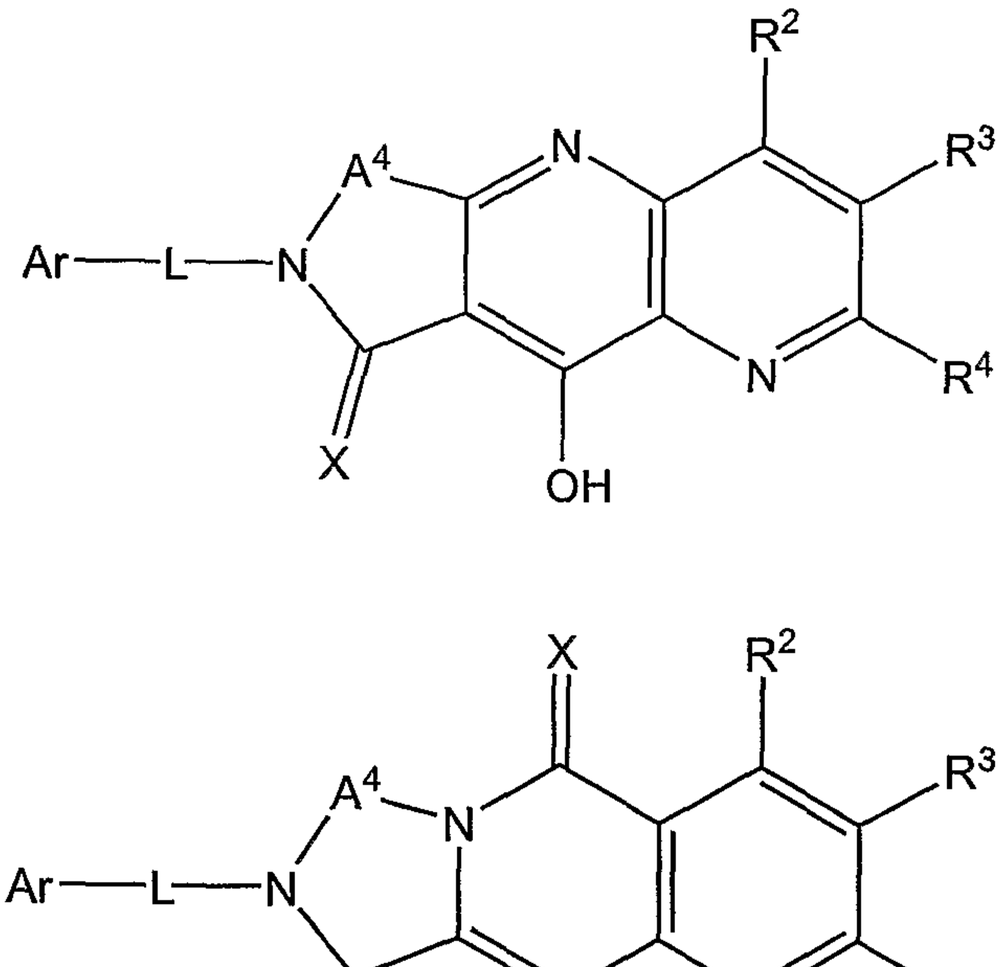
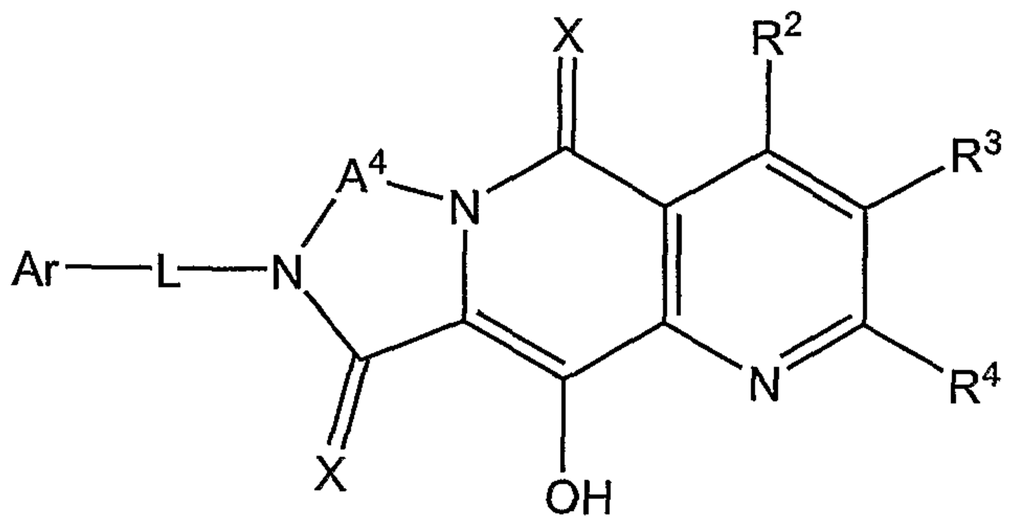
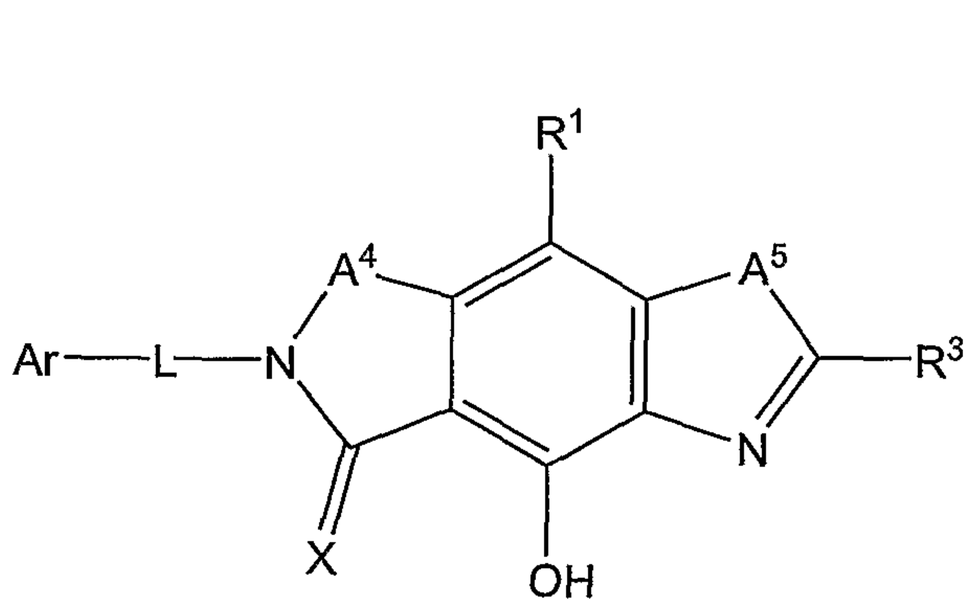


Formula I compounds of the invention include the following structures:

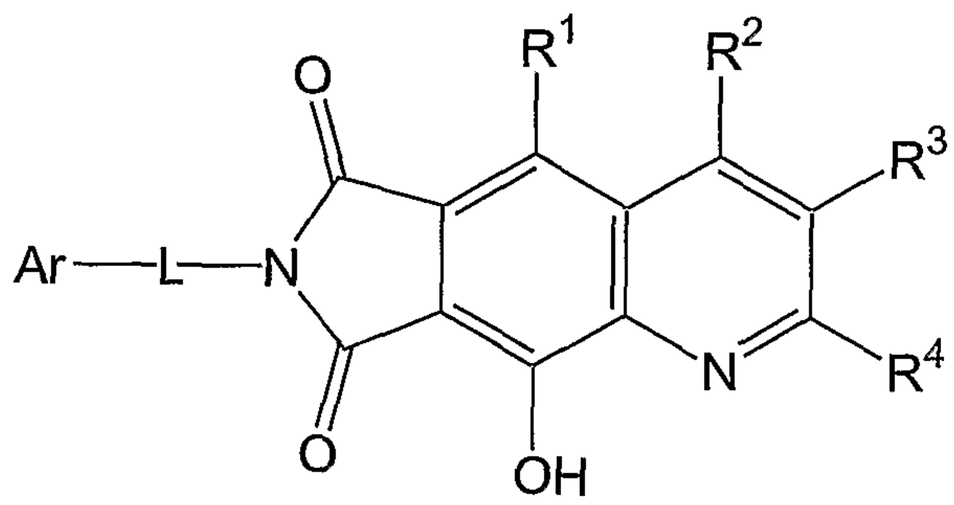




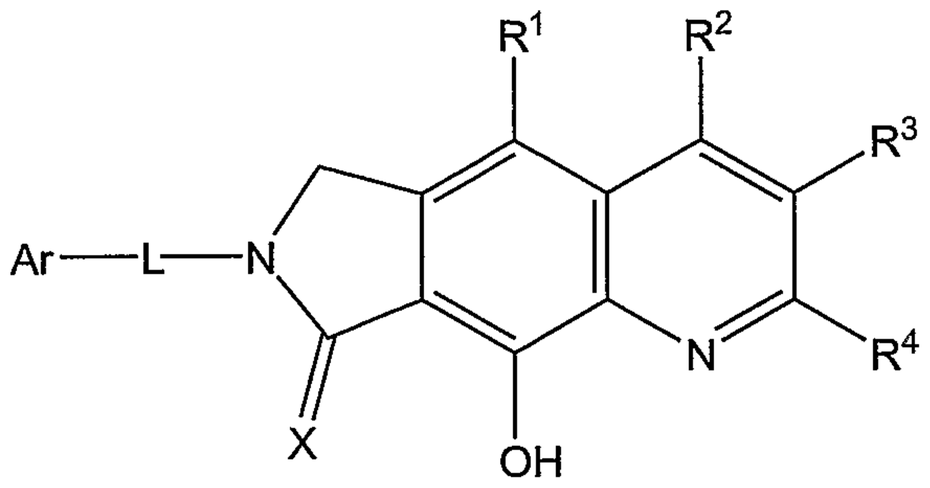




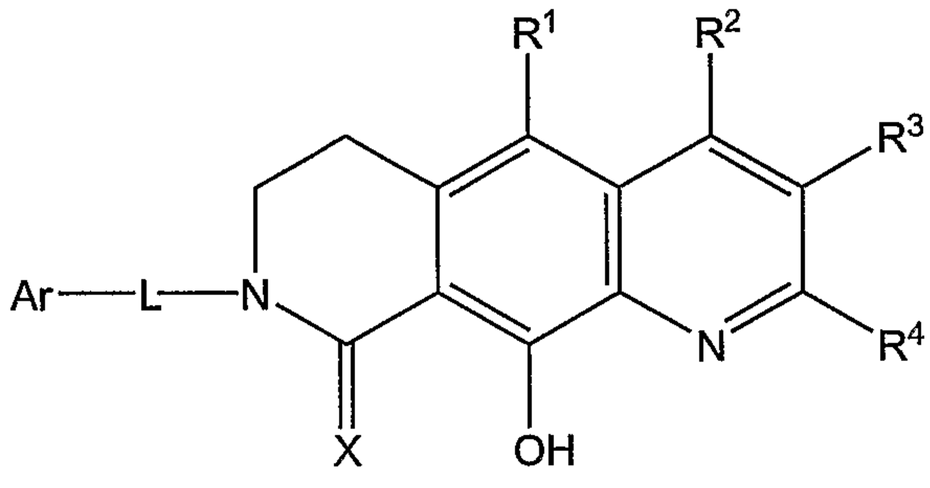
Formula I compounds thus include the following succinimide structure:



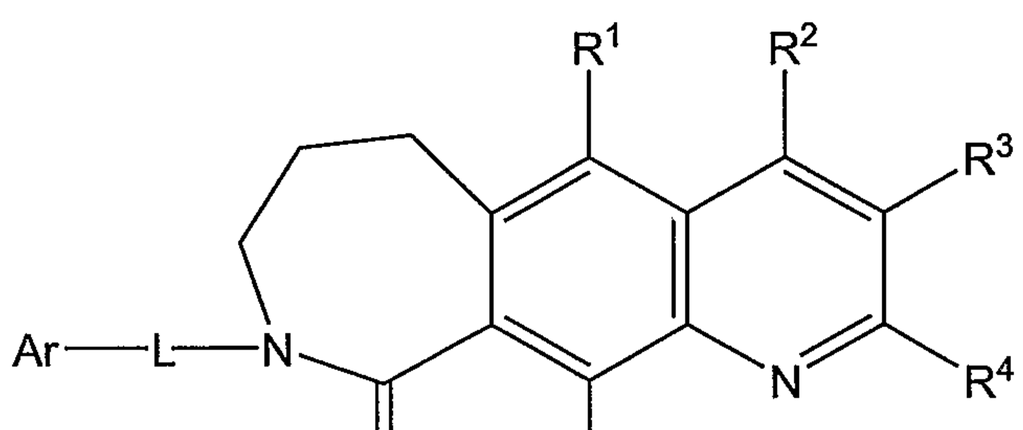
Embodiments of Formula I also include Ia-c where A^4 is CH_2, CH_2CH_2, and $CH_2CH_2CH_2$, respectively:



Ia

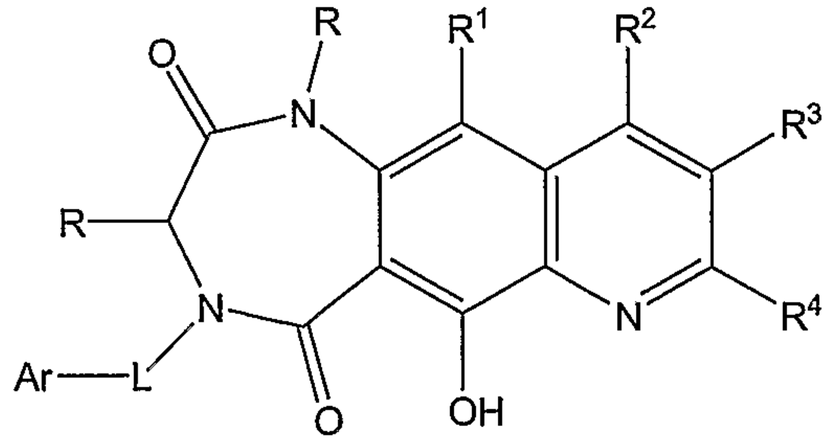


Ib



Ic

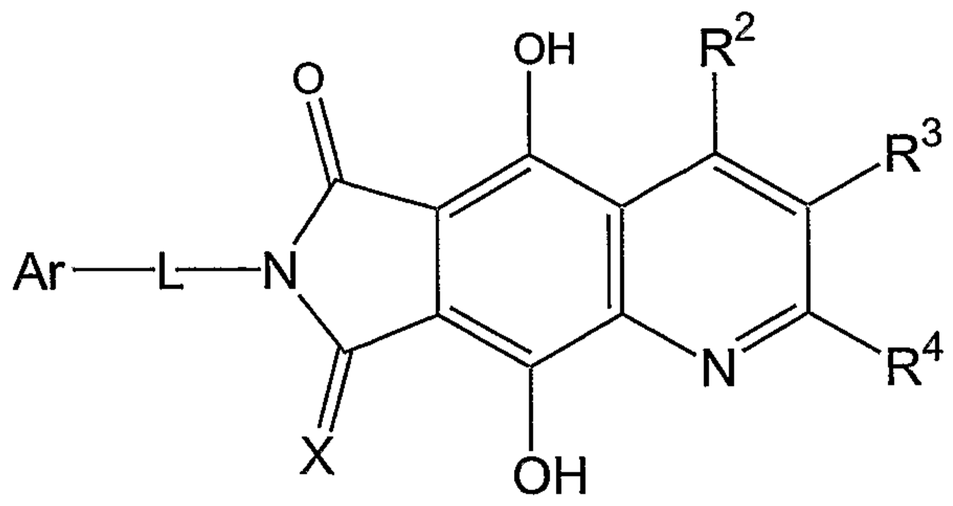
Where A^4 forms a seven-membered ring, the 7 membered ring may be comprised of a second amide group, as shown by exemplary Formula Id:



Id

One aspect of the invention includes compounds with a cyclic imide group, e.g. 5,9-dihydroxy-pyrrolo[3,4-*g*]quinoline-6,8-dione (Myers, etal U.S. Patent No.

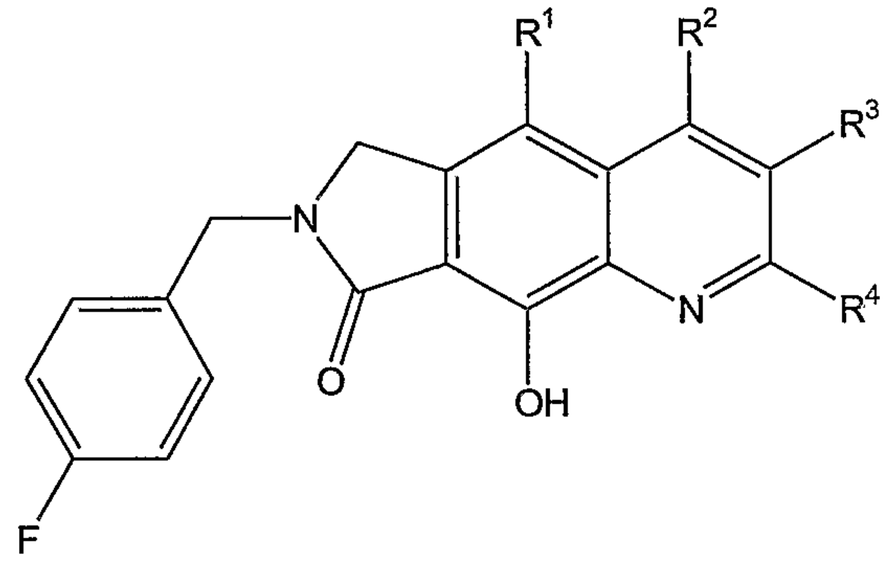
5,252,560; Robinson, U.S. Patent No. 5,854,275), where A is C(=O) and X is O, as in formula Ie:



Ie

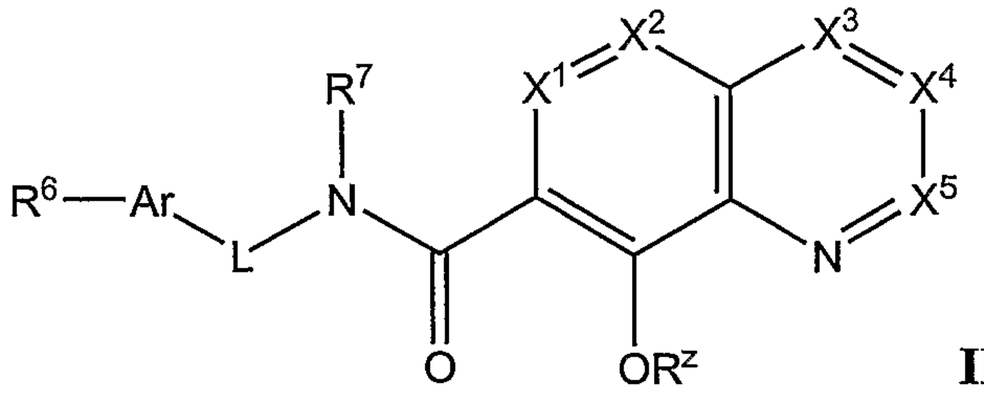
Along with other compounds of the invention, the cyclic imide group of Formula Ie provides functionality which may be in a pre-organized state for optimized HIV integrase inhibition relative to compounds without the cyclic imide group (Anthony, etal WO 02/30931; Zhuang, etal "Design and synthesis of 8-hydroxy-1,6-naphthyridines as novel HIV-1 integrase inhibitors" Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, Sept. 27-30, 2002).

Formula Ia compounds include the following amide structure:



Group II

In one aspect, the invention includes phosphonate analogs of aza-quinolinol compounds (Zhuang et al (2003) *J. Med. Chem.* 46(4):453-456; Zouhiri et al (2000) *J. Med. Chem.* 43(8):1533-1540; Ouali et al (2000) *J. Med. Chem.* 43(10)1949-1957; d'Angelo et al (2001) *Pathol. Biol.* 49:237-246; Mekouar et al (1998) *J. Med. Chem.* 41:2846-2857; WO 03/62204; WO 03/016315 A1; WO 03/016309 A1; WO 03/016294 A1; WO02/070486 A1; WO 02/055079; WO 02/030930; WO 02/030931; WO 02/30426) represented by the Formula II:



II

wherein:

X^1 is CR^1, NR, or N;

X^2 is CR^2, NR, or N;

X^3 is CR^3, NR, or N;

X^4 is CR^4, NR, or N;

X^5 is CR^5, NR, or N;

at least one of X^1, X^2, X^3, X^4, and X^5 is NR or N;

R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently selected from H, F, Cl, Br, I, OH, amino ($-NH_2$), ammonium ($-NH_3^+$), alkylamino, dialkylamino, trialkylammonium, C_1-C_8 alkyl, C_1-C_8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, C_1-C_8 alkylsulfonate, C_1-C_8 alkylamino, 4-dialkylaminopyridinium, C_1-C_8 alkylhydroxyl, C_1-C_8 alkylthiol, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide ($-SOAr$), arylthio ($-SAr$), sulfonamide ($-SO_2NR_2$), alkylsulfoxide ($-SOR$), formyl ($-CHO$), ester ($-C(=O)OR$), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile ($-CN$), azido ($-N_3$), nitro ($-NO_2$), C_1-C_8 alkoxy ($-OR$), C_1-C_8 alkyl, C_1-C_8 substituted alkyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heteroaryl, and C_2-C_{20} substituted heteroaryl, phosphonate, phosphate, polyethyleneoxy, and a prodrug moiety.

R is independently selected from H, C_1-C_8 alkyl, C_1-C_8 substituted alkyl, C_2-C_{18} alkenyl, C_2-C_{18} substituted alkenyl, C_2-C_{18} alkynyl, C_2-C_{18} substituted alkynyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heteroaryl, and C_2-C_{20} substituted heteroaryl.

Alternatively, R, R^1, R^2, R^3, R^4, R^5, R^6, or R^7 may independently comprise A^1, A^3 or $L-A^3$.

At least one of R, R^1, R^2, R^3, R^4, R^5, R^6, and R^7 comprises a phosphonate group. The phosphonate group may be a prodrug moiety. The phosphonate group may be directly attached to a ring carbon (CR^1, CR^2, CR^3, CR^4 or CR^5) of Formula II.

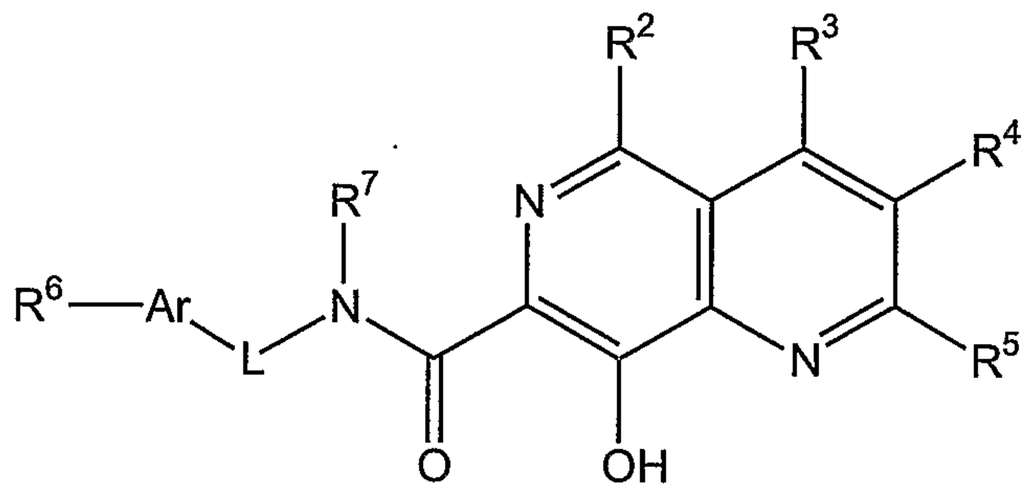
R^z is H; a protecting group selected from benzyhydryl ($CHPh_2$), trialkylsilyl (R_3Si), 2-trimethylsiloxyethyl, alkoxymethyl (CH_2OR), and ester ($C(=O)R$); or a prodrug moiety;

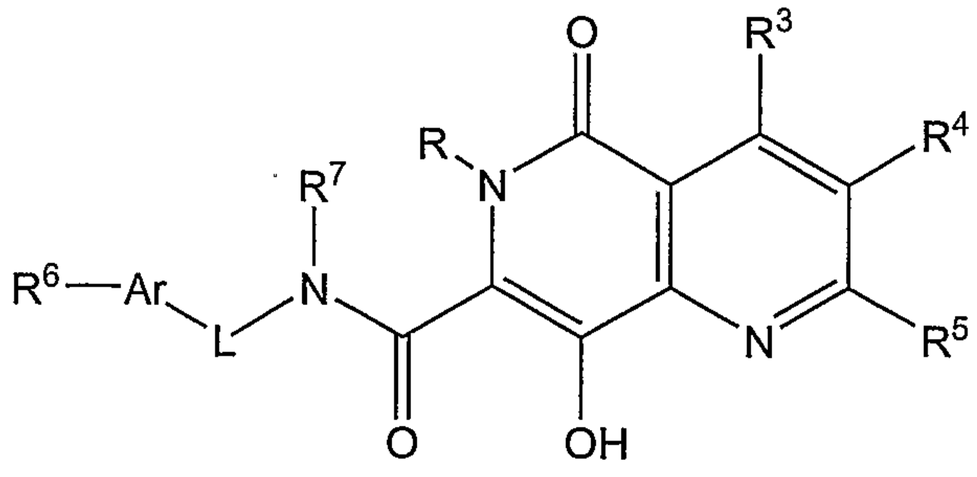
L is a bond or any linker which covalently attaches the Ar group to the tricyclic scaffold. For example, L may be a bond, O, S, S(=O) (sulfoxide), $S(=O)_2$ (sulfone), $S(=O)_2NR$ (sulfonamide), N–OR, C_1–C_{12} alkylene, C_1–C_{12} substituted alkylene, C_2–C_{12} alkenylene, C_2–C_{12} substituted alkenylene, C_2–C_{12} alkynylene, C_2–C_{12} substituted alkynylene, C(=O)NH, C(=O), $C(=O)NH(CH_2)_n$, or $(CH_2CH_2O)_n$, where n may be 1, 2, 3, 4, 5, or 6.

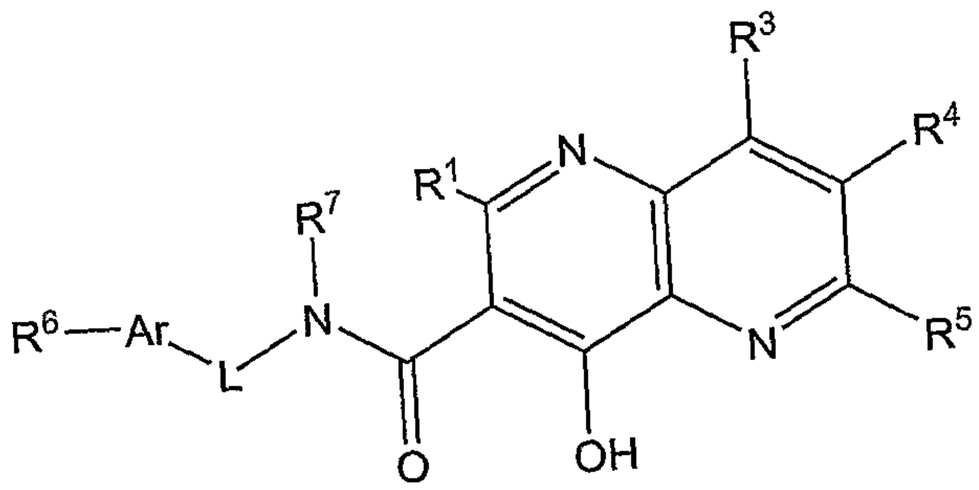
Ar groups may be any saturated, unsaturated or aromatic ring or ring system comprising a mono- or bicyclic carbocycle or heterocycle, e.g. 3 to 10 ring atoms. The rings are saturated when containing 3 ring atoms, saturated or mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when containing 6 ring atoms.

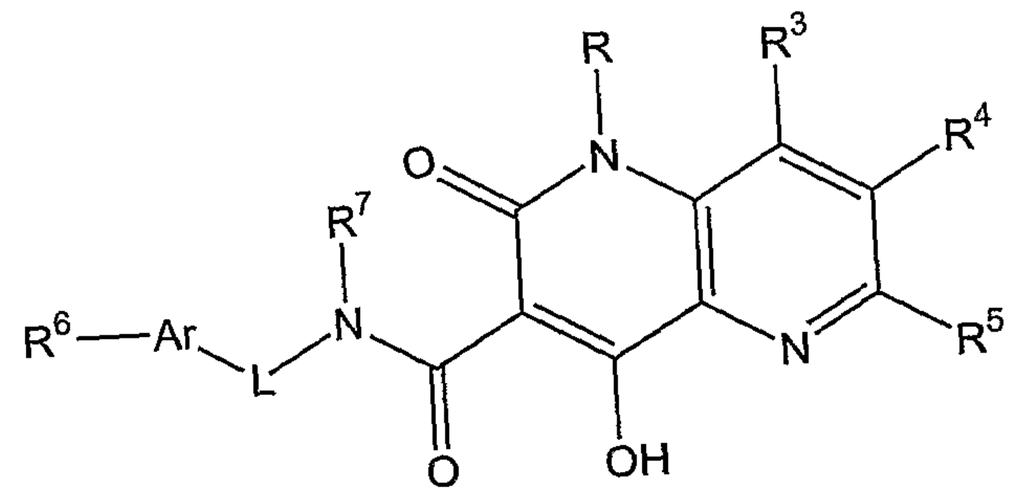
Ar is covalently attached to L and to one or more R^6.

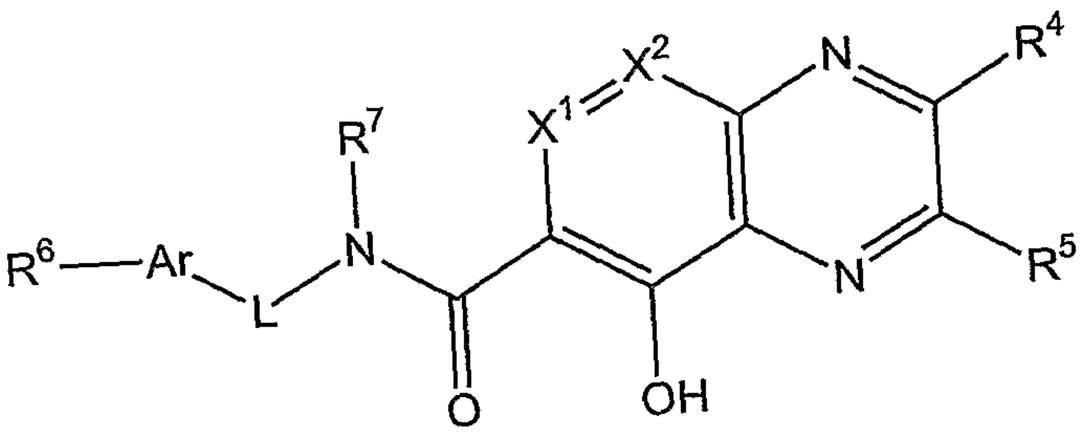
Exemplary structures within Formula II include the following:

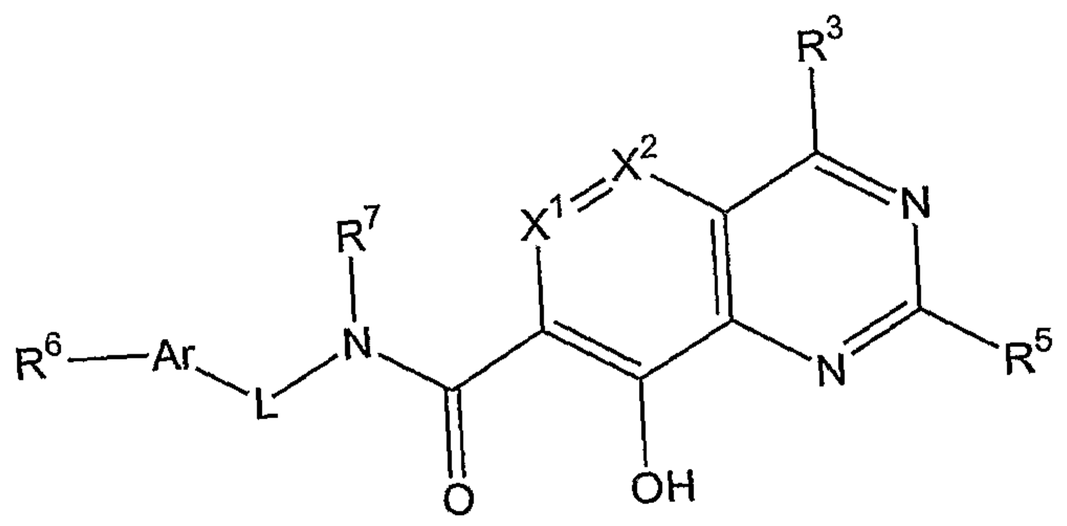


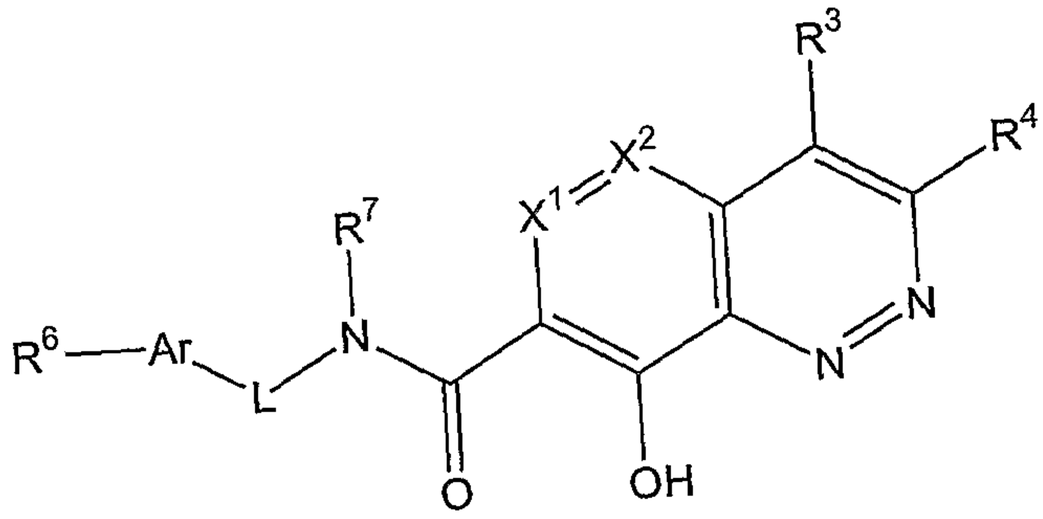




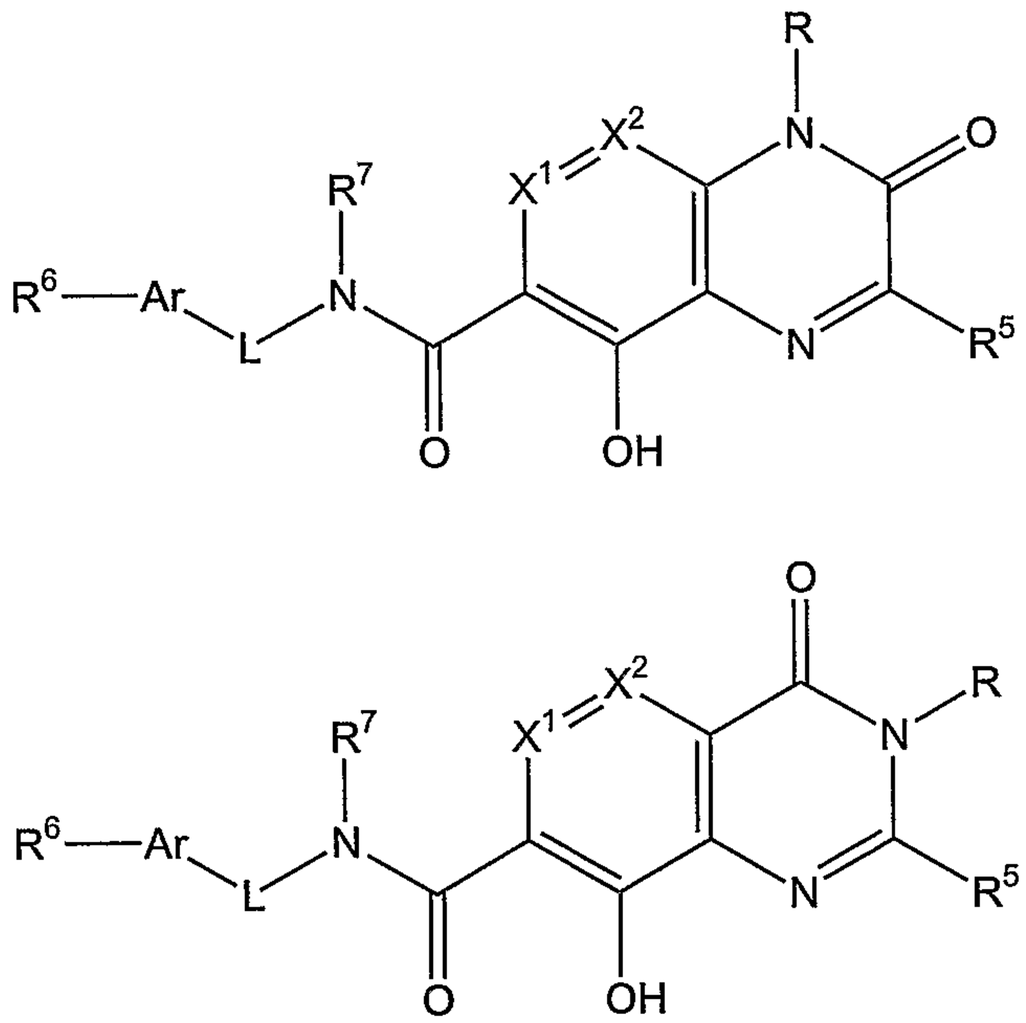






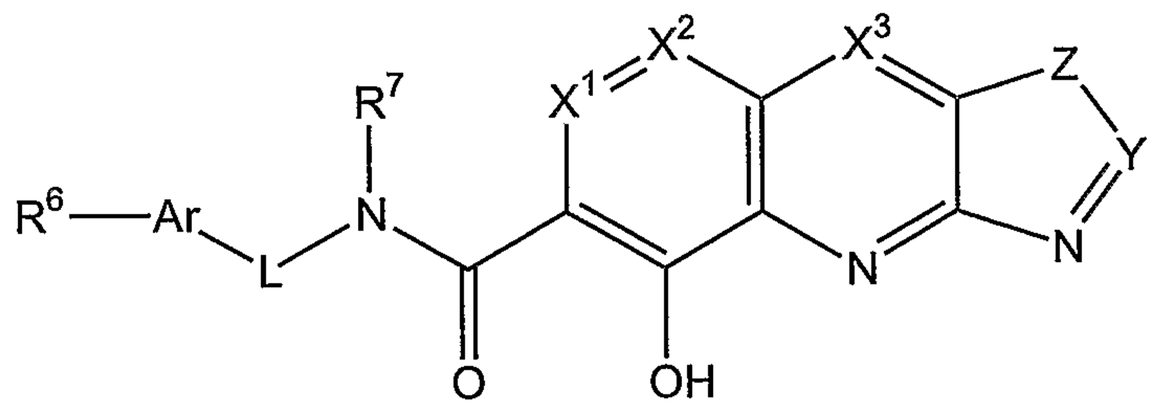


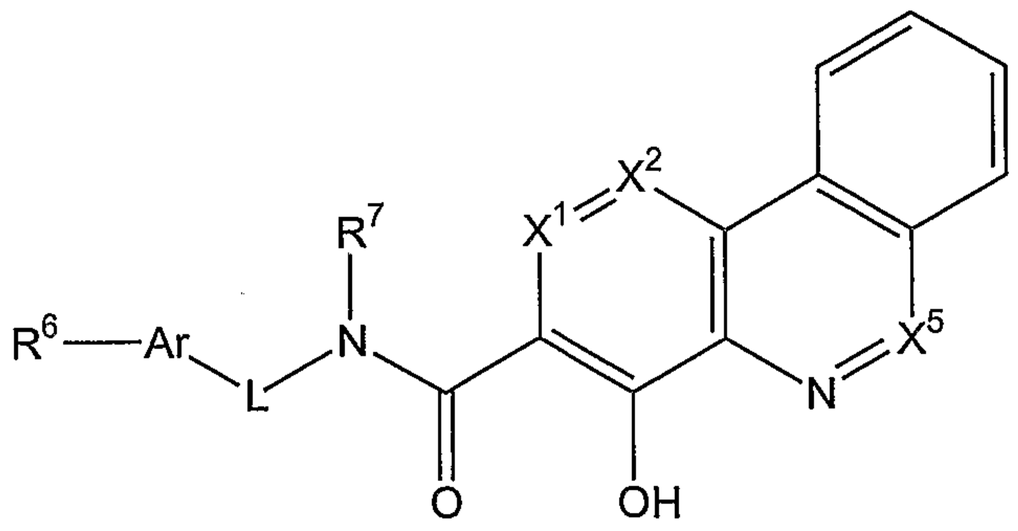
5

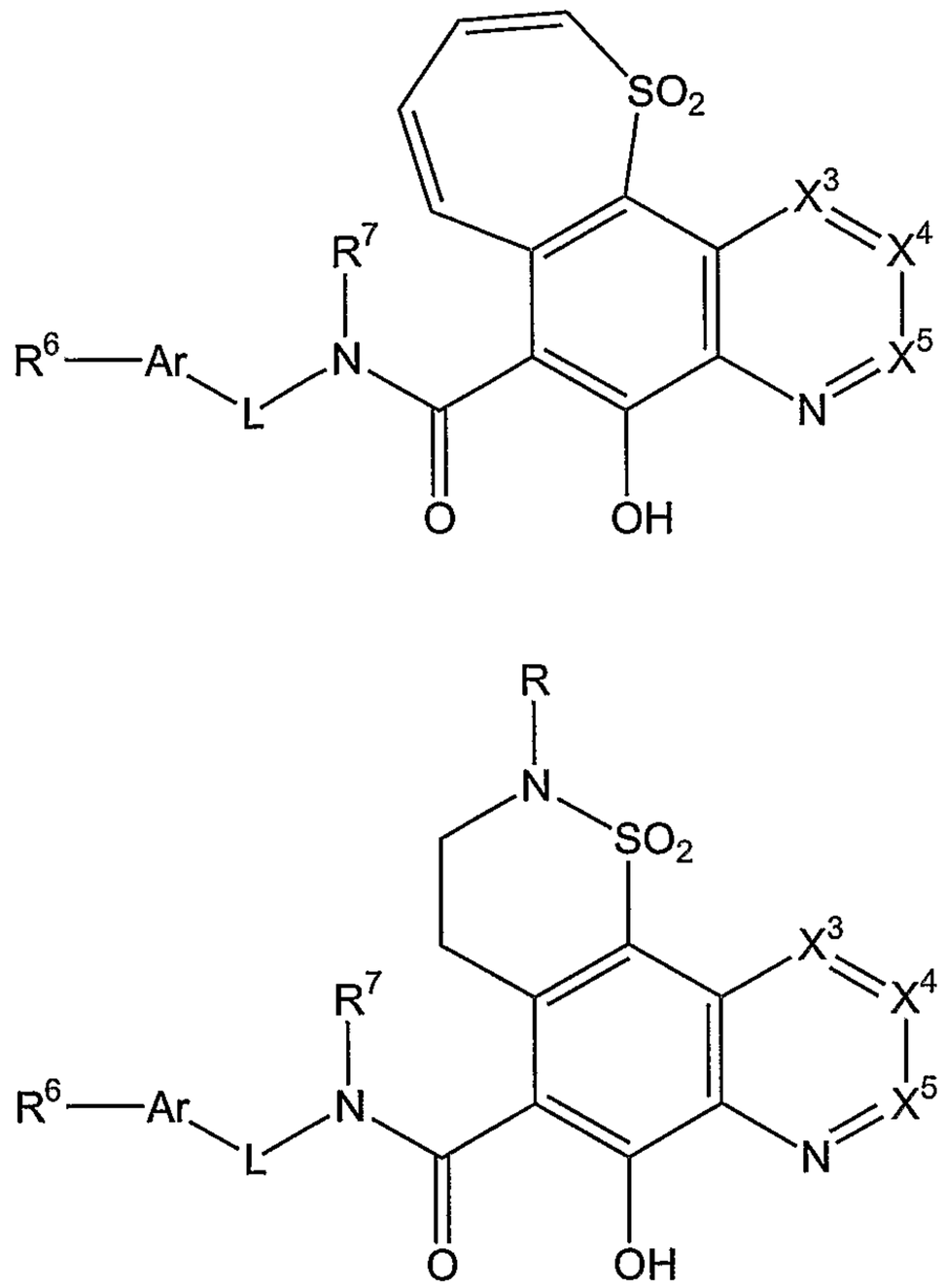


When X^1 is CR^1 and when X^2 is CR^2, then CR^1 and CR^2 together may form a ring. When X^3 is CR^3 and when X^4 is CR^4, then CR^3 and CR^4 together may form a ring. When X^4 is CR^4 and X^5 is CR^5, then CR^4 and CR^5 together may form a ring. The ring may be 5, 6, or 7-membered. The ring may be all carbon atoms or it may have one or more heteroatoms selected from nitrogen, oxygen, and sulfur.

Exemplary structures when CR^4 and CR^5 form a ring include the following:



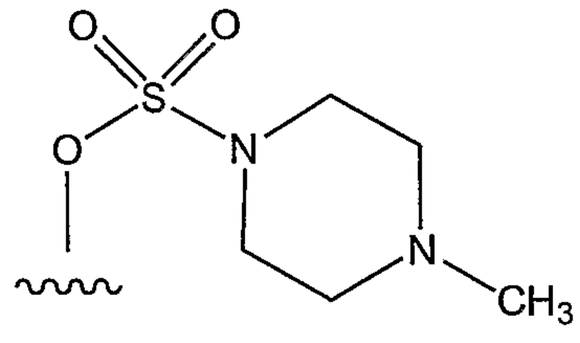




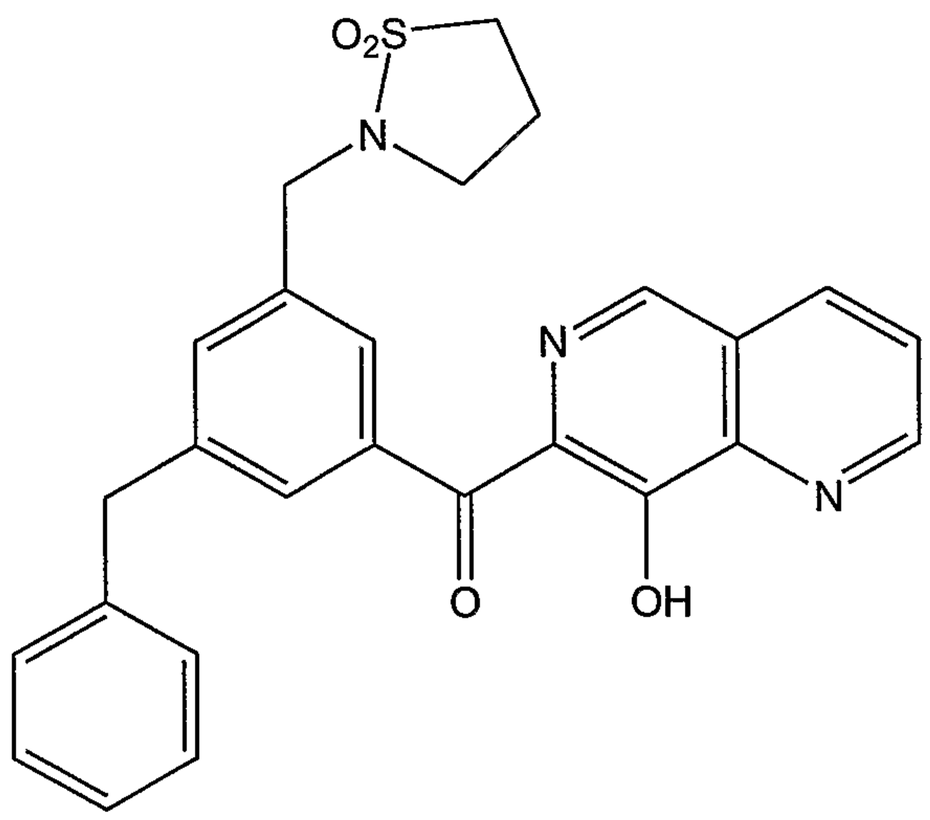
Y is CR^5, NR or N. Z is a moiety forming a five, six, or seven membered ring. For example, Z may be O, S, NR, CR_2, CROR, CROC(=O)R, C(=O), C(=S), CRSR, C(=NR_2), C=CR_2, CR_2–CR_2, CR=CR, NR–CR_2, N=CR, N=N, SO_2–NR, C(=O)CR_2, S(=O)CR_2, SO_2CR_2, C(=O)NR, CR_2–CR_2–CR_2, CR=CR–CR_2, CRC(=O)NR, $CR_2SO_2CR_2$, CR_2SO_2NR, CRC(=S)NR, CR=N–CR_2, CR=N–NR, or N=CR–NR.

R^2 may be –H, –OH, –OC(=O)OR, –OC(=O)NR_2, –OC(=S)NR_2, –OC(=O)NRNR_2, –OC(=O)R, –C(=O)OR, –C(=O)NR_2, –C(=O)NRNR_2, –C(=O)R, –OSO_2NR_2 (sulfamate), –NR_2, –$NRSO_2R$, –NRC(=S)NR_2, –SR, –S(O)R, –SO_2R, –SO_2NR_2 (sulfonamide), –OSO_2R (sulfonate), –P(=O)$(OR)_2$, –P(=O)(OR)(NR_2), –P(=O)$(NR_2)_2$, –P(=S)$(OR)_2$, –P(=S)(OR)(NR_2), –P(=S)$(NR_2)_2$, and including prodrug substituted forms thereof.

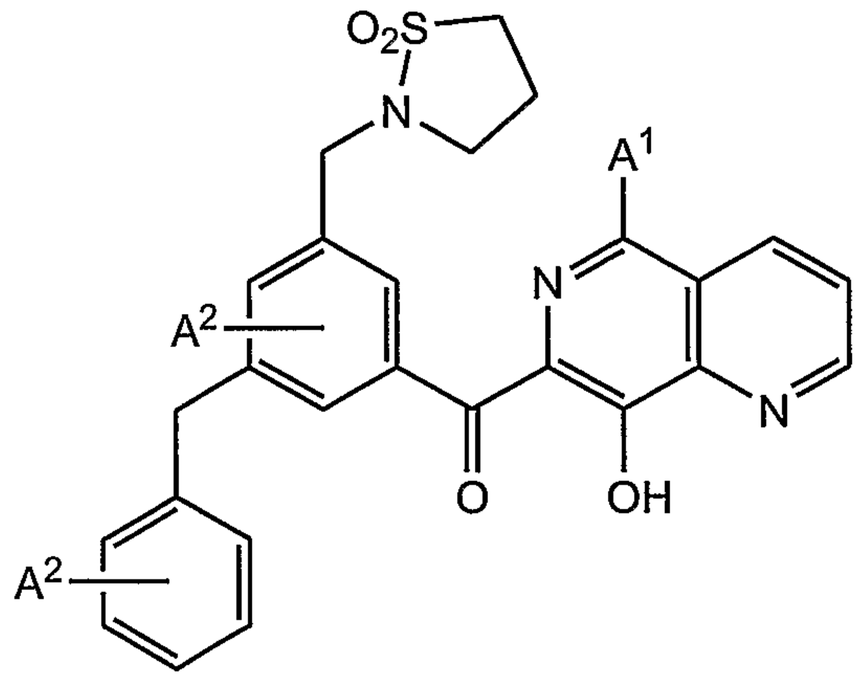
R^2 may include a ring, e.g. 4-7 membered ring lactam or sultam, or piperazinyl sulfamate:

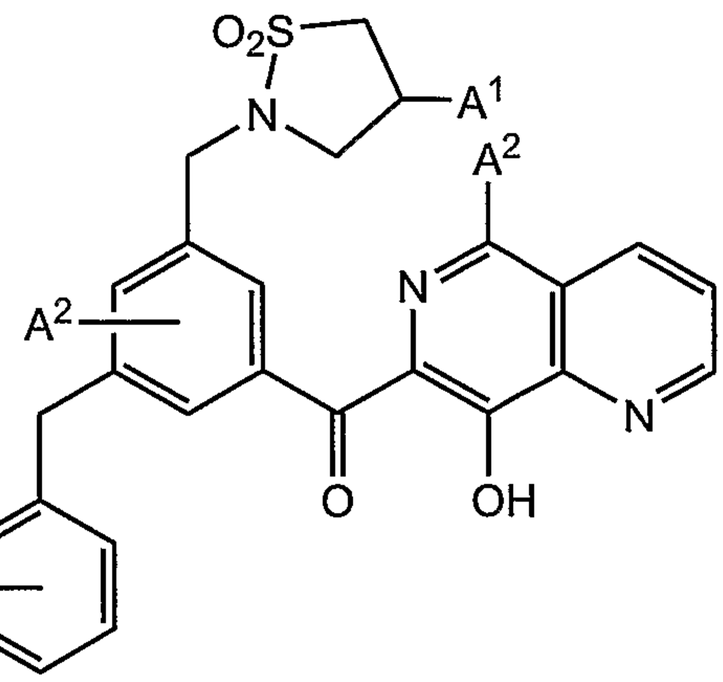


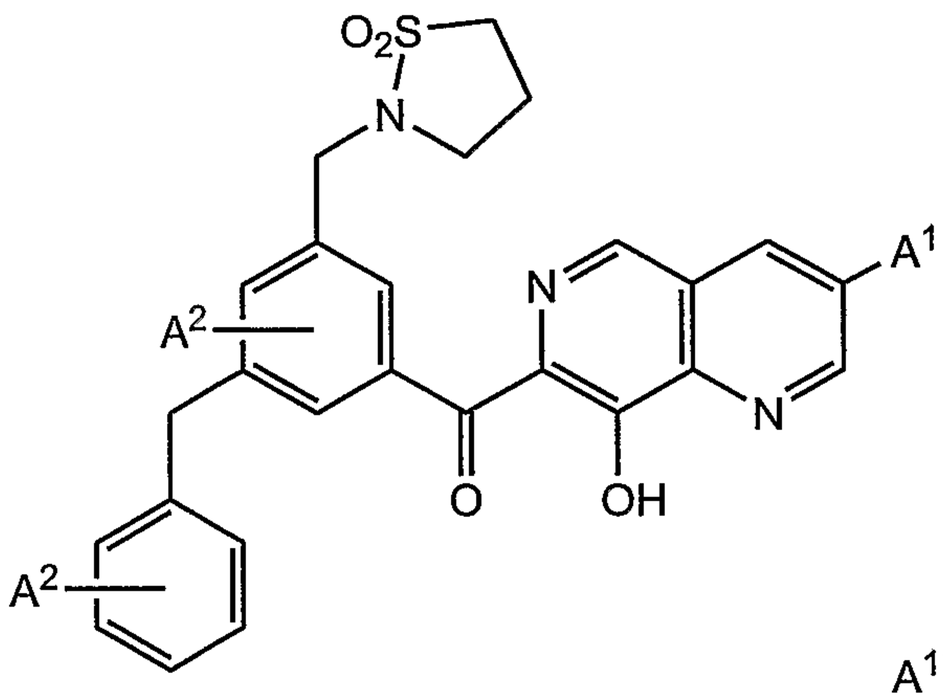
Exemplary embodiments of Formula II compounds include:

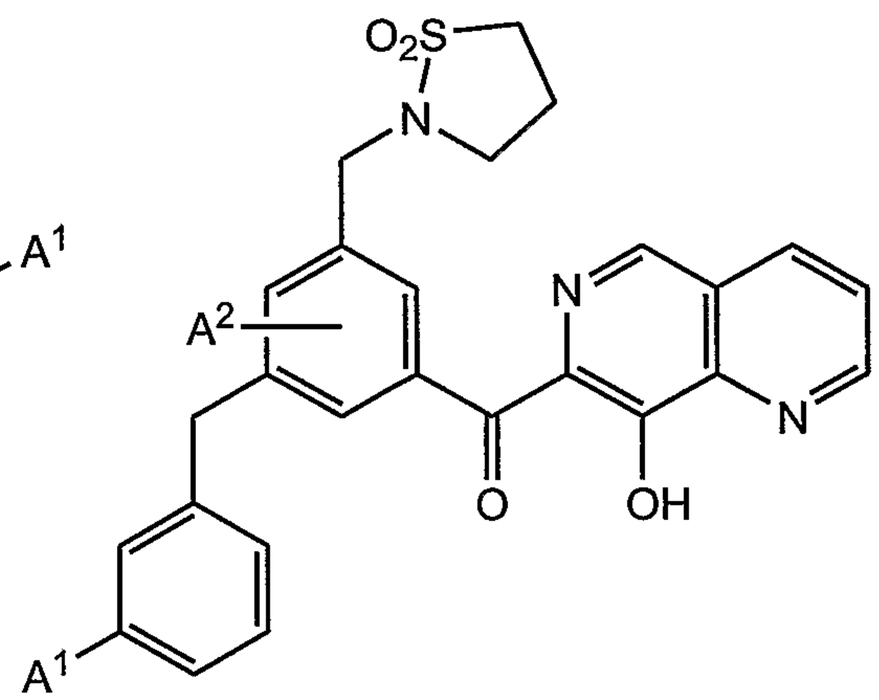


where at least one aryl or sultam ring carbon atom is substituted with an A^1 group, and any aryl or sultam ring carbon atom may be substituted with an A^2 group, including the exemplary structures:



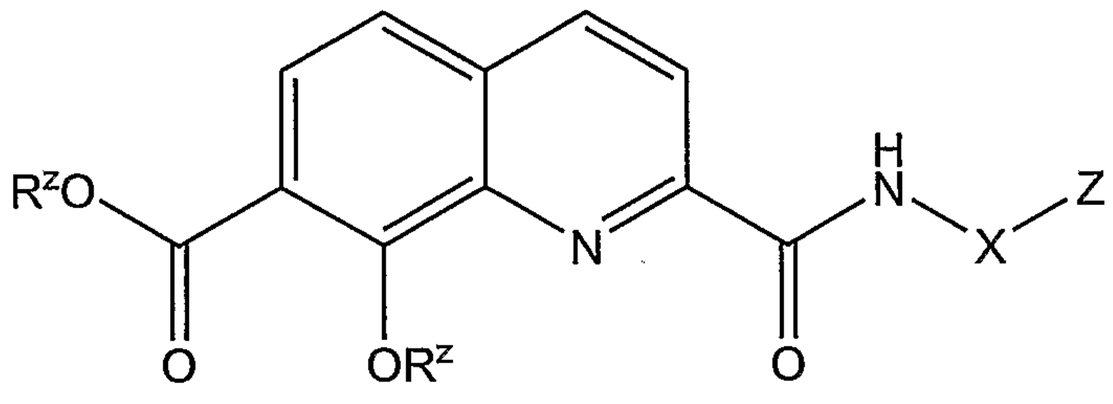






Group III

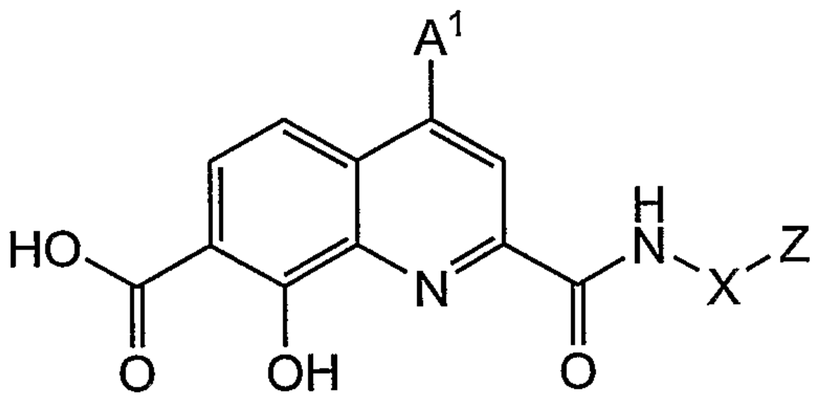
In one aspect, the invention includes phosphonate analogs of quinoline compounds (WO 03/031413 A1) represented by the Formula III:

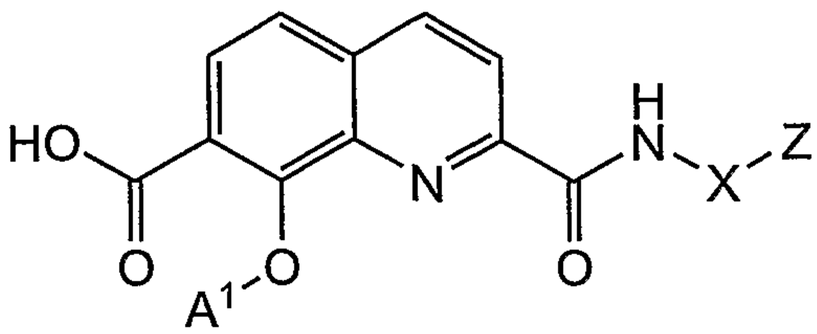


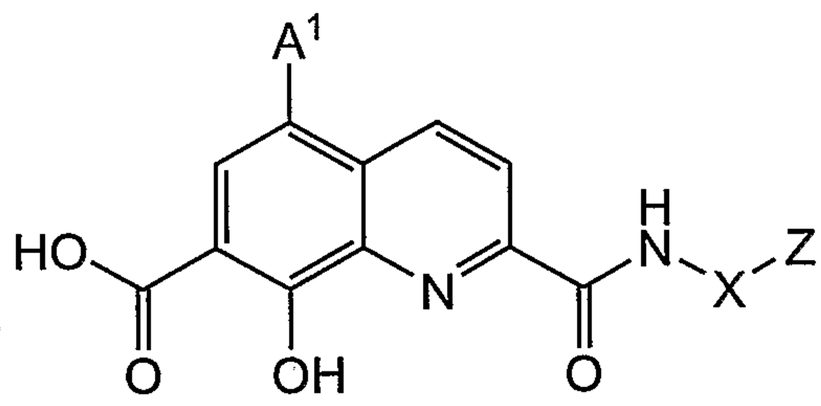
III

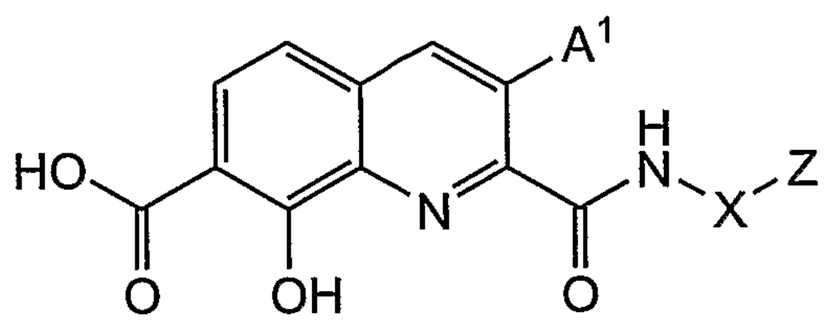
wherein X is L and Z is R^6-Ar as defined in Formula II. R^z is H; a protecting group selected from benzyhydryl ($CHPh_2$), trialkylsilyl (R_3Si), 2-trimethylsiloxyethyl, alkoxymethyl (CH_2OR), and ester (C(=O)R); or a prodrug moiety. The aryl carbons and amide nitrogen may be further substituted as defined in the following embodiments of Formula III.

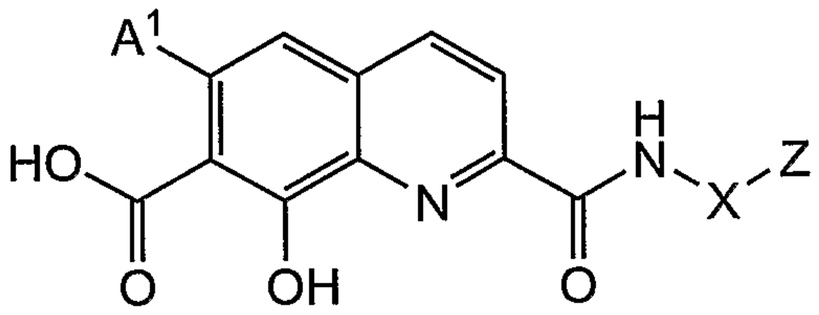
Embodiments of Formula III include the structures:

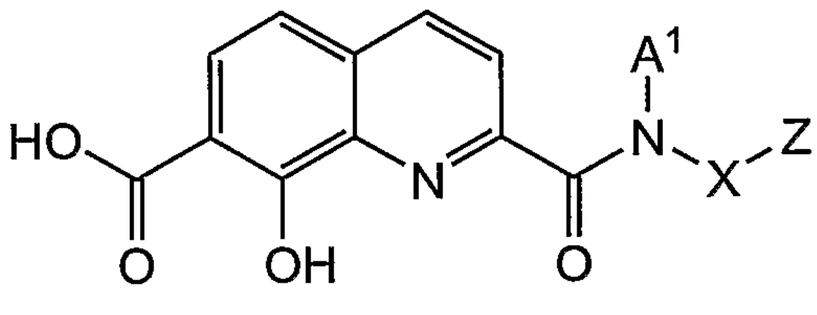


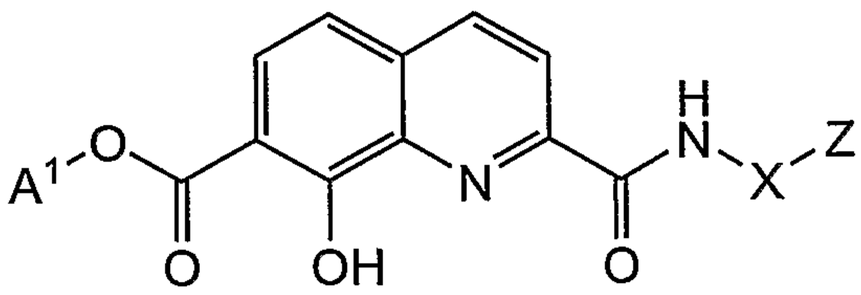




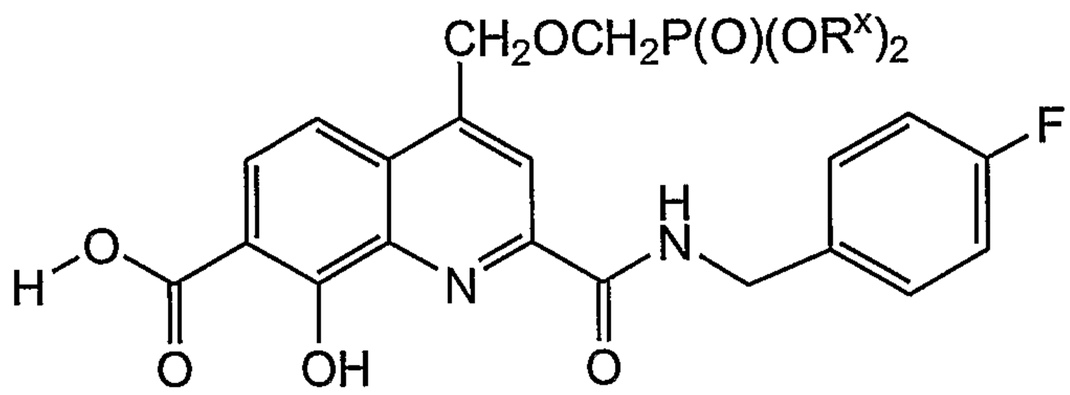


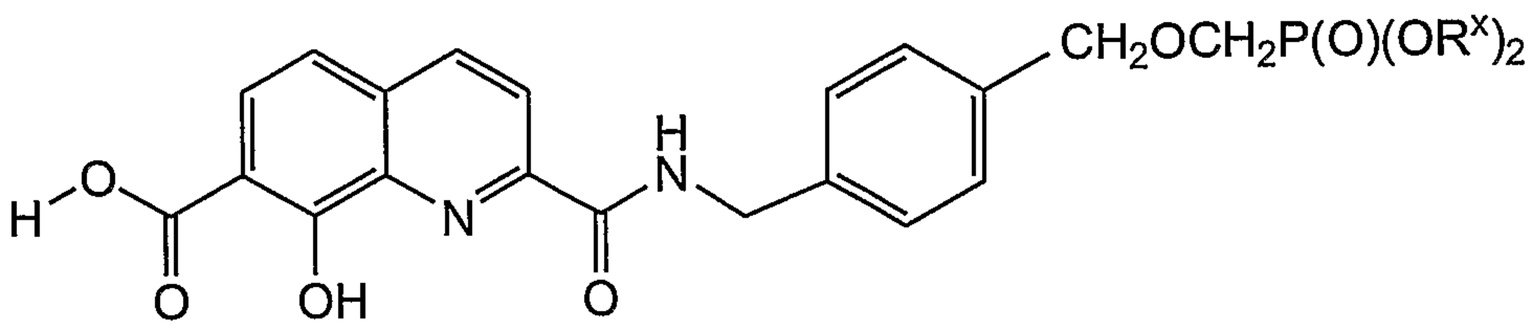






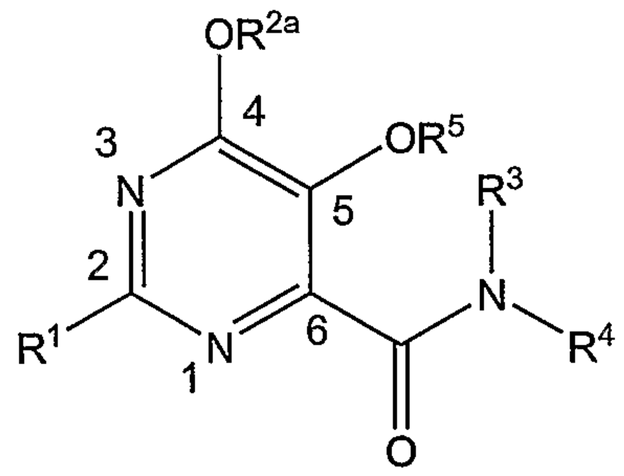
Further embodiments of Formula III compounds include the following:





Group IV

In one aspect, the invention includes phosphonate analogs of 4,5-dihydroxypyrimidine, 6-carboxamide compounds (WO 03/035076 A1) having Formula IV:



IV

wherein:

R^1 is selected from H, F, Cl, Br, I, OH, OR, amino ($-NH_2$), ammonium ($-NH_3^+$), alkylamino (–NHR), dialkylamino ($-NR_2$), trialkylammonium ($-NR_3^+$), carboxyl ($-CO_2H$), sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, 4-dialkylaminopyridinium, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide (–SOAr), arylthio (–SAr), sulfonamide ($-SO_2NR_2$), alkylsulfoxide (–SOR), formyl (–CHO), ester ($-CO_2R$), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile (–CN), azido ($-N_3$), nitro ($-NO_2$), C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocycle, and C_2–C_{20} substituted heterocycle, phosphonate, phosphate, polyethyleneoxy, a protecting group, and a prodrug moiety;

R^{2a} and R^5 are each independently selected from H, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, 4-dialkylaminopyridinium, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide (–SOAr), arylthio (–SAr), sulfonamide ($-SO_2NR_2$), alkylsulfoxide (–SOR), formyl (–CHO), ester ($-CO_2R$), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile (–CN), azido ($-N_3$), nitro ($-NO_2$), C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocycle, and C_2–C_{20} substituted heterocycle, phosphonate, phosphate, polyethyleneoxy, a protecting group, and a prodrug moiety;

R^{2b}, R^3, and R^4 are each independently selected from H, OH, OR, amino ($-NH_2$), ammonium ($-NH_3^+$), alkylamino (–NHR), dialkylamino ($-NR_2$), trialkylammonium ($-NR_3^+$), carboxyl ($-CO_2H$), sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, 4-dialkylaminopyridinium, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide (–SOAr), arylthio (–SAr), sulfonamide ($-SO_2NR_2$), alkylsulfoxide (–SOR), formyl (–CHO), ester ($-CO_2R$), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile (–CN), azido ($-N_3$), nitro ($-NO_2$), C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocycle, and C_2–C_{20} substituted heterocycle, phosphonate, phosphate, polyethyleneoxy, a protecting group, and a prodrug moiety;

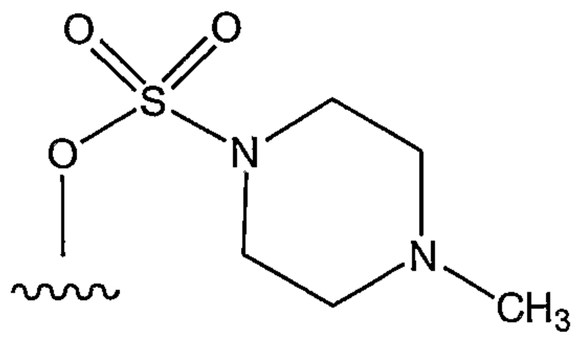
R is independently selected from H, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl.

Alternatively, R, R^1, R^{2a}, R^3, R^4, or R^5 may independently comprise A^1, A^3 or $L–A^3$.

At least one of R, R^1, R^{2a}, R^3, R^4, and R^5 comprises a phosphonate group. The phosphonate group may be a prodrug moiety.

Embodiments of R^1, R^{2a}, R^{2b}, R^3, R^4, and R^5 include $-C(=S)NR_2$, $-C(=O)OR$, $-C(=O)NR_2$, $-C(=O)NRNR_2$, $-C(=O)R$, $-SO_2NR_2$, $-NRSO_2R$, $-NRC(=S)NR_2$, –SR, $-S(O)R$, $-SO_2R$, $-SO_2R$, $-P(=O)(OR)_2$, $-P(=O)(OR)(NR_2)$, $-P(=O)(NR_2)_2$, $-P(=S)(OR)_2$, $-P(=S)(OR)(NR_2)$, $-P(=S)(NR_2)_2$, and including prodrug substituted forms thereof.

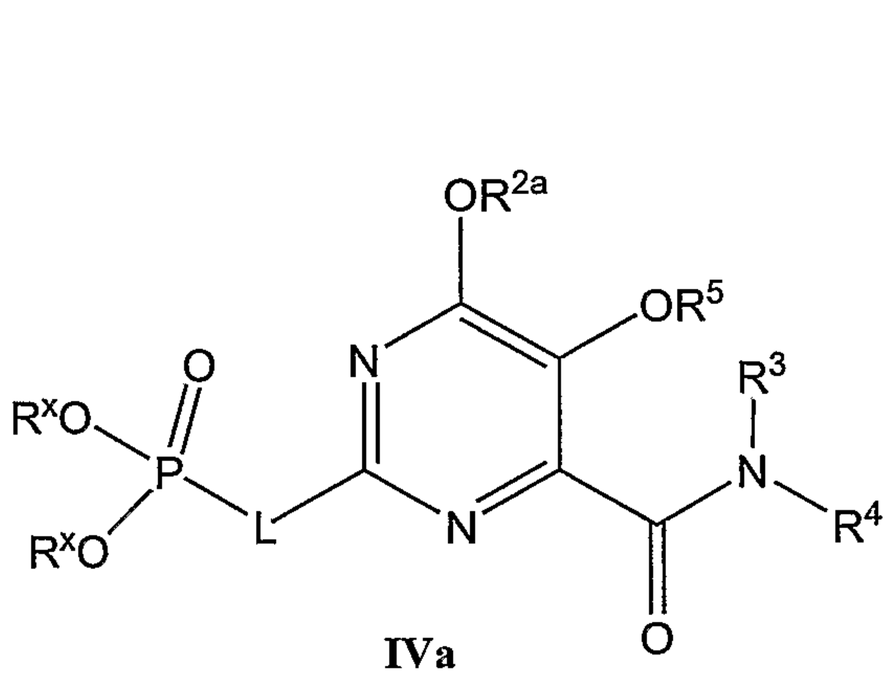
Embodiments of R^1, R^{2a}, R^{2b}, R^3, R^4, and R^5 may also individually or in combination form a ring, e.g. 4-7 membered ring lactam, carbonate, or sultam, or piperazinyl sulfamate:



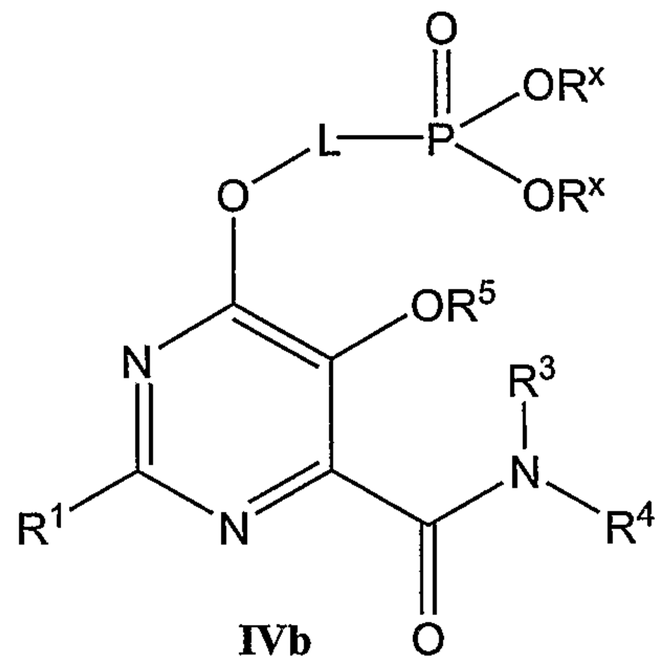
Embodiments of R^1 also include $-OC(=S)NR_2$, $-OC(=O)OR$, $-OC(=O)NR_2$, $-OC(=O)NRNR_2$, $-OC(=O)R$, $-OP(=O)(OR)_2$, $-OP(=O)(OR)(NR_2)$, $-OP(=O)(NR_2)_2$, $-OP(=S)(OR)_2$, $-OP(=S)(OR)(NR_2)$, $-OP(=S)(NR_2)_2$, and including prodrug substituted forms thereof.

A linker may be interposed between positions R^1, R^{2a}, R^3, R^4, or R^5 and substituent A^3, as exemplified in some structures herein as "L-A^3". The linker L may be O, S, NR, N–OR, C_1–C_{12} alkylene, C_1–C_{12} substituted alkylene, C_2–C_{12} alkenylene, C_2–C_{12} substituted alkenylene, C_2–C_{12} alkynylene, C_2–C_{12} substituted alkynylene, C(=O)NH, C(=O), $S(=O)_2$, $C(=O)NH(CH_2)_n$, and $(CH_2CH_2O)_n$, where n may be 1, 2, 3, 4, 5, or 6. Linkers may also be repeating units of alkyloxy (e.g. polyethylenoxy, PEG, polymethyleneoxy) and alkylamino (e.g. polyethyleneamino, Jeffamine™); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide. For example, the linker may comprise propargyl, urea, or alkoxy groups.

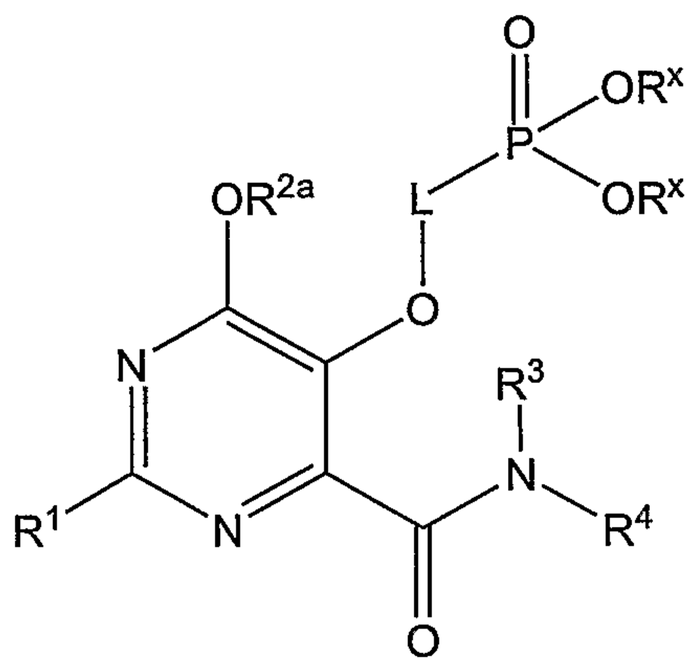
Exemplary structures within Formula IV include IVa, IVb, IVc, IVd:



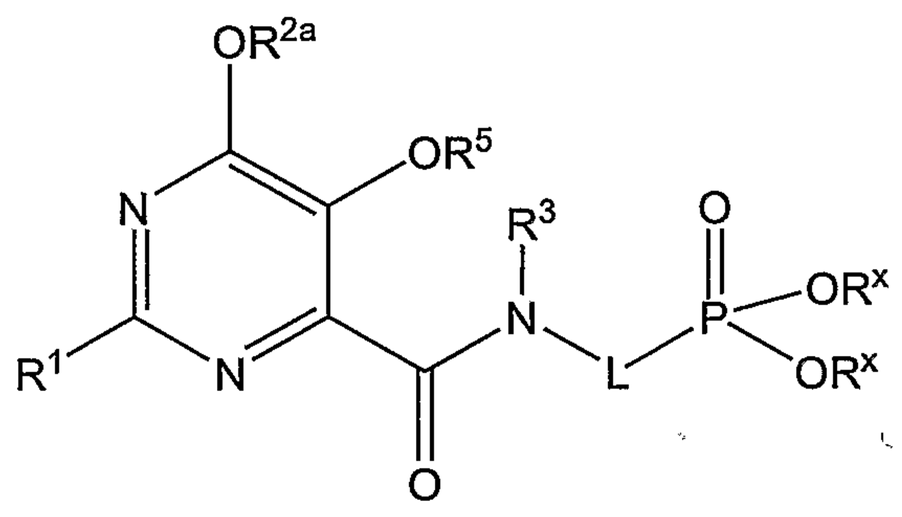
IVa



IVb



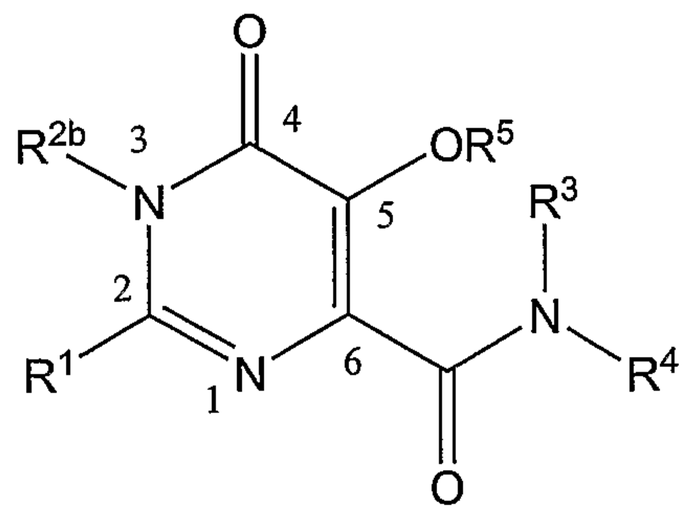
IVc



IVd

Group V

In one aspect, the invention includes phosphonate analogs of 3-N-substituted, 5-hydroxypyrimidinone, 6-carboxamide compounds (WO 03/035077 A1) having Formula V:



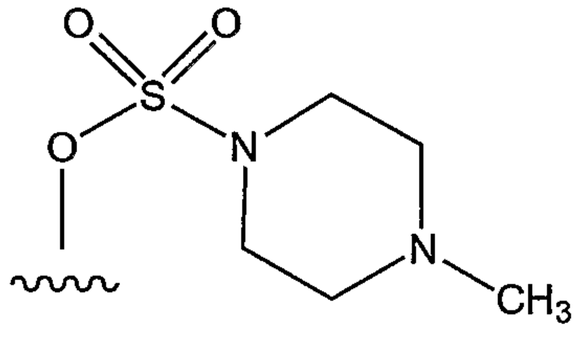
V

wherein R^1, R^{2b}, R^3, R^4, and R^5 are as defined for Formula IV. Alternatively, R, R^1, R^{2b}, R^3, R^4, or R^5 may independently comprise A^1, A^3 or $L–A^3$.

At least one of R, R^1, R^{2b}, R^3, R^4, and R^5 comprises a phosphonate group. The phosphonate group may be a prodrug moiety.

Embodiments of R^1, R^{2b}, R^{2b}, R^3, R^4, and R^5 include $-C(=S)NR_2$, $-C(=O)OR$, $-C(=O)NR_2$, $-C(=O)NRNR_2$, $-C(=O)R$, $-SO_2NR_2$, $-NRSO_2R$, $-NRC(=S)NR_2$, $-SR$, $-S(O)R$, $-SO_2R$, $-SO_2R$, $-P(=O)(OR)_2$, $-P(=O)(OR)(NR_2)$, $-P(=O)(NR_2)_2$, $-P(=S)(OR)_2$, $-P(=S)(OR)(NR_2)$, $-P(=S)(NR_2)_2$, and including prodrug substituted forms thereof.

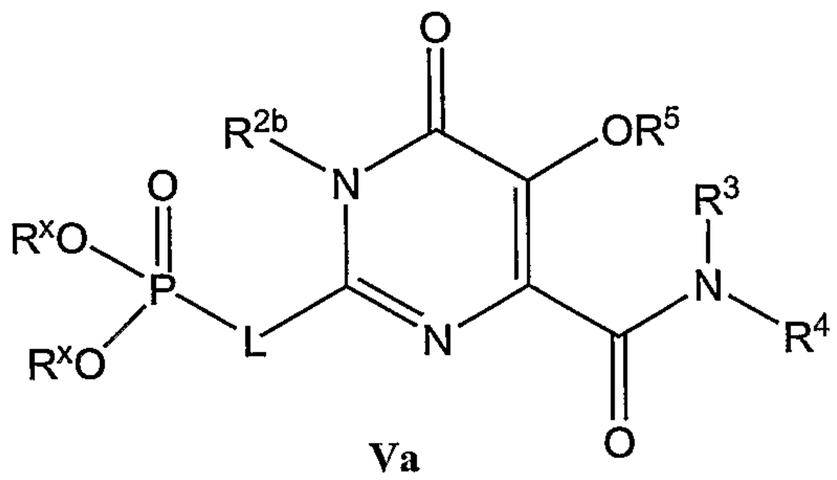
Embodiments of R^1, R^{2a}, R^{2b}, R^3, R^4, and R^5 may also individually or in combination form a ring, e.g. 4-7 membered ring lactam, carbonate, or sultam, or piperazinyl sulfamate:



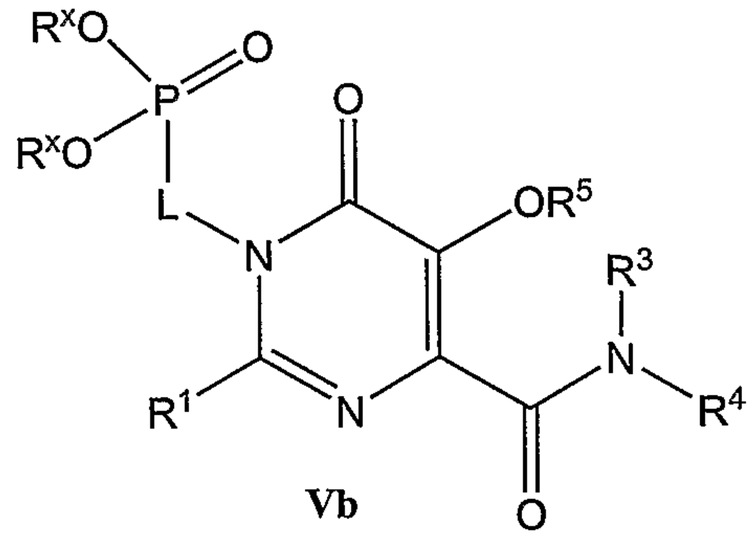
Embodiments of R^1 also include $-OC(=S)NR_2$, $-OC(=O)OR$, $-OC(=O)NR_2$, $-OC(=O)NRNR_2$, $-OC(=O)R$, $-OP(=O)(OR)_2$, $-OP(=O)(OR)(NR_2)$, $-OP(=O)(NR_2)_2$, $-OP(=S)(OR)_2$, $-OP(=S)(OR)(NR_2)$, $-OP(=S)(NR_2)_2$, and including prodrug substituted forms thereof.

A linker may be interposed between positions R^1, R^{2b}, R^3, R^4, or R^5 and substituent A^3, as exemplified in some structures herein as "L-A^3". The linker L may be O, S, NR, N–OR, C_1–C_{12} alkylene, C_1–C_{12} substituted alkylene, C_2–C_{12} alkenylene, C_2–C_{12} substituted alkenylene, C_2–C_{12} alkynylene, C_2–C_{12} substituted alkynylene, C(=O)NH, C(=O), $S(=O)_2$, $C(=O)NH(CH_2)_n$, and $(CH_2CH_2O)_n$, where n may be 1, 2, 3, 4, 5, or 6. Linkers may also be repeating units of alkyloxy (e.g. polyethylenoxy, PEG, polymethyleneoxy) and alkylamino (e.g. polyethyleneamino, Jeffamine™); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide. For example, the linker may comprise propargyl, urea, or alkoxy groups.

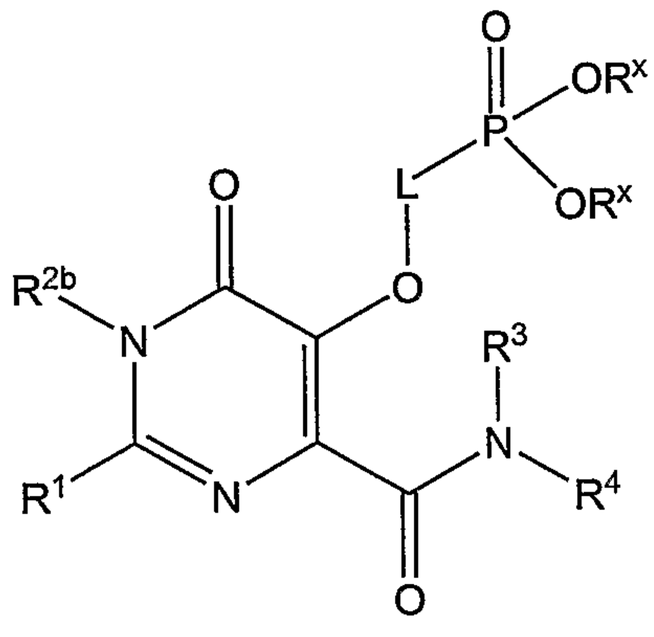
Exemplary structures within Formula V include Va, Vb, Vc, Vd:



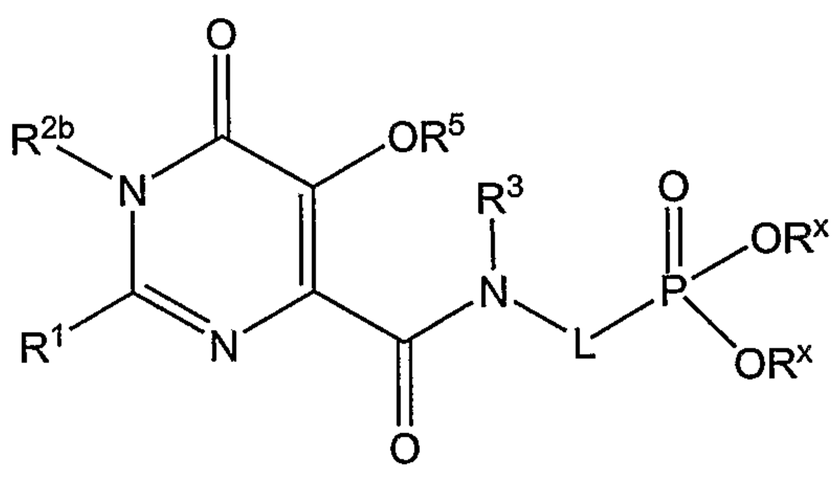
Va



Vb



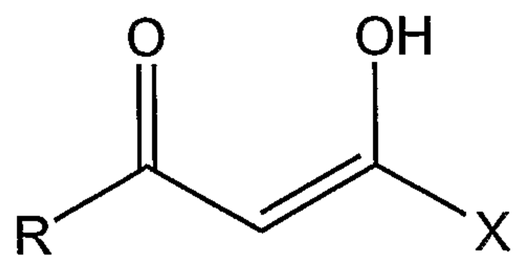
Vc



Vd

Group VI

In one aspect, the invention includes phosphonate analogs of 1,3 diketo compounds having Formula VI:



VI

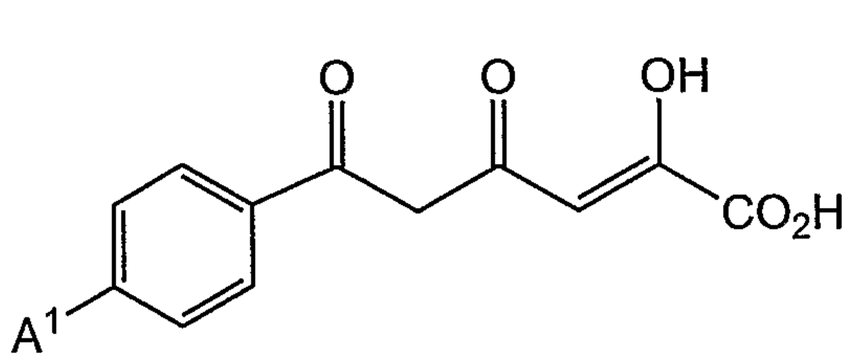
wherein

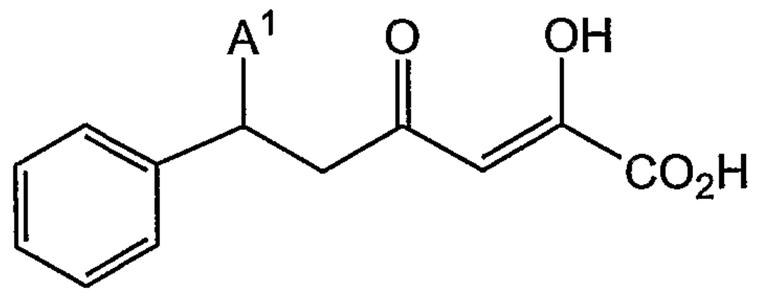
R is C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, or C_2–C_{20} substituted heteroaryl (Pais et al (2002) *Drugs of the Future* 27(11):1101-1111). Alternatively, R may be C_1–C_8 alkylamino, C_1–C_8 substituted alkylamino, C_2–C_{18} alkenylamino, C_2–C_{18} substituted alkenylamino, C_2–C_{18} alkynylamino, C_2–C_{18} substituted alkynylamino, C_6–C_{20} arylamino, C_6–C_{20}

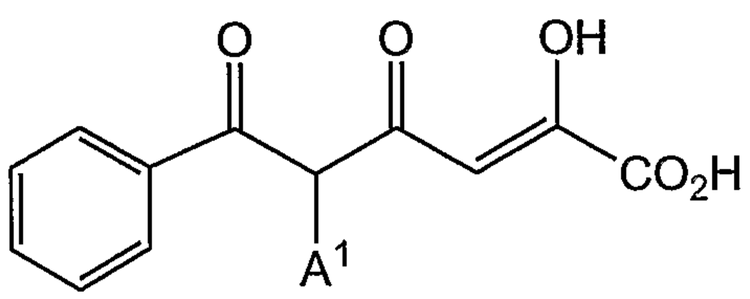
substituted arylamino, C_6–C_{20} arylalkylamino, C_6–C_{20} substituted arylalkylamino, C_2–C_{20} heteroarylamino, or C_2–C_{20} substituted heteroarylamino, whereby the amide is formed (WO 04/004657; WO 01/96283; WO 01/98248). Exemplary Formula VI compounds include where R is benzylamino, thiophenyl, thioimidazolyl, benzothiophenyl, napthothiophenyl, pyrrolidinyl, pyrazolyl, indanyl, indolyl, sesamyl, and benzoxazolyl.

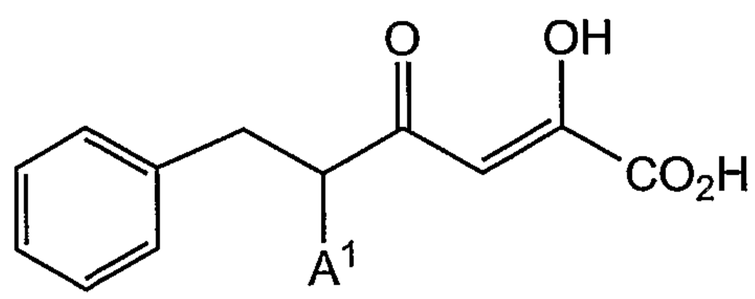
X is: (VIa) a carboxylic acid or ester group (Zhang et al (2003) *Bioorganic & Medicinal Chemistry Letters* 13(6):1215-1219; Pais et al (2002) *Jour. Med. Chem.* 45(15):3184-3194; Reinke et al (2002) *Antimicrob. Agents and Chemo.* 46(10):3301-3303; Marchand et al (2002) *Jour. Biological Chem.* 277(15):12596-112603; Hazuda et al (2000) *Science* 287(5453):646-650; Espeseth et al (2000) *Proc. Natl. Acad. Sci. USA* 97(21):11244-11249; Wai et al (2000) *J. Med. Chem.* 43(26):2923-2926; US 6548546; WO 03/016266 A1; WO 03/049695 A2; WO 03/049690 A2; WO 00/06529, WO 99/62513, WO 01/96283; WO 01/98248); (VIb) a moiety with an acidic proton such as tetrazole or triazole (Pluymers et al (2002) *Antimicrob. Agents and Chemo.* 46(10):3292-3297; WO 99/50245, WO 00/39086); (VIc) a substituted amide (WO 01/17968, WO 03/16266); (Vd) aryl (WO 99/62520); and (VIe) heteroaryl (WO 01/096329; WO 99/62513, WO 99/62520, WO 99/62897, WO 01/00578).

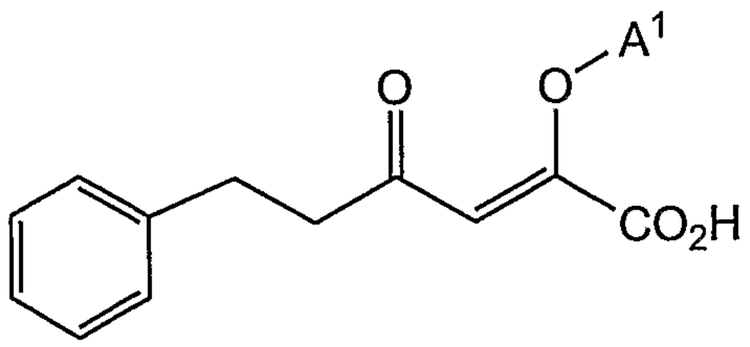
Embodiments of Formula VI compounds include:

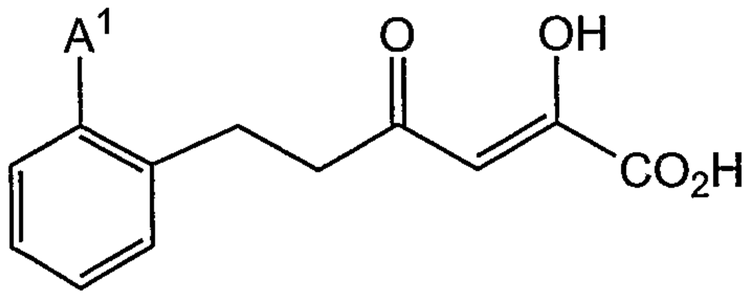




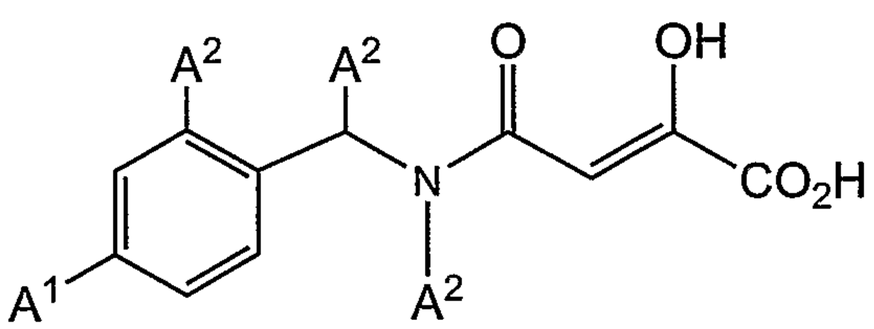


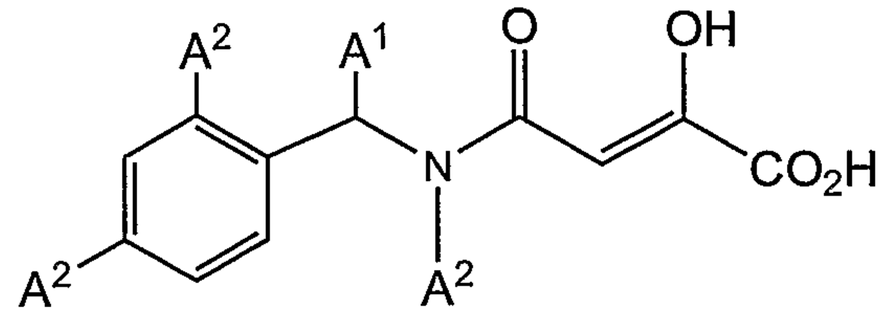


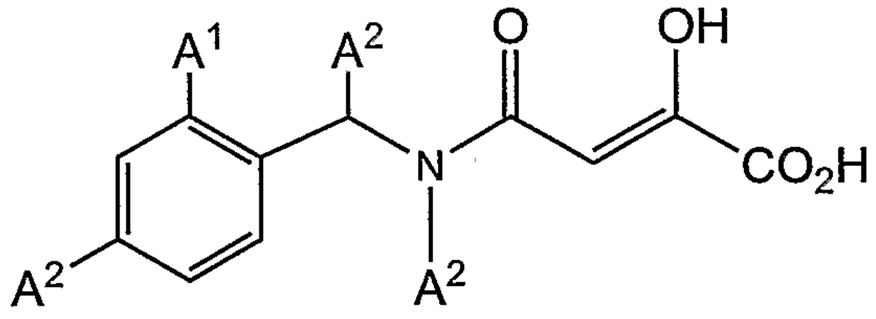


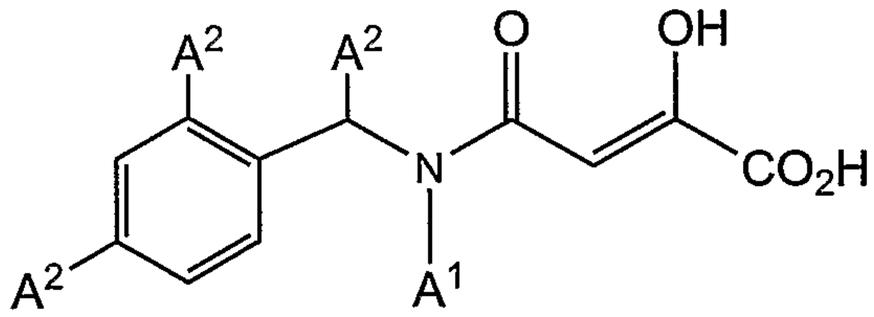


Embodiments of Formula VI compounds also include:

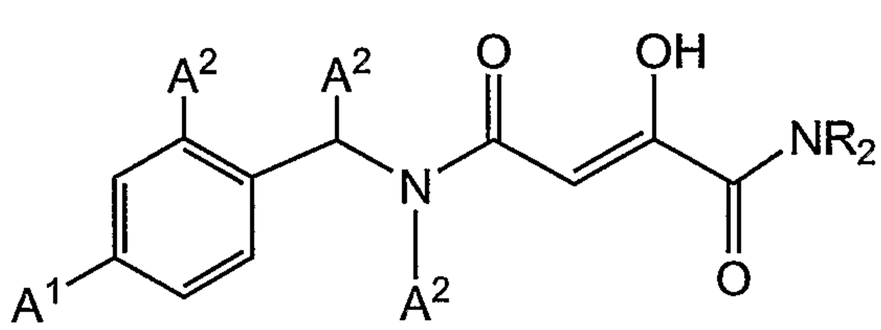


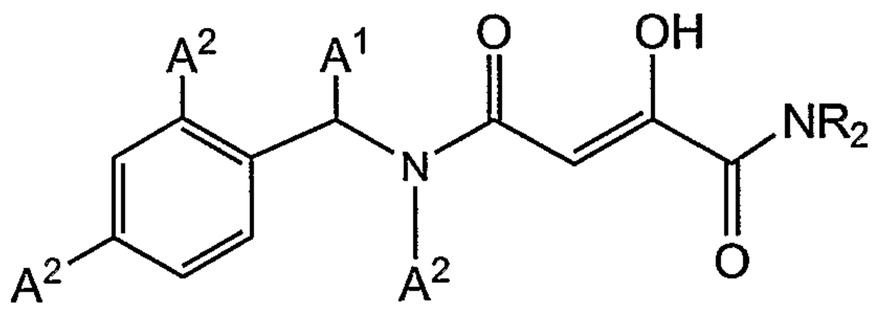


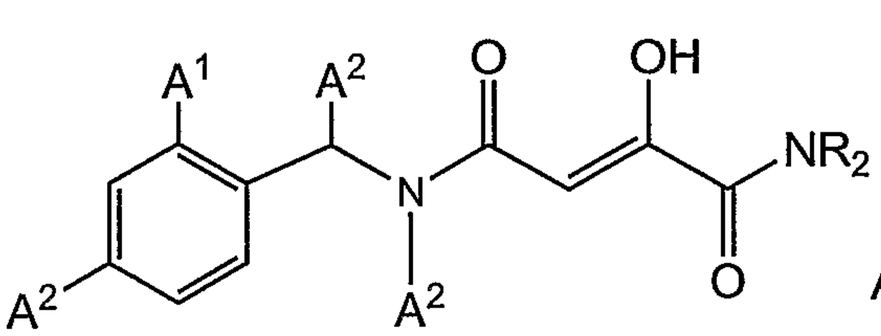


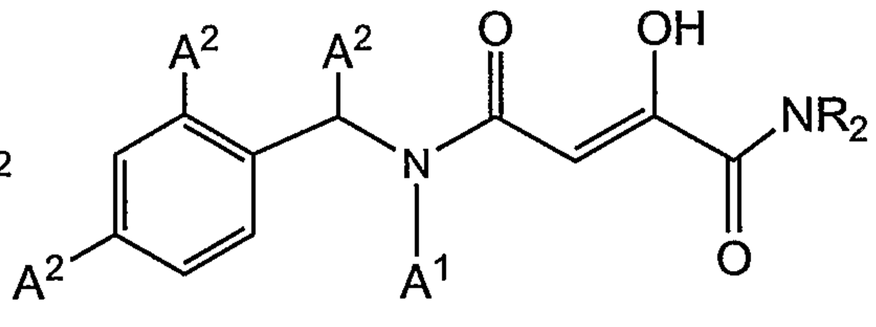


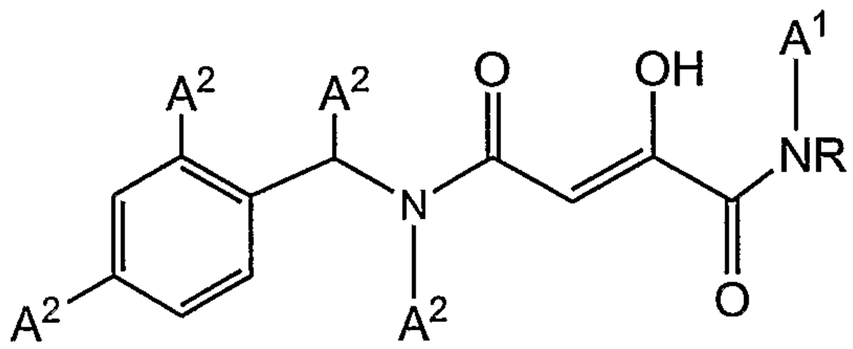
Embodiments of Formula VI compounds also include:











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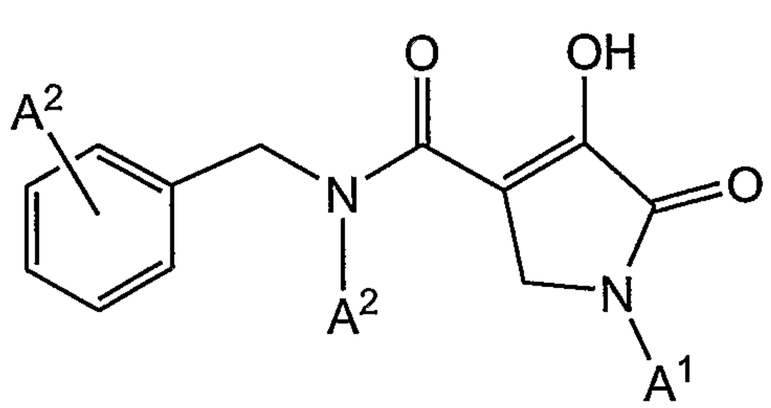
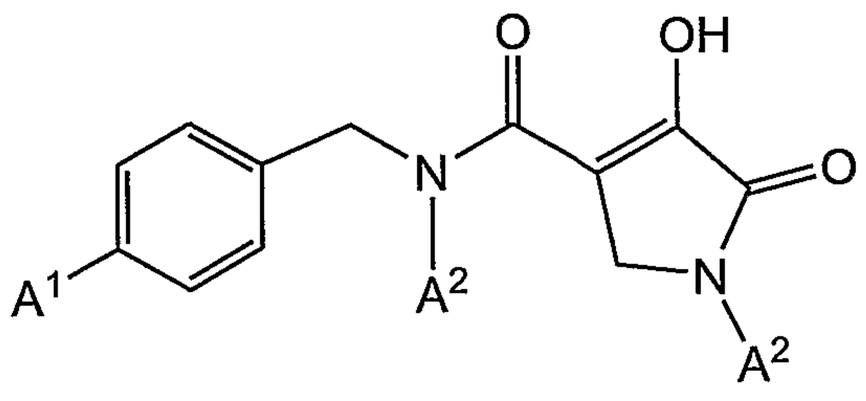
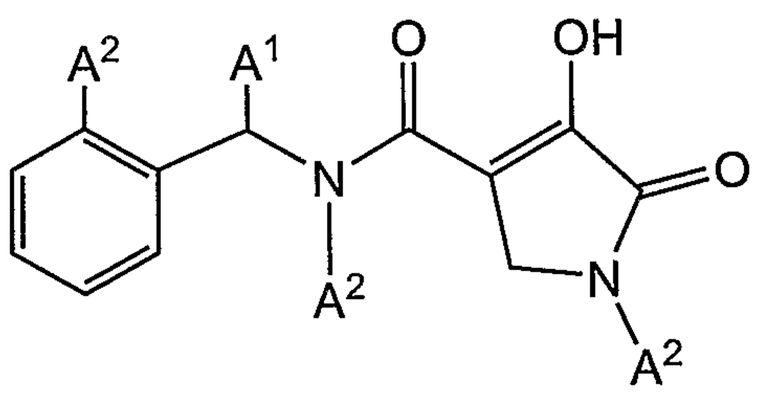
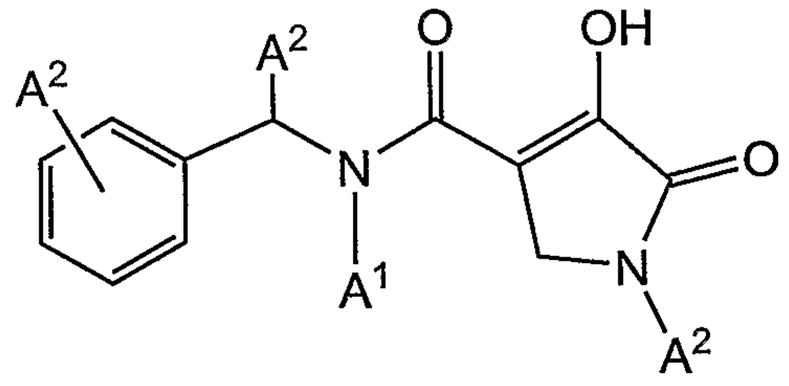
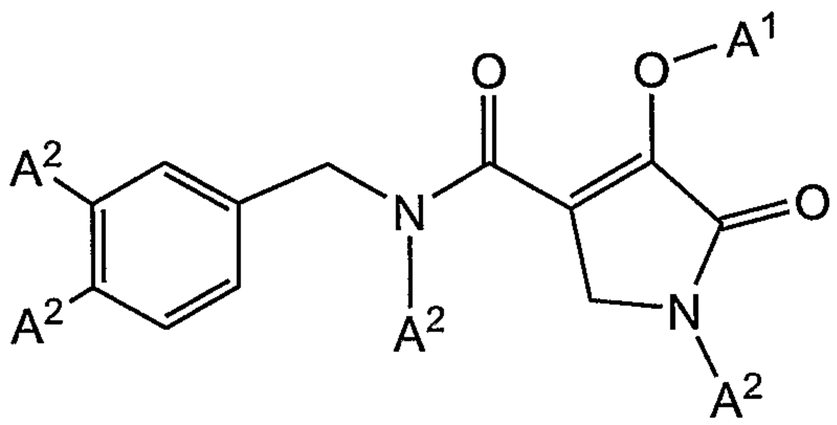
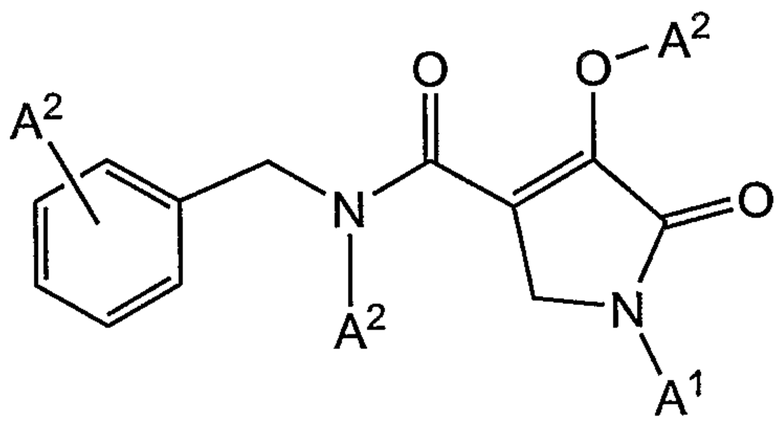




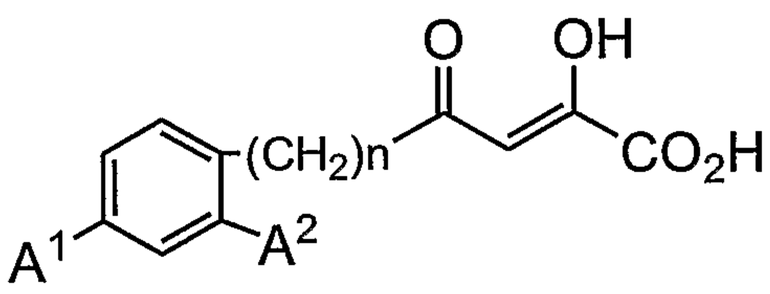


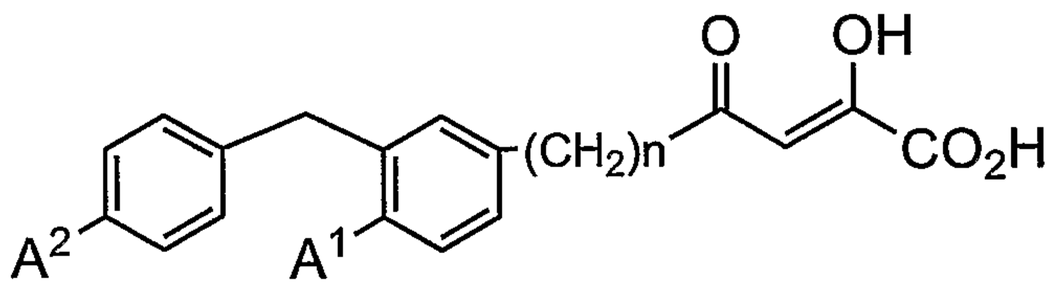


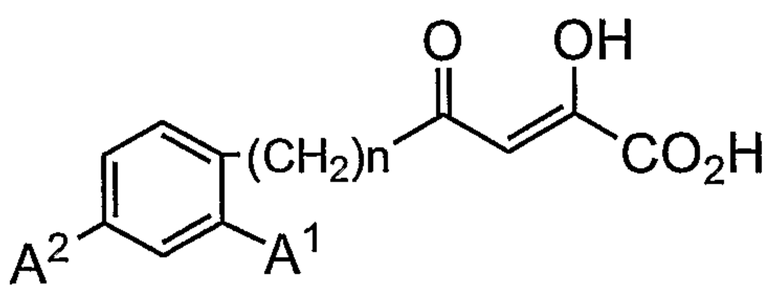


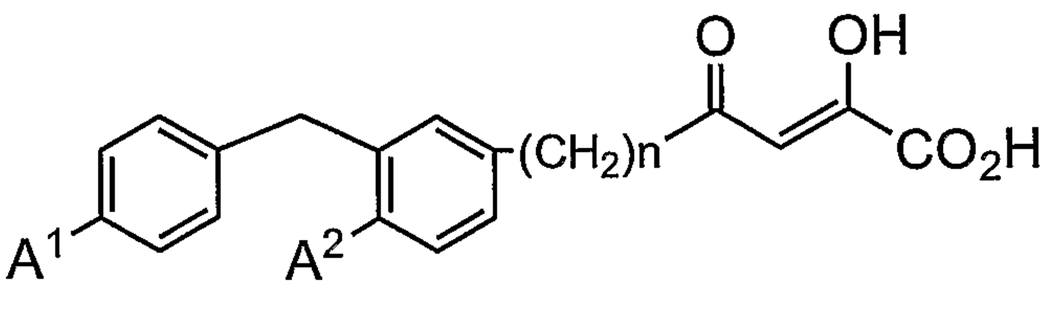


Embodiments of Formula VI compounds also include:



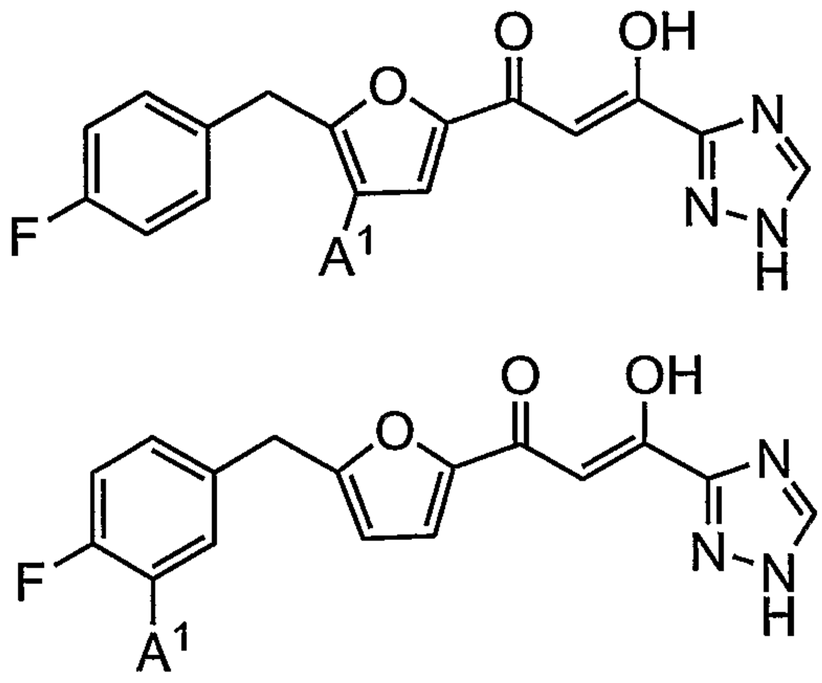


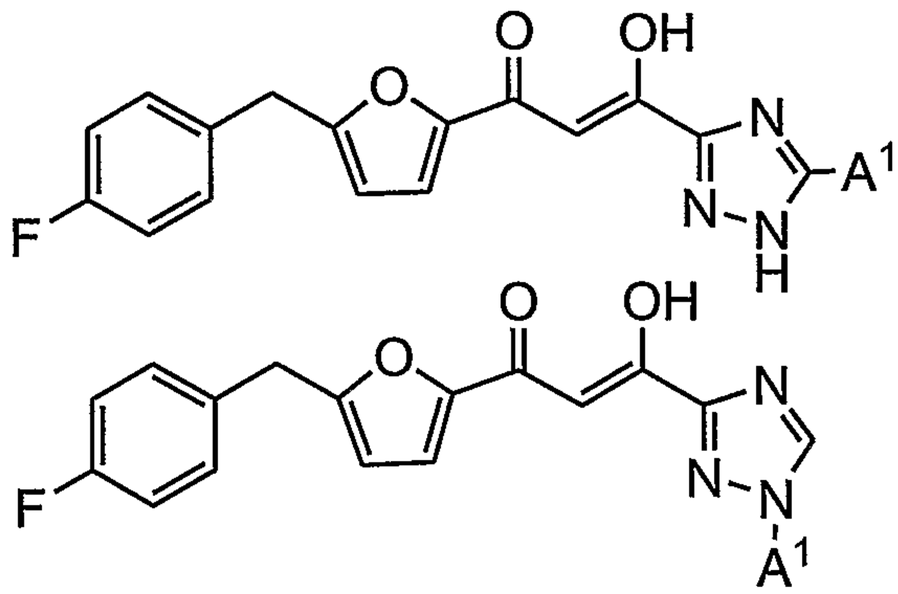




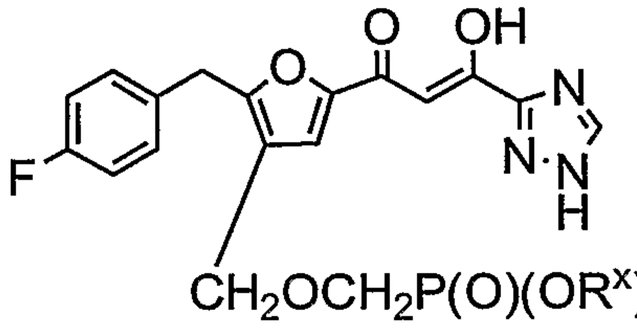
where n may be 1, 2, 3, 4, 5, or 6.

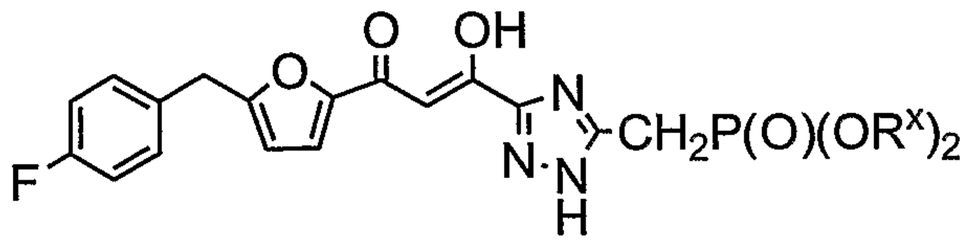
Embodiments of Formula VI compounds also include:

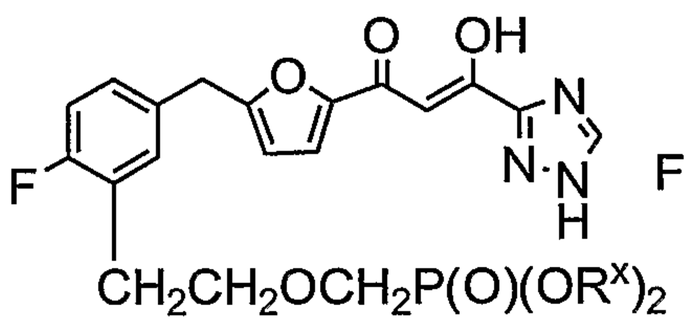


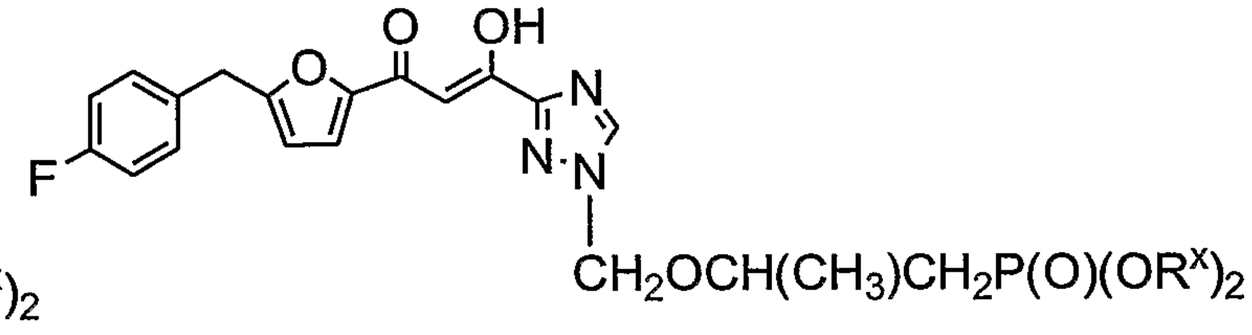


Embodiments of Formula VI compounds also include:

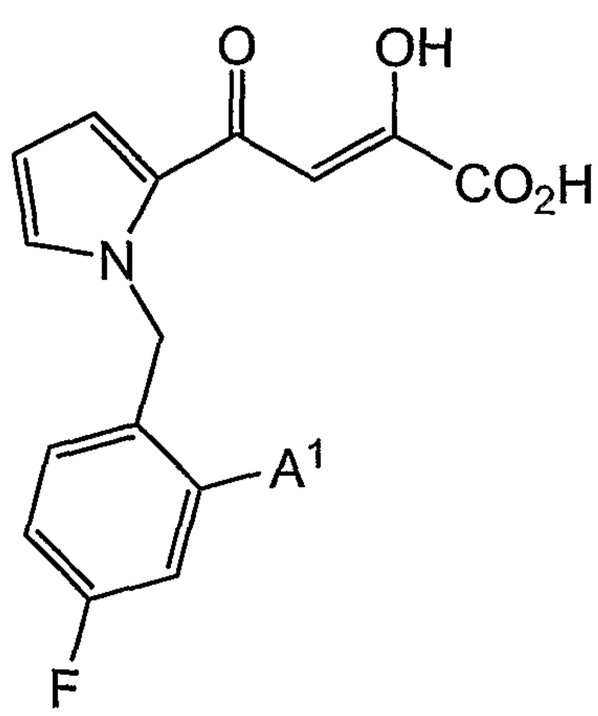


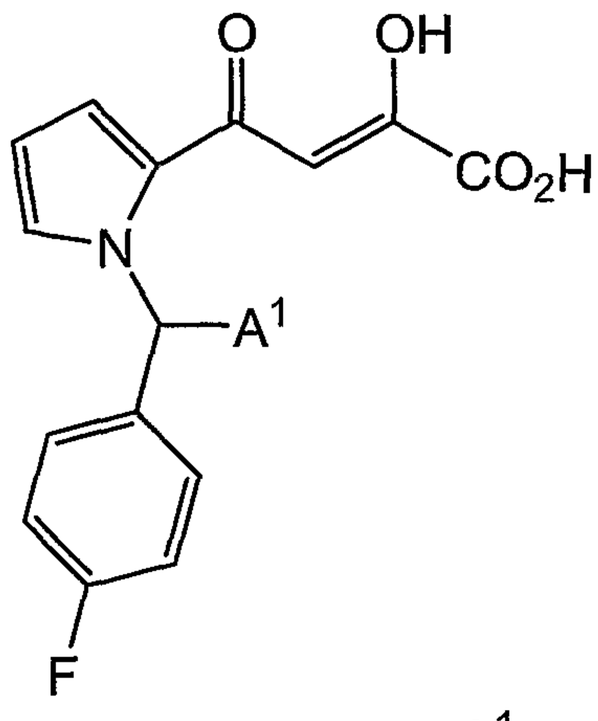


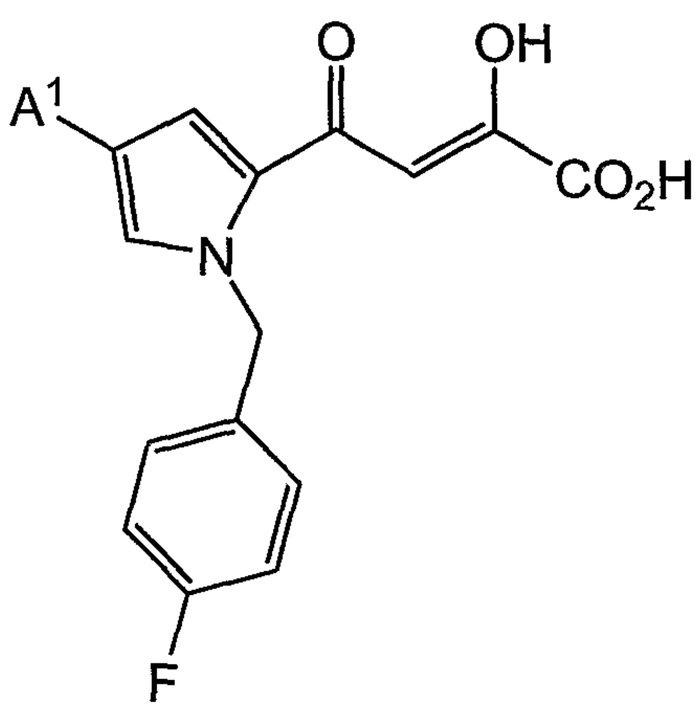


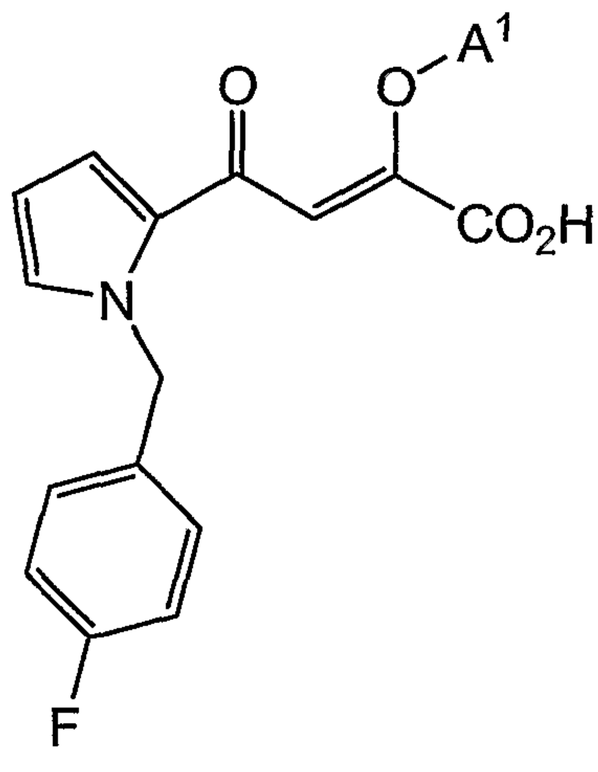


Embodiments of Formula VI compounds also include:









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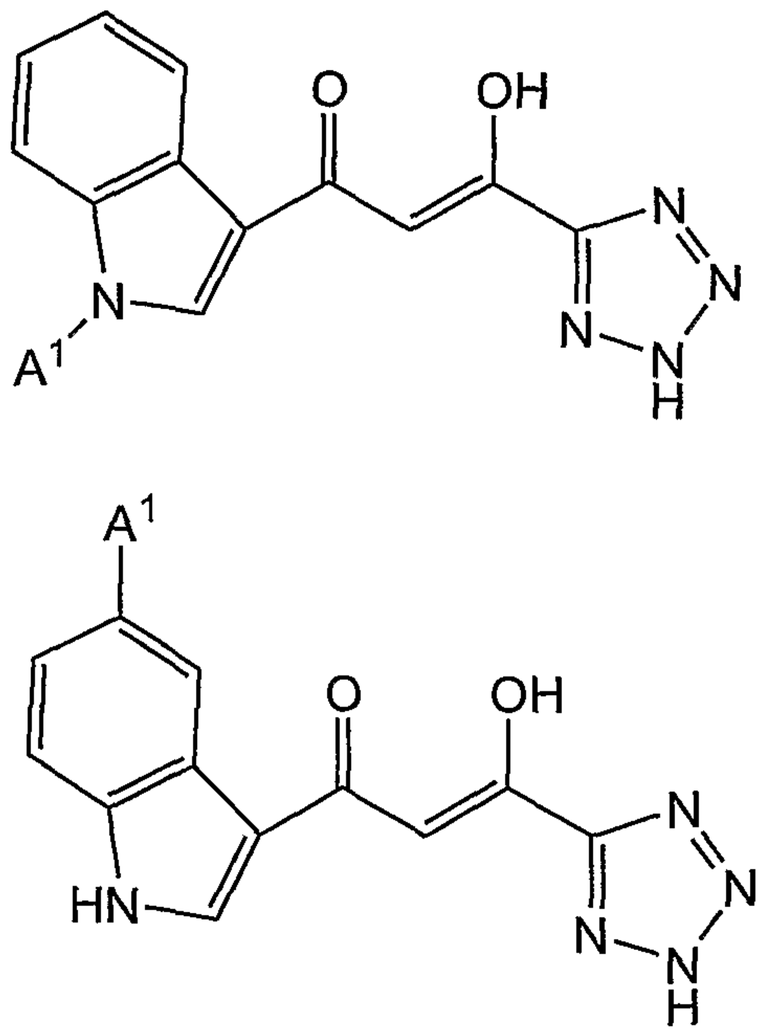
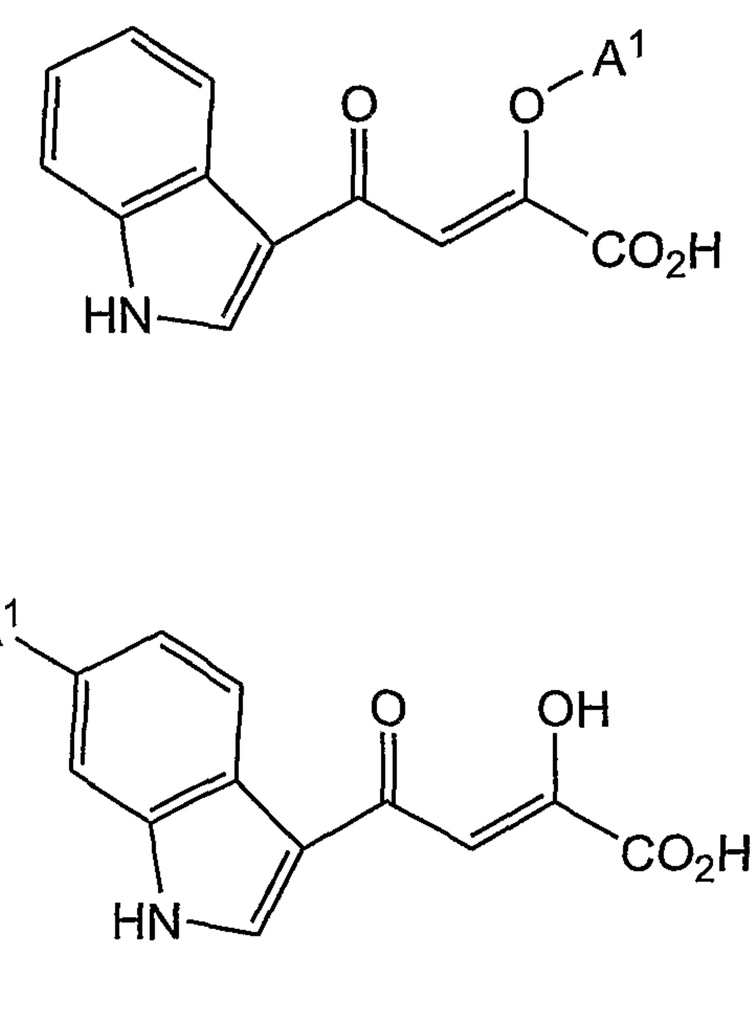
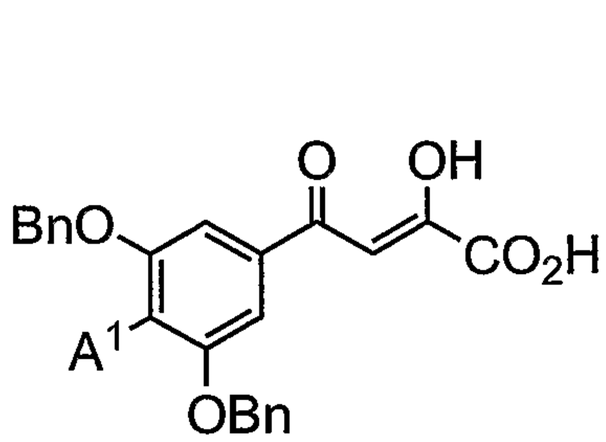
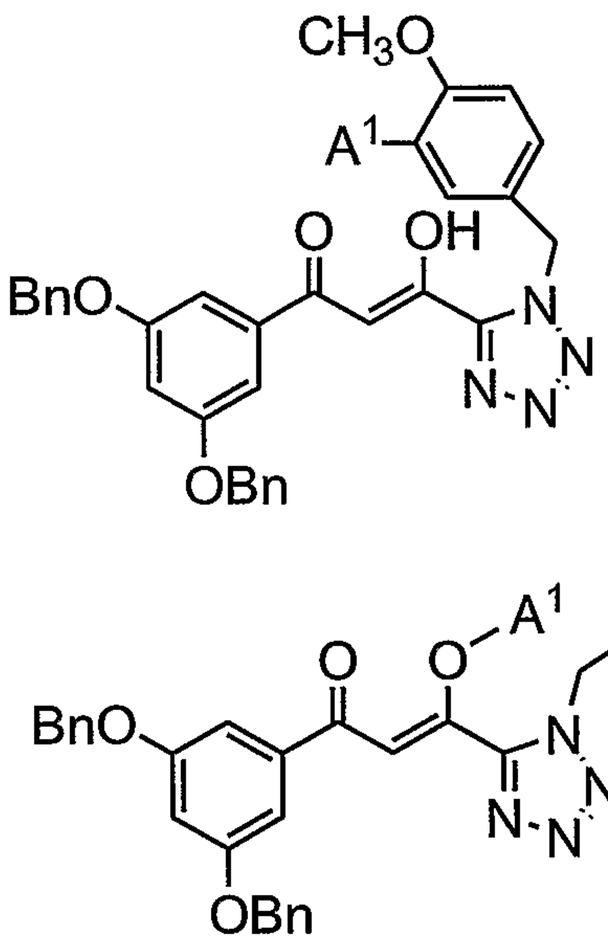
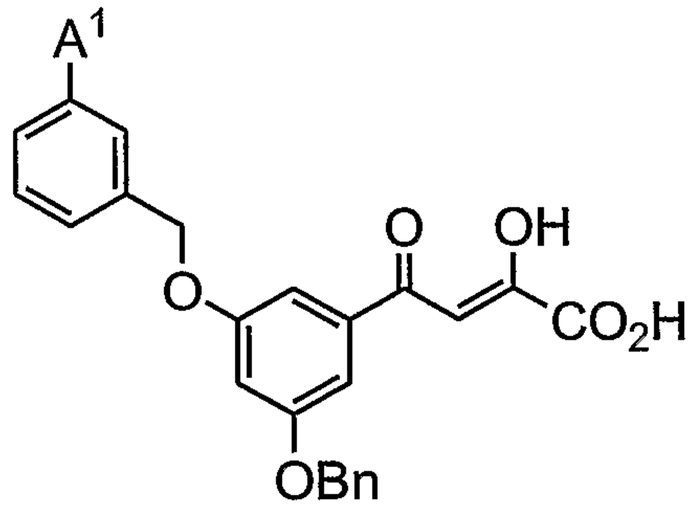


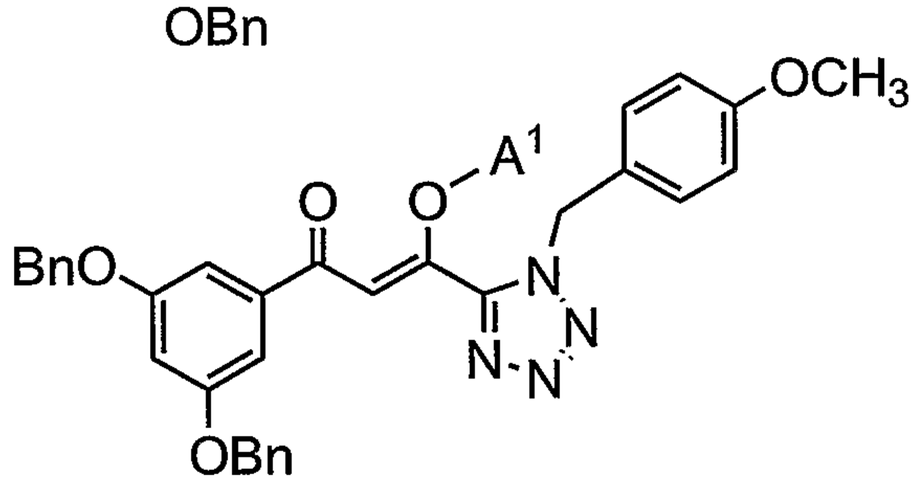


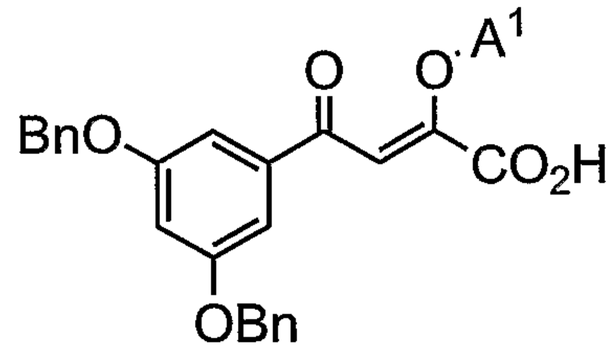
Embodiments of Formula VI compounds also include:

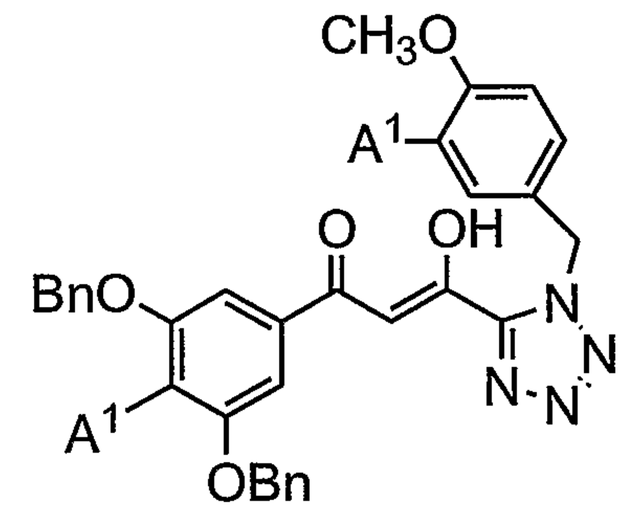




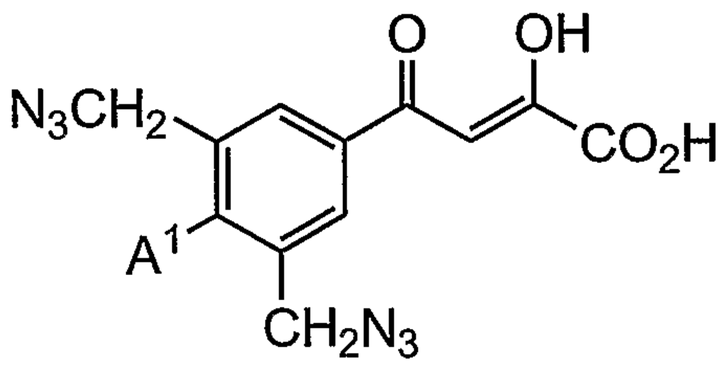


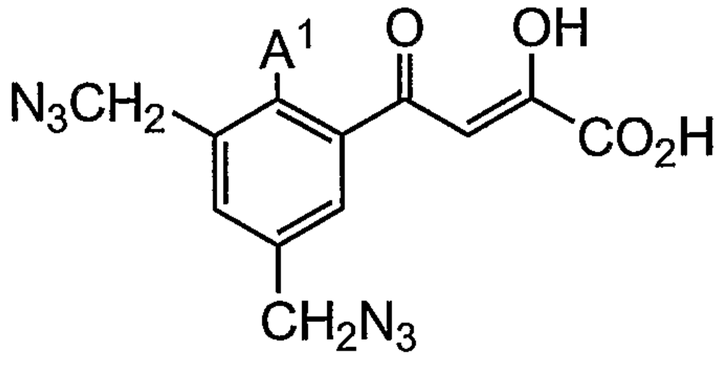


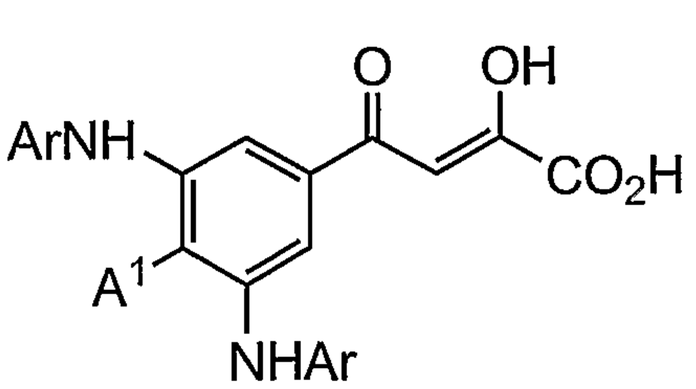


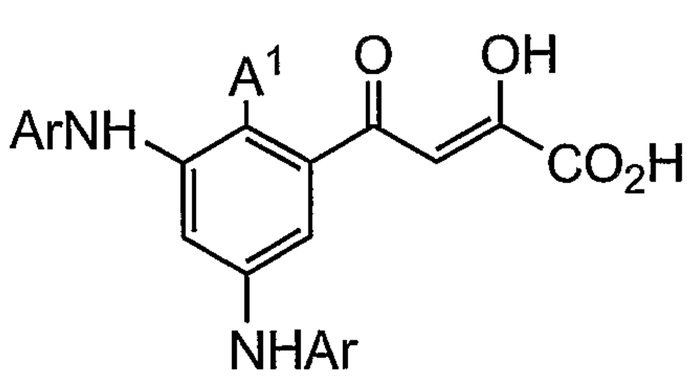


Embodiments of Formula VI compounds also include:



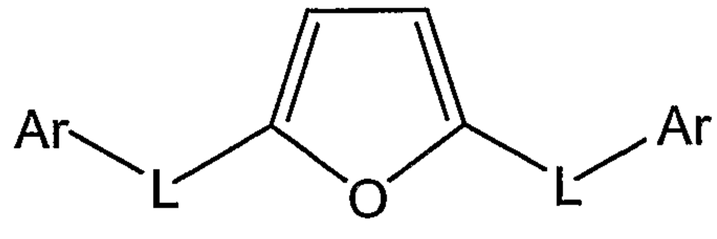






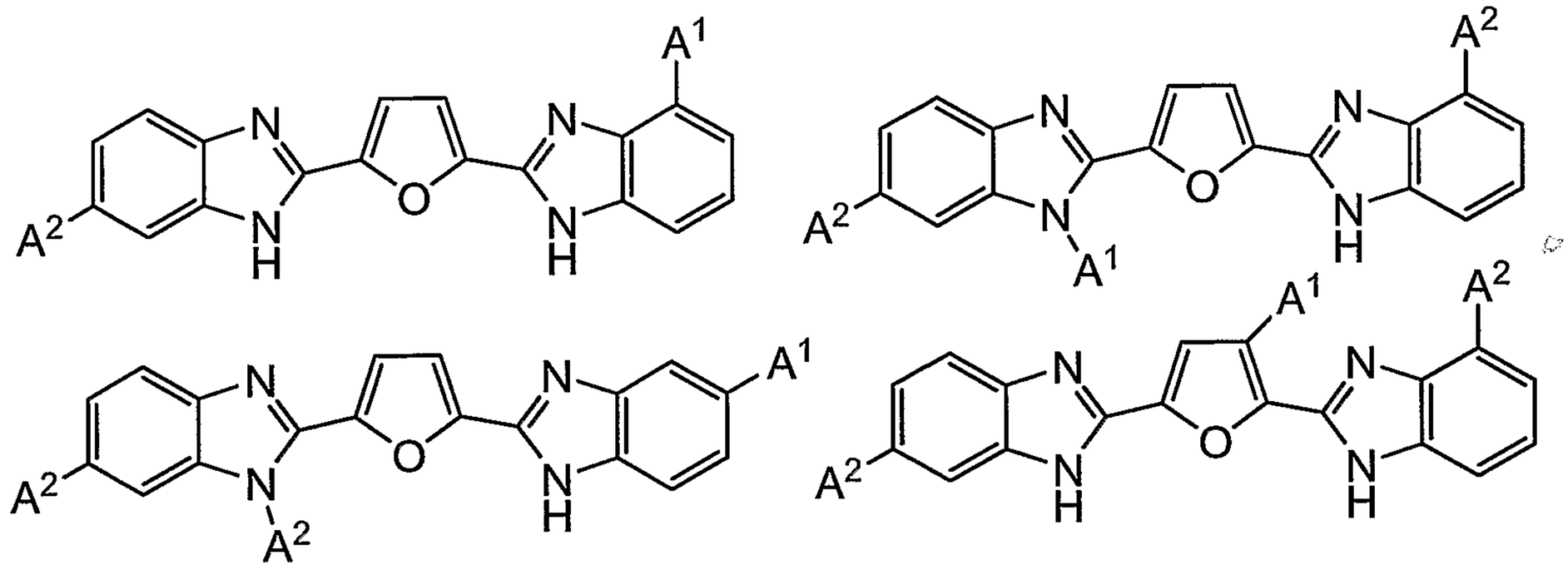
Group VII

In one aspect, the invention includes phosphonate analogs of 2,5 diarylsubstituted, furan compounds having Formula VII:

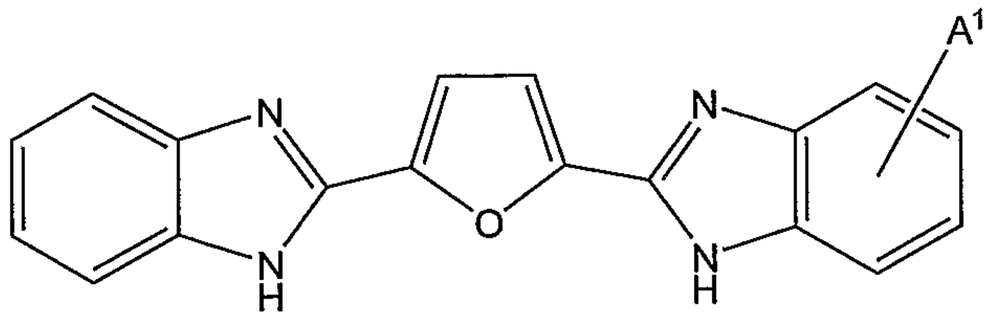


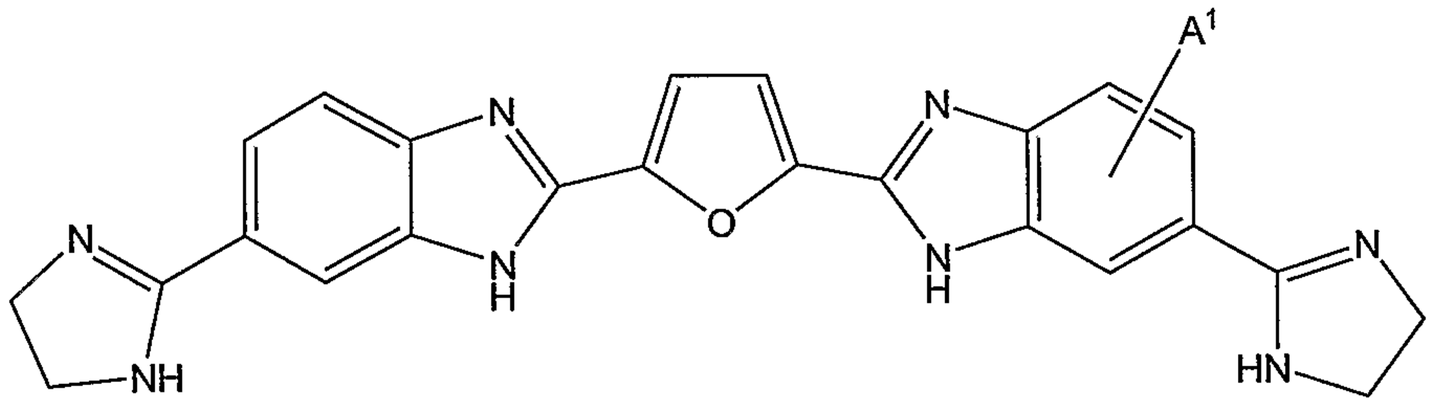
VII

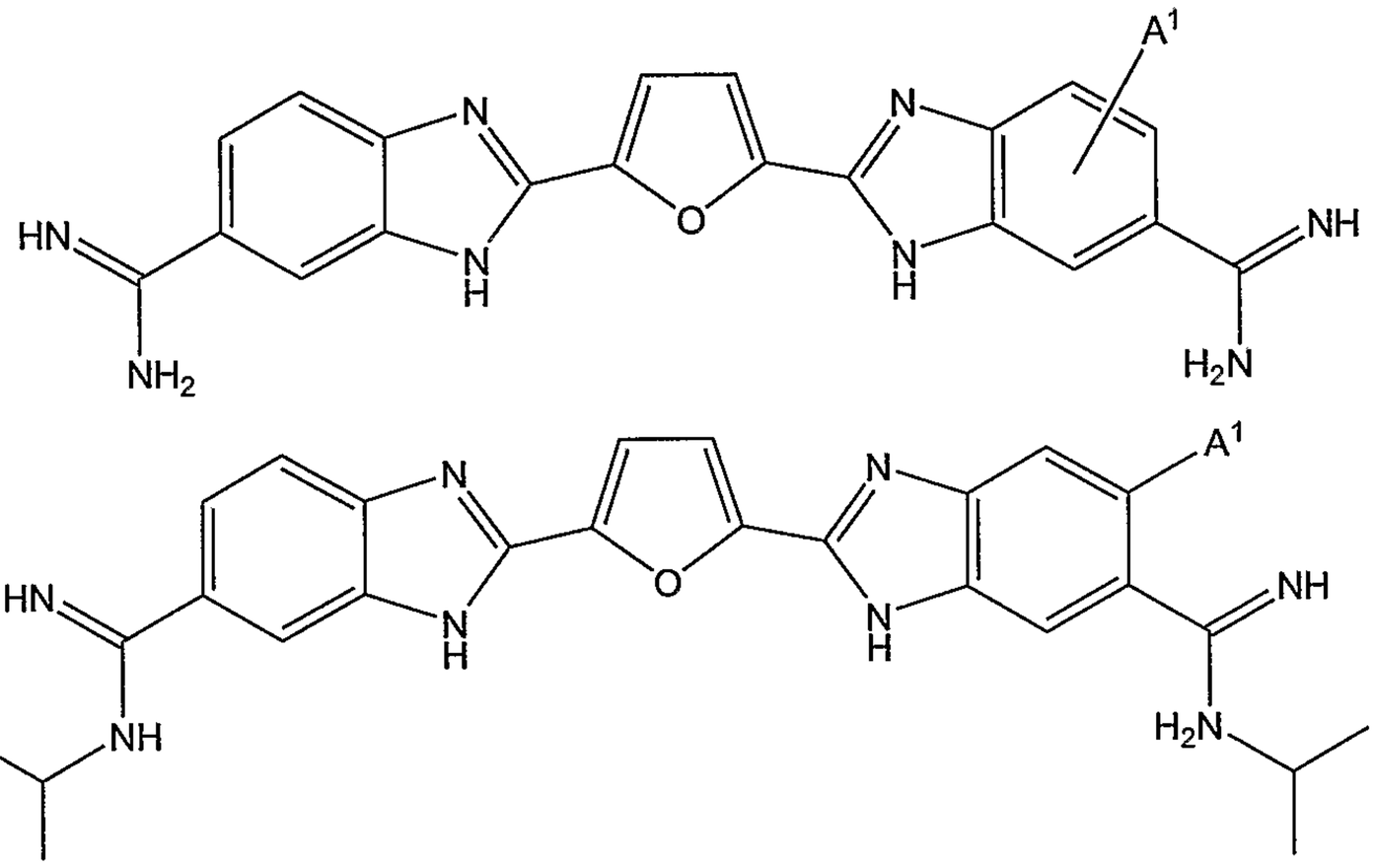
Embodiments of Formula VII compounds include:



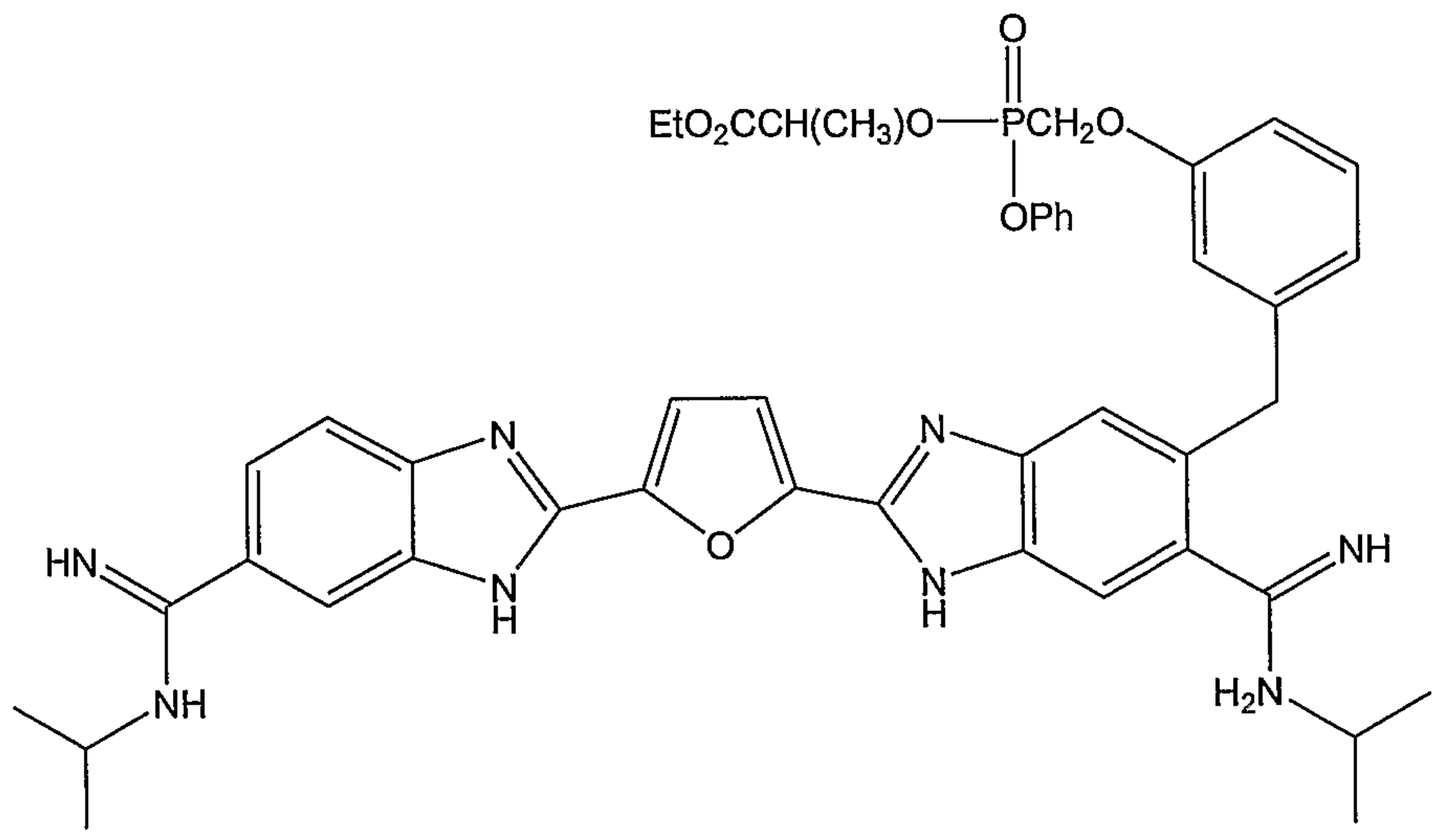
Embodiments of Formula VII compounds also include:





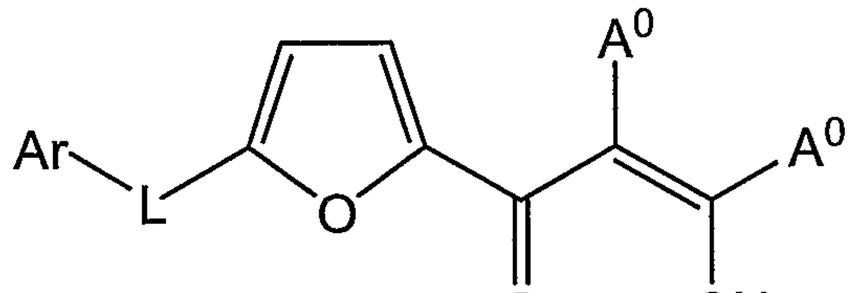


5 Further embodiments of Formula VII compounds include:



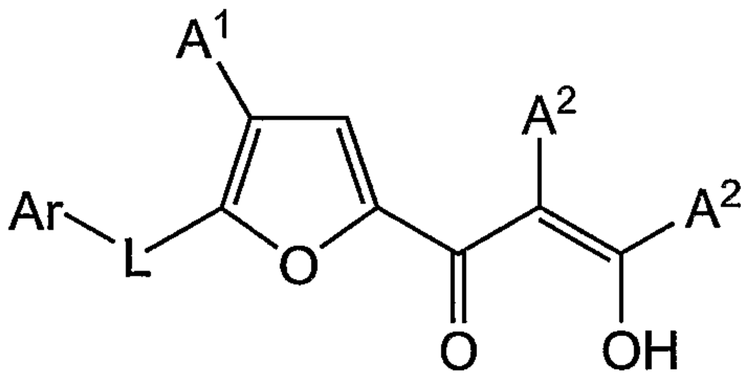
Group VIII

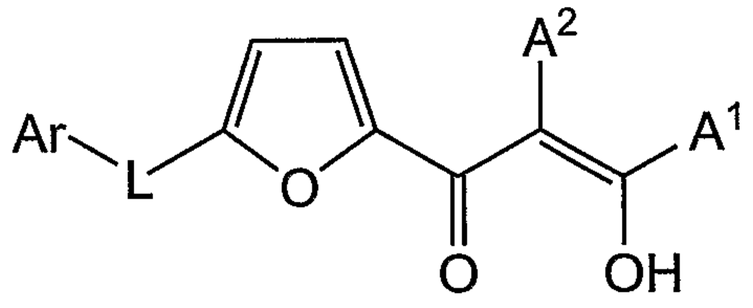
In one aspect, the invention includes phosphonate analogs of 2,5 substituted, diketo-furan compounds (WO 03/016275 A1) having Formula VIII:

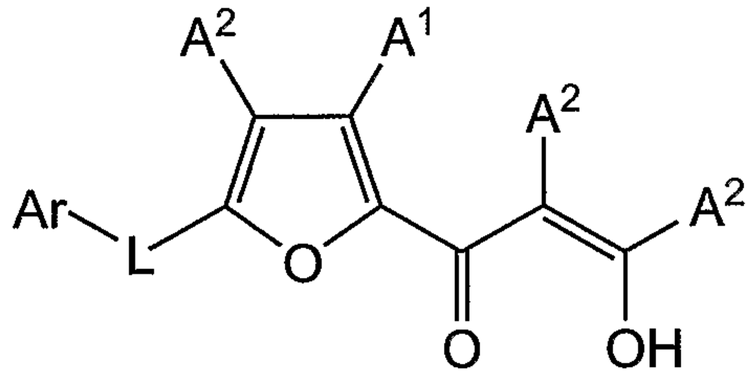


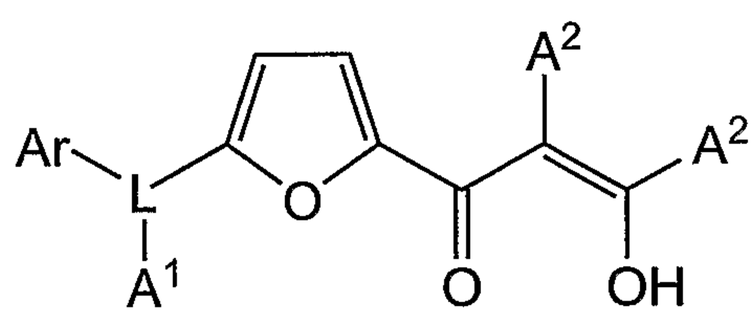
VIII

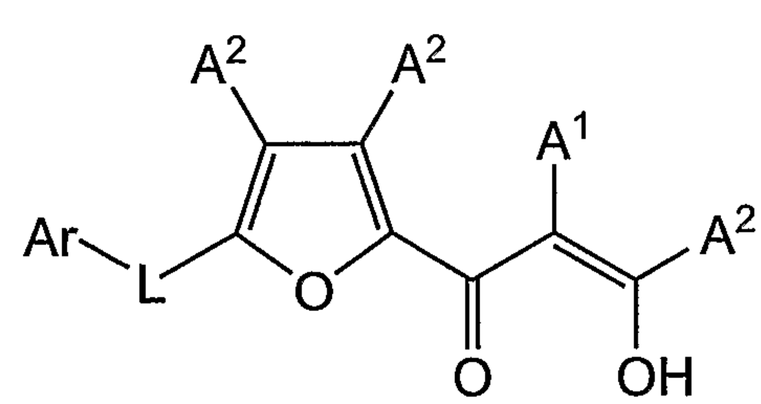
Embodiments of Formula VIII include the structures:

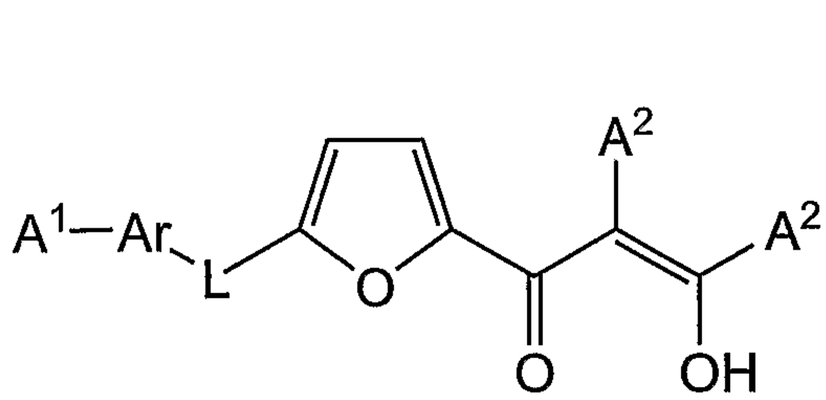




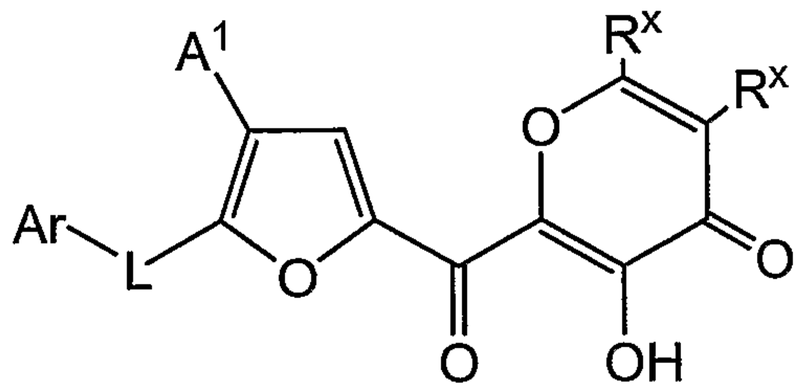


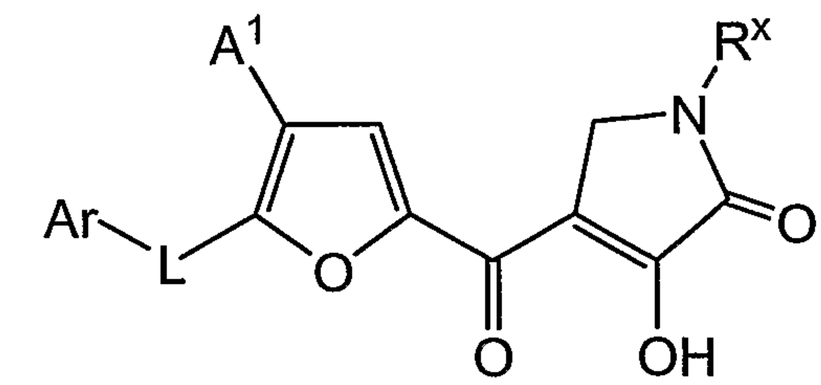


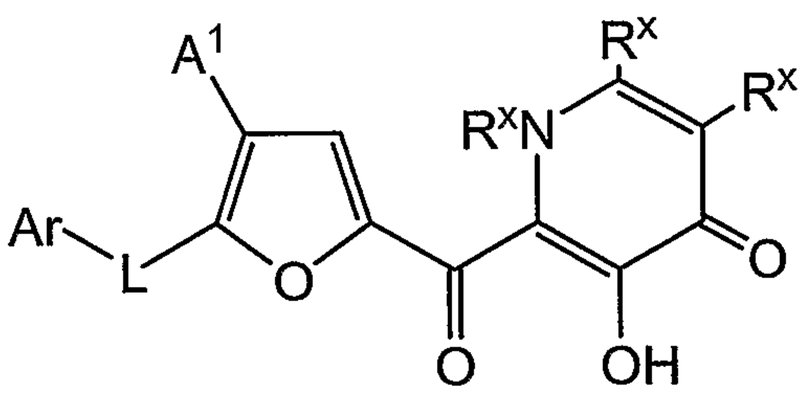


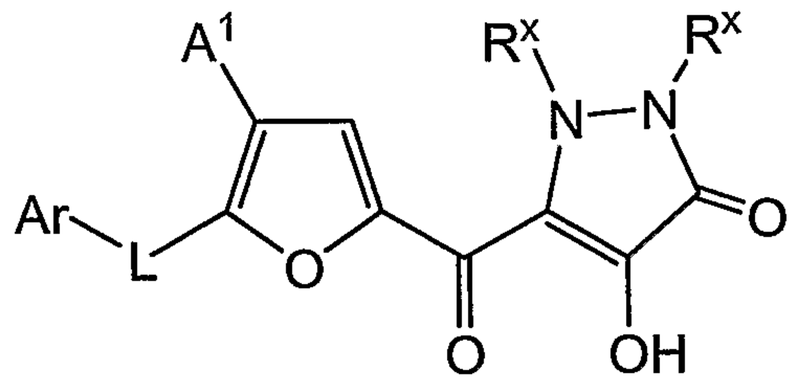


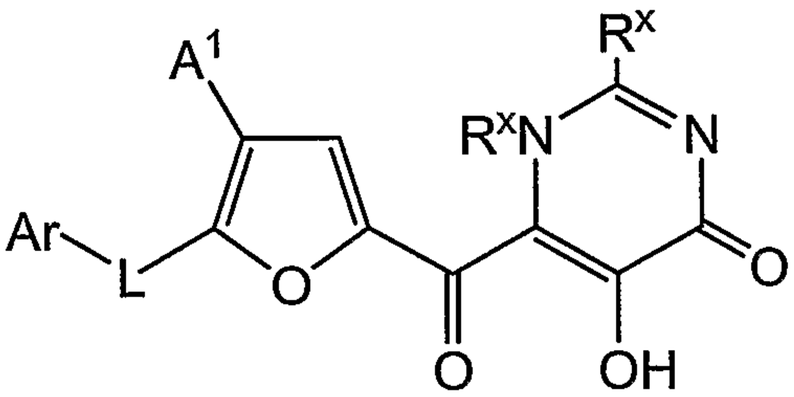
Embodiments of Formula VIII also include the structures:

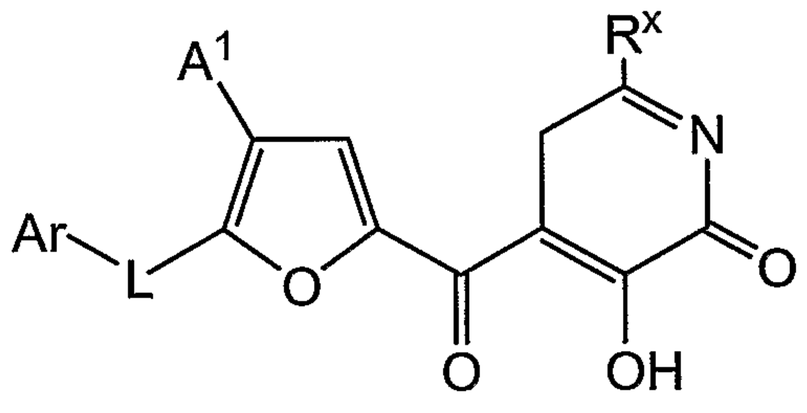


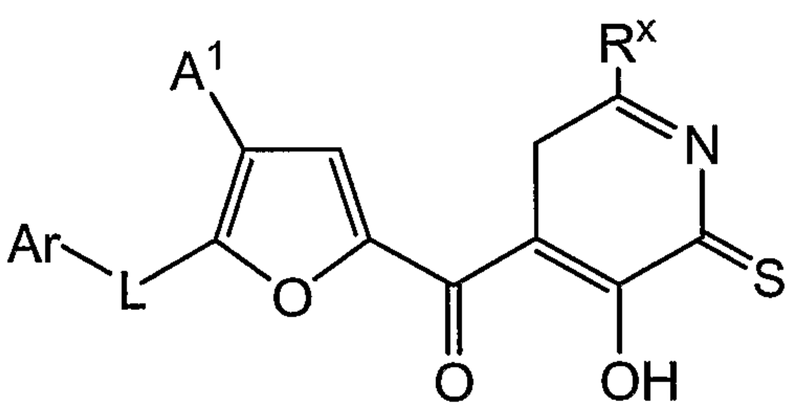


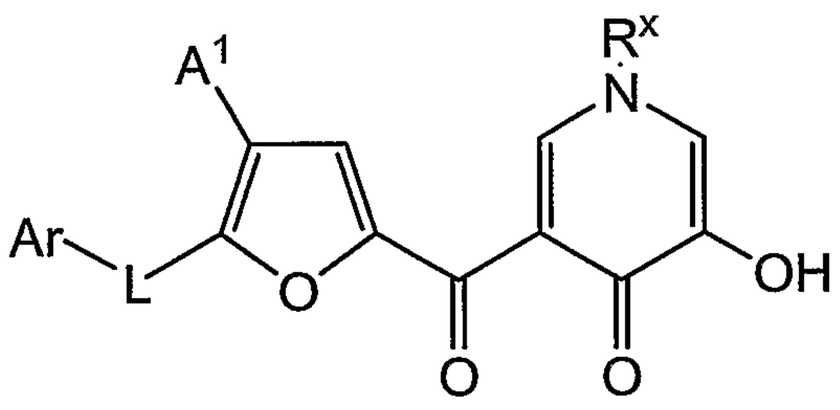




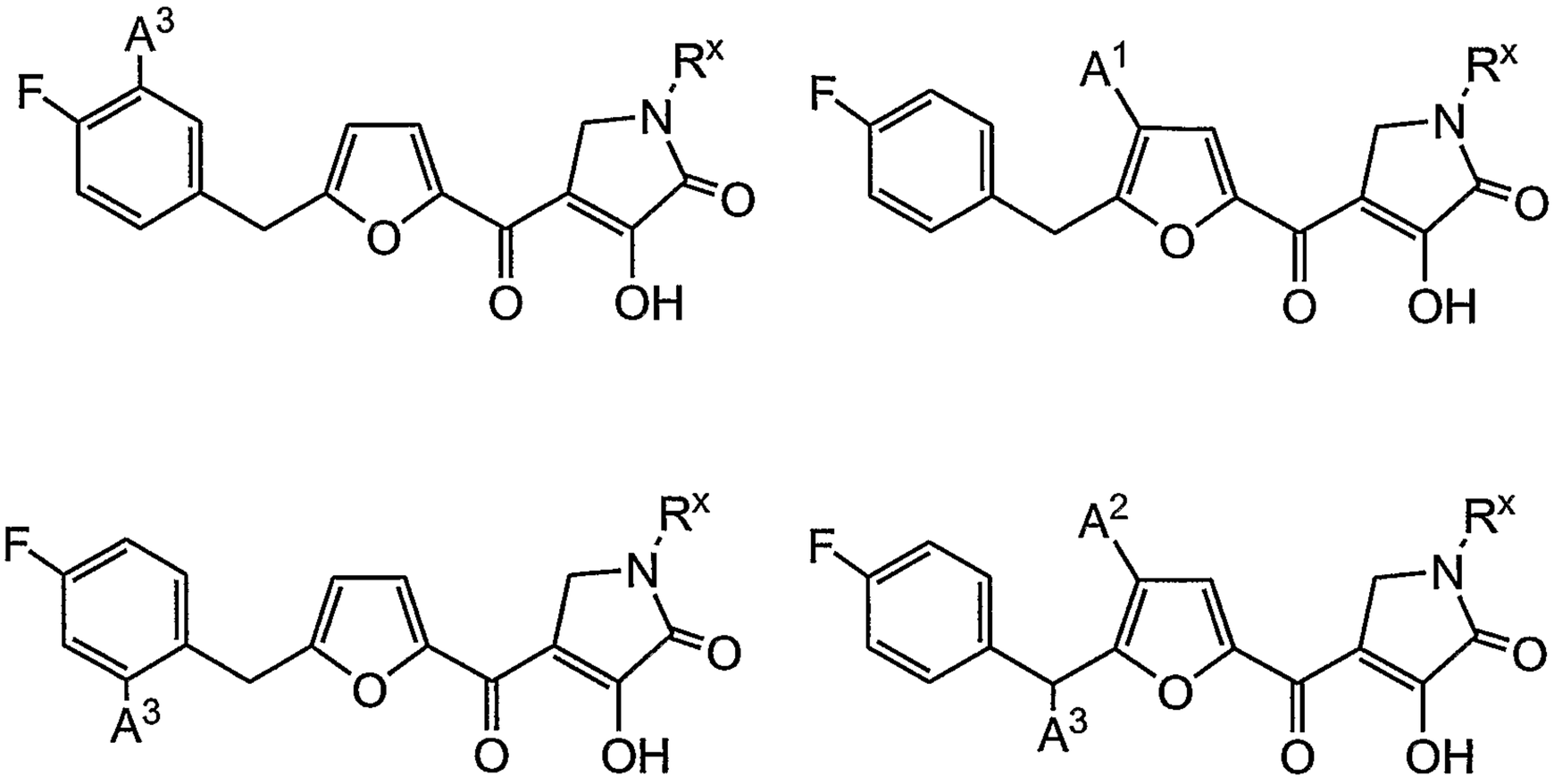






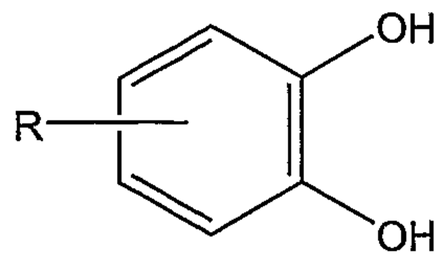


Embodiments of Formula VIII also include the structures:



Group IX

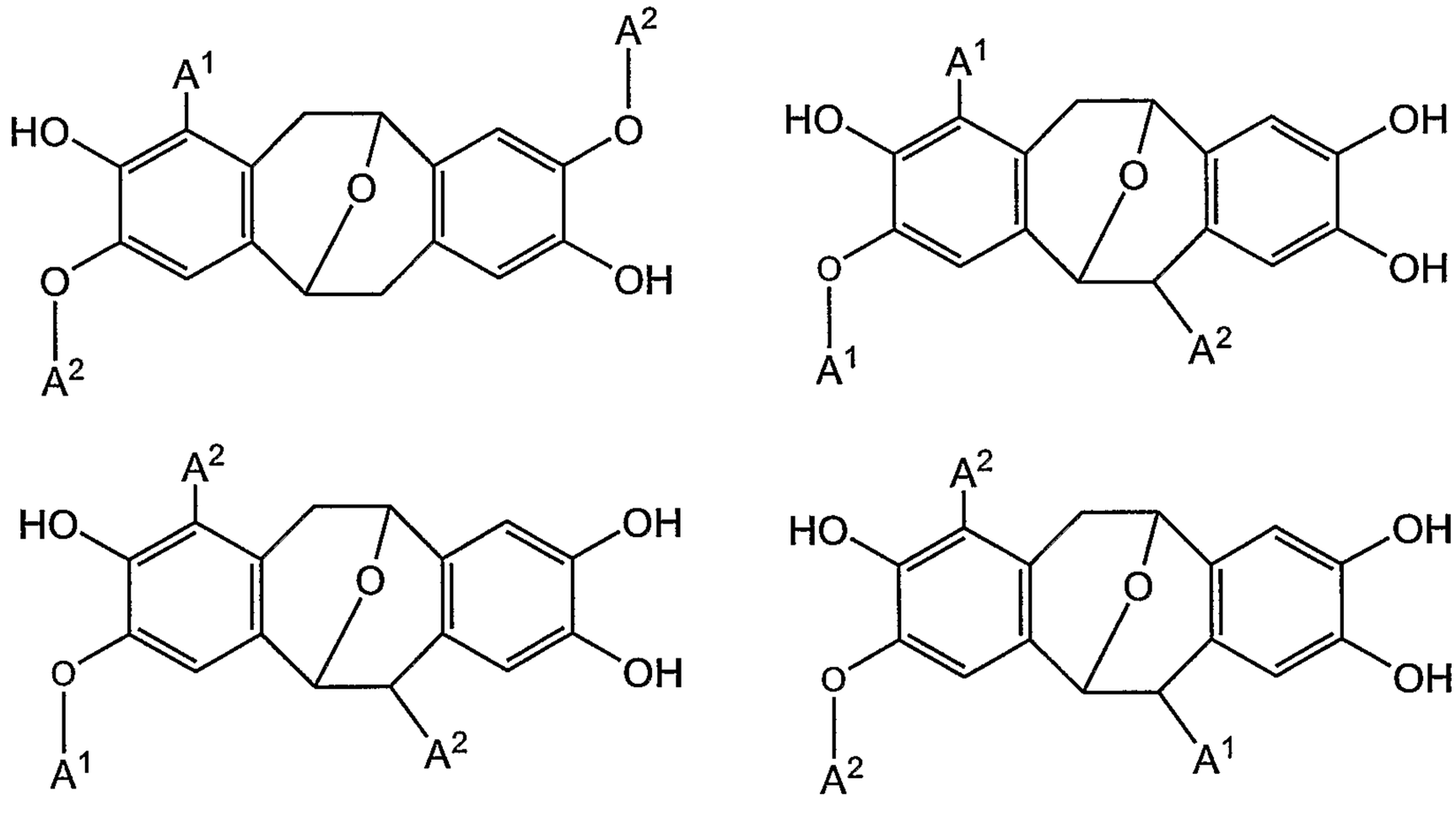
In one aspect, the invention includes phosphonate analogs of catechol compounds (Dupont et al (2001) *Bioorganic & Medicinal Chemistry Letters* 11(24):3175-3178; Neamati et al (1997) *Drug Discovery Today* 2:487-498; Neamati et al (2000) *Adv. Pharmacol.* 49:147-165; Fesen et al (1993) *Proc. Natl. Acad. Sci USA* 90:2399-2403; Lafemina et al (1995) *Antimicrob. Agents Chemother.* 39:320-324; Eich et al (1996) *J. Med. Chem.* 39(1):86-95; Pommier et al (1997) *Antiviral Chem. Chemother.* 8:463-483; Pommier et al (1999) *Adv. Virus Res.* 52:427-458; Fesen et al (1994) *Biochem. Pharmacol.* 48:595-608; McDougall et al (1998) *Antimicrob. Agents Chemother.* 42:140-146; Mazumder et al (1995) *Biochem. Pharmacol.* 49:1165-1170; Pfeifer et al (1992) *J. Pharm. Med.* 2:75-97; Mazumder et al (1997) *J. Med. Chem.* 40:3057-3063; Zhao et al (1997) *J. Med. Chem.* 40:1186-1194; Neamati et al (1997) *Antimicrob. Agents Chemother.* 41:385-393; Neamati et al (1997) *Mol. Pharmacol.* 52:1041-1055; Molteni et al (2000) *J. Med. Chem.* 43(10):2031-2039; US 6362165; GB 2271566), including caffeic acid phenylethyl ester (CAPE) compounds (Patil et al (2003) Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003; having Formula IX:



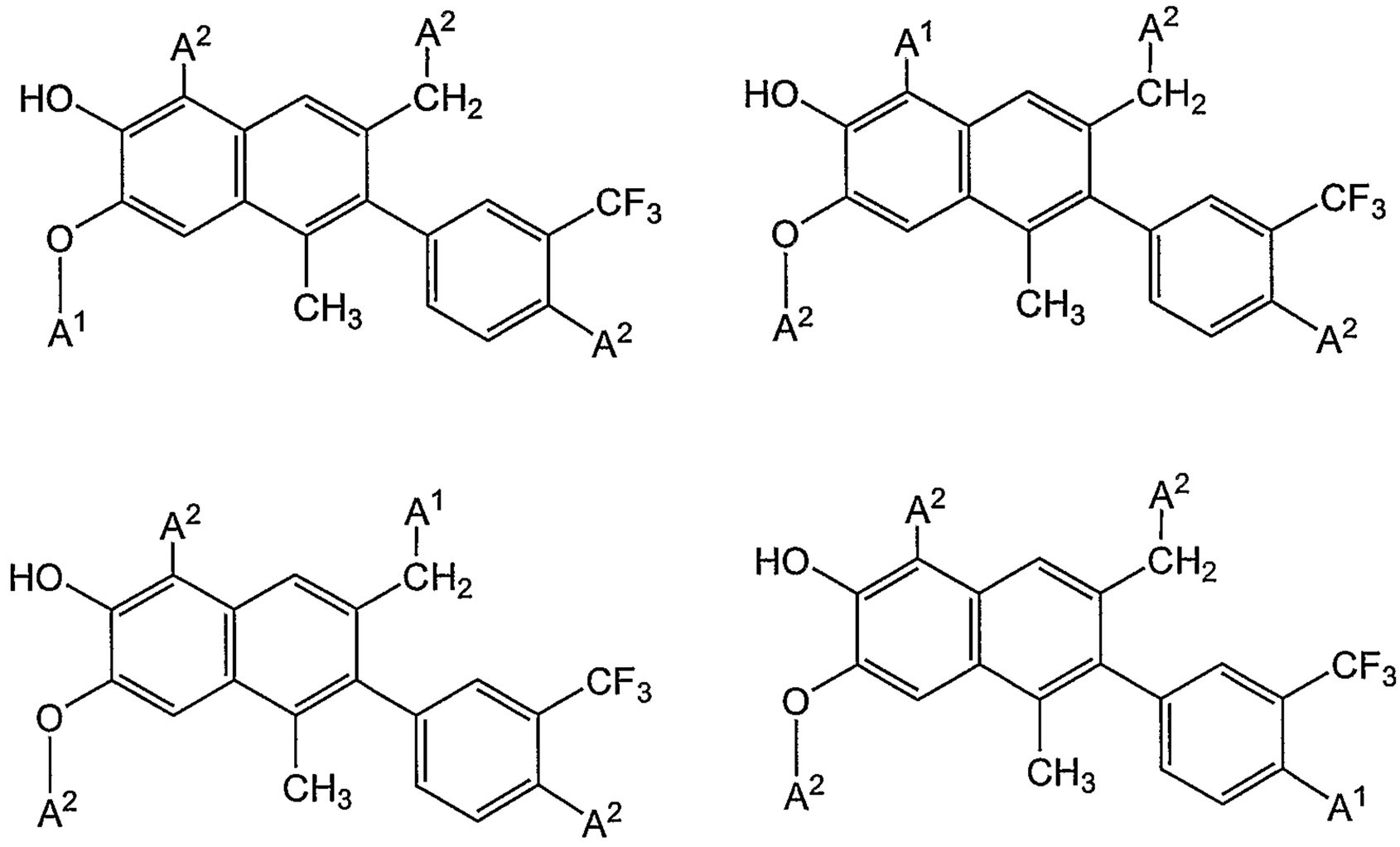
IX

where R is a variety of scaffolds that is covalently attached to the catechol moiety through a single bond or a fused ring system.

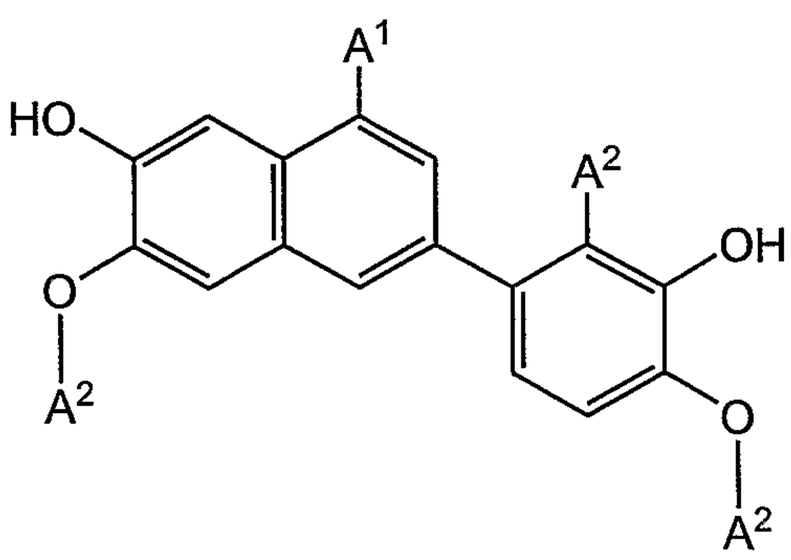
Embodiments of Formula IX include the structures:

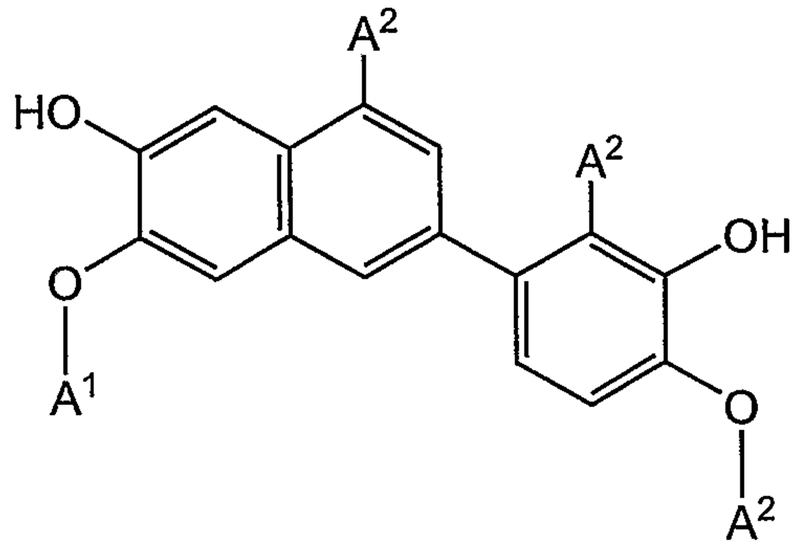


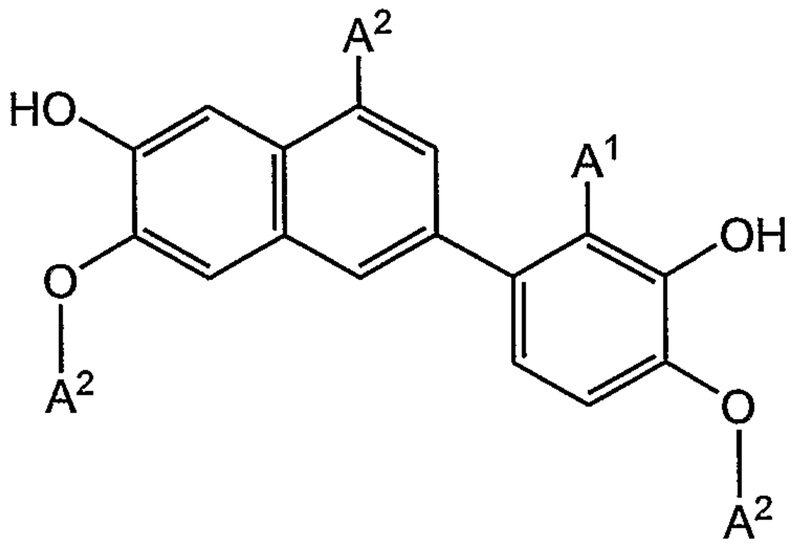
Embodiments of Formula IX also include the structures:

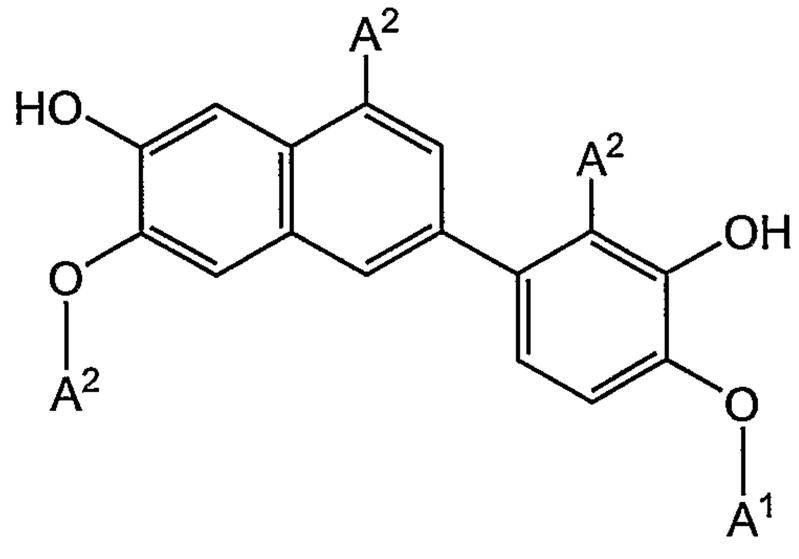


Embodiments of Formula IX also include the structures:

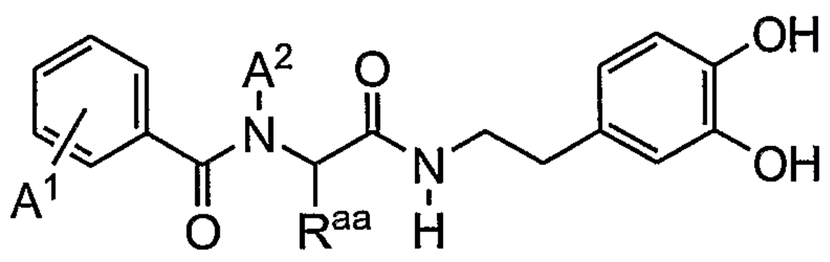


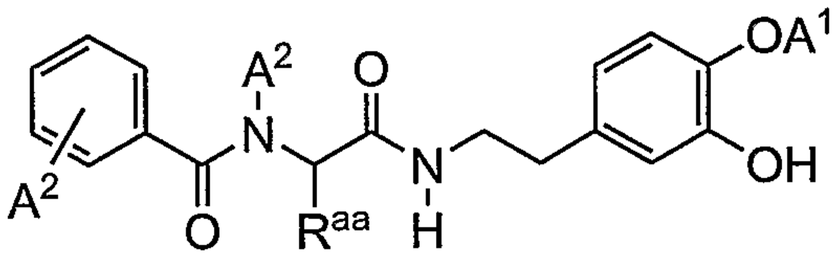


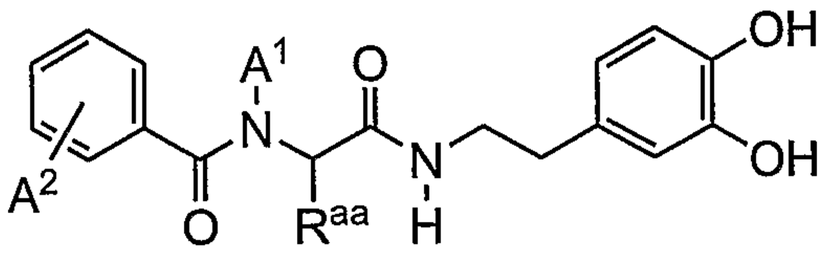


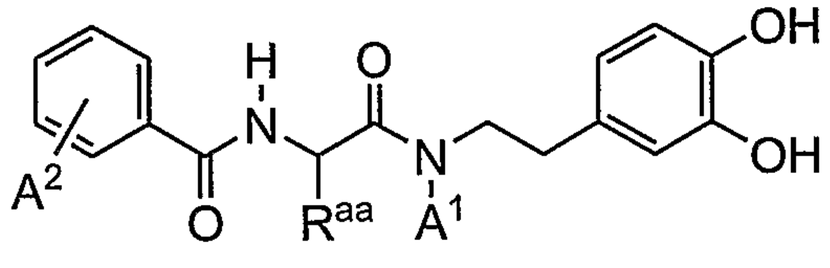


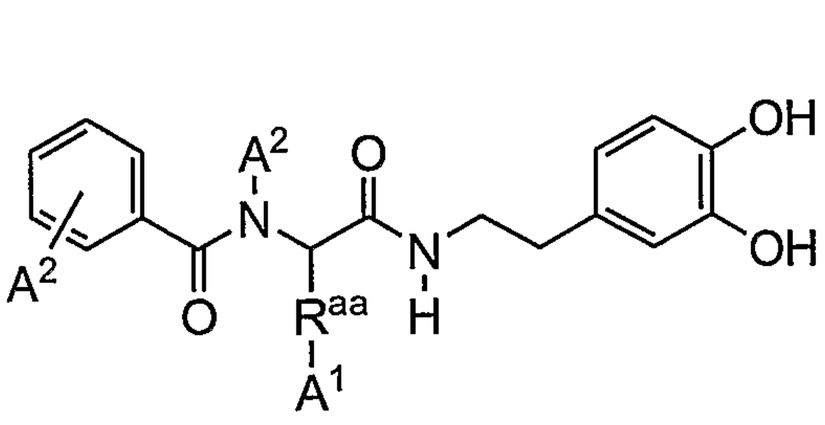
Embodiments of Formula IX also include the dopamine phosphonate structures:

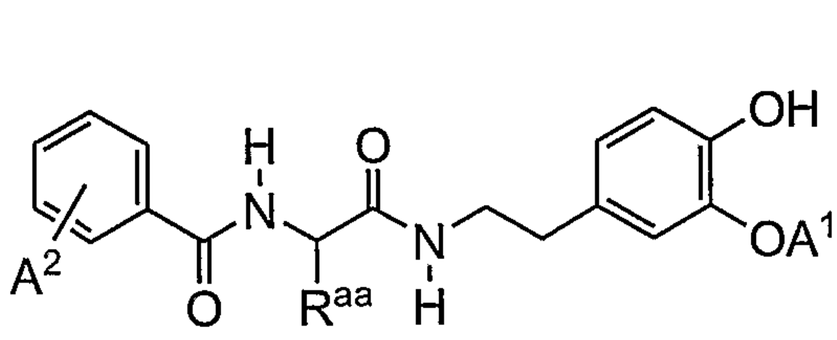






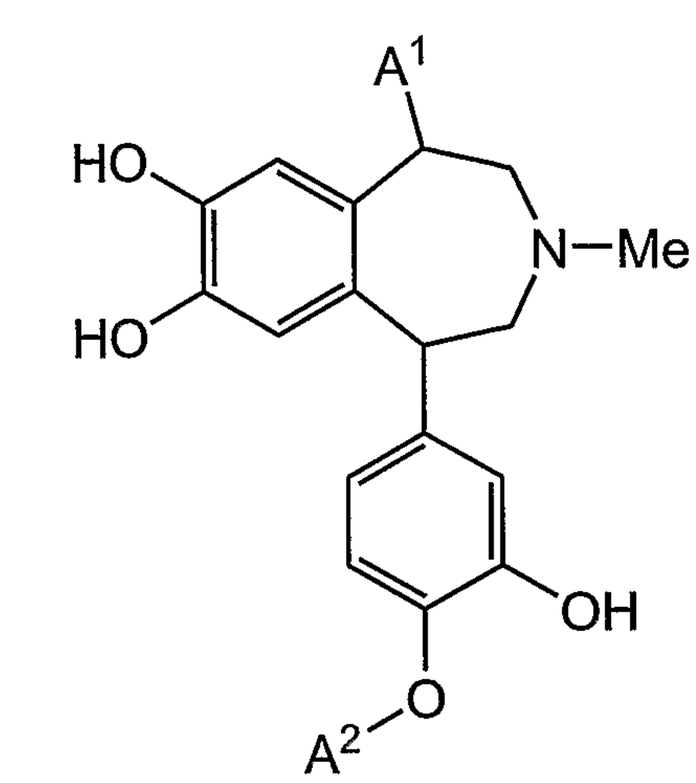


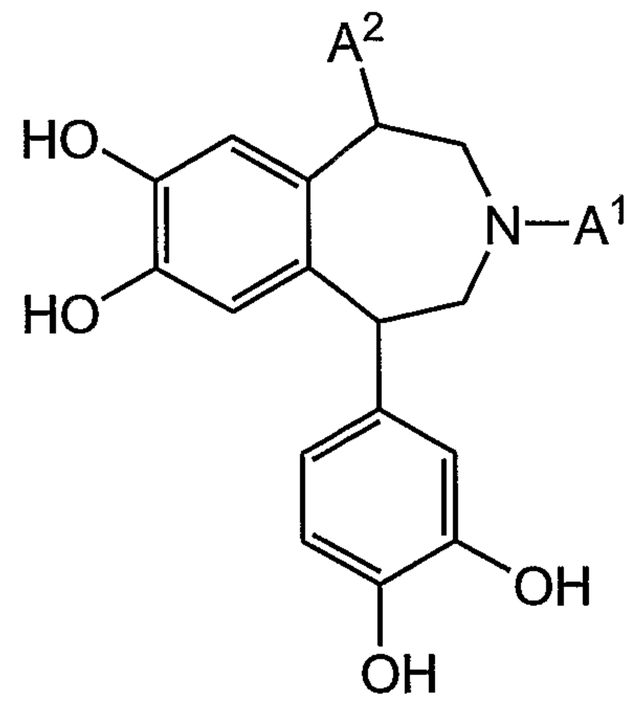


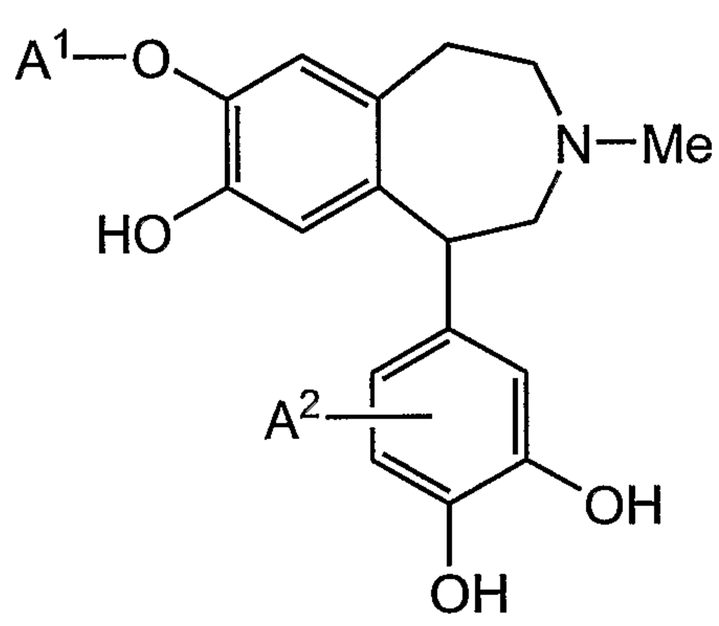


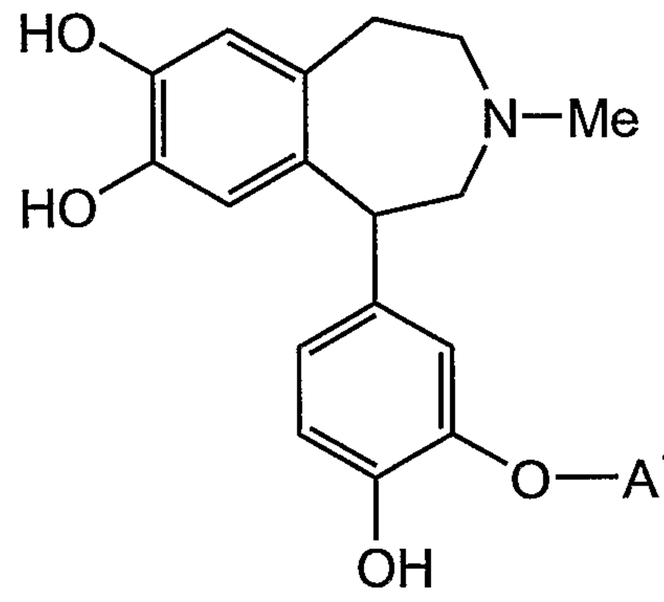
where R^{aa} is an amino acid side chain, including proline.

Embodiments of Formula IX also include the bis catechol, β-conidendrol phosphonate structures:







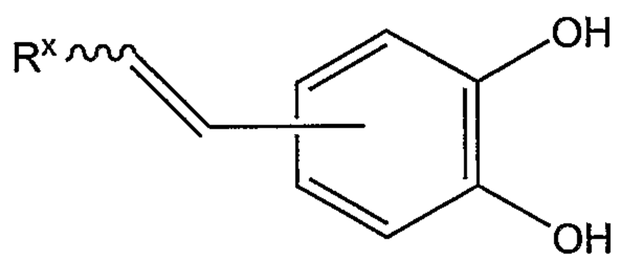


Group X

Catechol compounds IX include phosphonate analogs of styryl catechol compounds (Di Santo et al (2003) *Pure and Applied Chemistry* 75(2-3):195-206; Xu et al (2003) *Bioorganic & Medicinal Chemistry* 11(17):3589-3593); Lamidey et al (2002) *Helv. Chim. Acta* 85(8):2328-2334; Zouhiri et al (2000) *J. Med. Chem.* 43(8):1533-1540; Zouhiri et al (2001) *Tetrahedron Letters* 42(46):8189-8192; Ouali et al (2000) *J. Med. Chem.* 43(10)1949-1957; Mazumder et al (1997) *J. Med. Chem.* 40:3057-3063; Mekouar et al (1998) *J. Med. Chem.* 41:2846-2857; Pommier et al (2000) *Antiviral Res.* 47(3):139-148; Mazumder et al (1995) *Biochemistry* 34:15111-15122; Yoo et al (2003) *Farmaco* 58(12):1243-1250; Lee et al (2002) *Archiv der Pharmazie* (Weinheim, Germany), 335(6):277-282; WO 98/45269; WO 99/48371; WO 00/63152; WO 99/66942; WO 01/00199; WO 00/59867; WO 00/77013)

including analogs of chicoric acid (Reinke et al (2002) *Jour. Med. Chem.* 45(17):3669-3683; Robinson et al (1996) *Proc. Natl. Acad. Sci. USA* 93:6326-6331; Robinson et al (1996) *Mol. Pharmacol.* 50:846-855) and lithospermic acid (Abd-Elazem et al (2002) *Antiviral Research* 55(1):91-106; WO 02/026726).

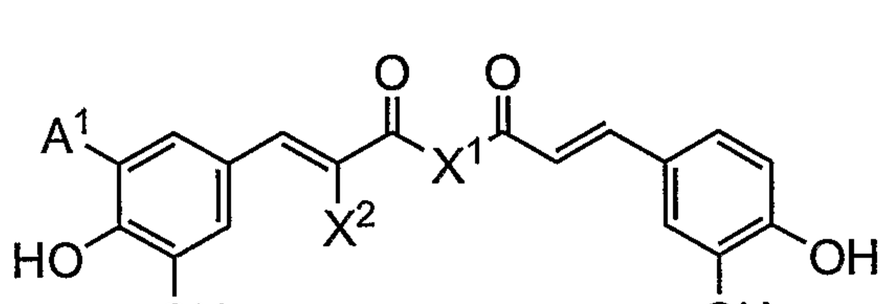
Phosphonate analogs of styryl catechol compounds generally have Formula X:

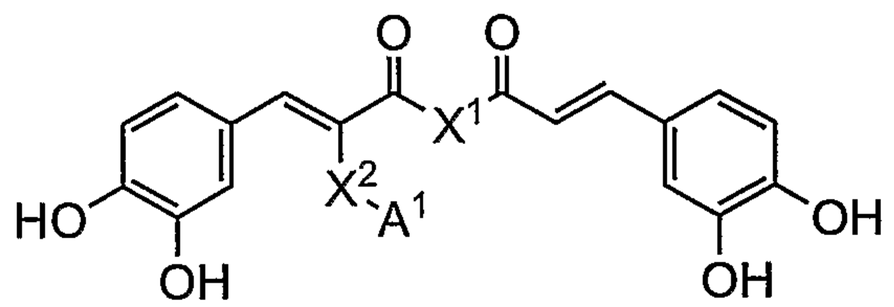


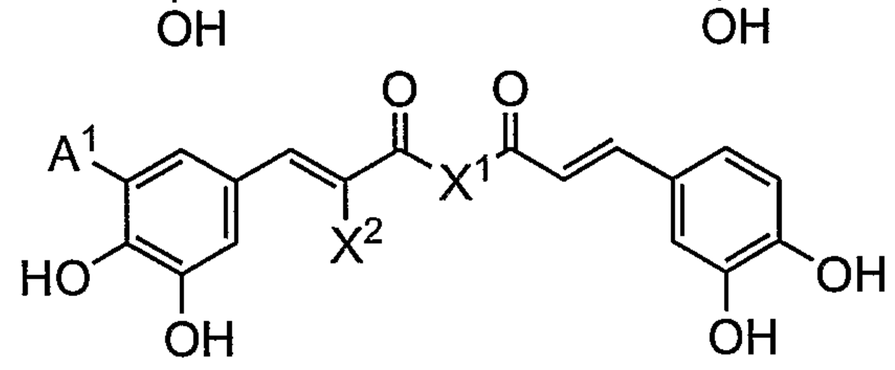
X

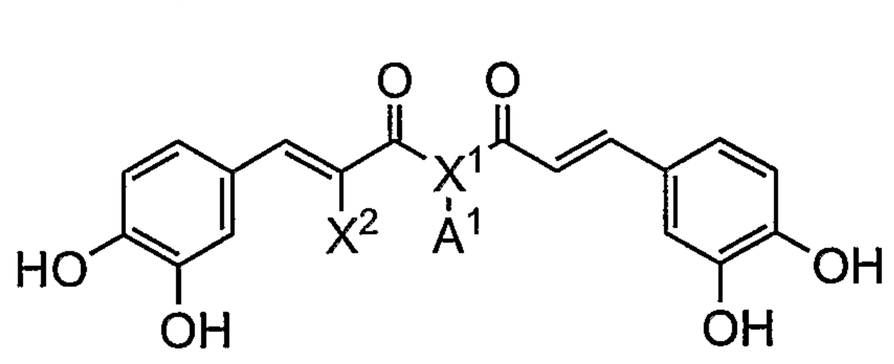
where R^x is a variety of scaffolds that is covalently attached to the catechol moiety through a single bond or a fused ring system.

Embodiments of Formula X compounds include:



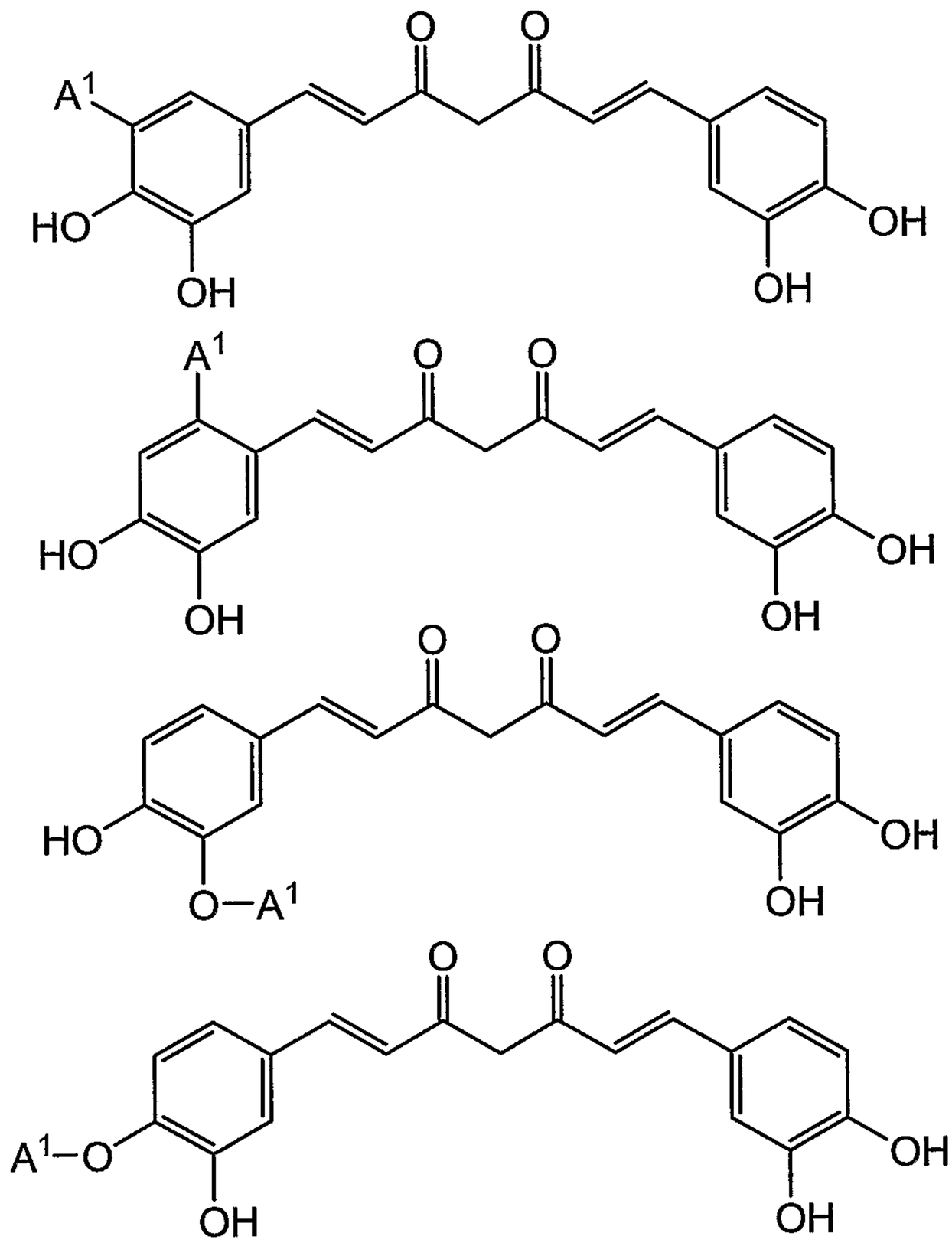






where X^1 is –NH(CH2)nNH– where n is 1-6, alkylarylene, or arylene, and X^2 is CN, Br, or OH, and any carbon or hydroxyl oxygen atom may be independently substituted with A^2.

Embodiments of Formula X compounds also include:



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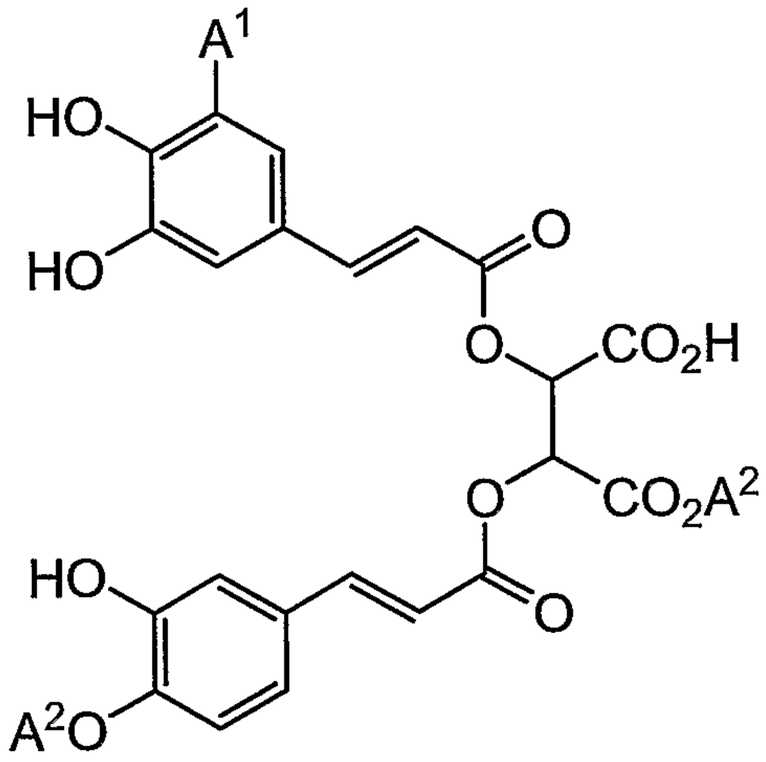

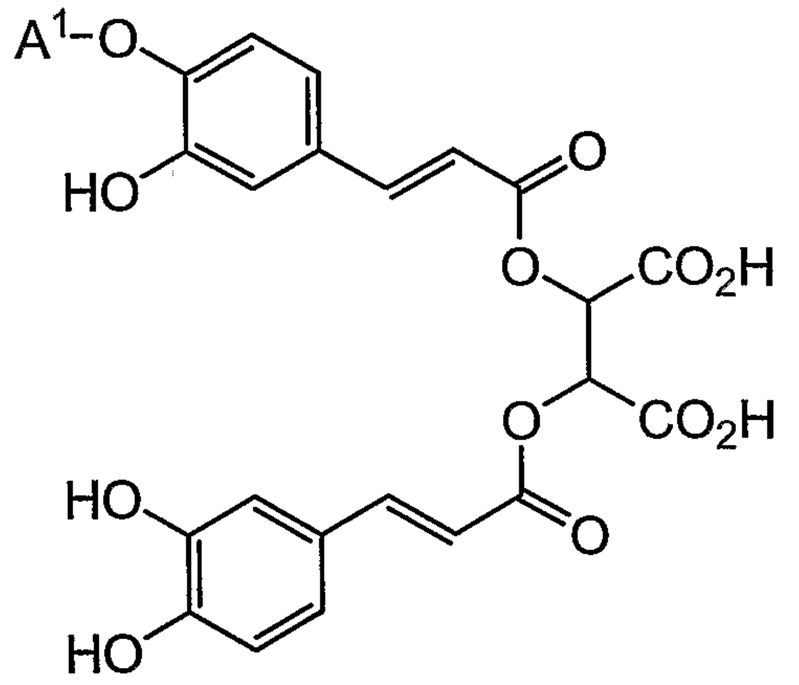

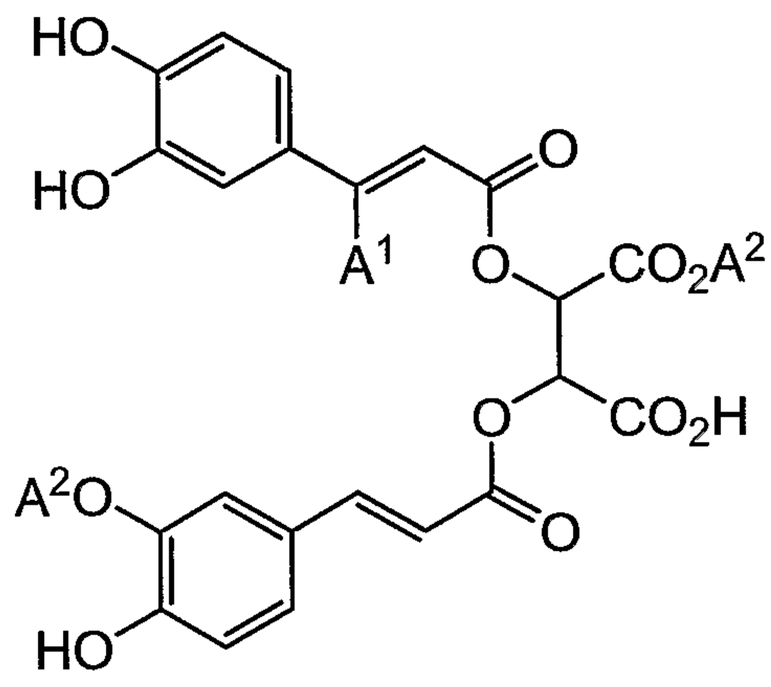

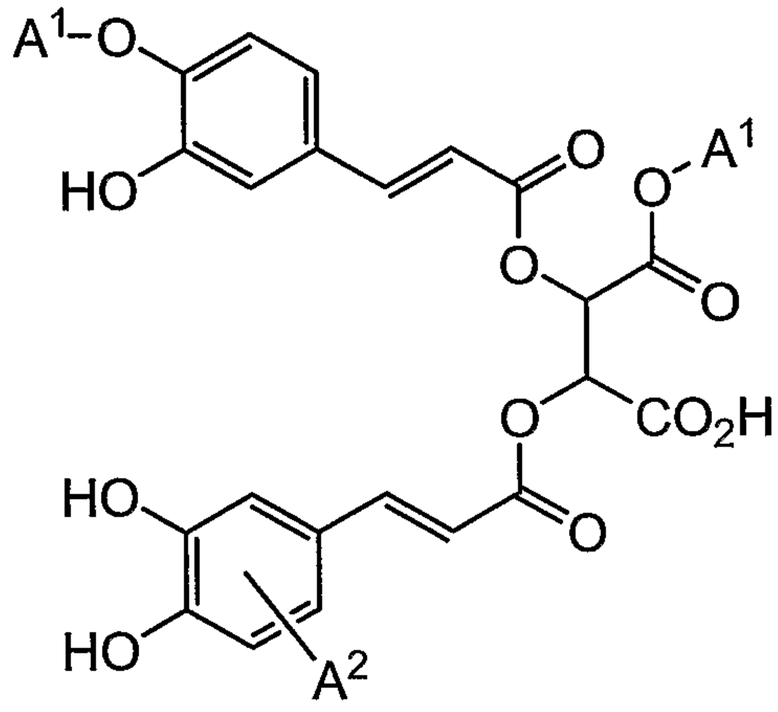

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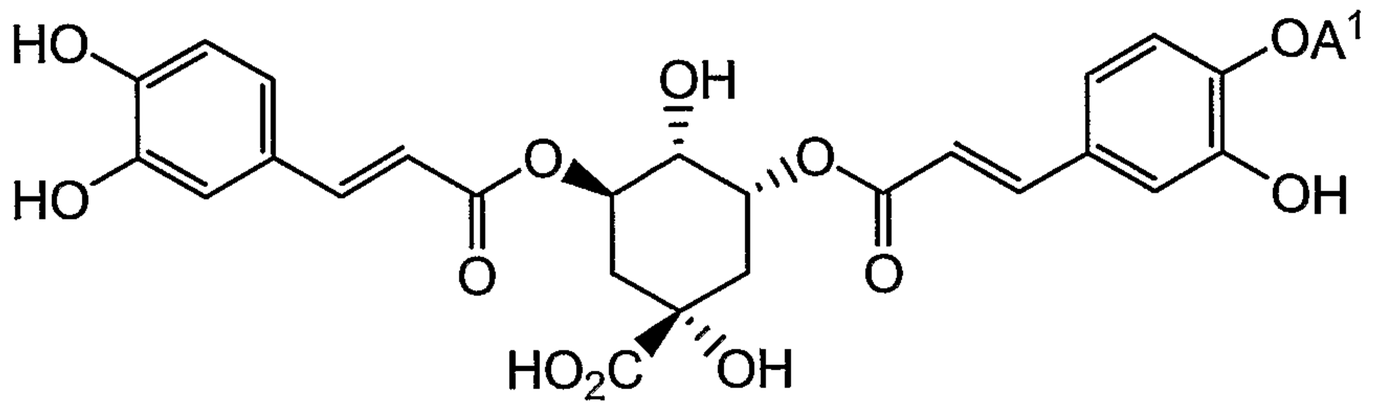

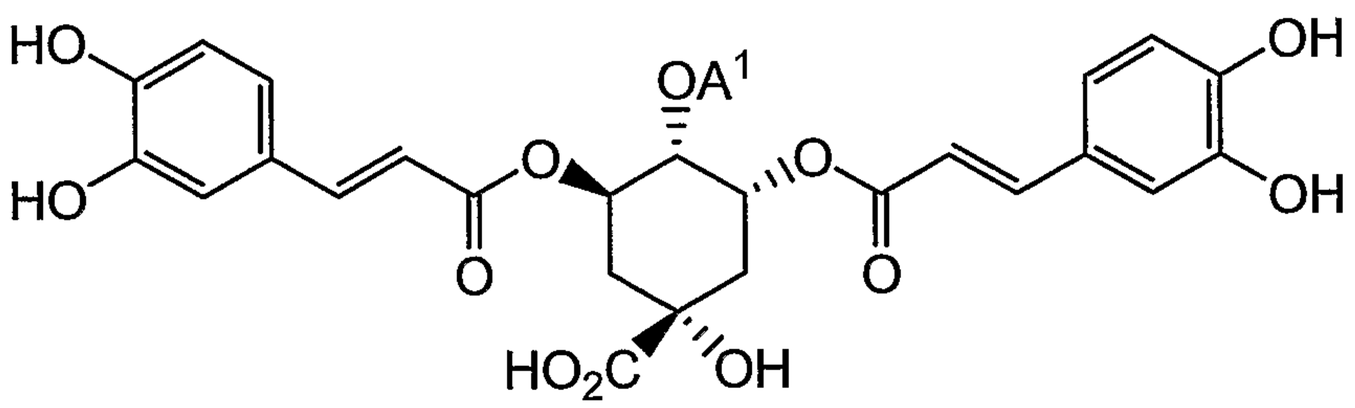

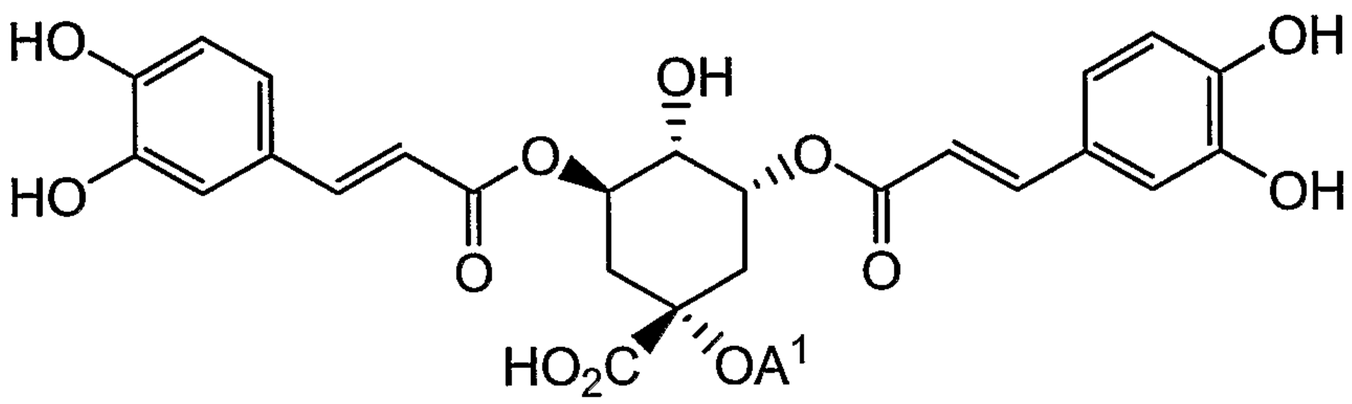

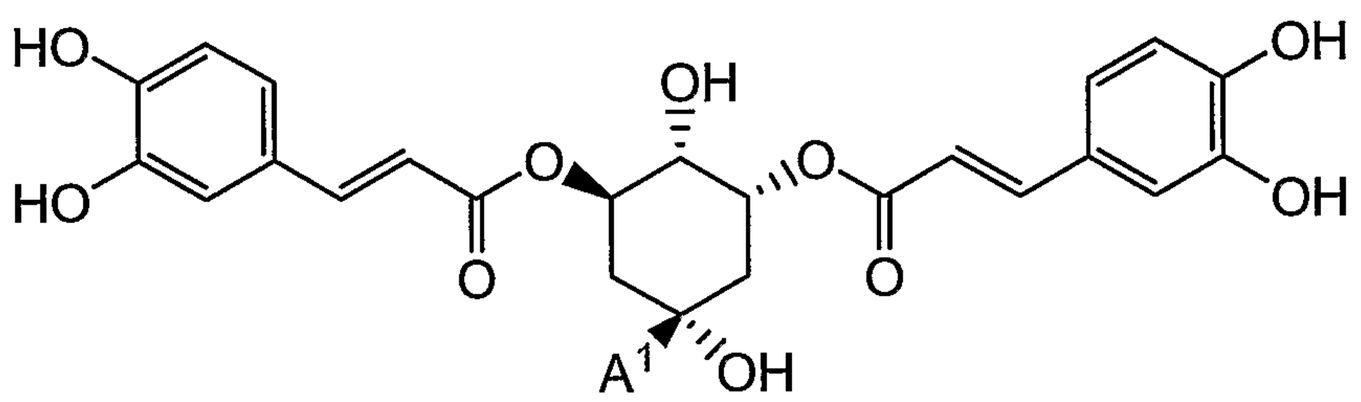

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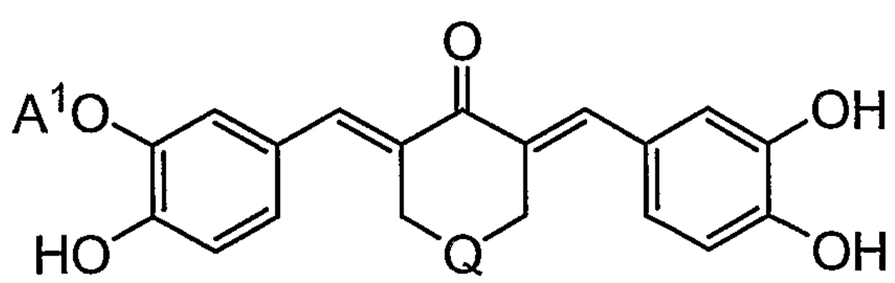
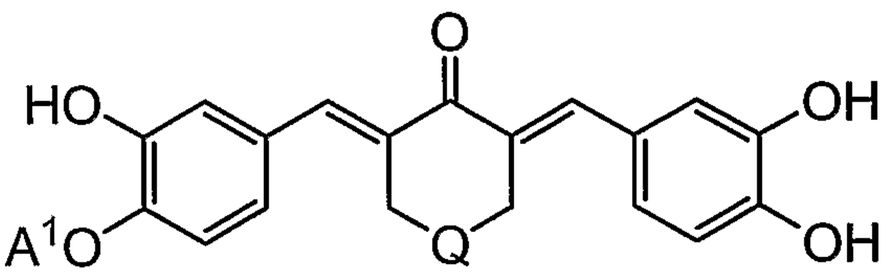
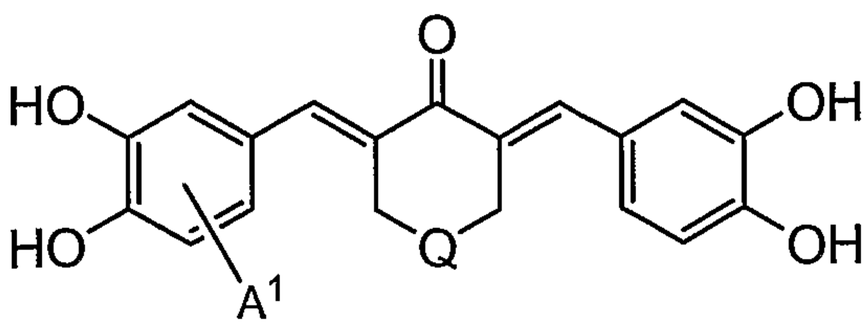
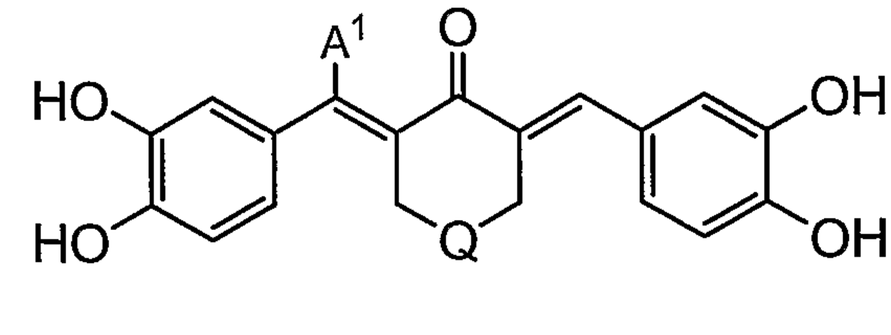


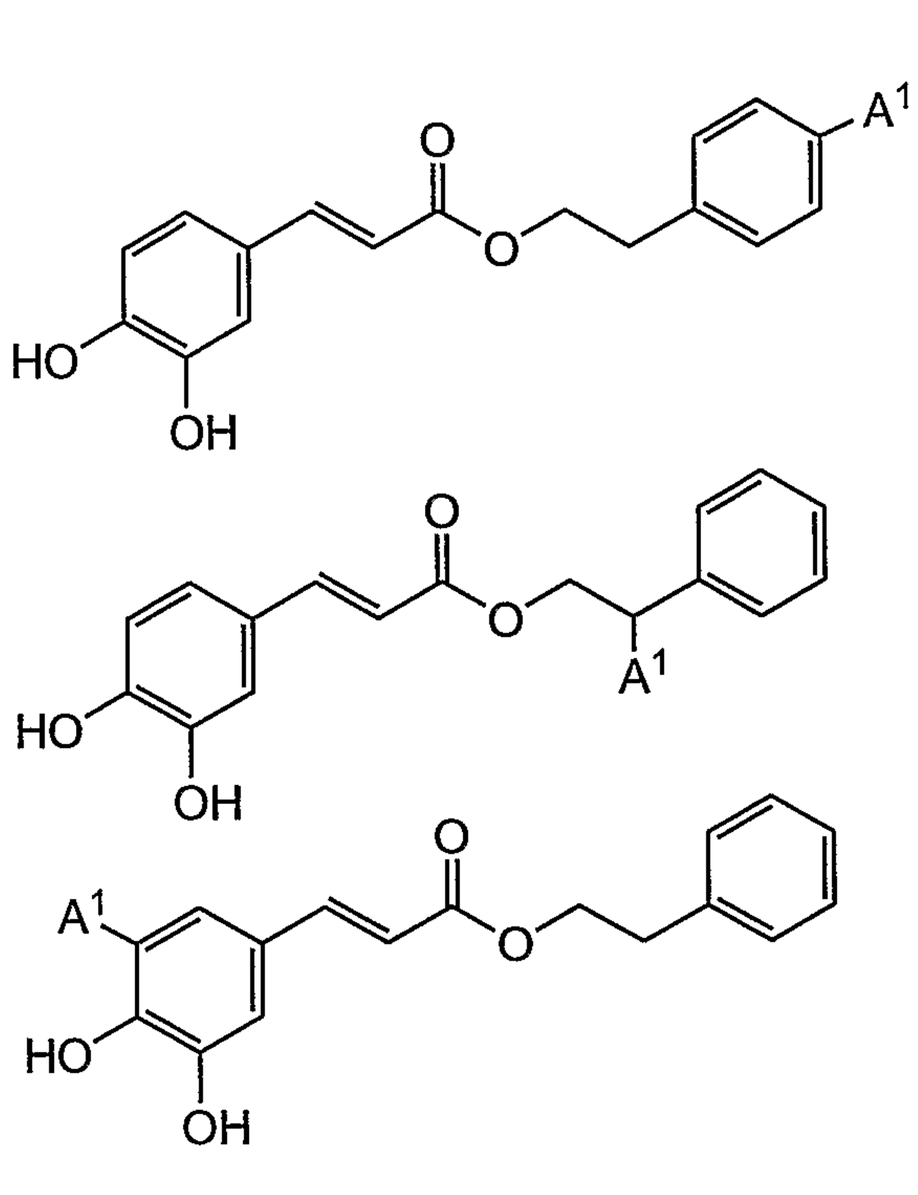


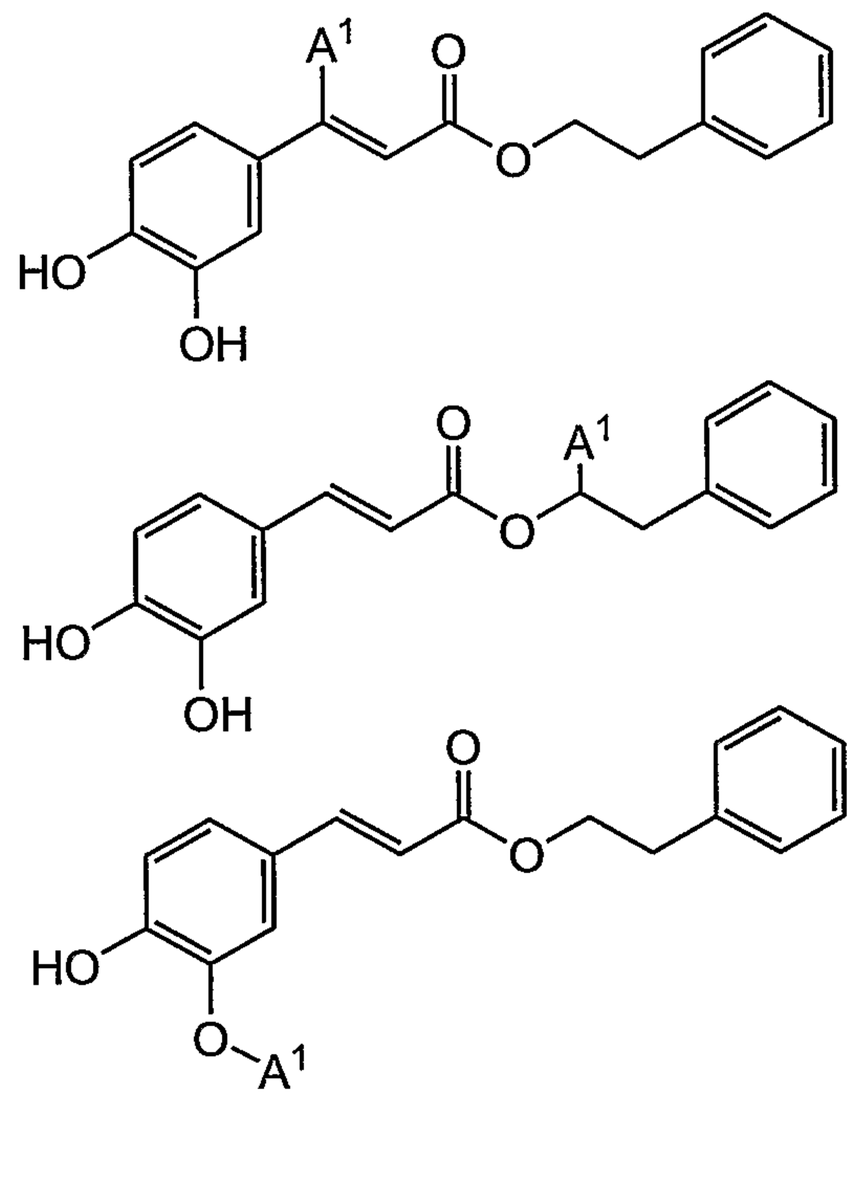




where Q is CH_2, O, S, NH, or NR.

Embodiments of Formula X compounds also include:





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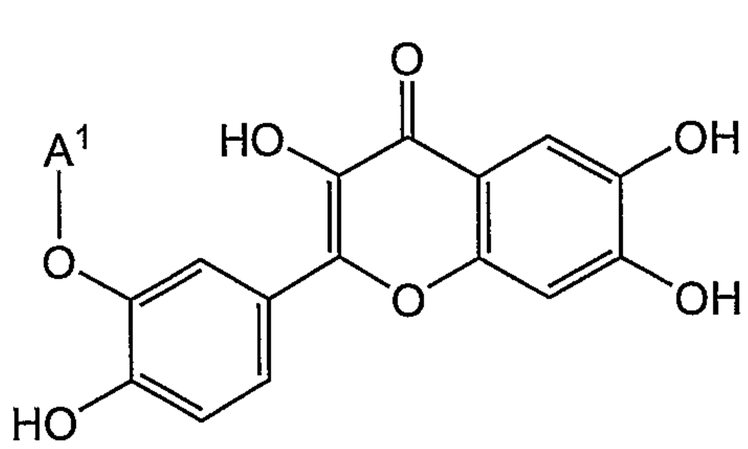

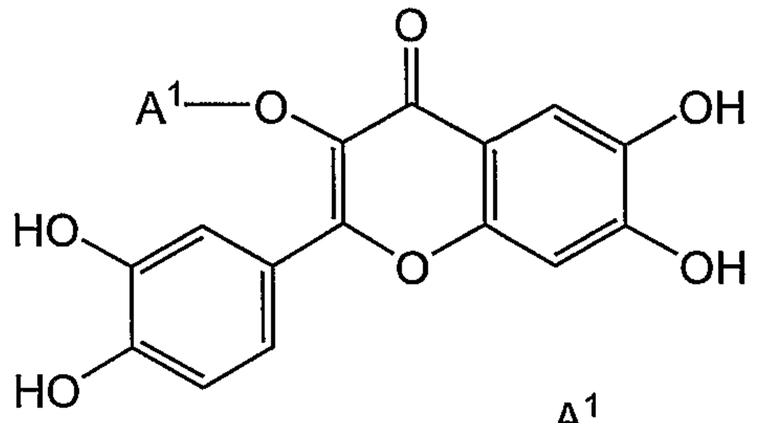

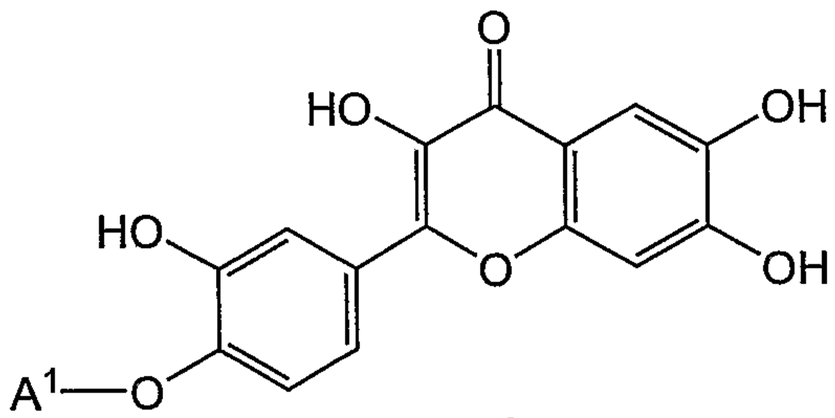

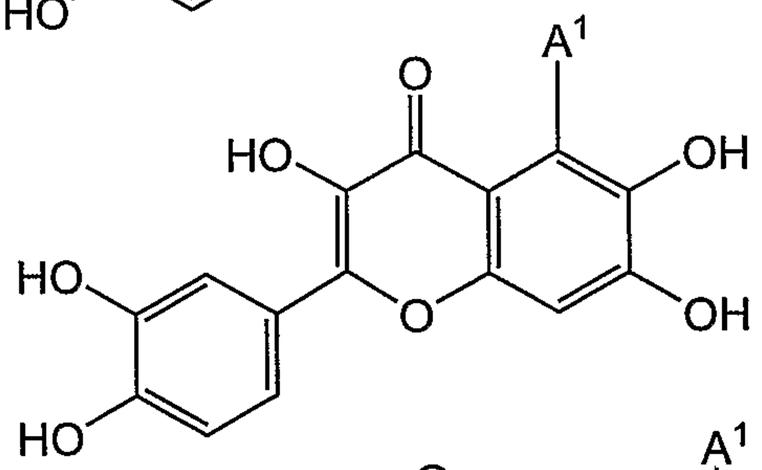

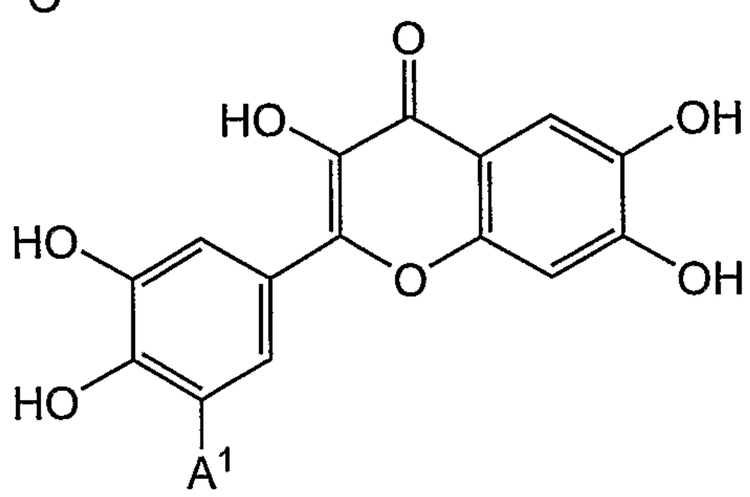

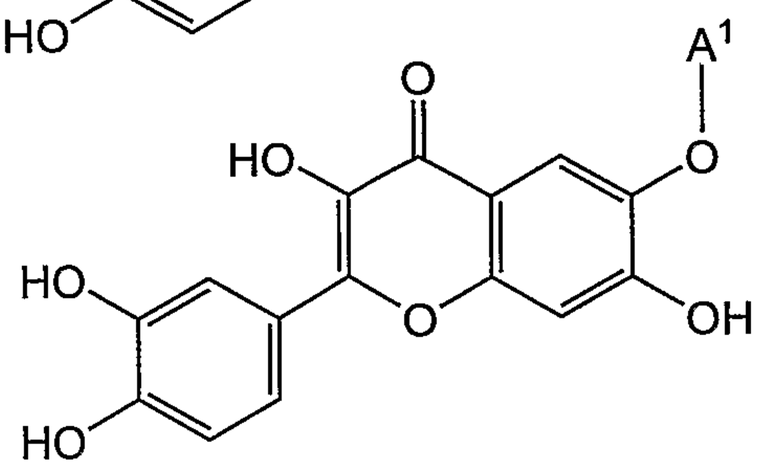

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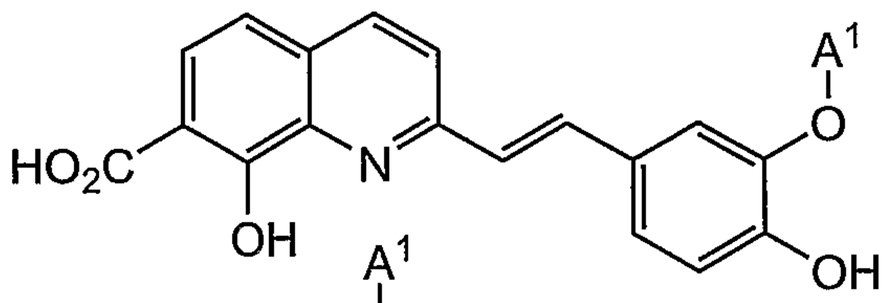

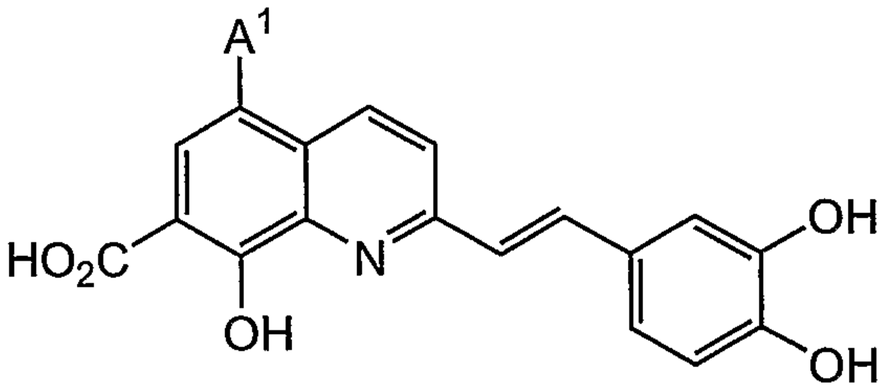

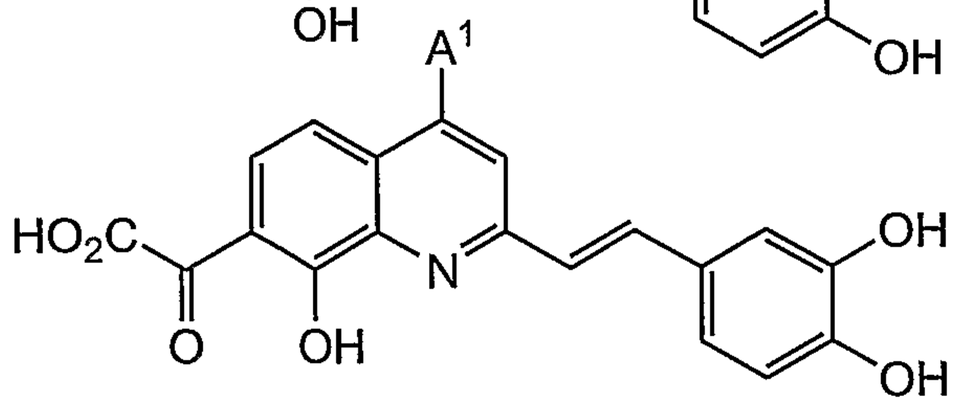

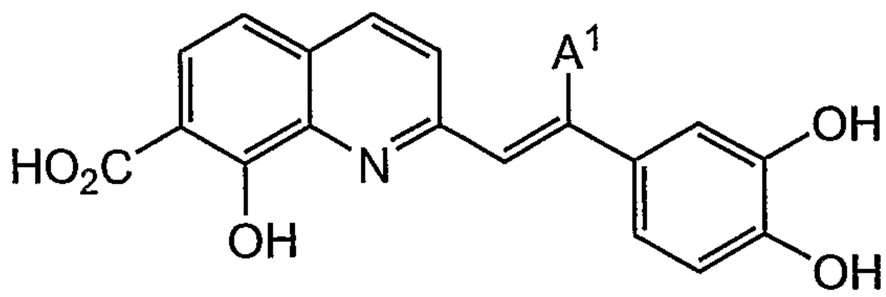

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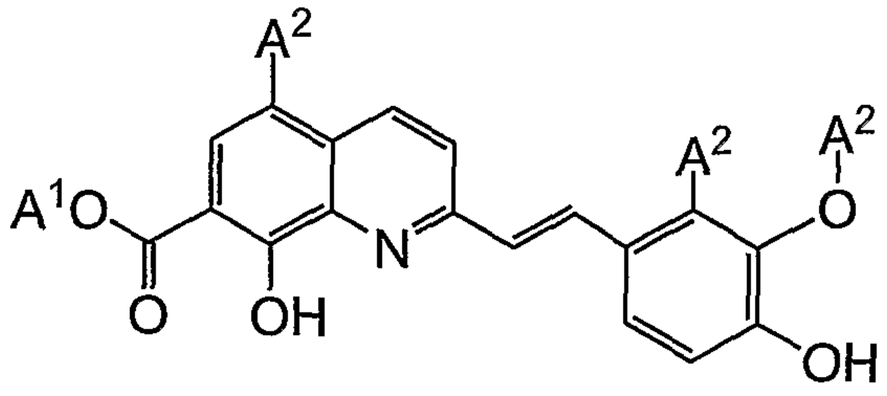

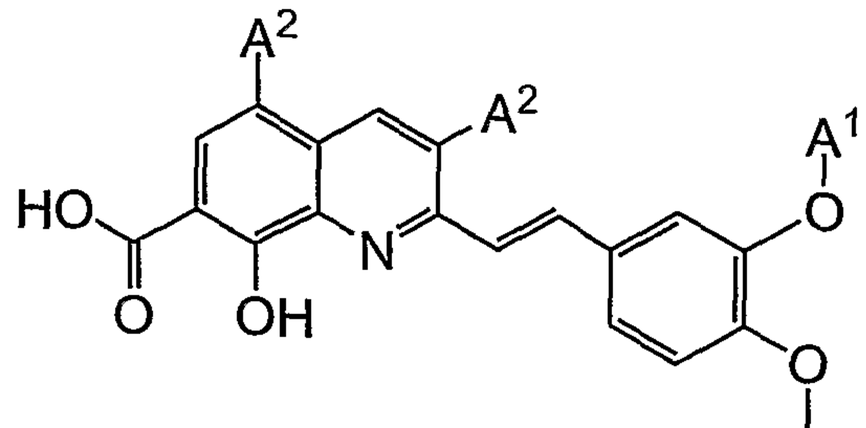

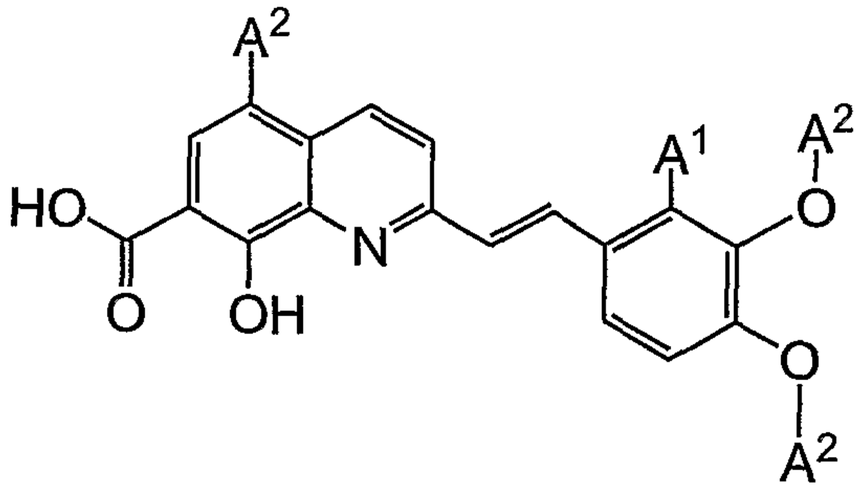

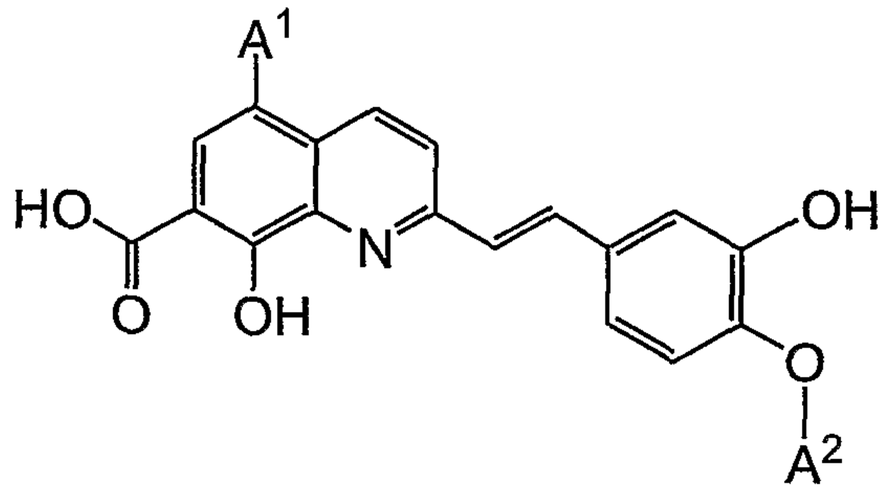

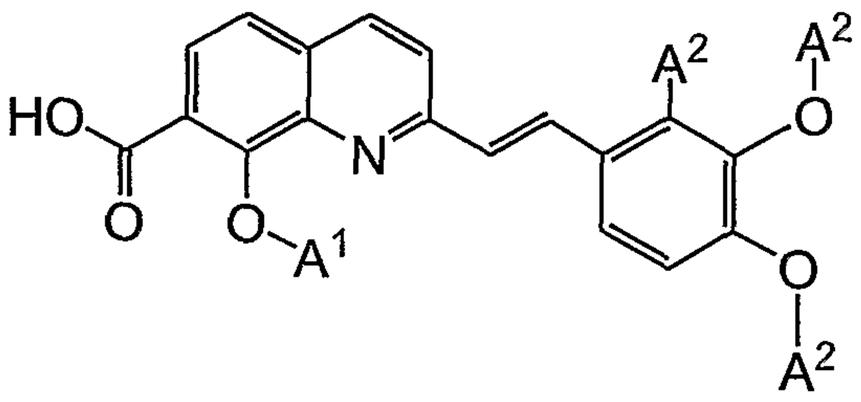

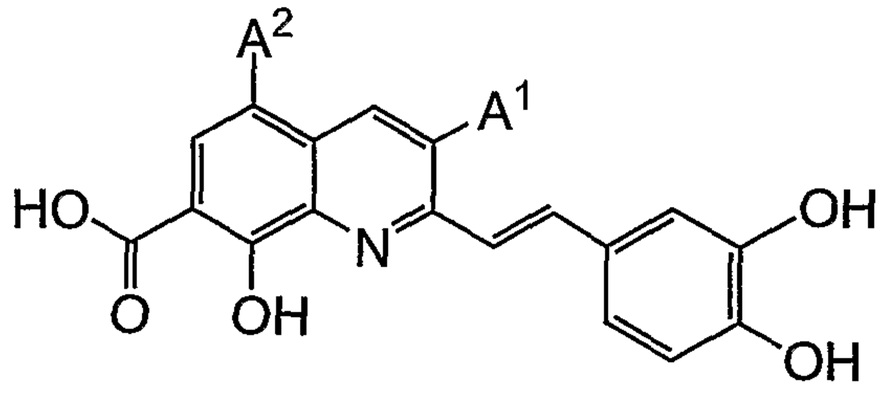

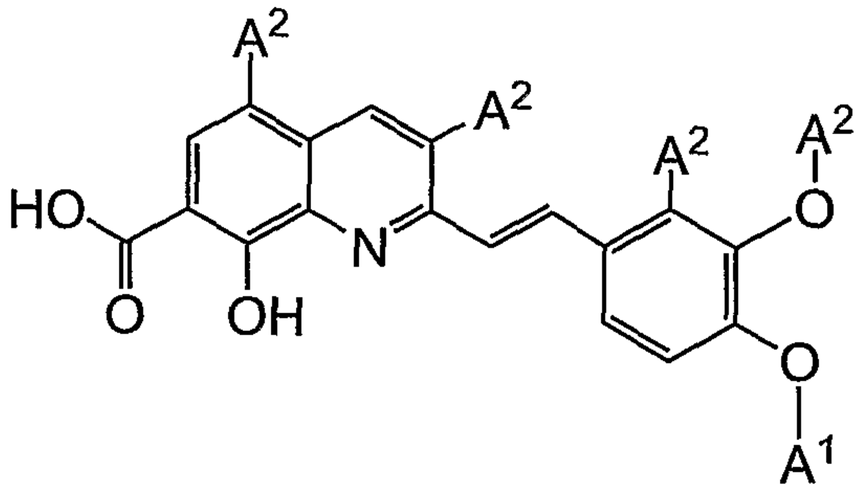

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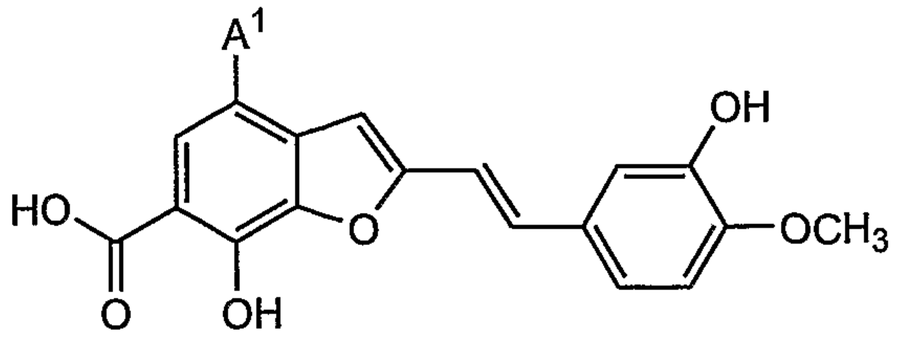
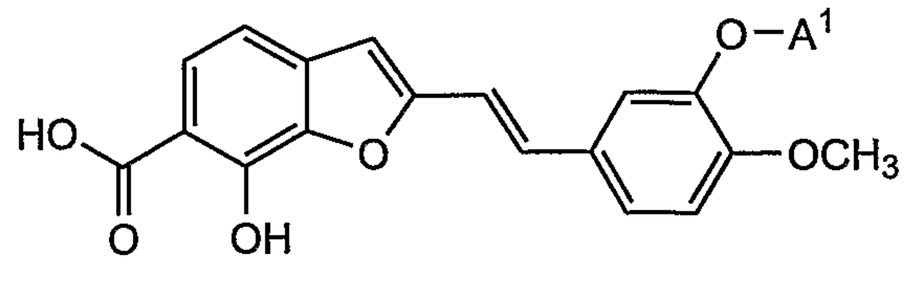
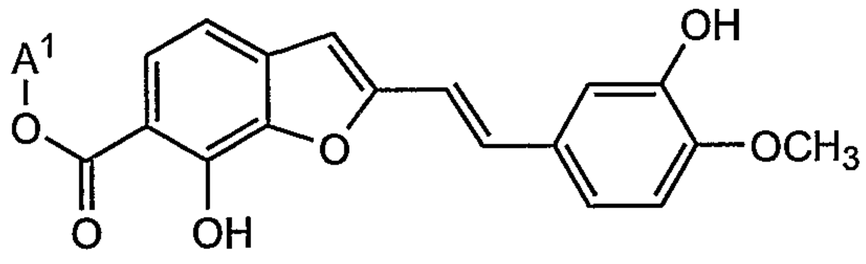
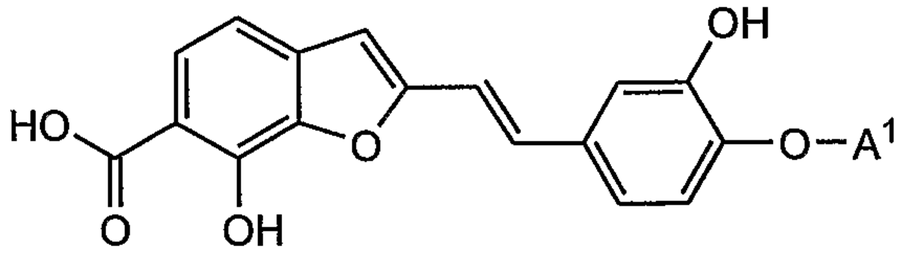
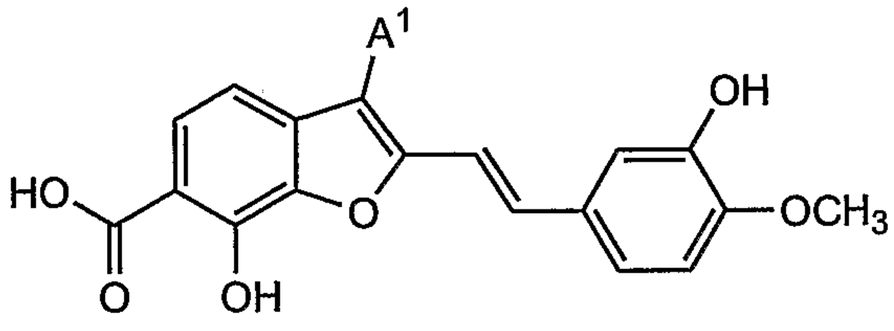
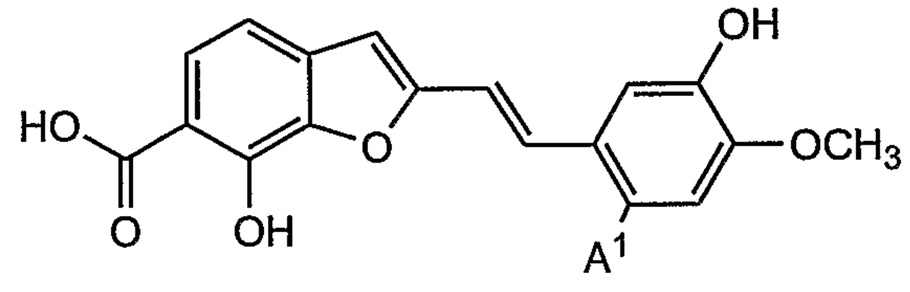




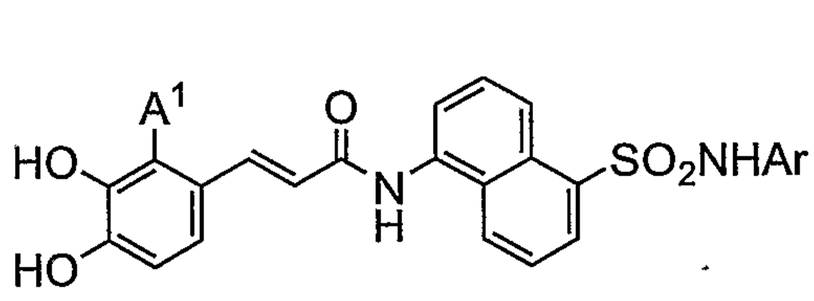


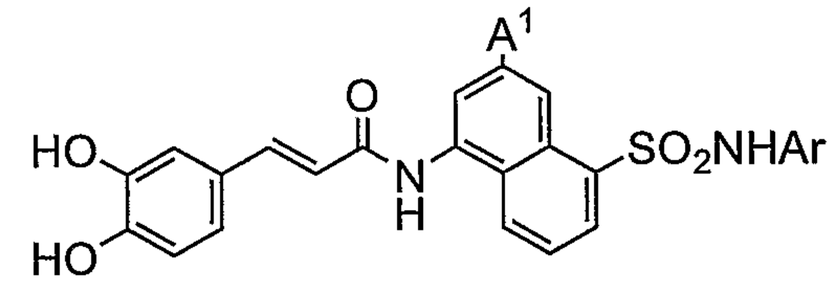


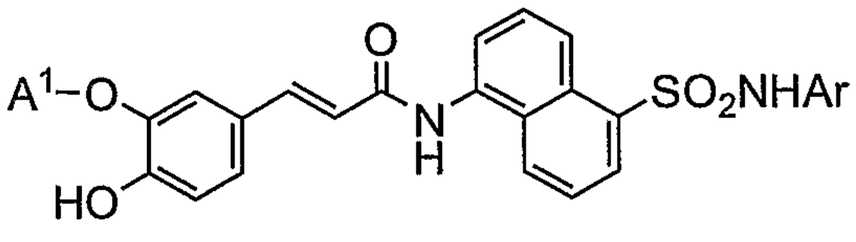


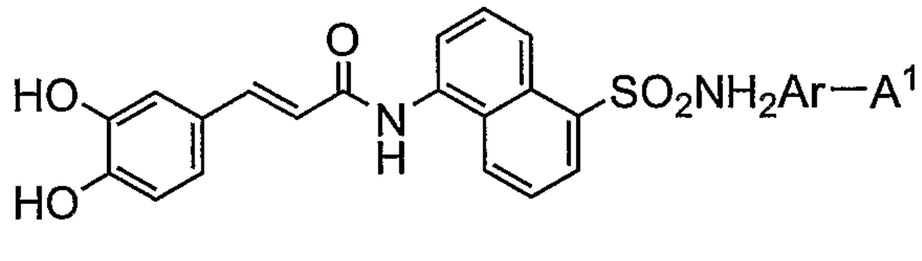


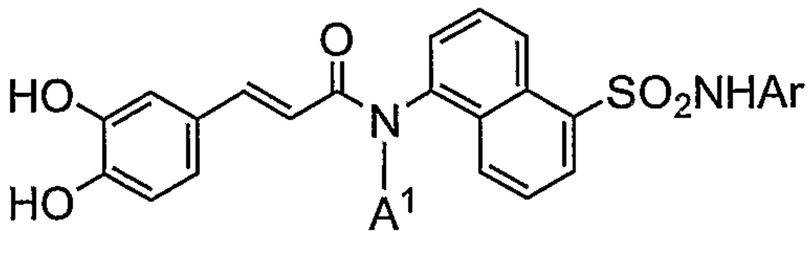
Embodiments of Formula X compounds also include:

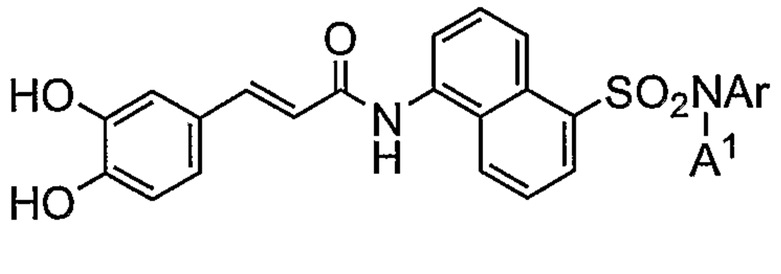






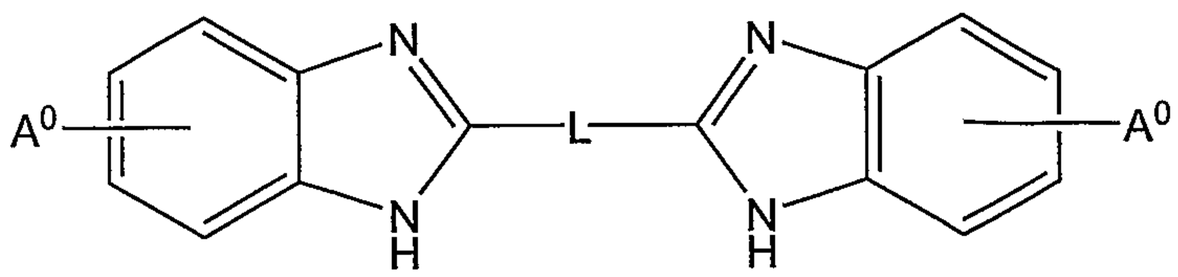






Group XI

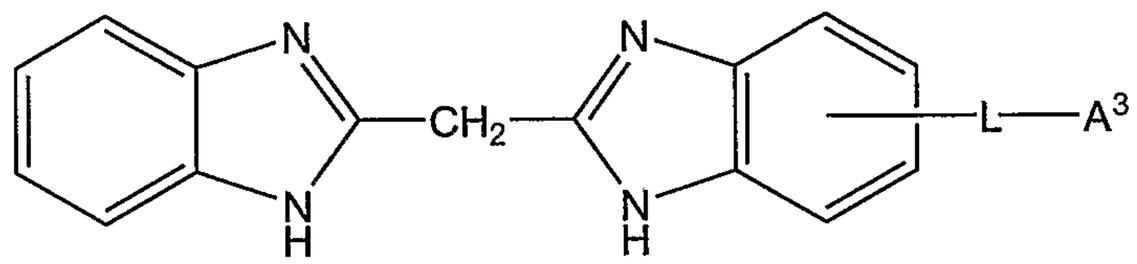
In one aspect, the invention includes phosphonate analogs of benzimidazole compounds (WO 02/070491 A1) and bis-benzimidazole compounds (WO 95/08540; WO 95/19772; WO 98/38170; Pluymers et al (2000) *Mol. Pharmacol.* 58:641-648) having Formula XI:

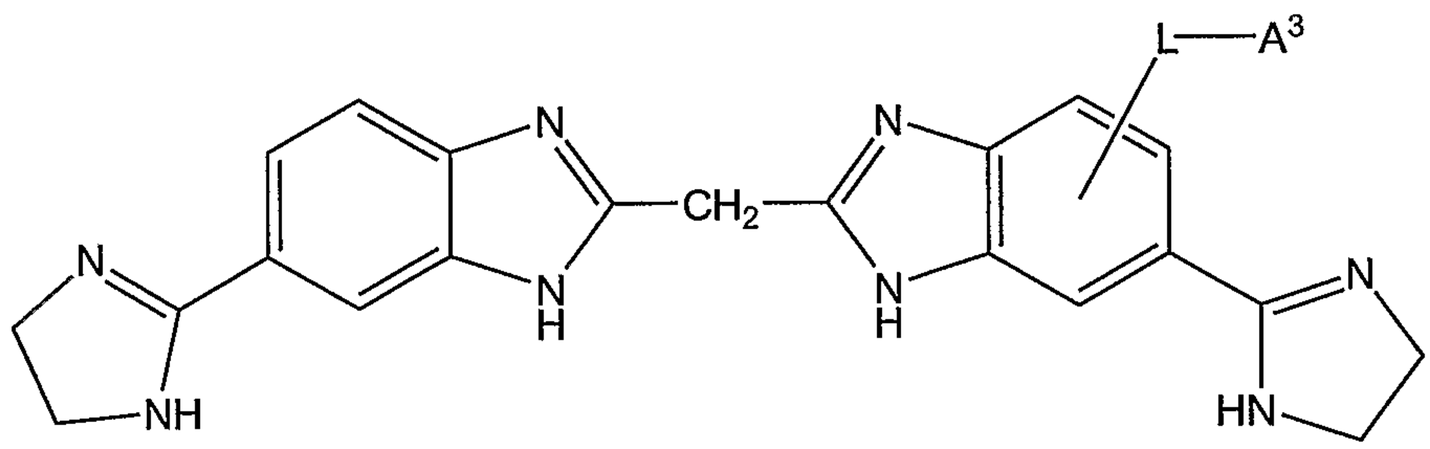


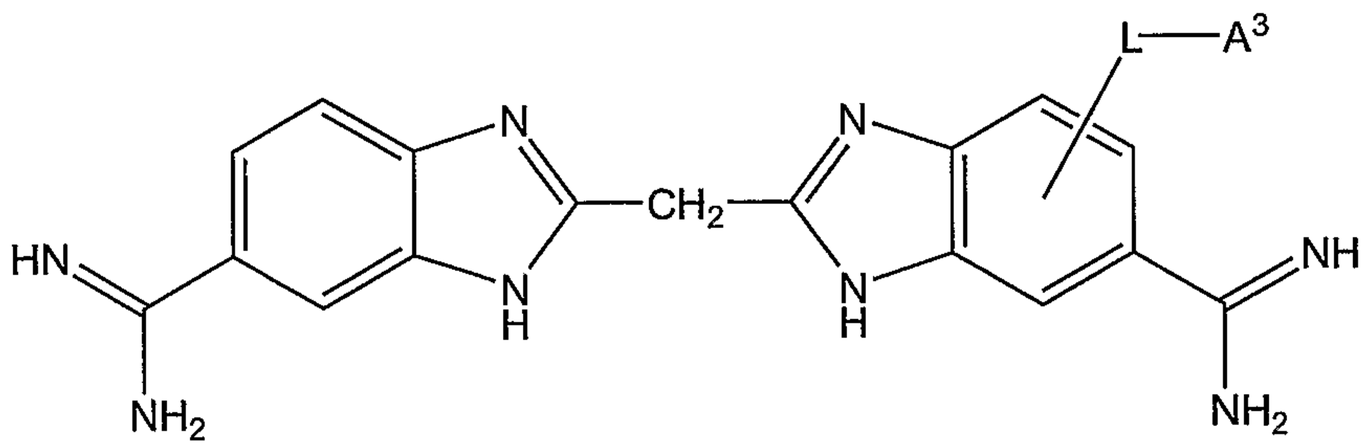
XI

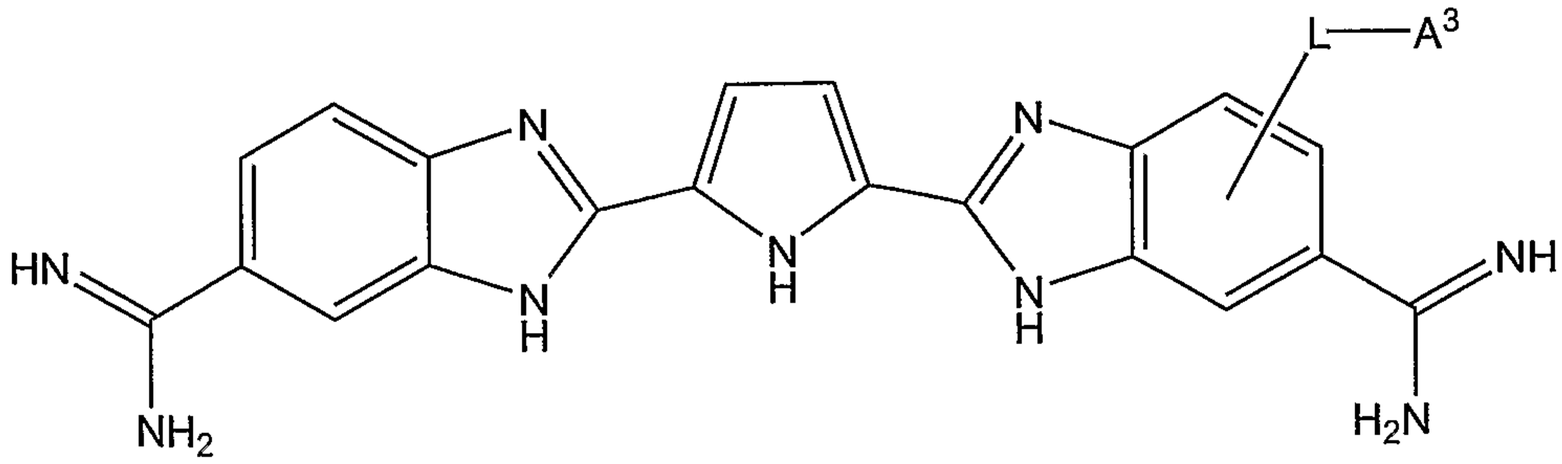
where Formula XI compounds may be further subsituted with fused ring systems, and L is a linker.

Embodiments of Formula XI compounds include:

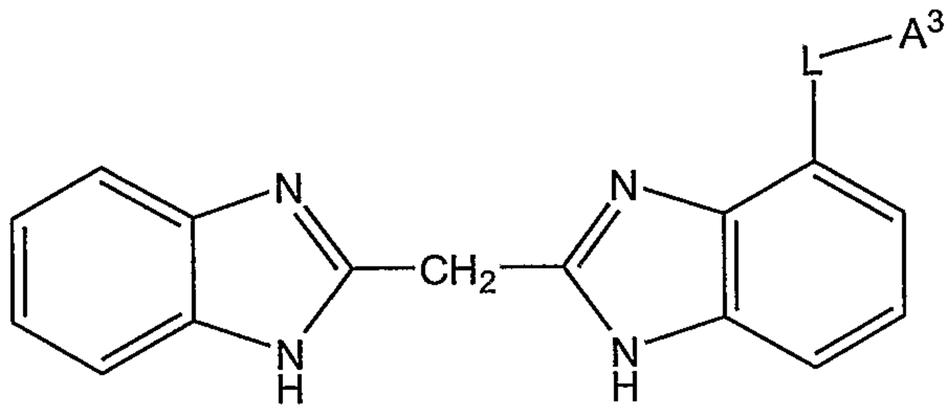


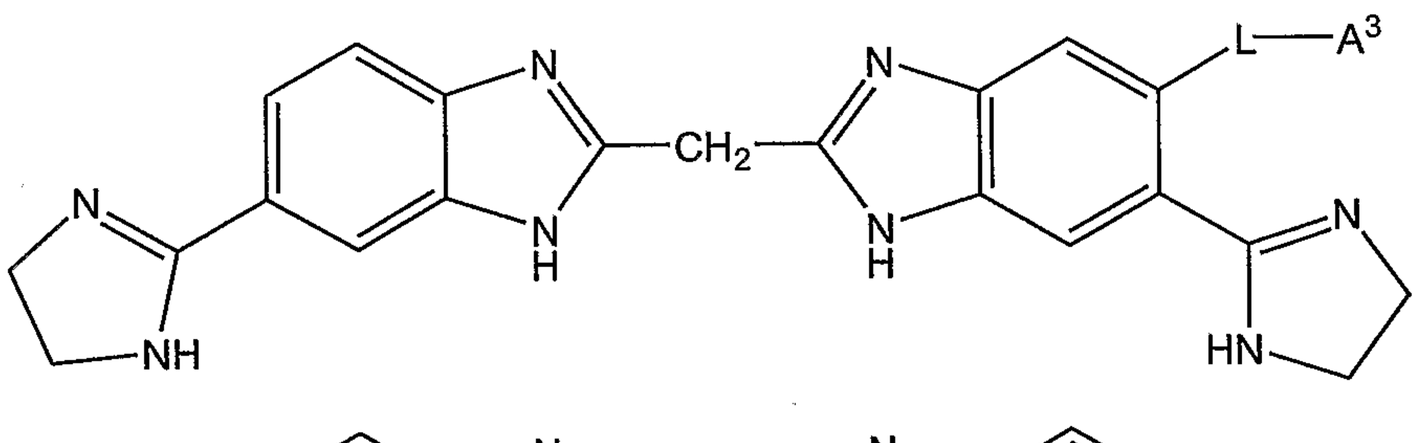


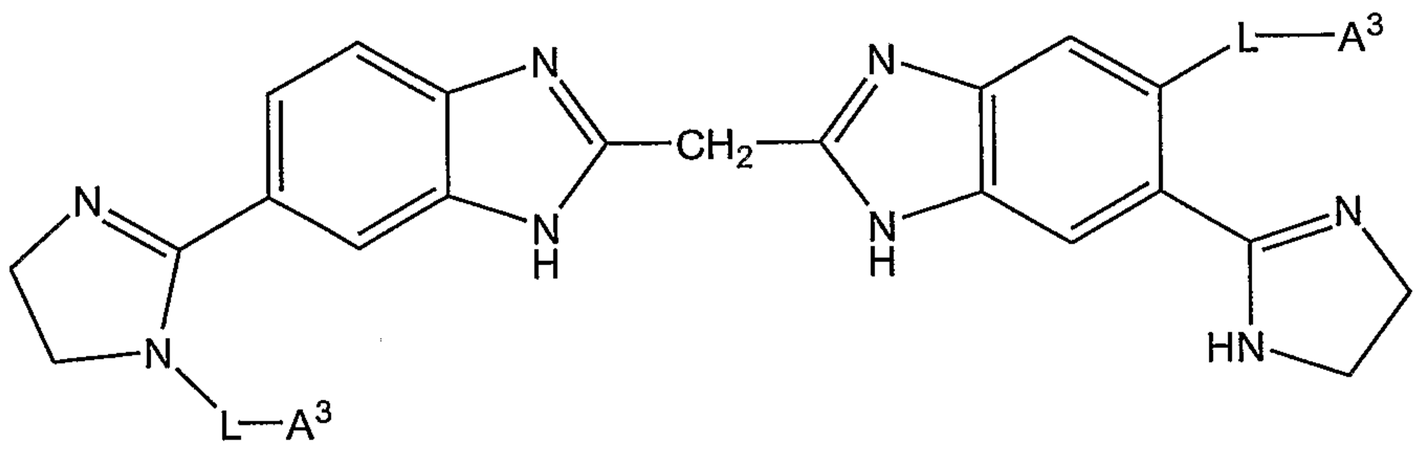




Further embodiments of Formula XI compounds include:

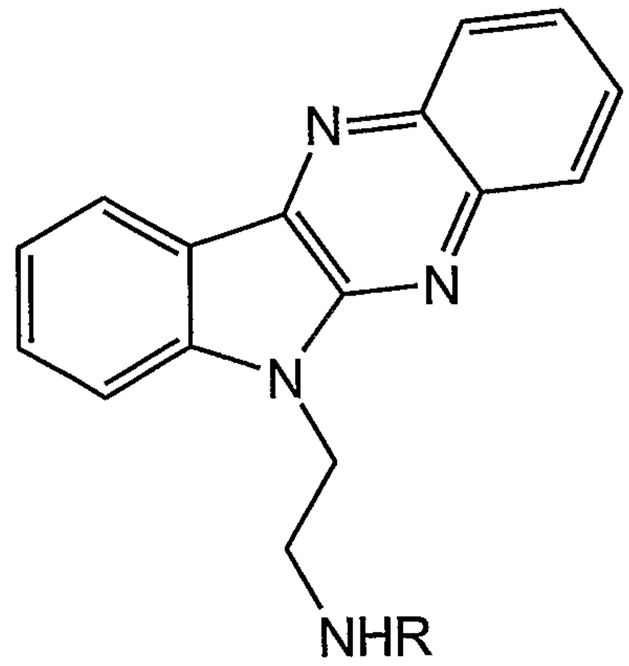






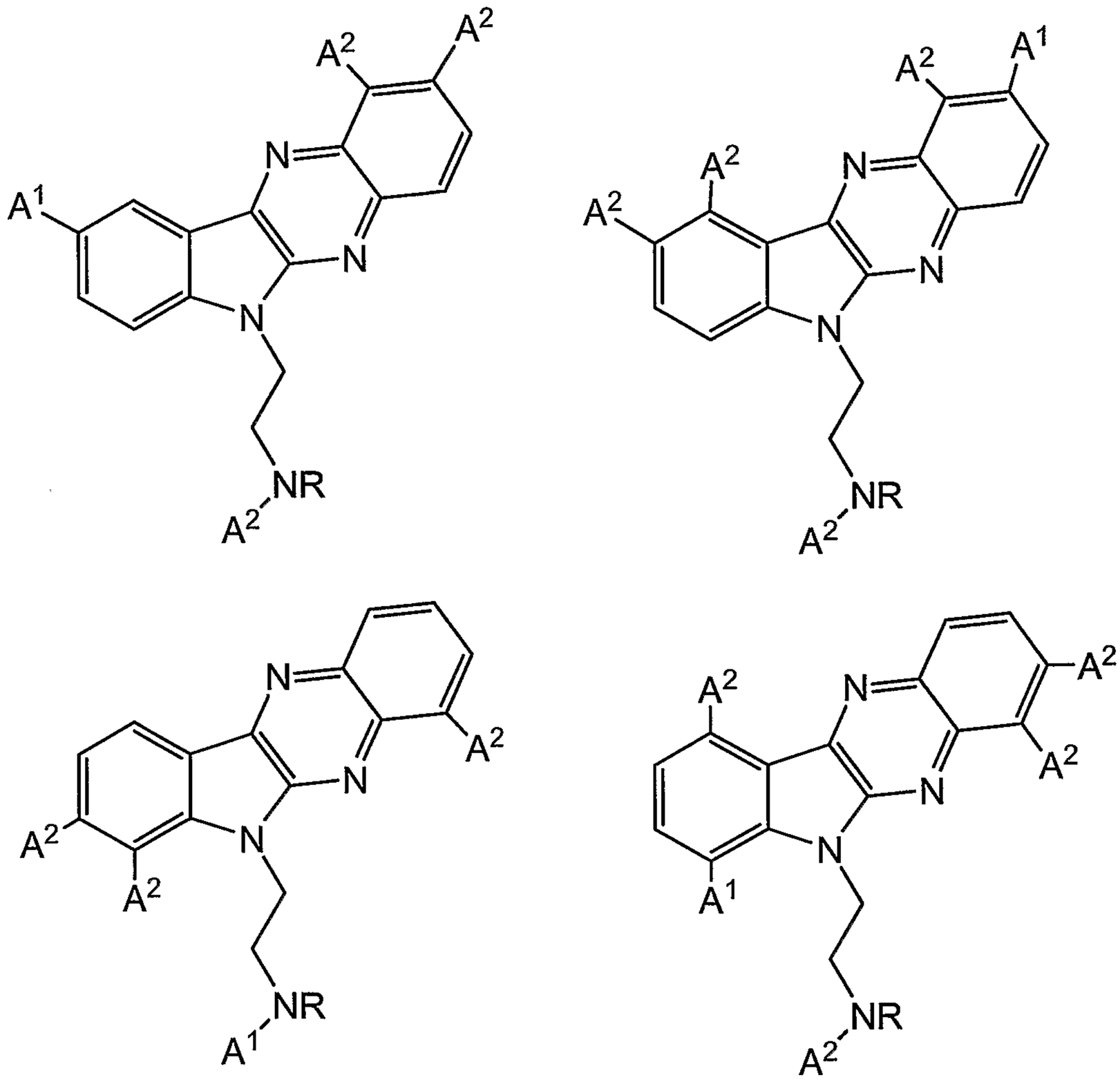
Group XII

In one aspect, the invention includes phosphonate analogs of indoloquinoxaline compounds (WO 96/00067) having Formula XII:



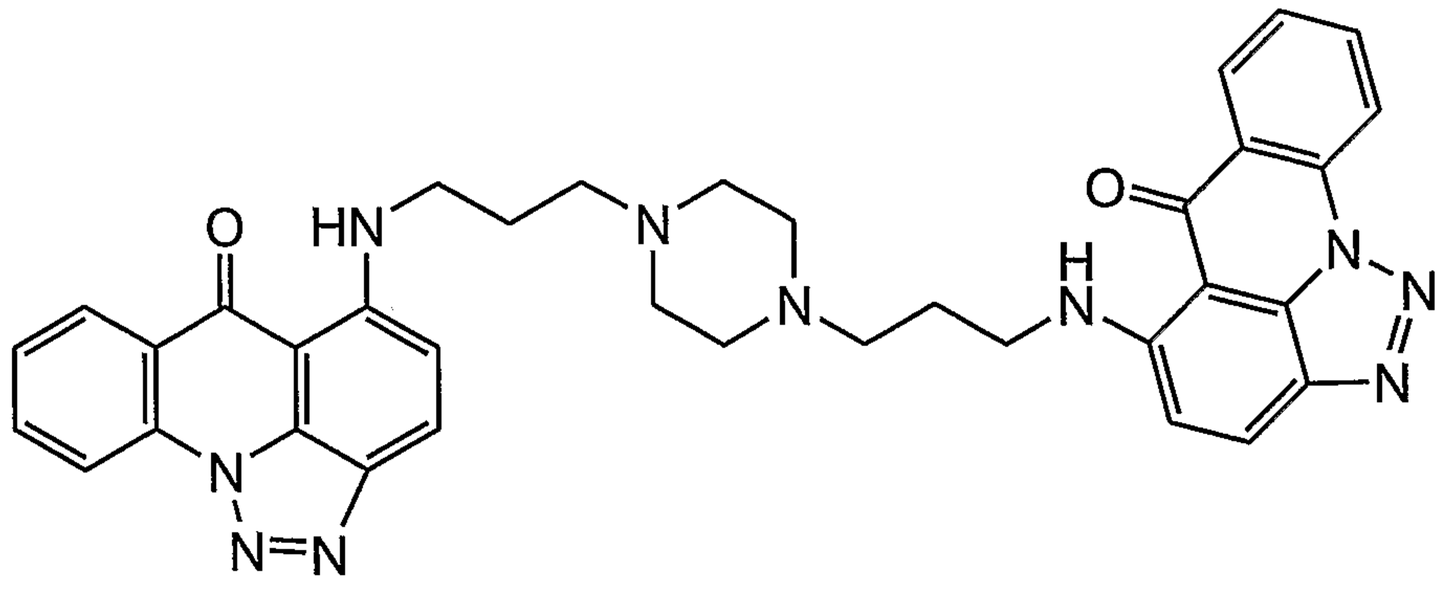
XII

Embodiments of Formula XII compounds include:



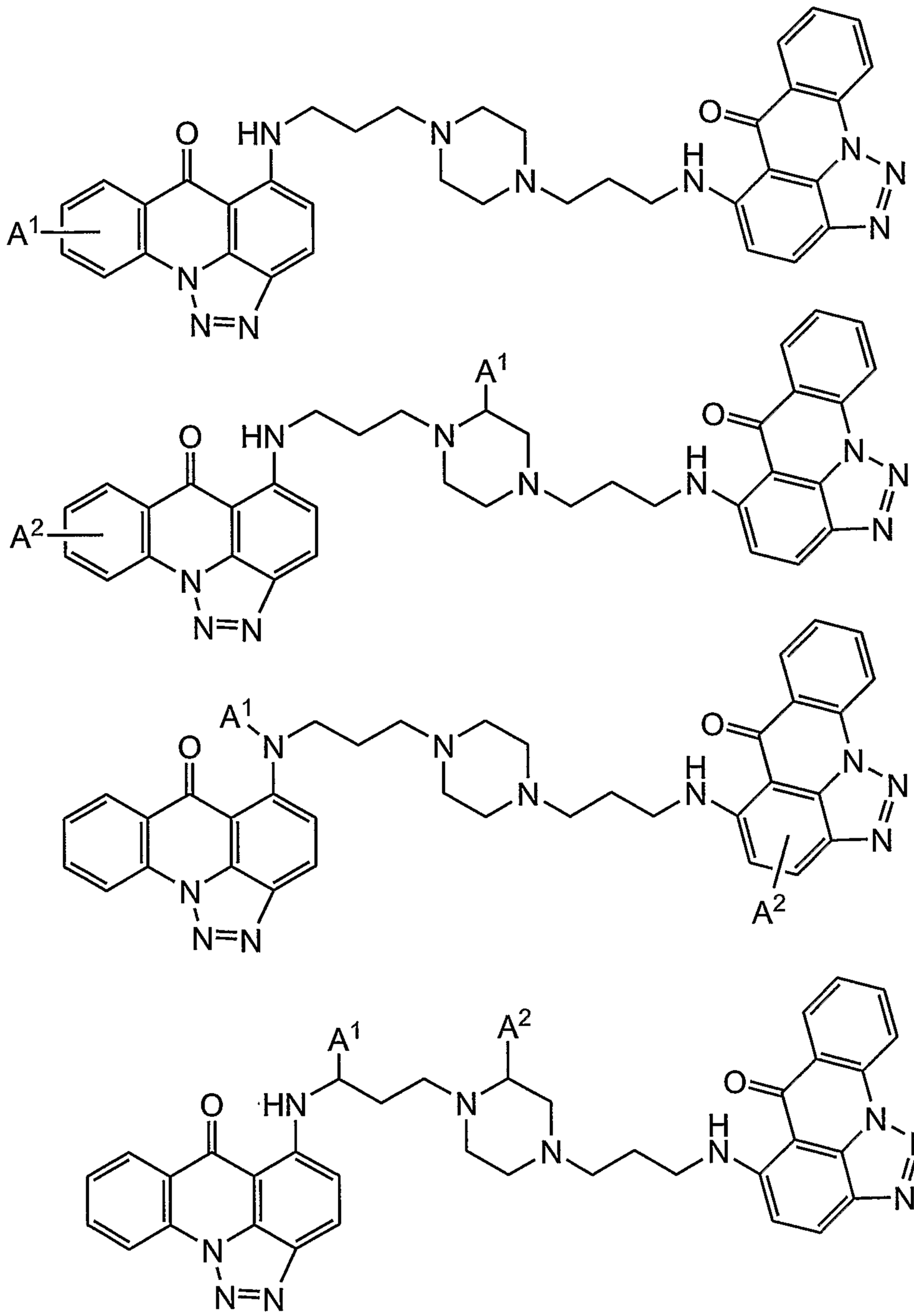
5 Group XIII

In one aspect, the invention includes phosphonate analogs of acridine compounds (Thale et al (2002) *J. Org. Chem.* 67:9384-9391) including phosphonate analogs of bis-acridine compounds (Turpin et al (1998) *Antimicrob. Agents Chemother*. 42:487-494; WO 97/38999) having Formula XIII:



10 **XIII**

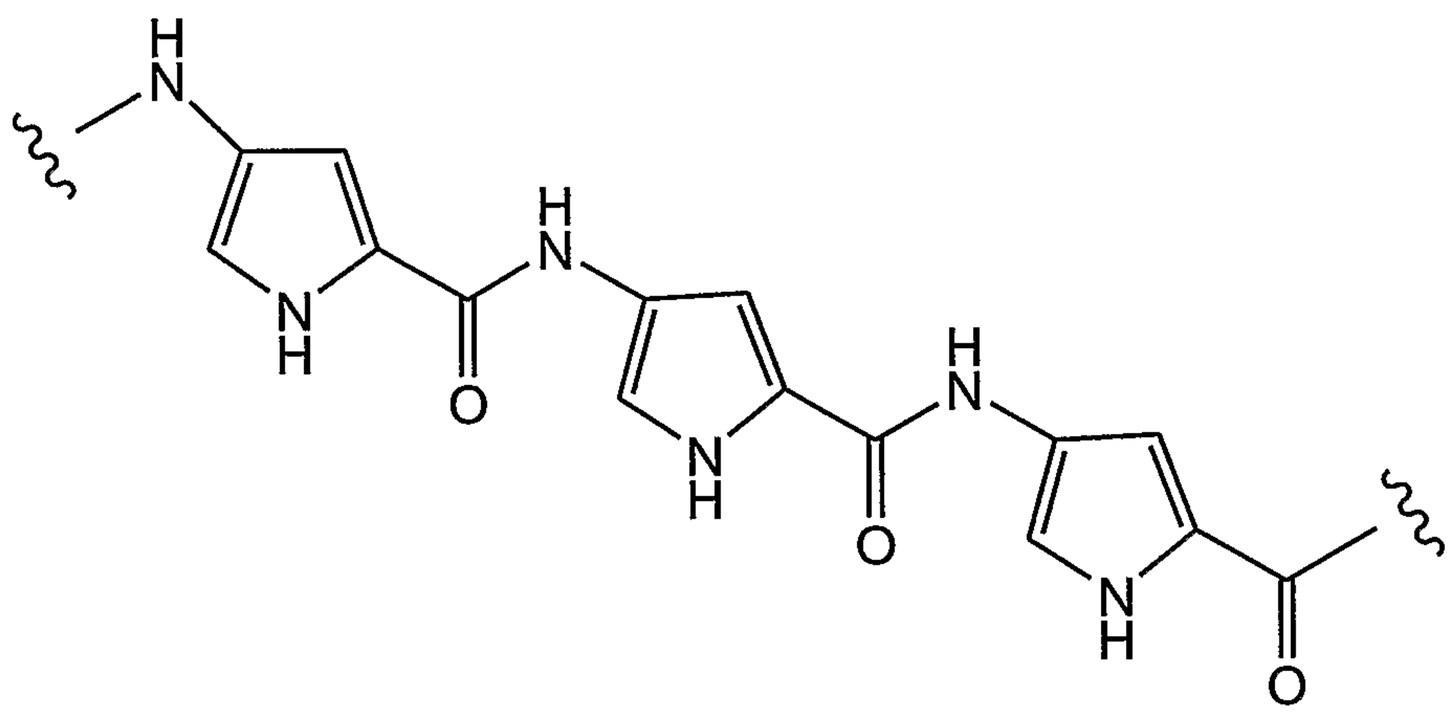
Embodiments of Formula XIII compounds include:



Group XIV

In one aspect, the invention includes phosphonate analogs of polyamide, DNA binding compounds (Fesen et al (1993) *Proc. Natl. Acad. Sci. USA* 90:2399-2403; Carteau et al (1993) *Biochem. Biophys. Res. Commun.* 192:1409-1414; Carteau et al (1994) *Biochem. Pharmacol.* 47:1821-1826; Mazumder et al (1995) *AIDS Res. Hum.*

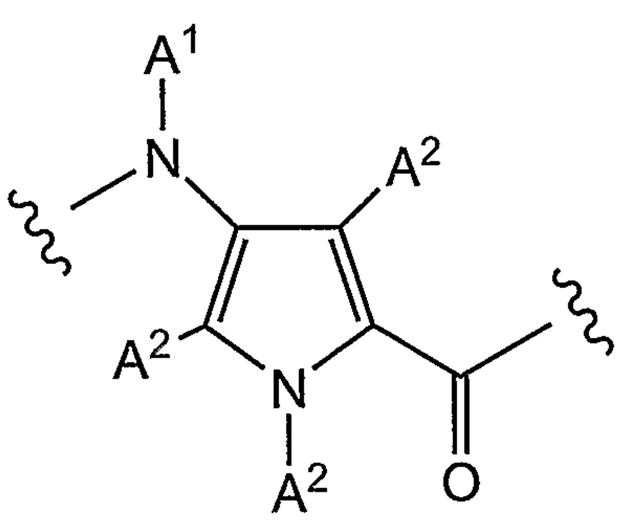
Retroviruses 11:115-125; Bouziane et al (1996) *J. Biol. Chem.* 271:10359-10364; Billich et al (1992) *Antiviral Chem. Chemother.* 3:113-119; Ryabinin et al (2000) *Eur. J. Med. Chem.* 35(11):989-1000), , such as polypyrrole amide phosphonate oligomers (Neamati et al (1998) *Mol. Pharmacol.* 54:280-290; Wang et al (1992) *J. Med. Chem.* 35:2890-2897) having Formula XIV:

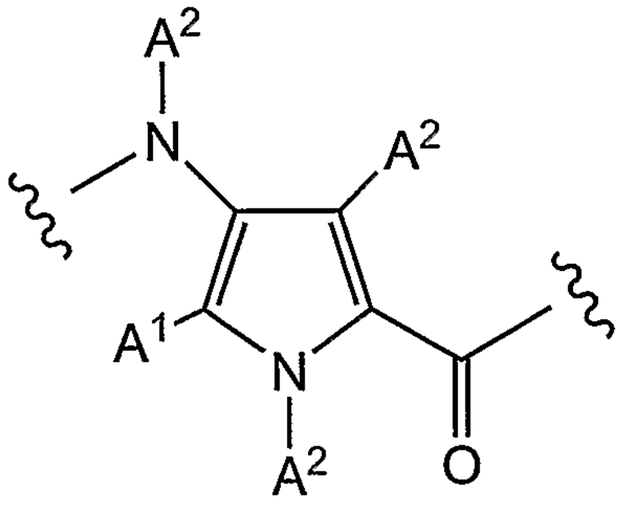


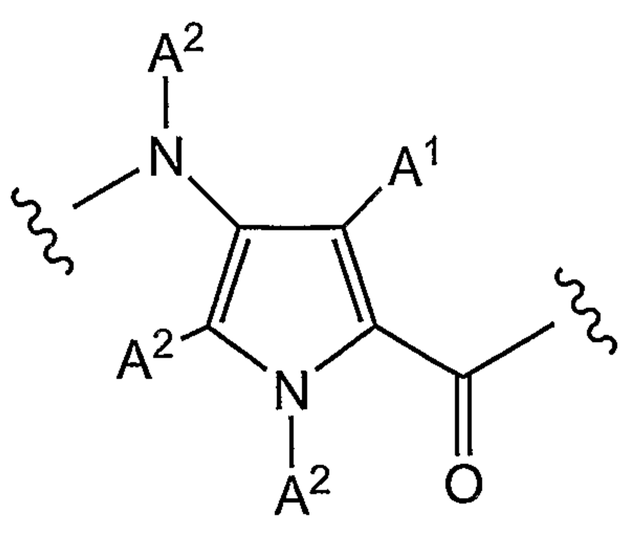
XIV

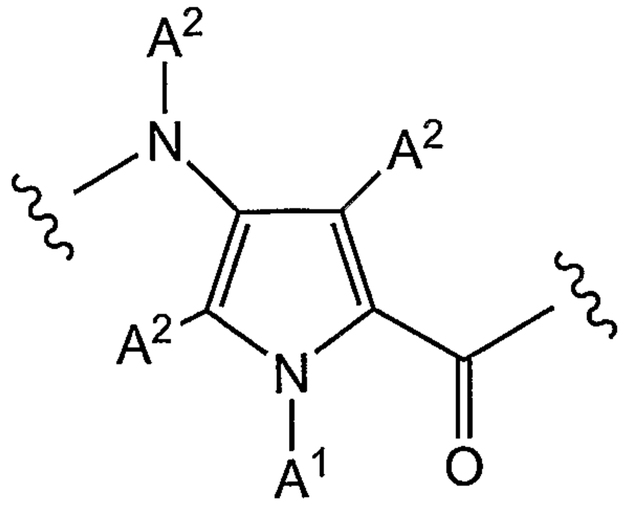
where the wavy lines indicate the depicted structure is a substructure of a repeating polymer molecule.

Embodiments of Formula XIV compounds include:





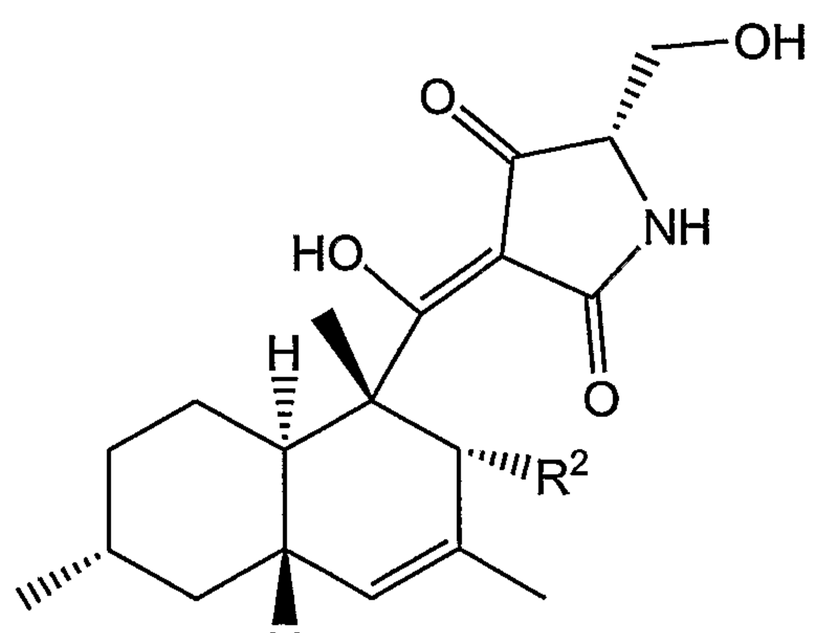




where one or more of the pyrrole amide monomer units in the polypyrrole amide molecule are substituted at one or more locations with a phosphonate group.

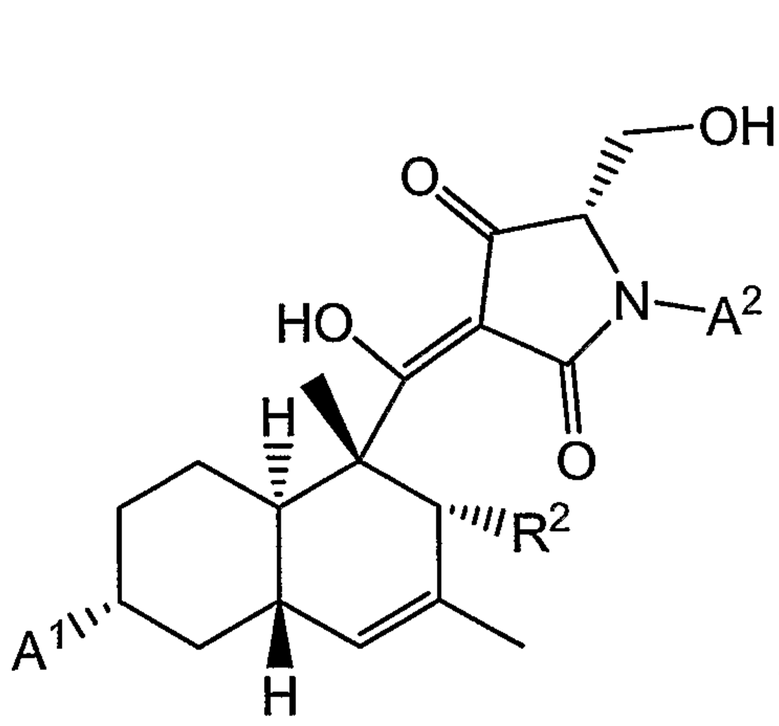
Group XV

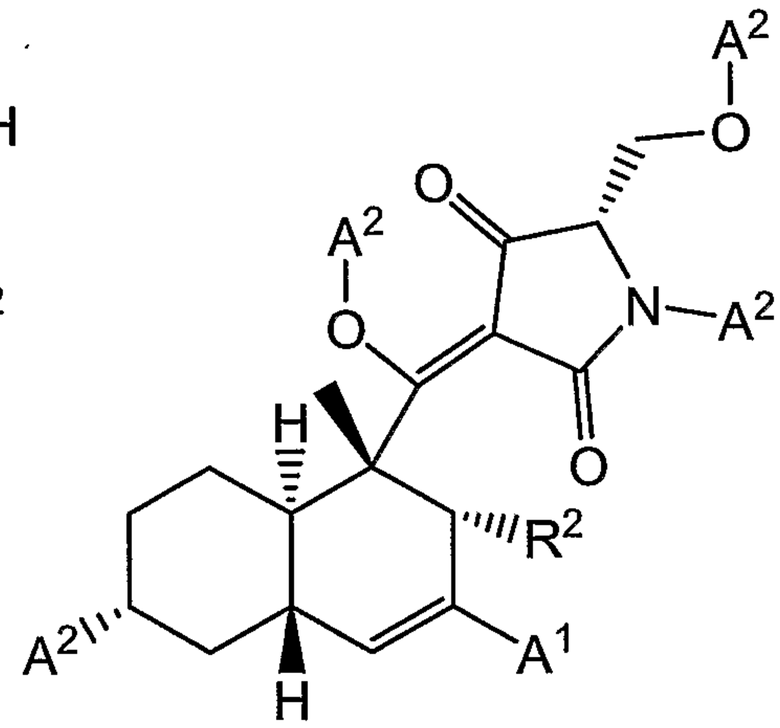
In one aspect, the invention includes phosphonate analogs of [6,6] bicyclic compounds (Hazuda et al (1999) *Antiviral. Chem. Chemother.* 10:63; US 6541515; Singh et al (1998) *Tetrahedron Lett.* 39:2243-2246; GB 2306476; US5759842), including integramycins (Singh et al (2002) *Organic Letters* 4(7):1123-1126) and fungal metabolites having Formula XV:

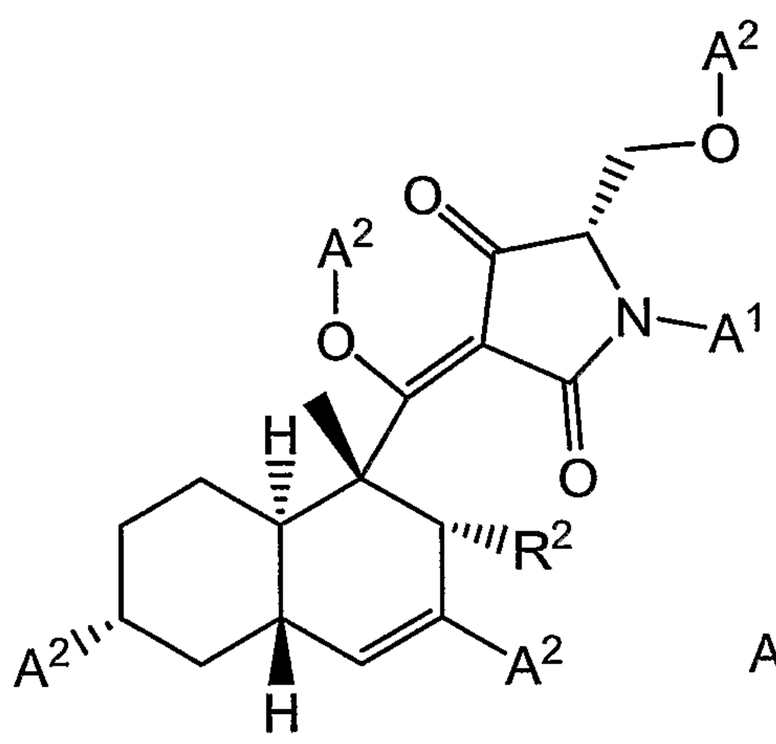


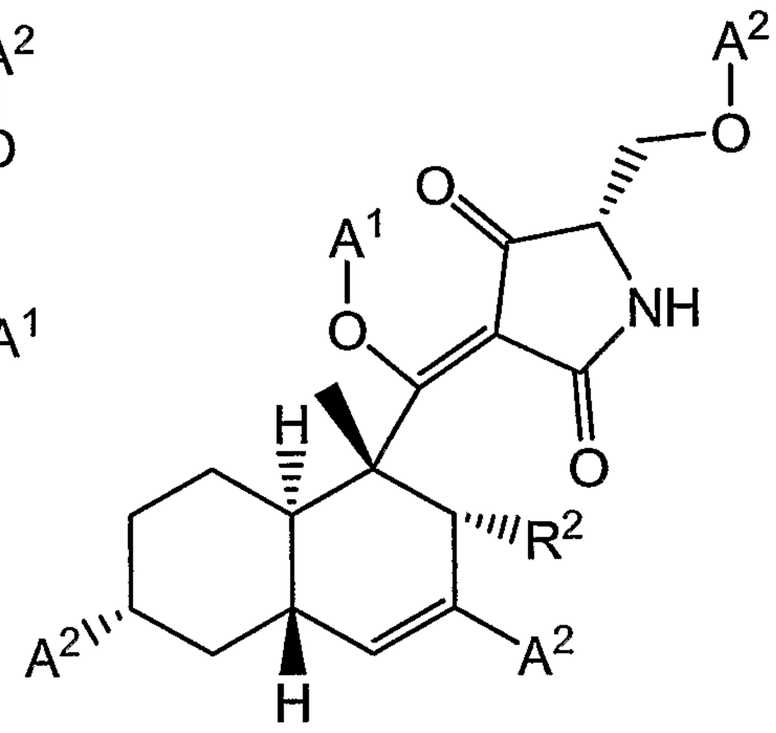
XV

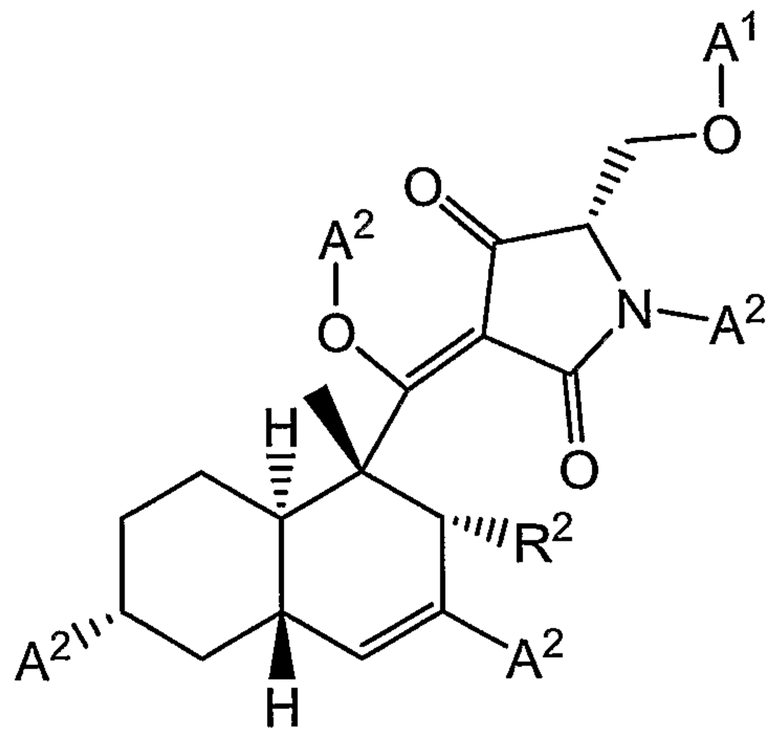
Embodiments of Formula XV compounds include:



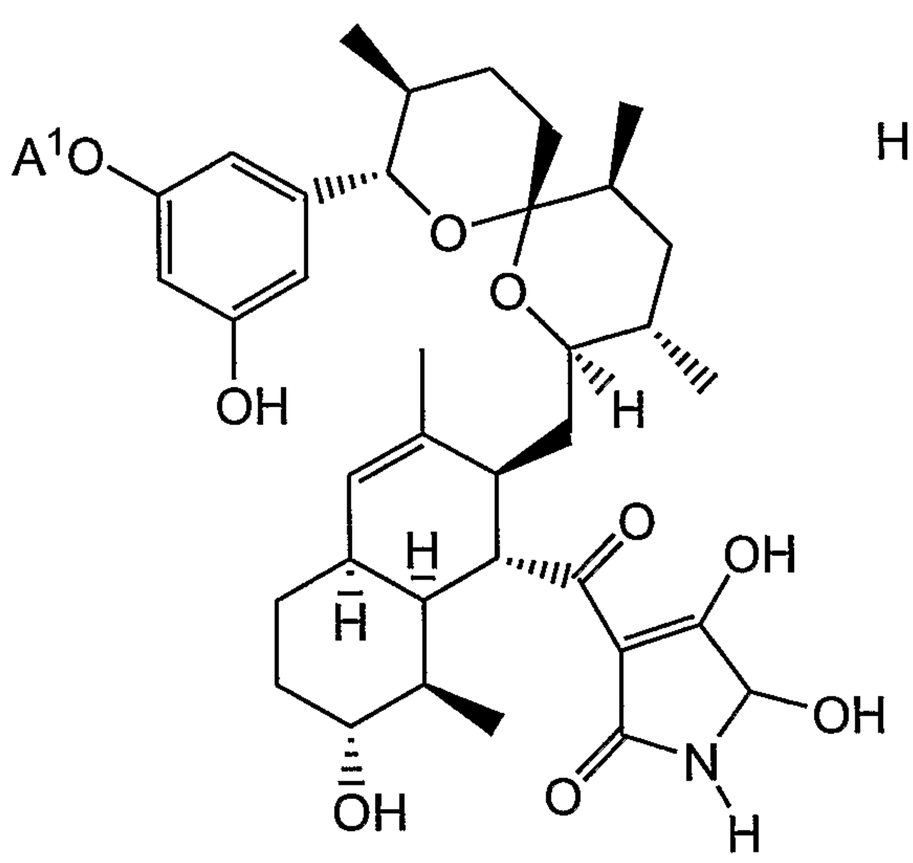


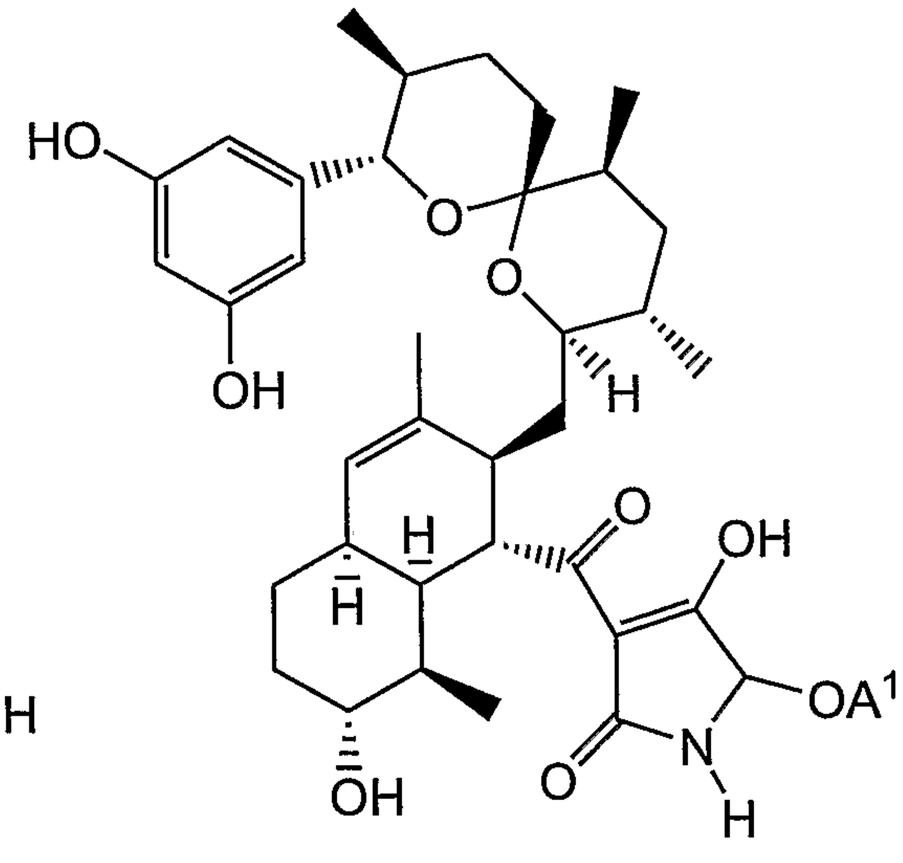


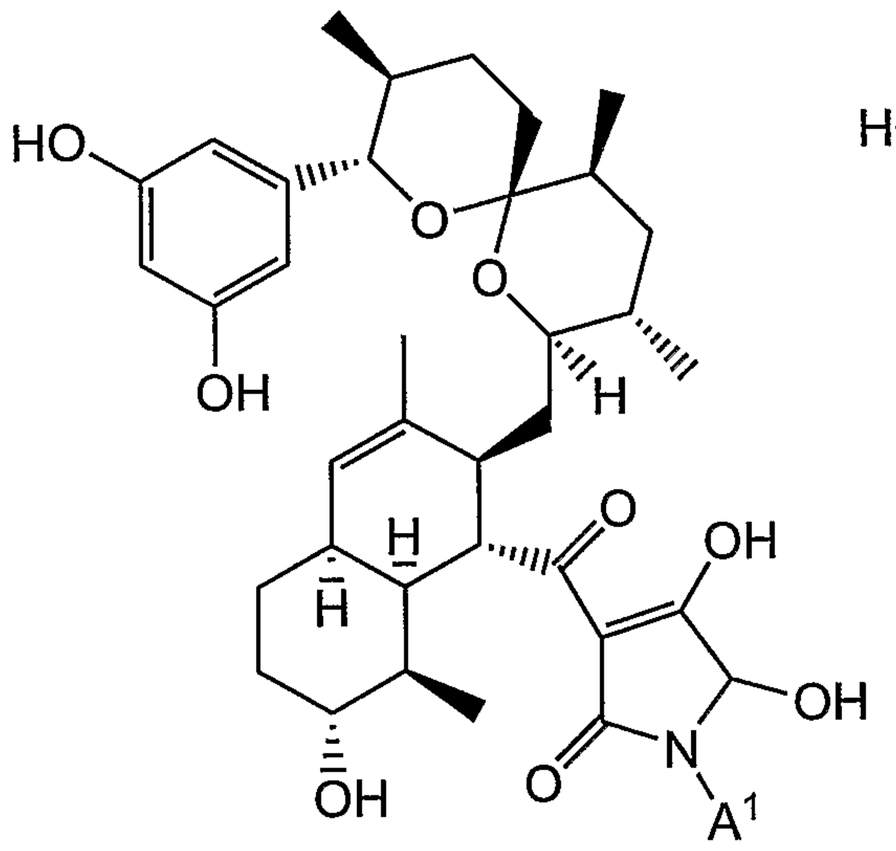


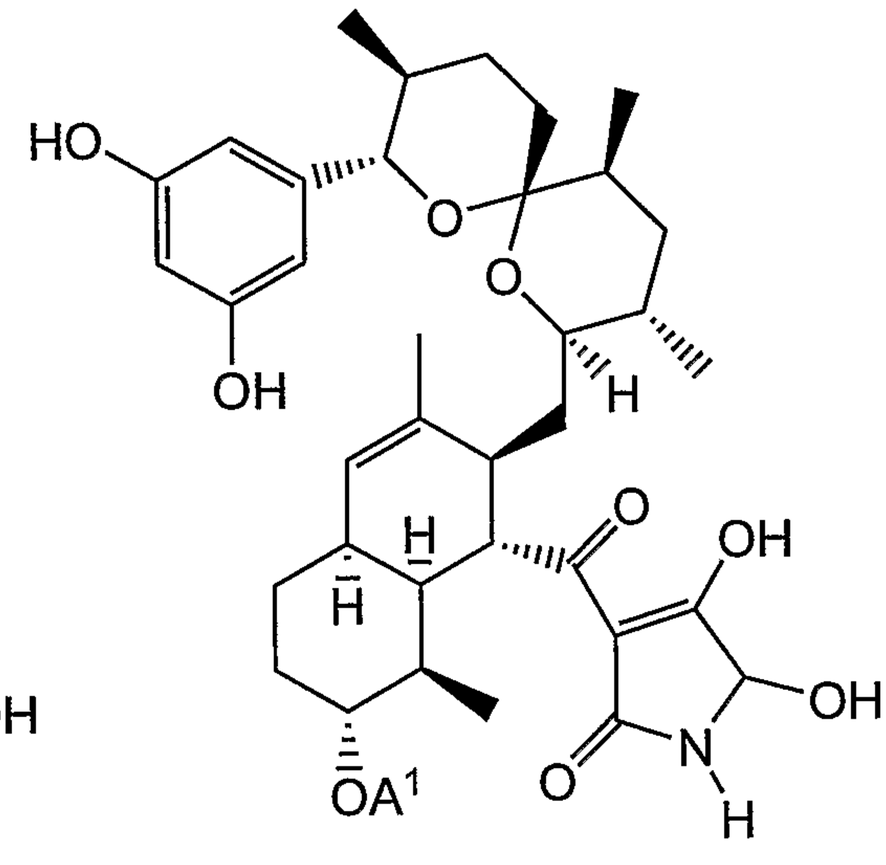


Embodiments of integramycin phosphonate Formula XV compounds also include:

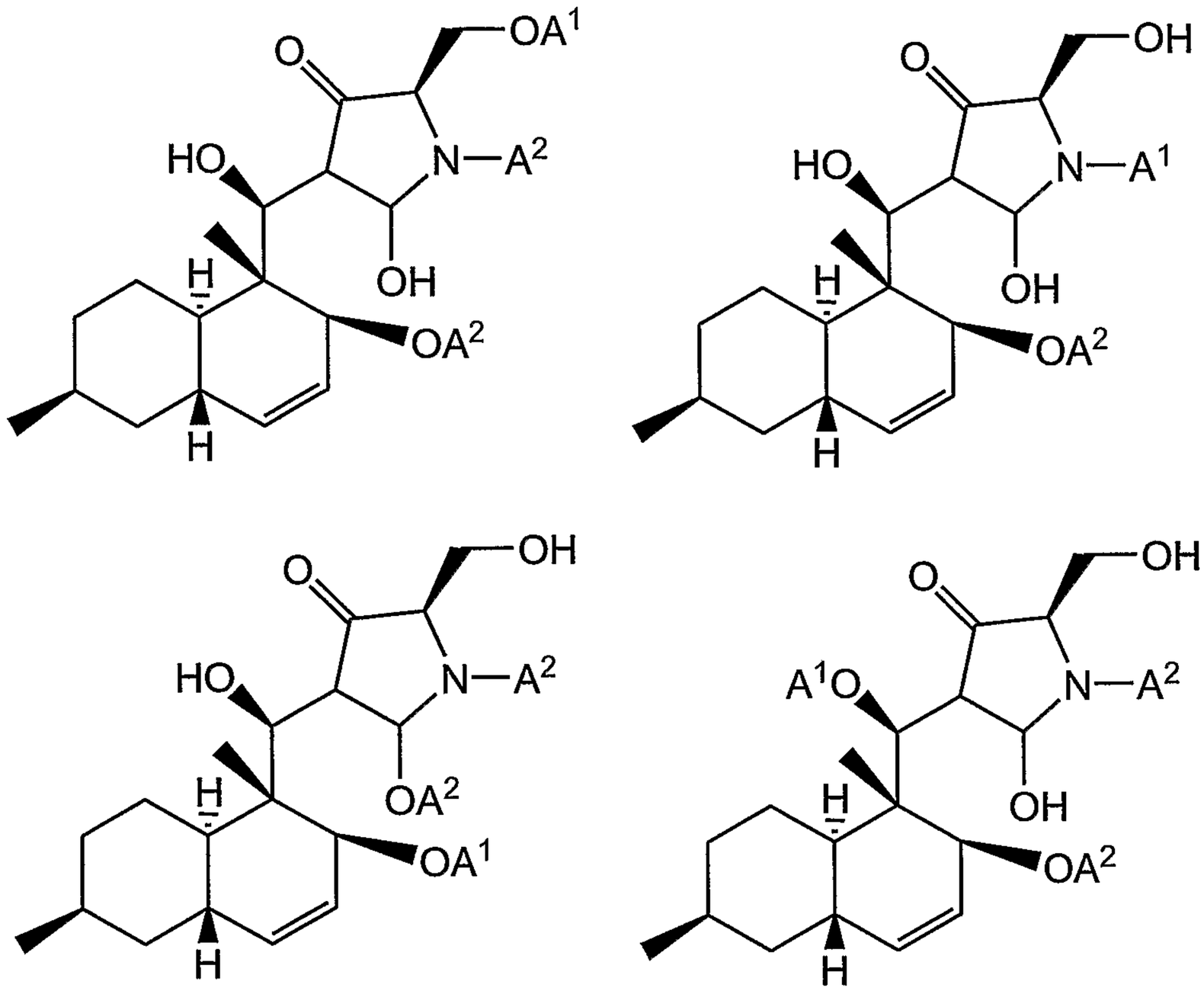






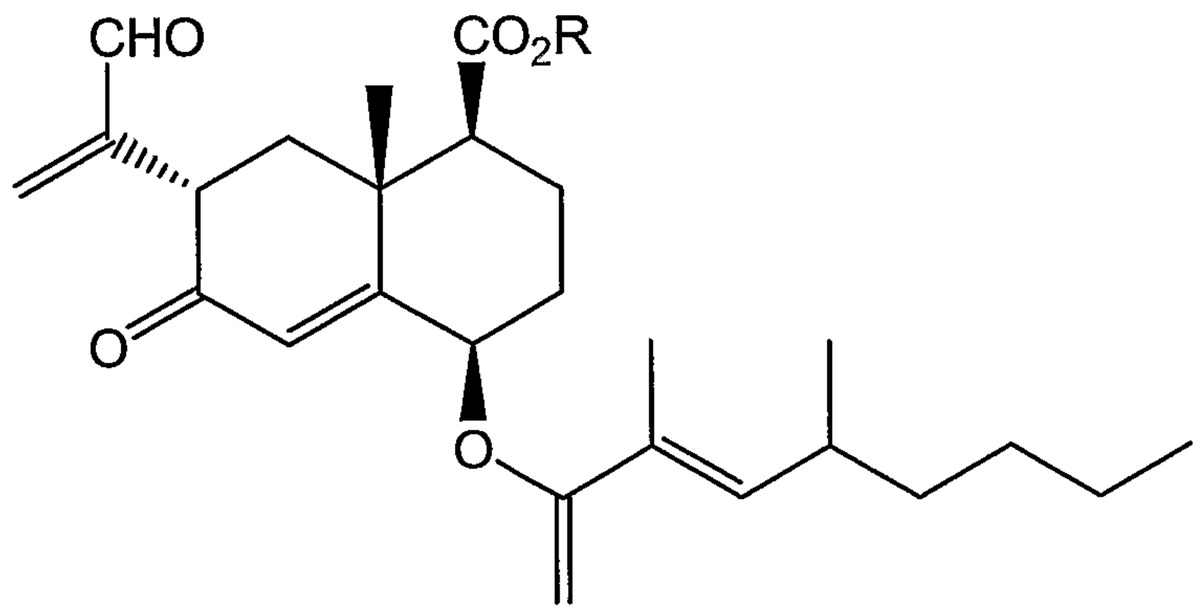


Embodiments of Formula XV compounds include phosphonate equicetin compounds having the structures:



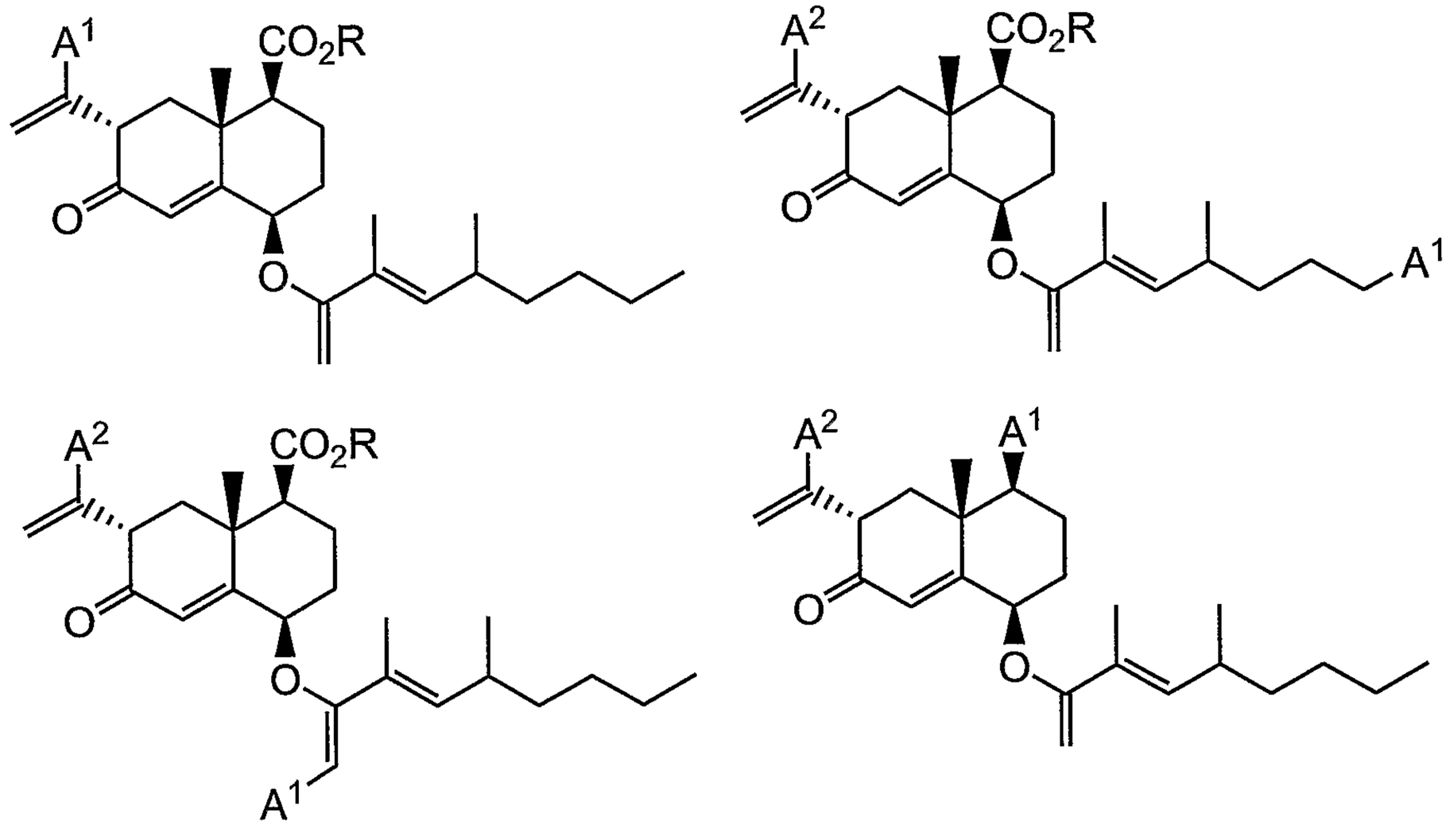
Group XVI

In one aspect, the invention includes phosphonate analogs of [6,6] bicyclic terpenoid compounds (GB 2319026) having Formula XVI:



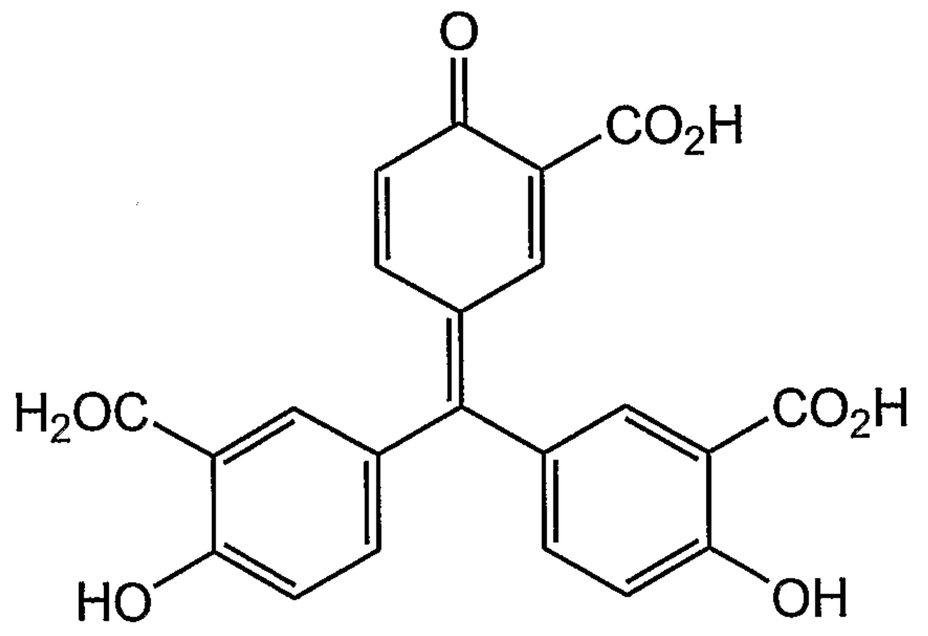
XVI

Embodiments of Formula XVI compounds include phosphonate [6,6] bicyclic terpenoid compounds having the structures:



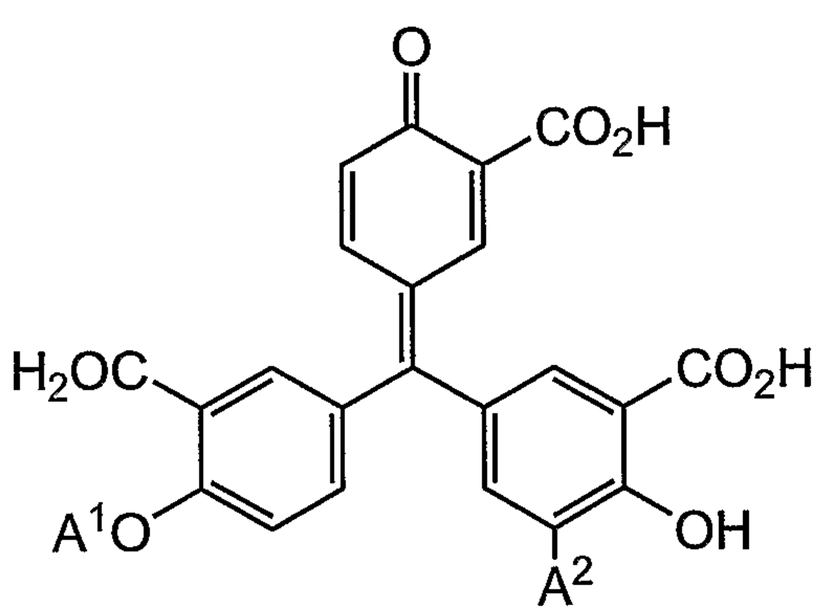
Group XVII

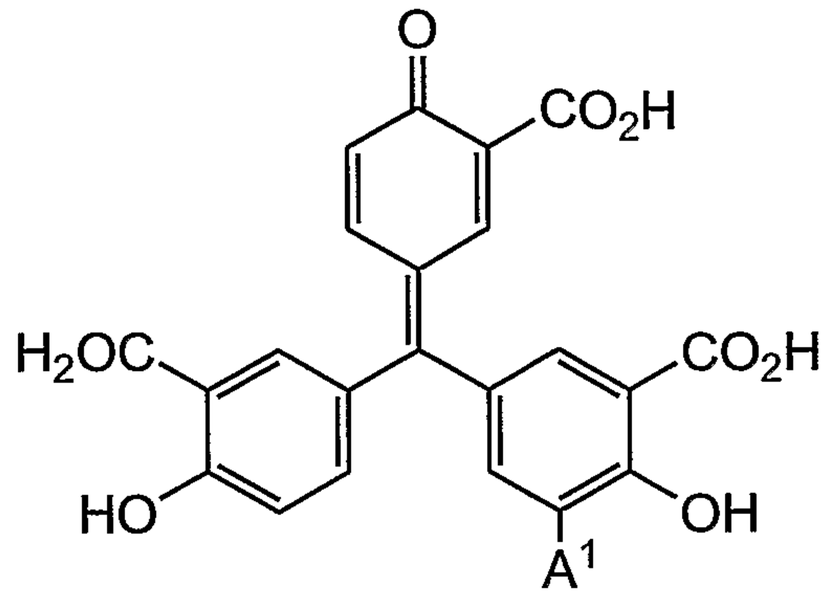
In one aspect, the invention includes phosphonate analogs of aurintricarboxylic acid compounds (Cushman et al (1992) *Biochem. Biophys. Res. Commun.* 185:85-90; Cushman et al (1995) *J. Med. Chem.* 38:443-452; Cushman et al (1991) *J. Med. Chem.* 34(1):337-342) having Formula XVII:

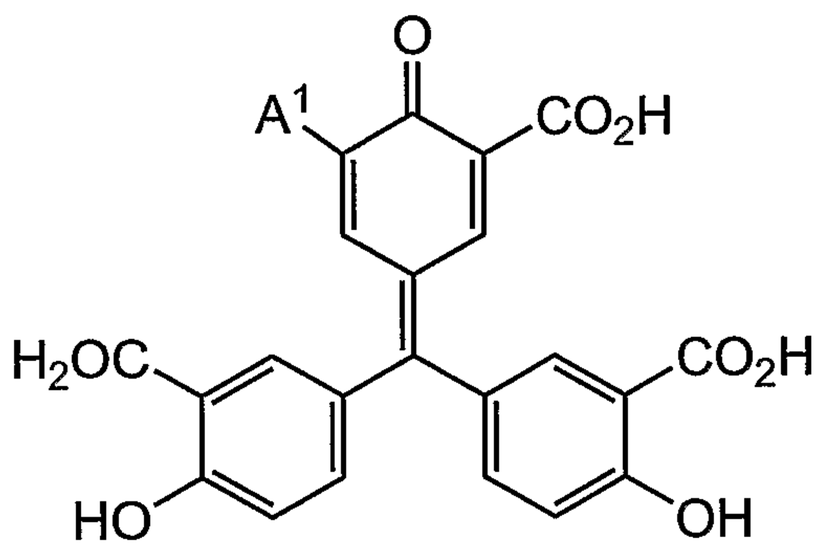


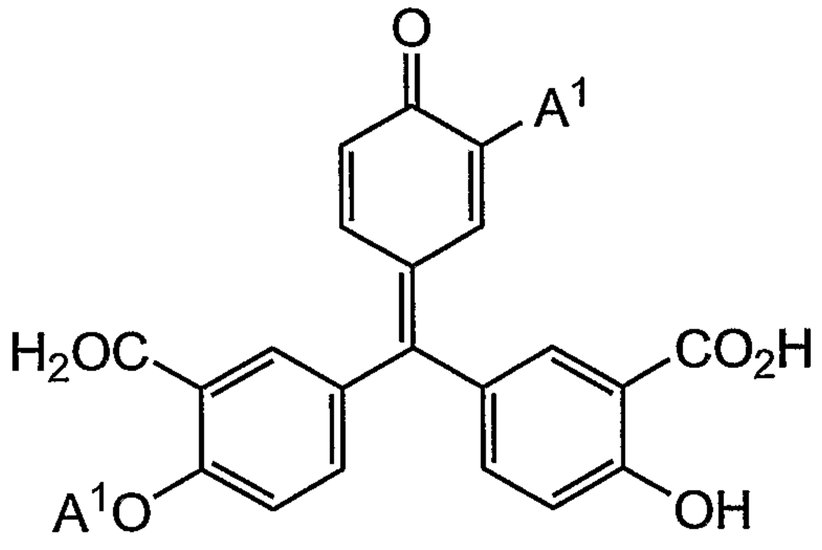
XVII

Embodiments of Formula XVII compounds include phosphonate aurintricarboxylic acid compounds having the structures:



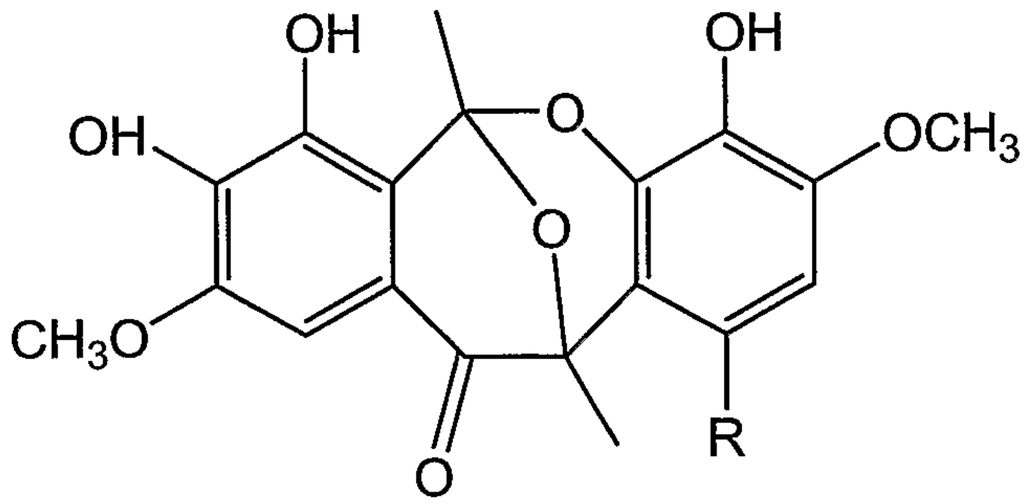






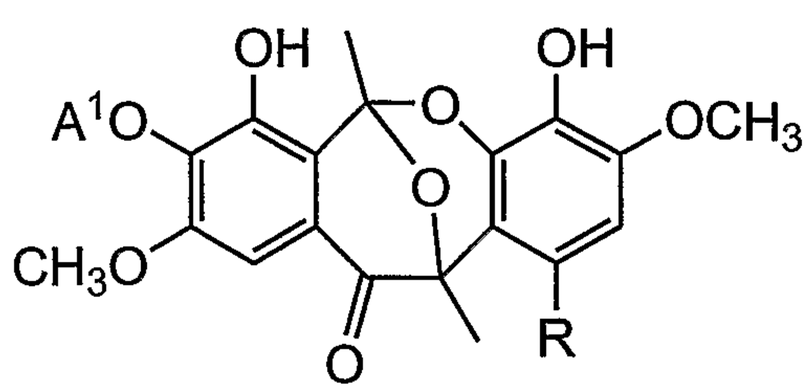
Group XVIII

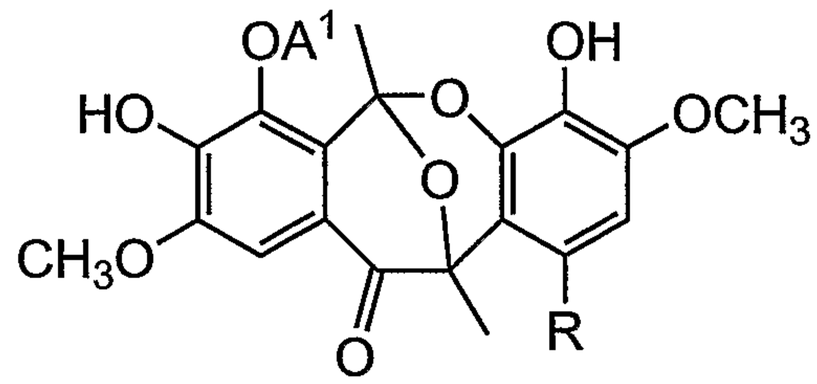
In one aspect, the invention includes phosphonate analogs of integrastatin compounds (Foot et al (2003) *Organic Letters* 5(23):4441-444; Singh et al (2002) *Tetrahedron Lett.* 43:2351-2354; WO 01/09114) having Formula XVIII:

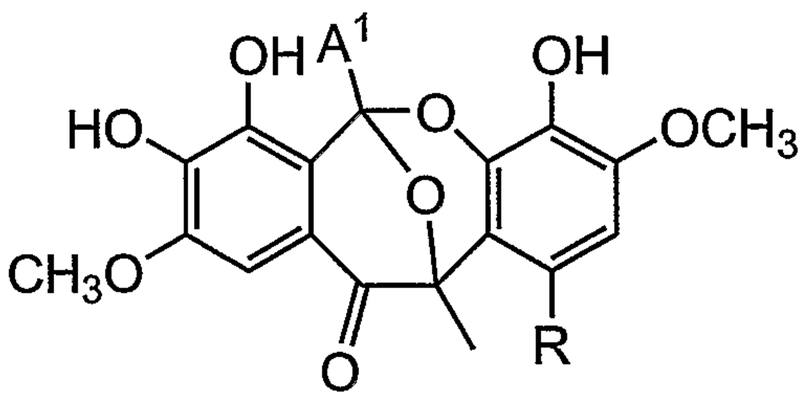


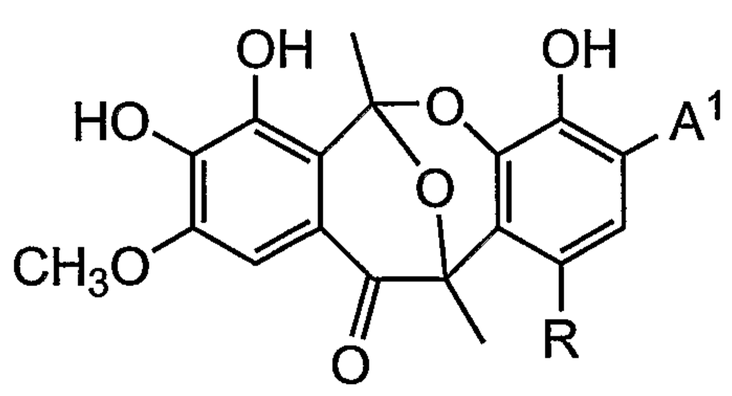
XVIII

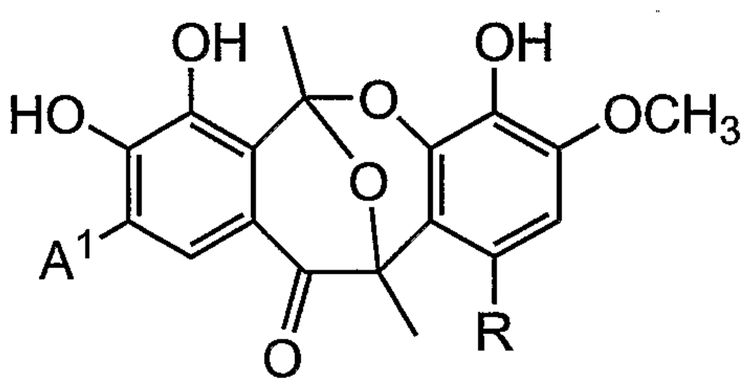
Embodiments of Formula XVIII compounds include phosphonate integrastatin compounds having the structures:

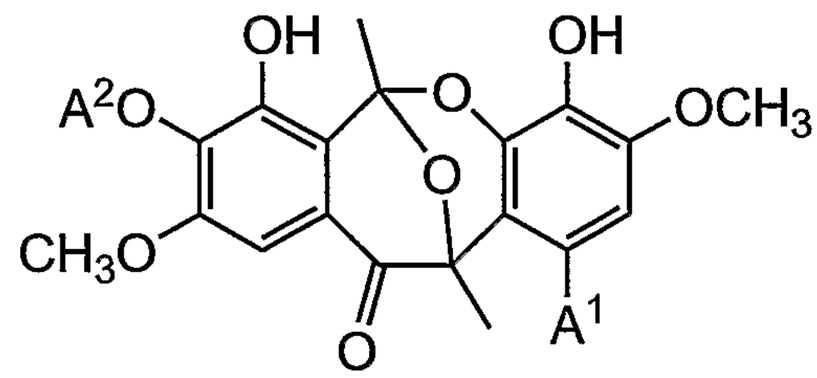






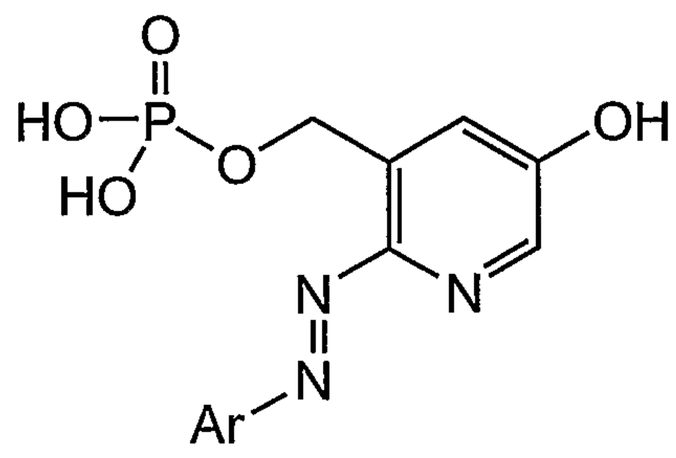






5 Group XIX

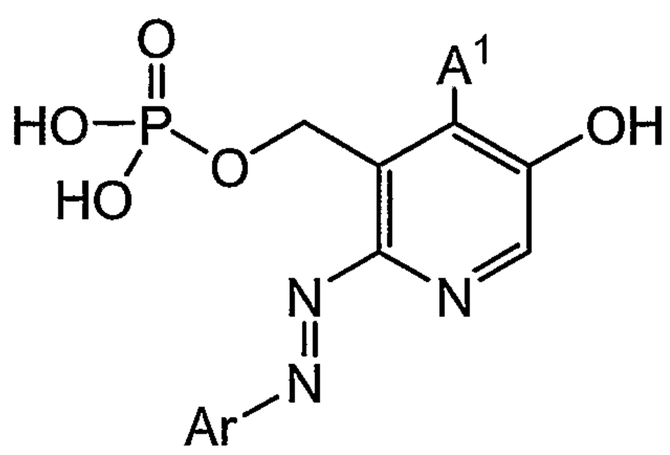
In one aspect, the invention includes phosphonate analogs of 6-(arylazo)pyridoxal-5-phosphate compounds (WO 03/082881 A2) having Formula XIX:

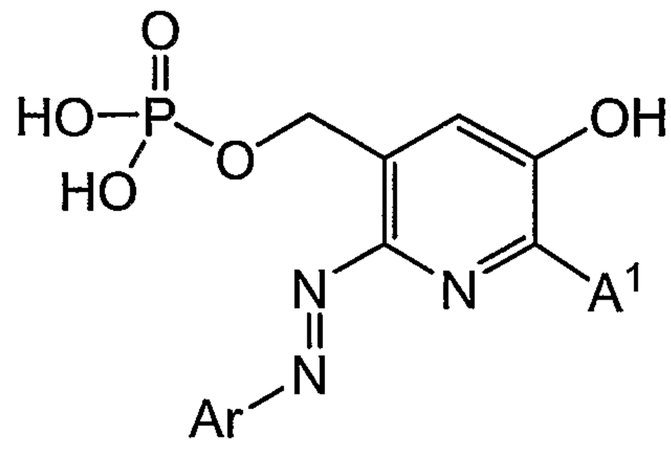


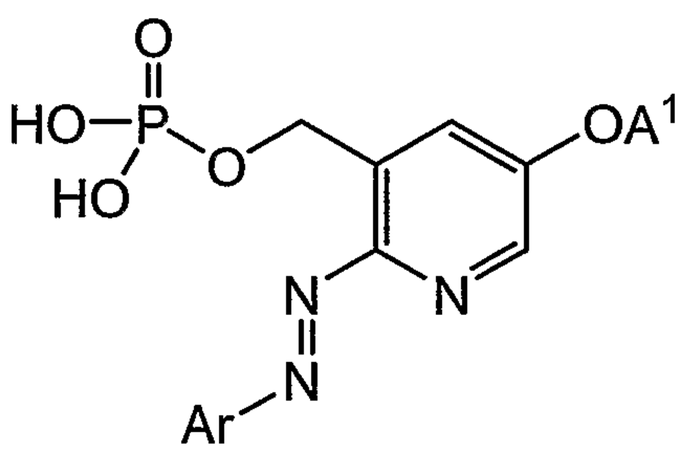
XIX

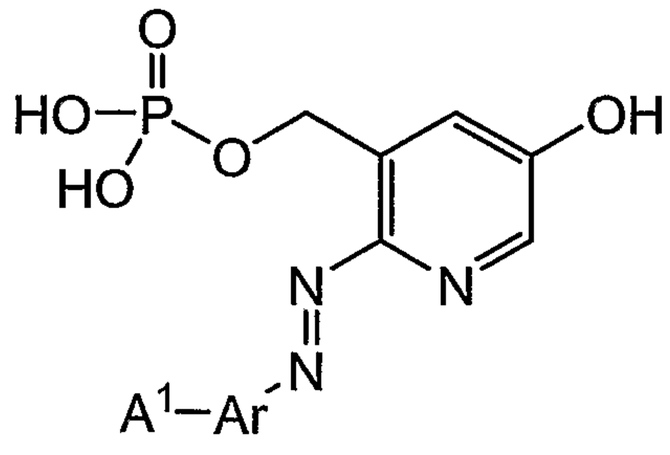
10

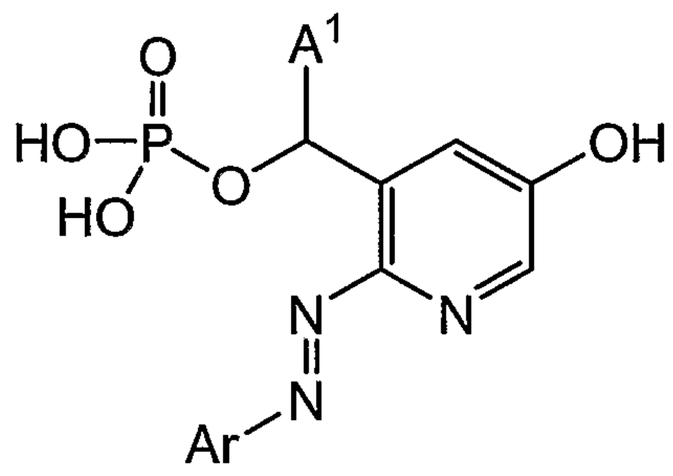
Embodiments of Formula XIX compounds include phosphonate 6-(arylazo)pyridoxal-5-phosphate compounds having the structures:

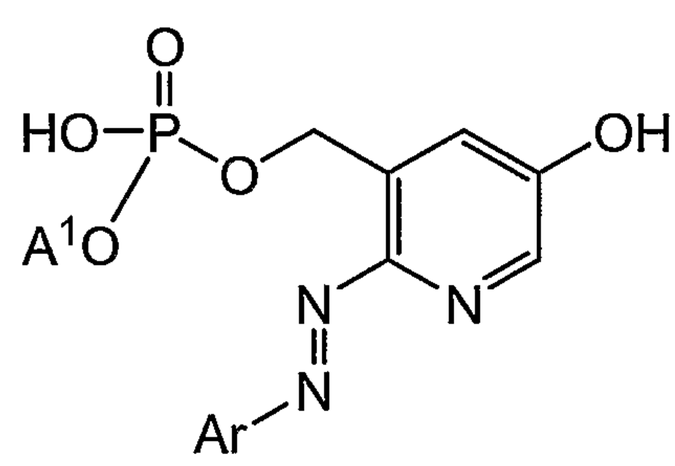












5 Group XX

In one aspect, the invention includes phosphonate analogs of 1,3-oxazine-, 1,3-thiazine-, pyran-, 1,4-oxazepine-, and 1,4-thiazepine-fused naphthalene compounds (WO 03/024941 A1) having Formula XX structures.

R^1 is H, (un)substituted C1-6 alkyl, halo, NO_2, NH_2, CO_2H, (un)substituted aryl, optionally benzene-fused 5- or 6-membered aromatic or saturated. heterocyclyl containing 1-3 heteroatoms selected from N, S, and O, (un)substituted aryl-carbonylamino;

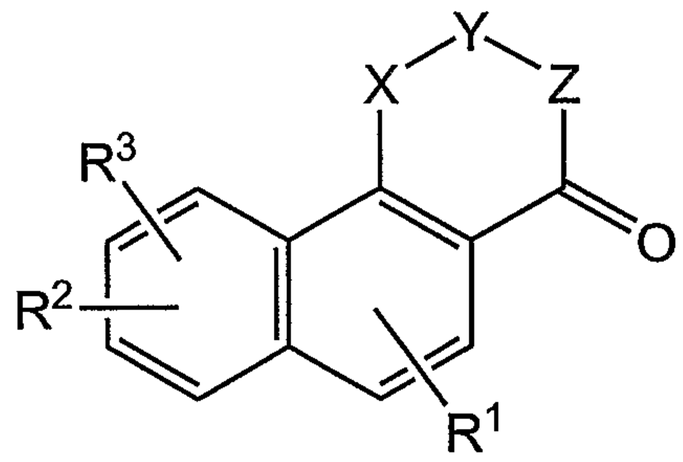
R^2 and R^3 are independently H, C_{1-6} alkyl or alkoxy, halo, NH_2, C_{1-6} alkylamino, di(C1-6 alkyl)amino, NO_2, CN, $CONH_2$, CO_2H, C_{2-7} alkylcarbonylamino,

C_{3-13} alkoxycarbonylaminoalkoxy, C_{1-6} aminoalkoxy, C_{3-13} alkylcarbonylaminoalkoxy;

X = O, S;

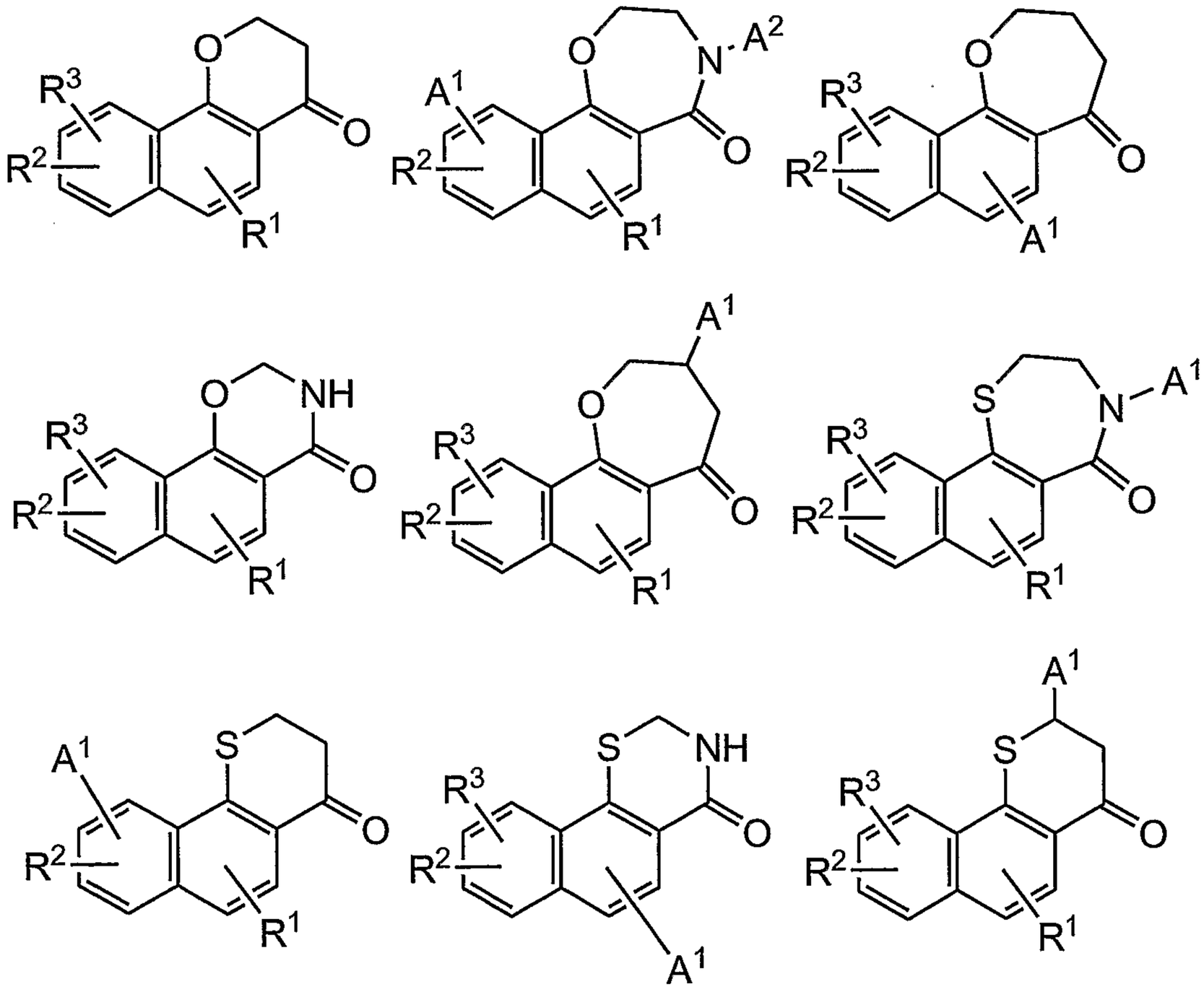
Y = CR^4R^5, $CR^4R^5CH_2$, $CH_2CR^4R^5$ wherein R^4, R^5 = H, C1-6 alkyl, CO_2H, C_{2-6} alkoxycarbonyl, optionally substituted aryl, C_{2-7} alkoxycarbonylalkyl, hydroxyalkyl, C_{3-7} cycloalkyl-alkyl, or arylalkyl; and

Z = CH_2, (un)substituted NH.



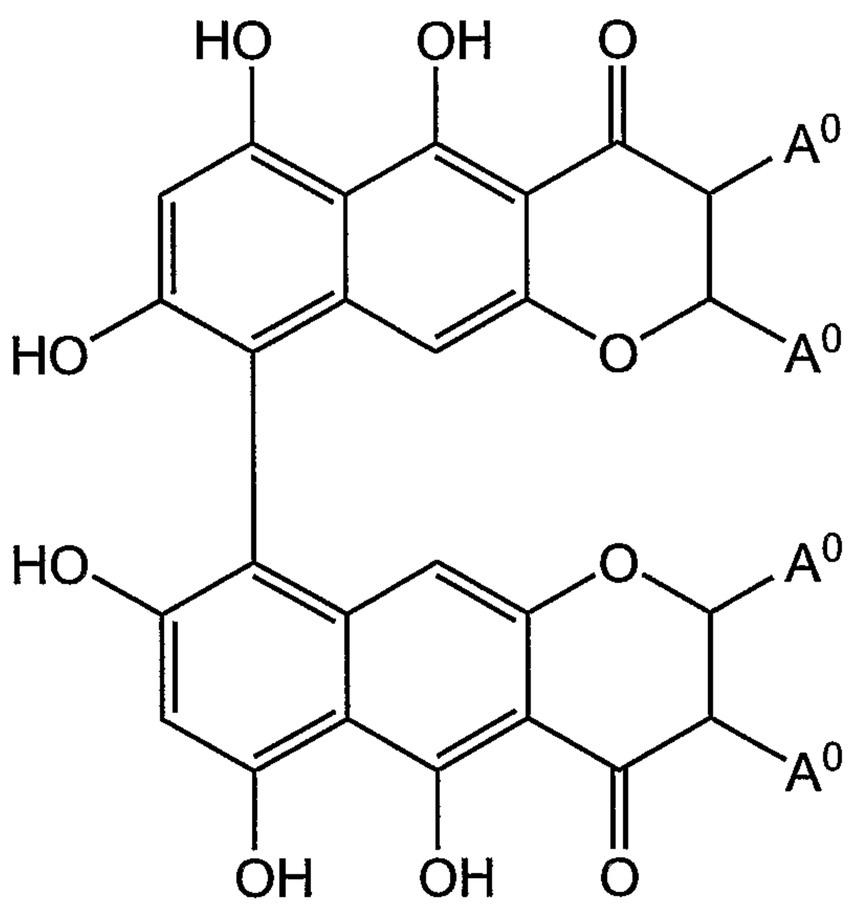
XX

Embodiments of Formula XX compounds include phosphonate 1,3-oxazine-, 1,3-thiazine-, pyran-, 1,4-oxazepine-, and 1,4-thiazepine-fused naphthalene compounds having the structures:



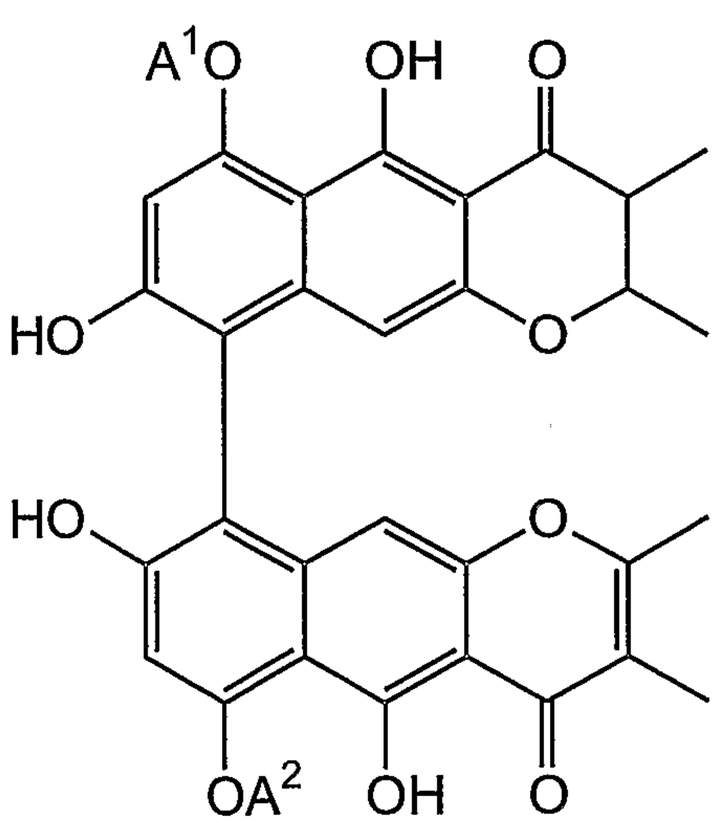
Group XXI

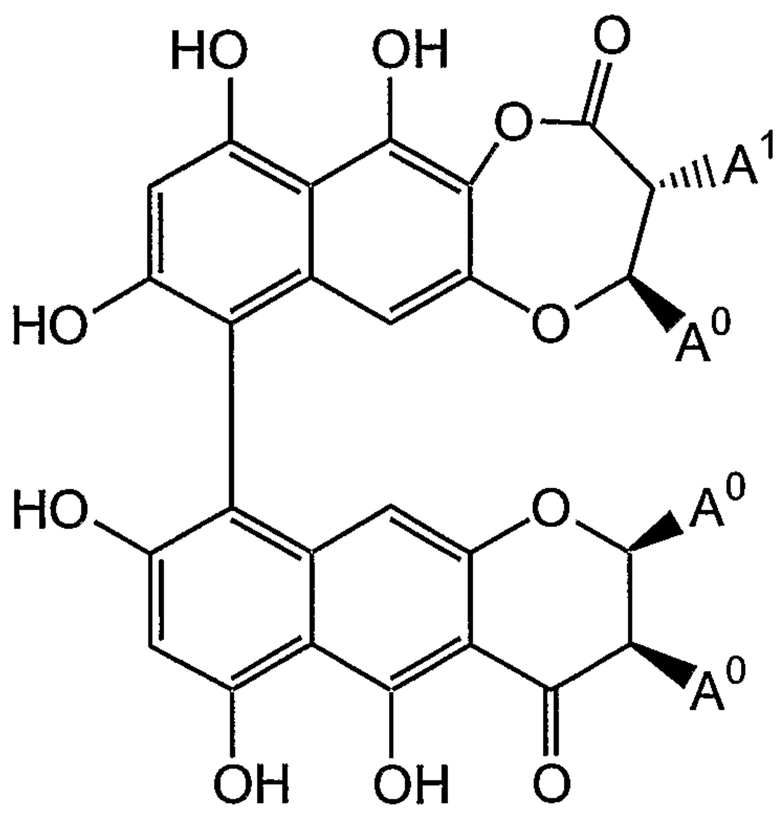
In one aspect, the invention includes phosphonate analogs of chaetochromin compounds derived from chaetochromin fermentation products and their chemically modified derivatives (WO 98/34932) including naphtho-γ-pyrones (Singh et al (2003) *Bioorganic & Med. Chemistry Letters* 13(4):713-717 having Formula XXI.



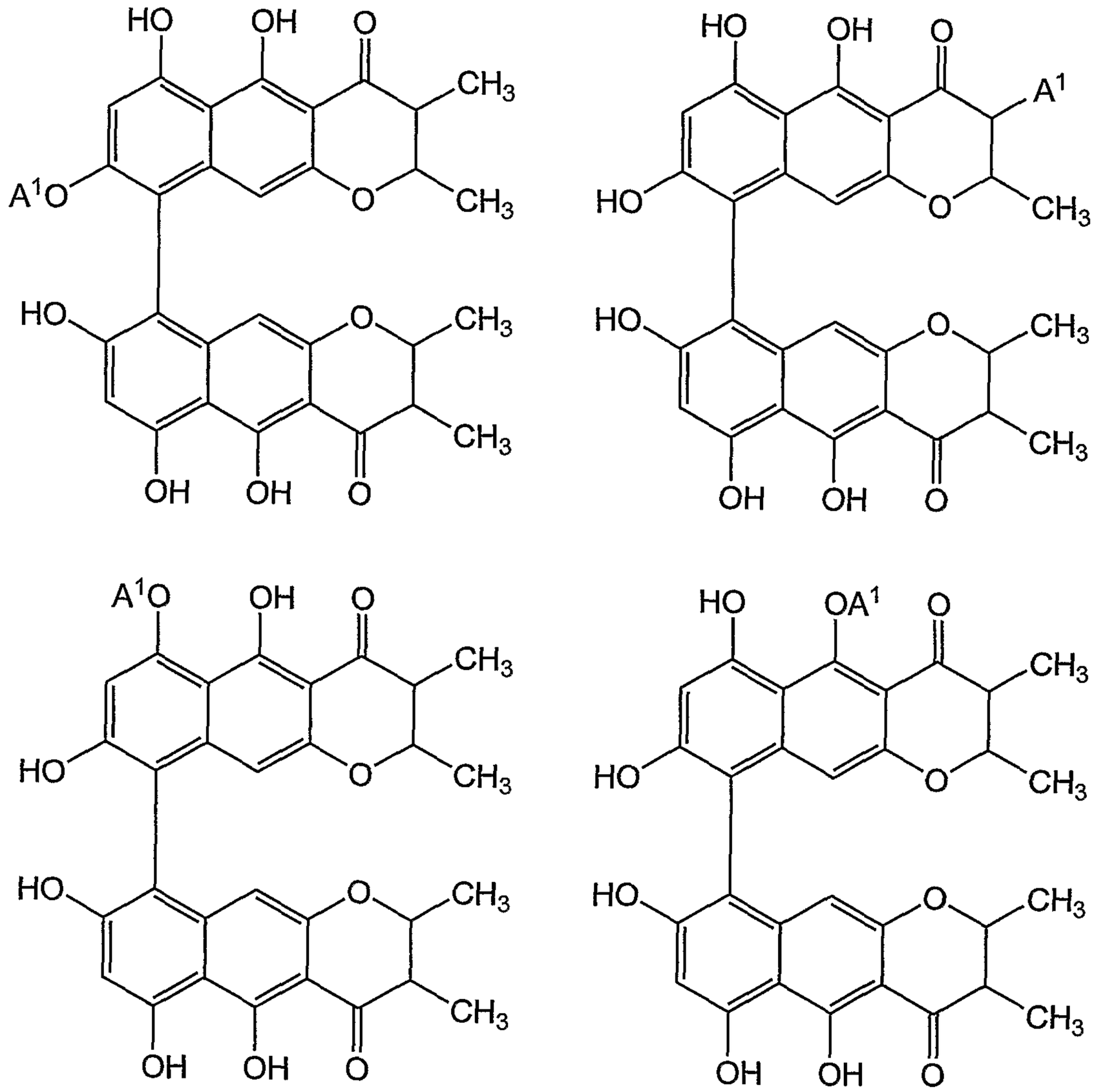
XXI

Formula XXI compounds further include phosphonate unsaturated (isochaetochromin D_1) and further oxidized lactone (oxychaeotochromin B) analogs of isochaetochromin B_1 and B_2 according to following structures:





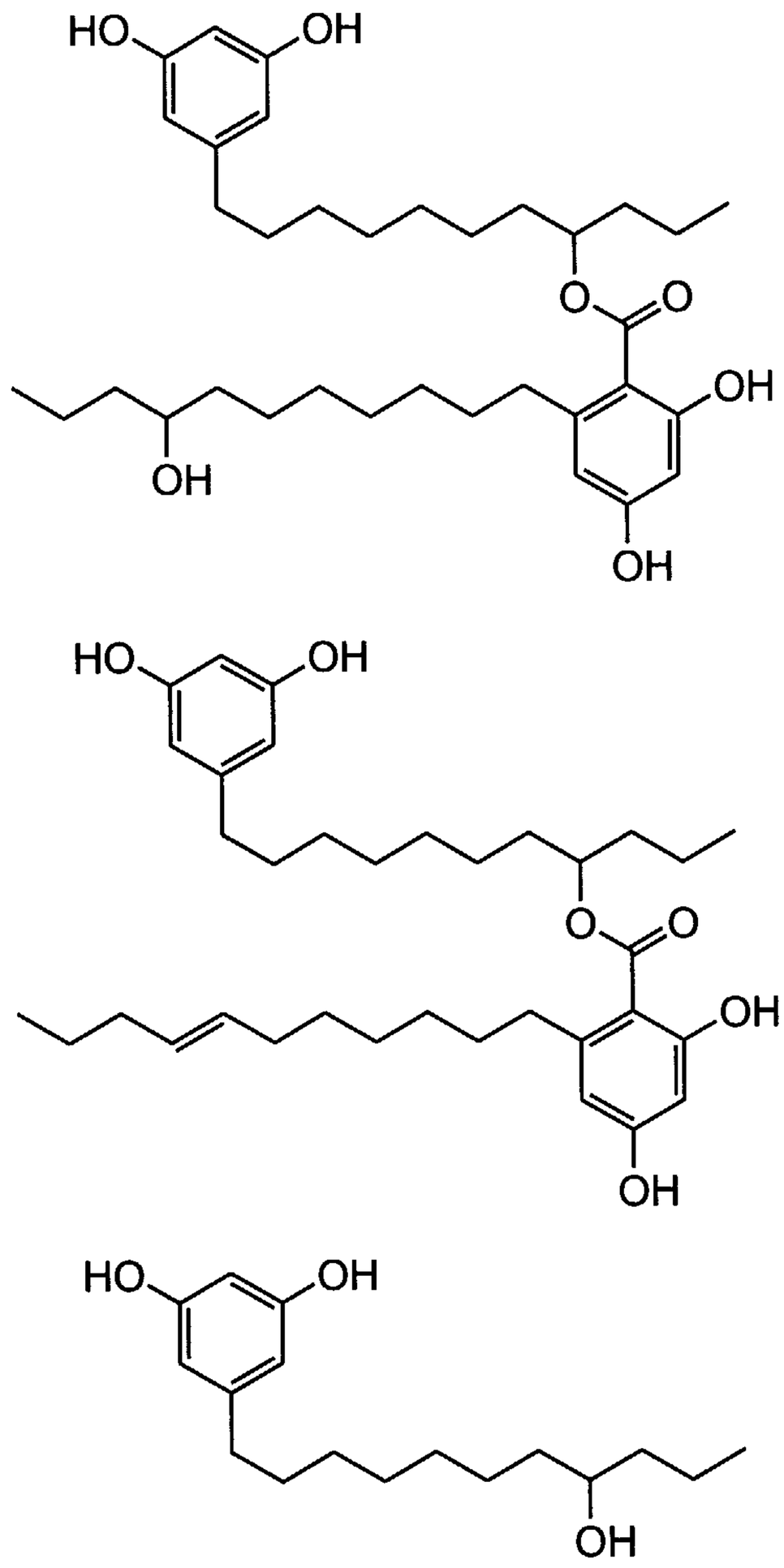
Embodiments of phosphonate analogs of chaetochromin compounds also include the structures:



The invention includes all rotational isomers, i.e. atropisomers, which may exist as stable enantiomers due to slow rotation around the single bond connecting the aryl rings of Formula XXI compounds.

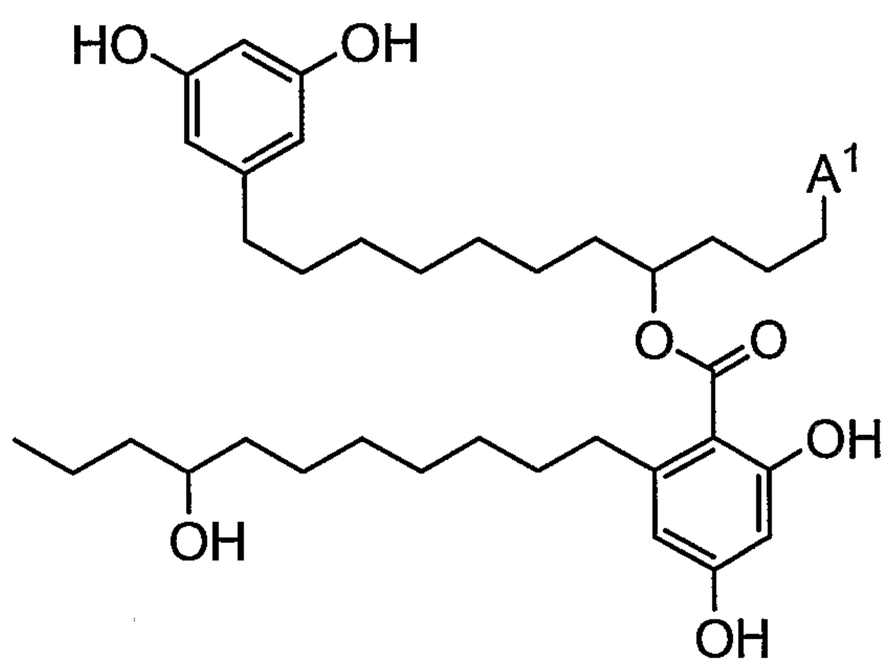
Group XXII

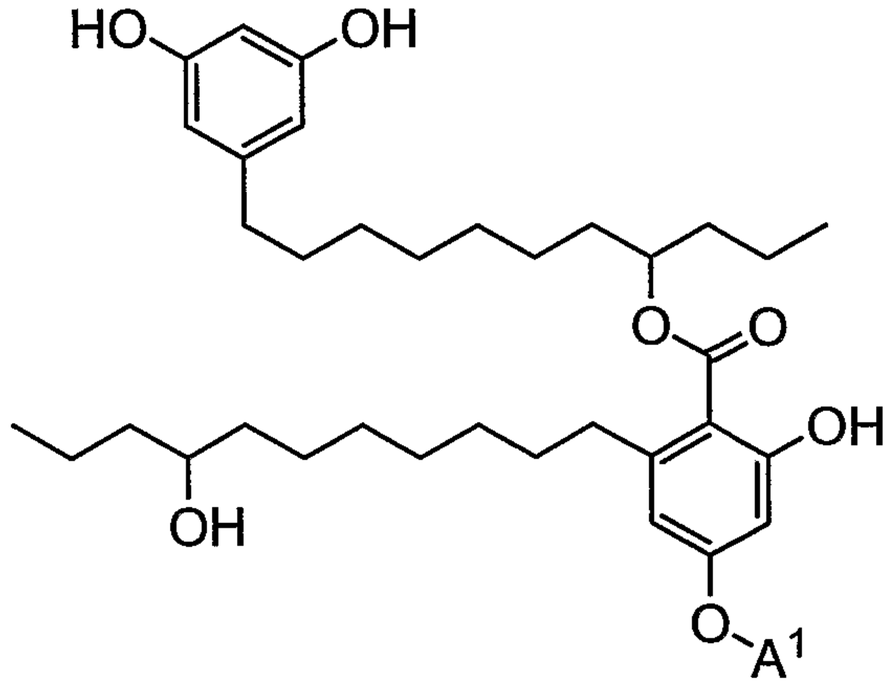
In one aspect, the invention includes phosphonate analogs of hydroxyphenylundecane compounds derived from fermentation products and their chemically modified derivatives (GB 2327674) including integracins (Singh et al (2002) *Tetrahedron Lett.* 43(9):1617-1620) having Formula XXII structures:

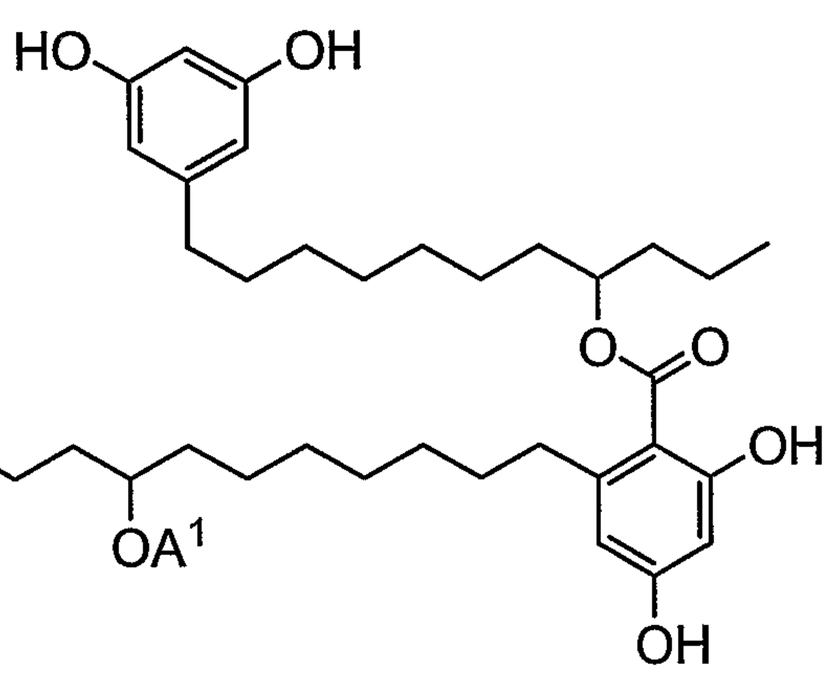


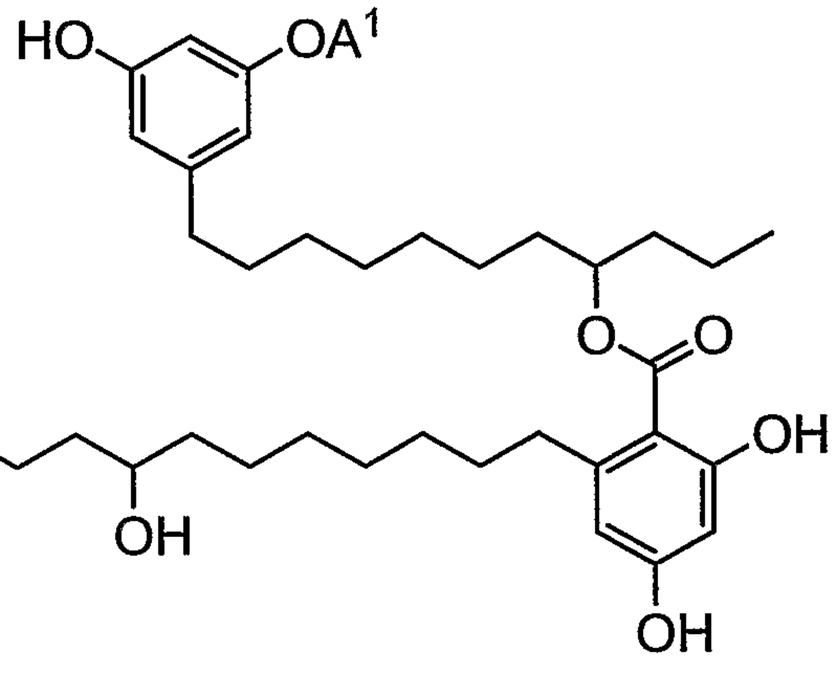
XXII

Embodiments of hydroxyphenylundecane phosphonate compounds Formula XXII include the structures:









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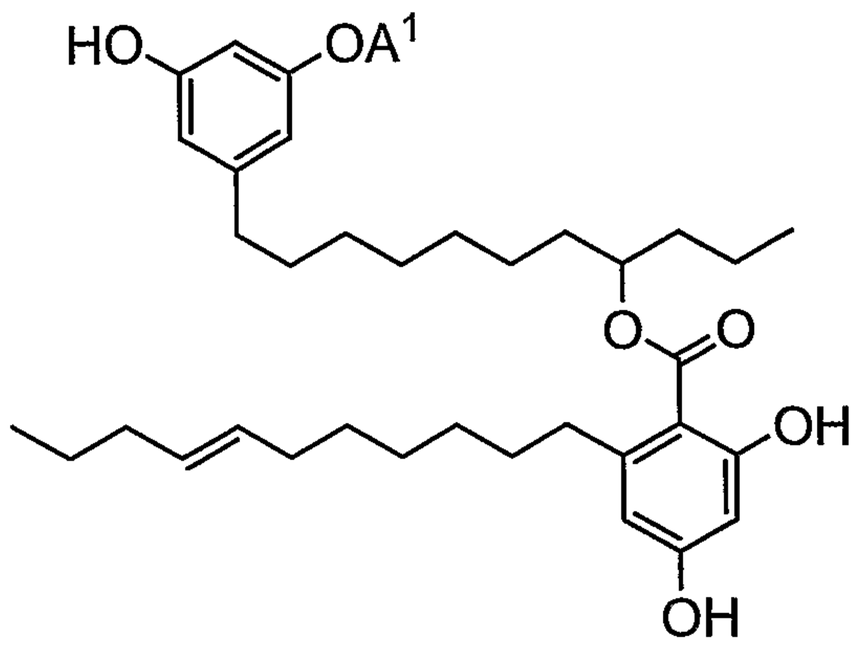
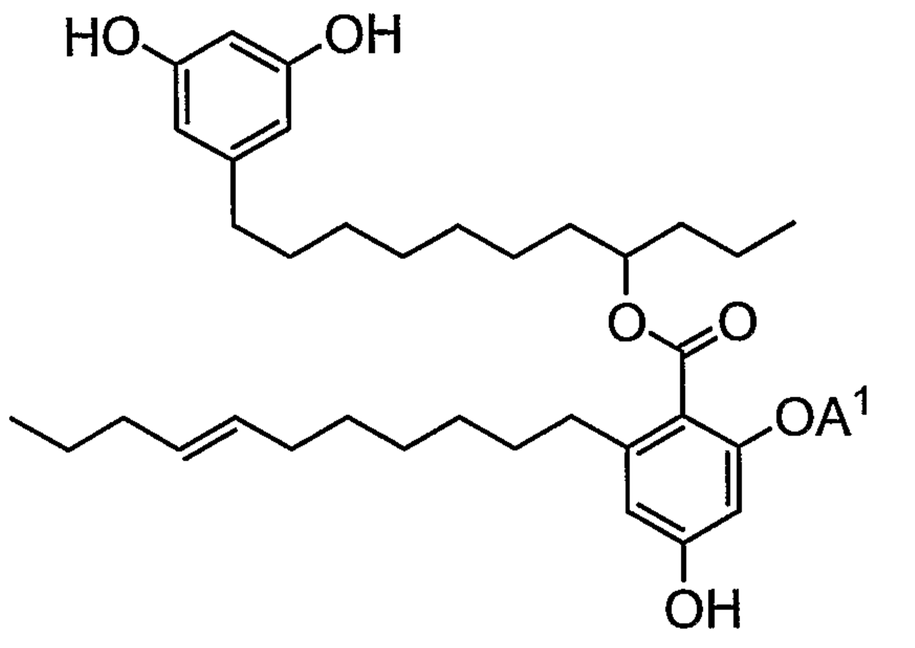
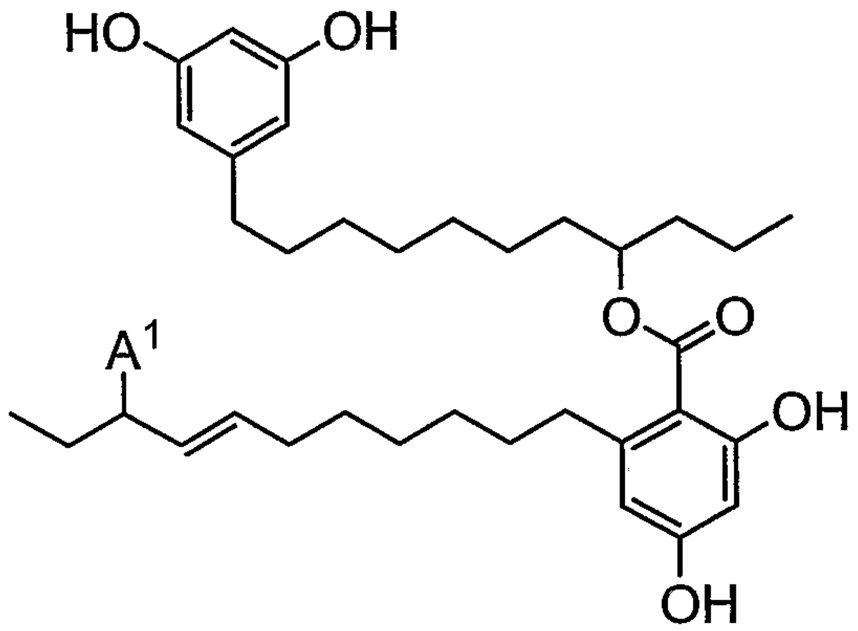
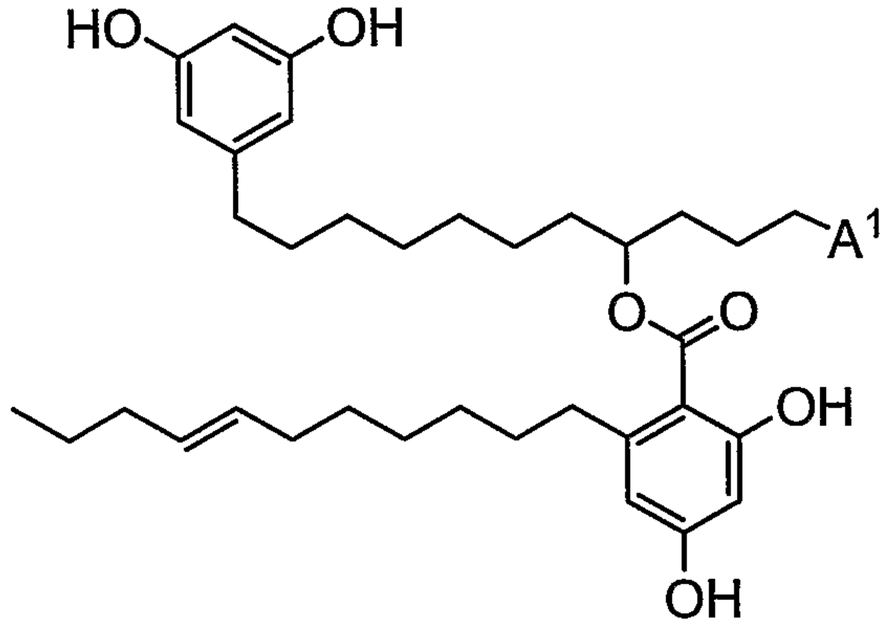
Embodiments of hydroxyphenylundecane phosphonate compounds Formula XXII also include the structures:

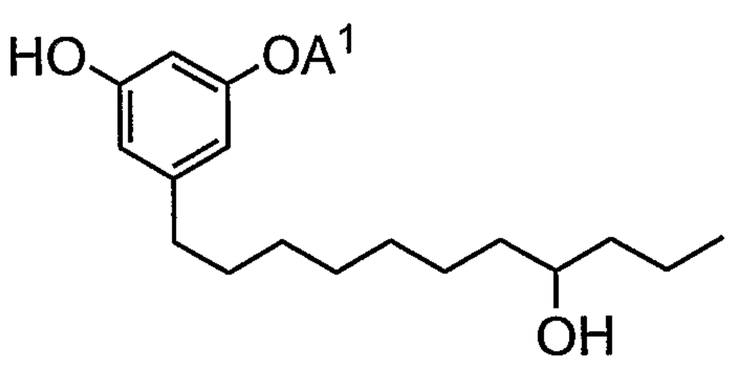


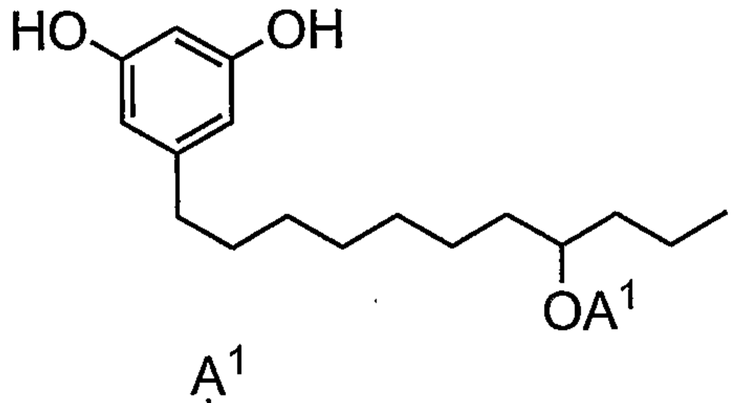


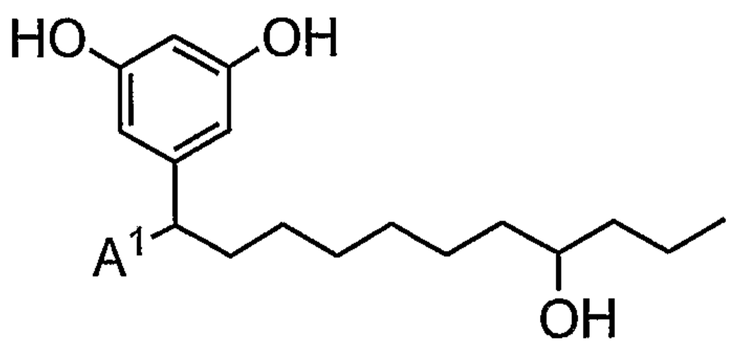


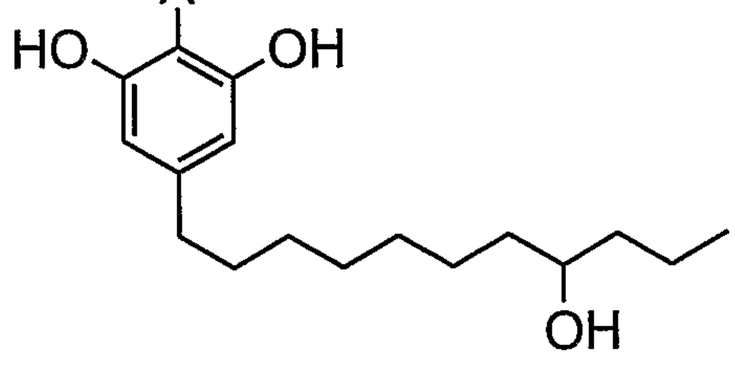


Embodiments of hydroxyphenylundecane phosphonate compounds Formula XXII also include the structures:





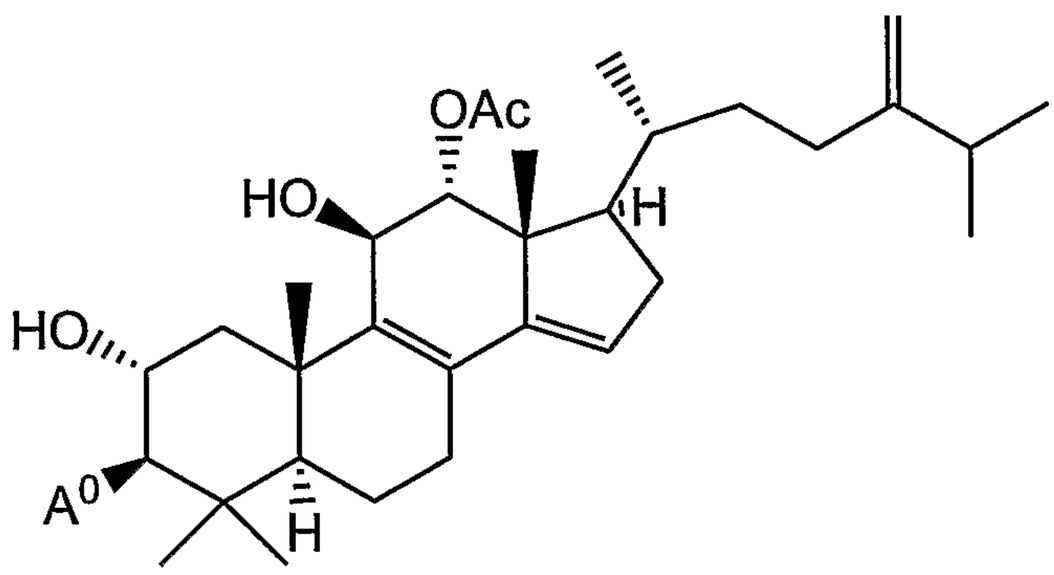




Group XXIII

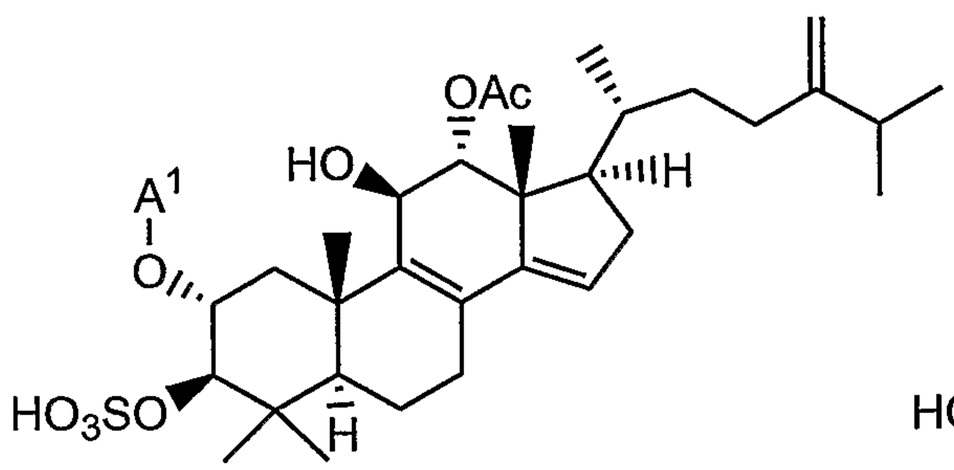
In one aspect, the invention includes phosphonate analogs of: (i) tetracyclic steroidal compounds derived from fermentation products and their chemically modified derivatives (Singh et al (2003) *Jour. of Natural Products* 66(10):1338-1344; WO 00/36132); and (ii) tetracyclic triterpenoid compounds, such as integracides (Singh et al (2003) *Bioorganic & Med. Chemistry* 11(7):1577-1582).

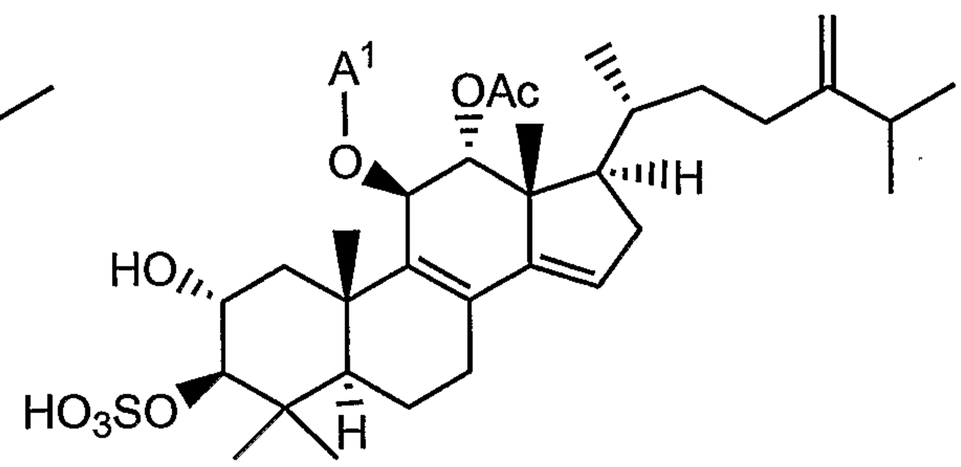
Embodiments of phosphonate integracide Formula XXIII compounds include the structure:

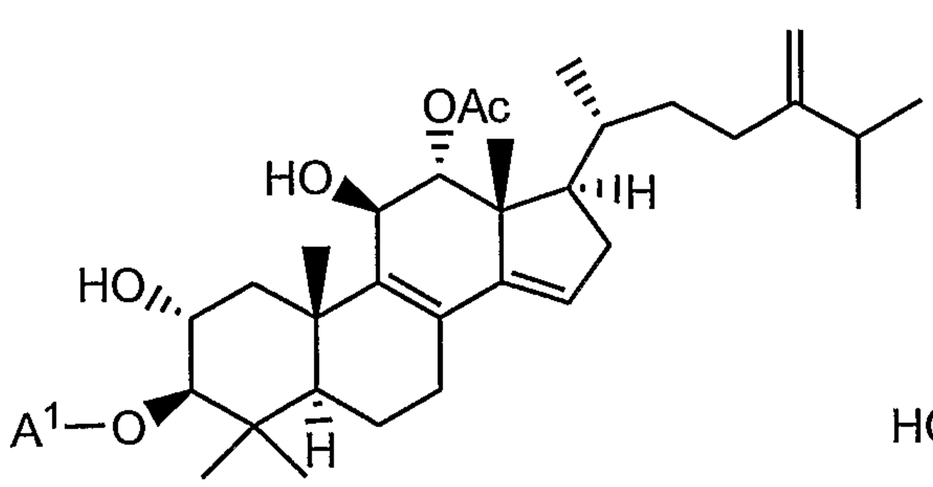


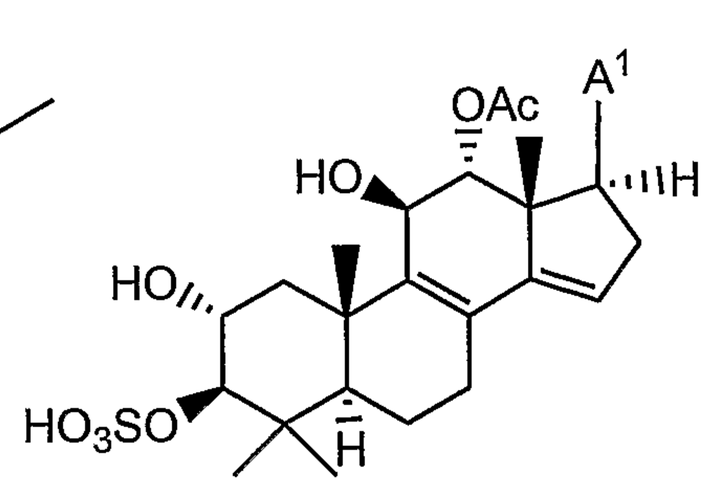
XXIII

where at least one carbon or oxygen atom is substituted with an A^1 group, and any aryl or sultam ring carbon atom may be substituted with an A^2 group, including the exemplary structures:

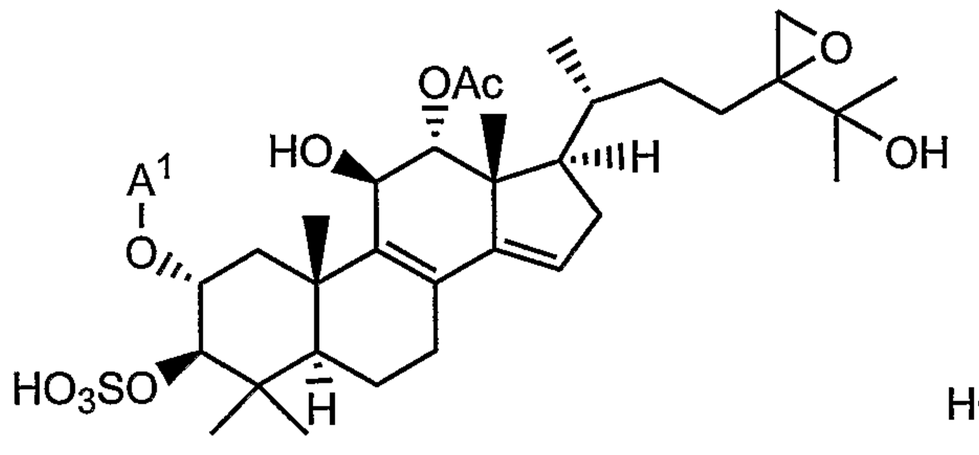


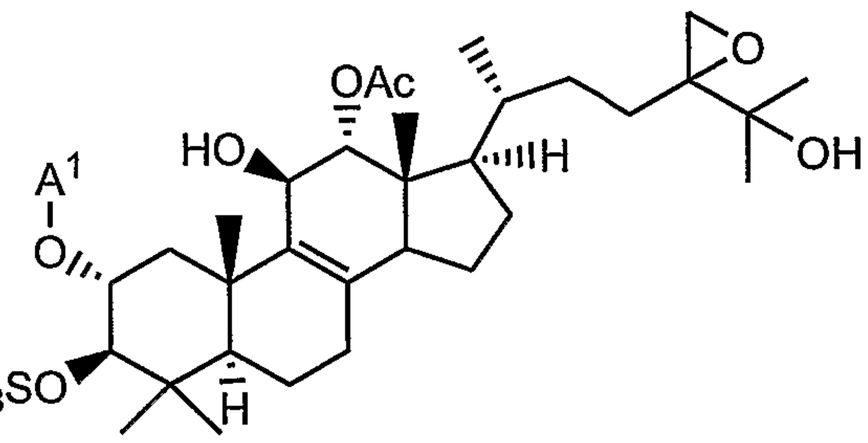


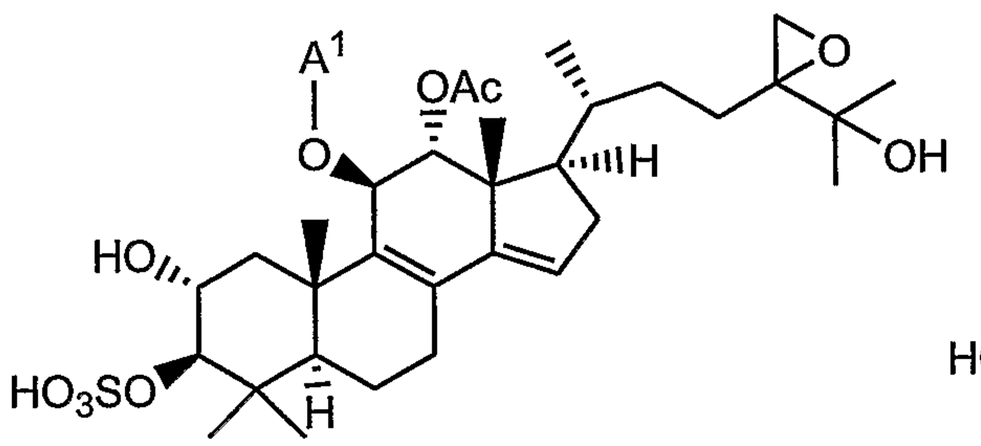


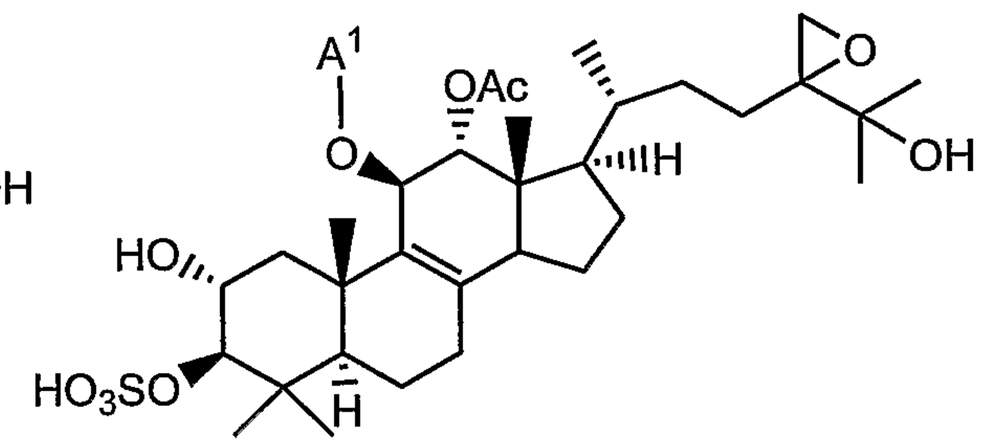


Embodiments of phosphonate integracide B Formula XXIII compounds also include the structures:









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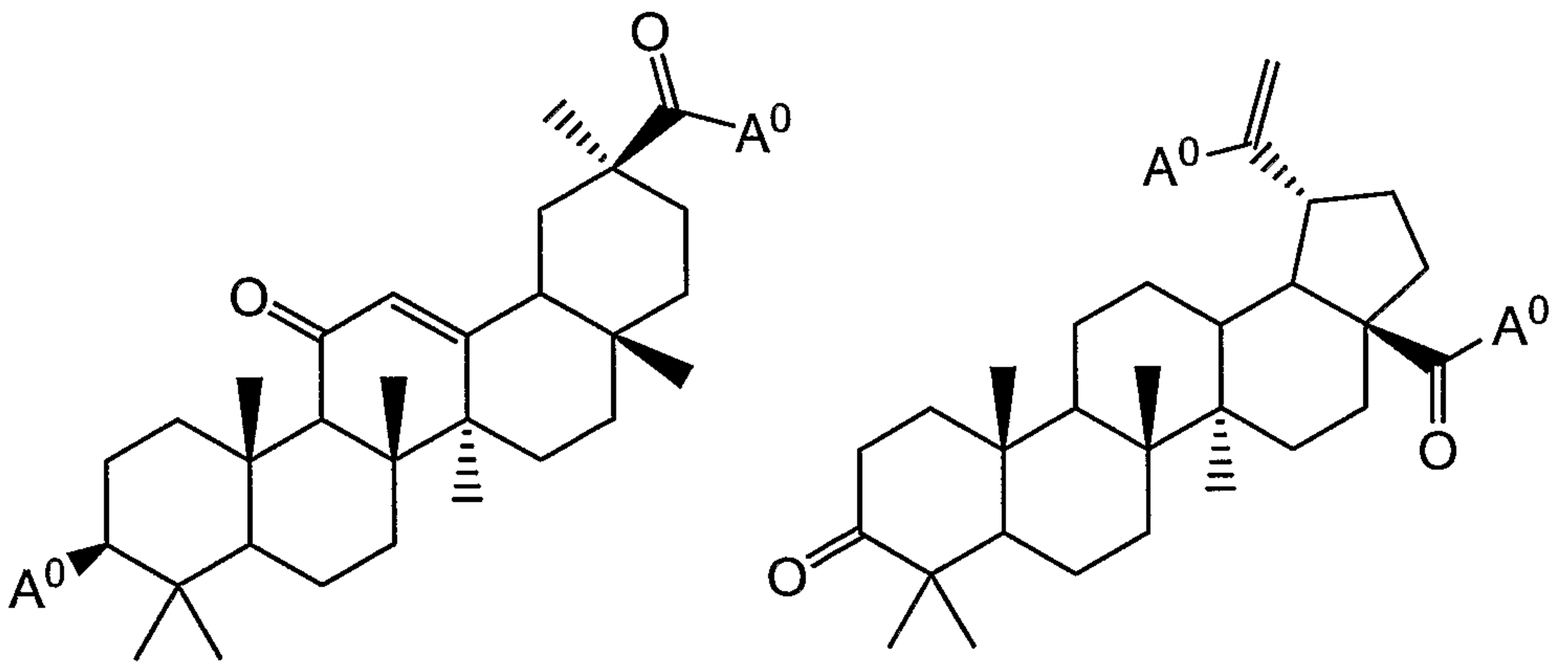
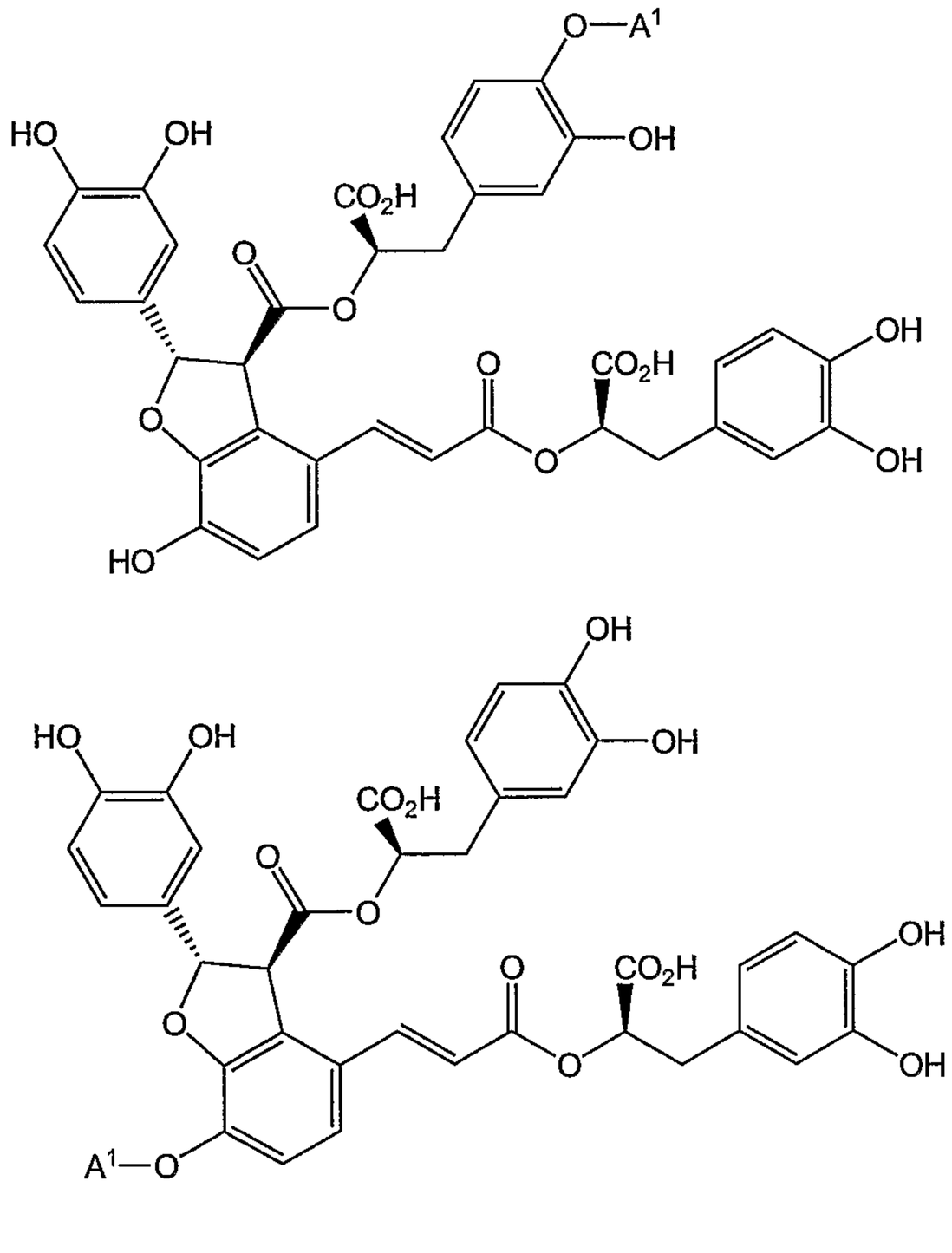
Group XXIV

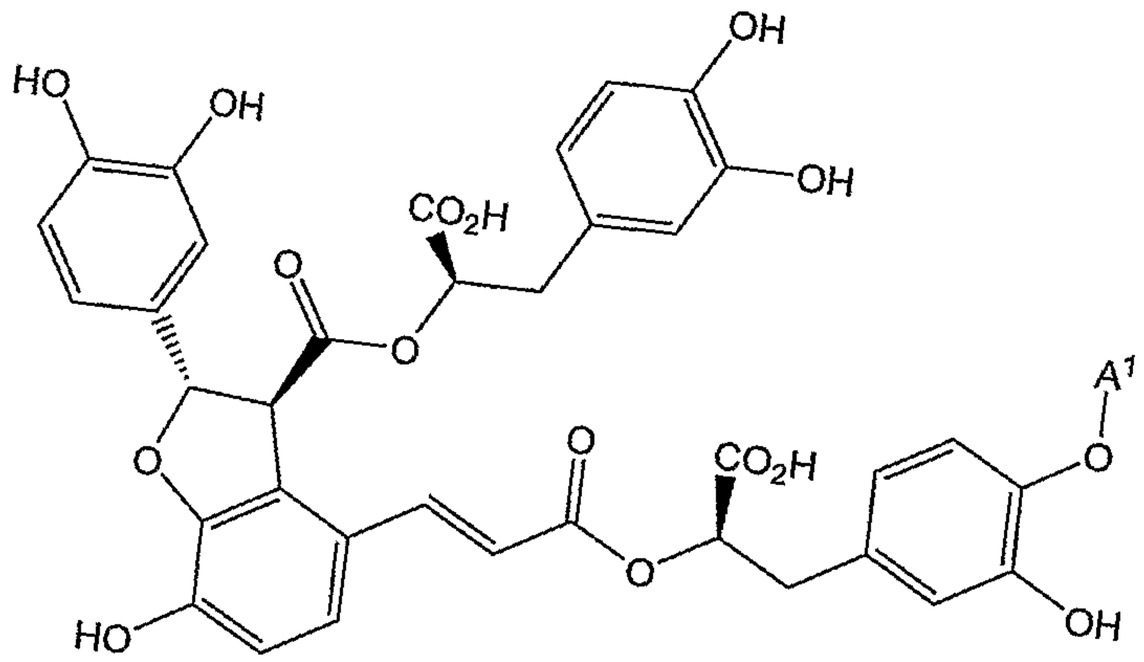
In one aspect, the invention includes phosphonate analogs of plant natural products including: (i) glycerrhenitic and betulonic acids (Semenova et al (2003) *Doklady Biochemistry and Biophysics* 391:218-220); (ii) compounds from Coleus parvifolius Benth. (Tewtrakul et al (2003) *Phytotherapy Research* 17(3):232-239); (iii) eudesmane-type sesquiterpenes and aporphine alkaloid lindechunines from Lindera chunii roots including hernandonine, laurolistine, 7-oxohernangerine and lindechunine A (Zhang et al (2002) *Chemical & Pharmaceutical Bulletin* 50(9):1195-1200); and (iv) lithospermic acid (Abd-Elazem et al (2002) *Antiviral Research* 55(1):91-106; WO 02/026726).

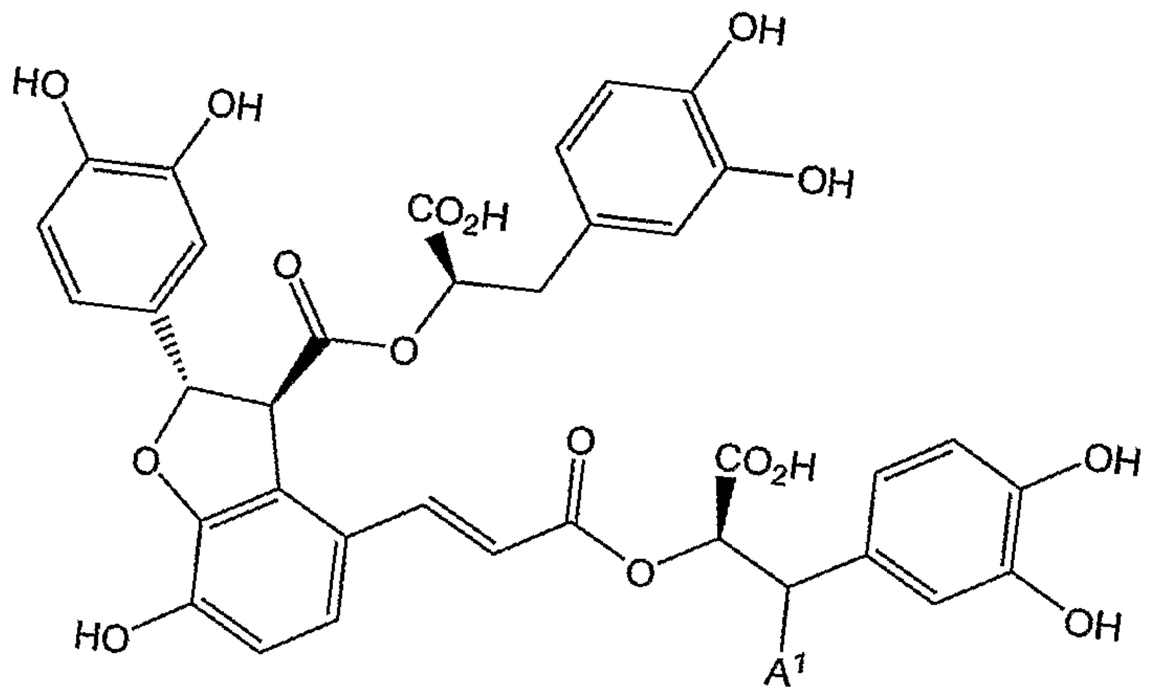
Embodiments of Formula XXIV glycerrhenitic and betulonic acid phosphonate compounds include the structures:



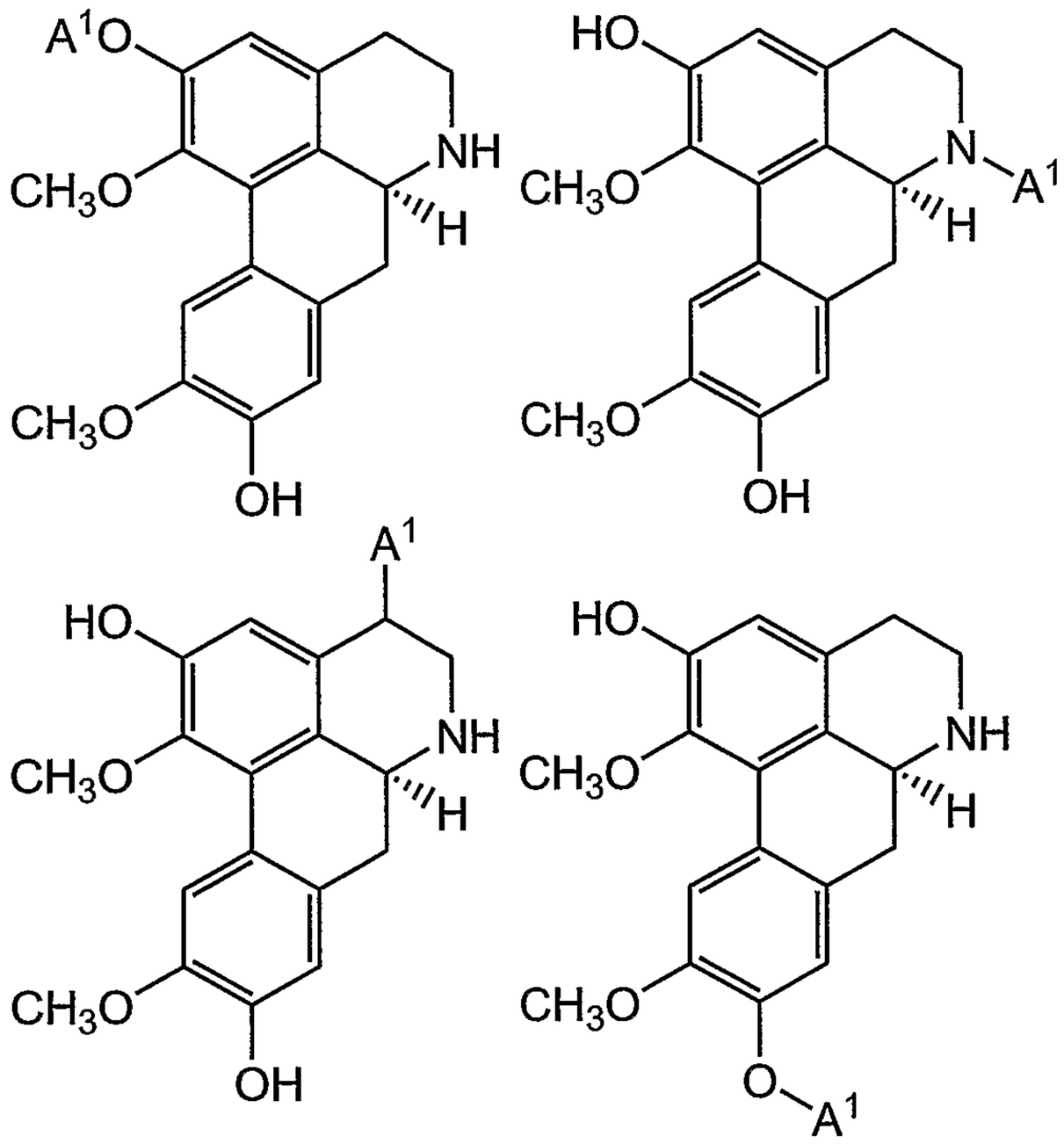
Embodiments of Formula XXIV compounds also include the structures:





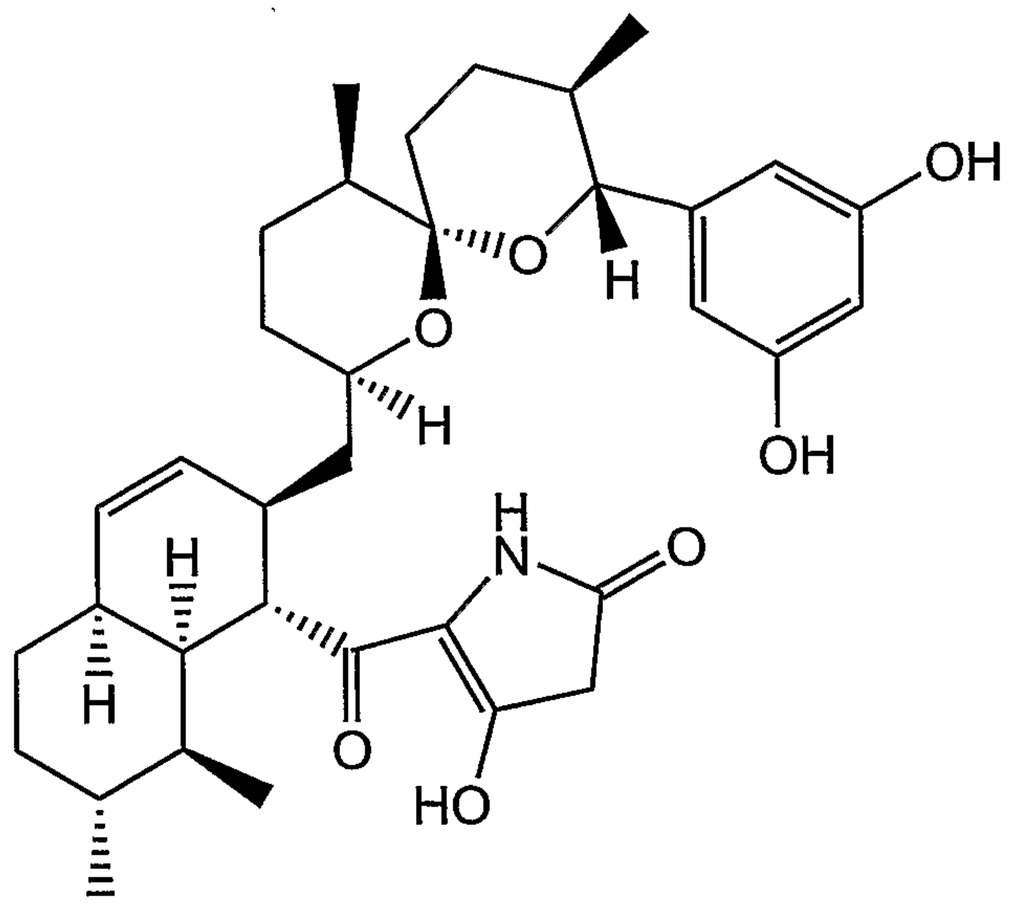


Embodiments of laurolistine phosphonate Formula XXIV compounds include the structures:



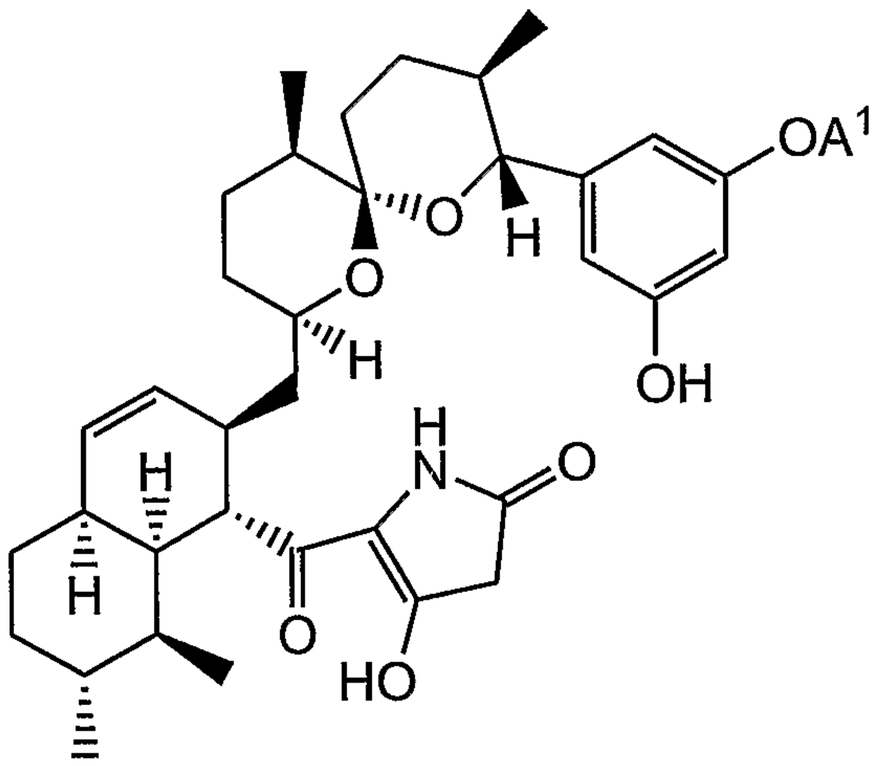
Group XXV

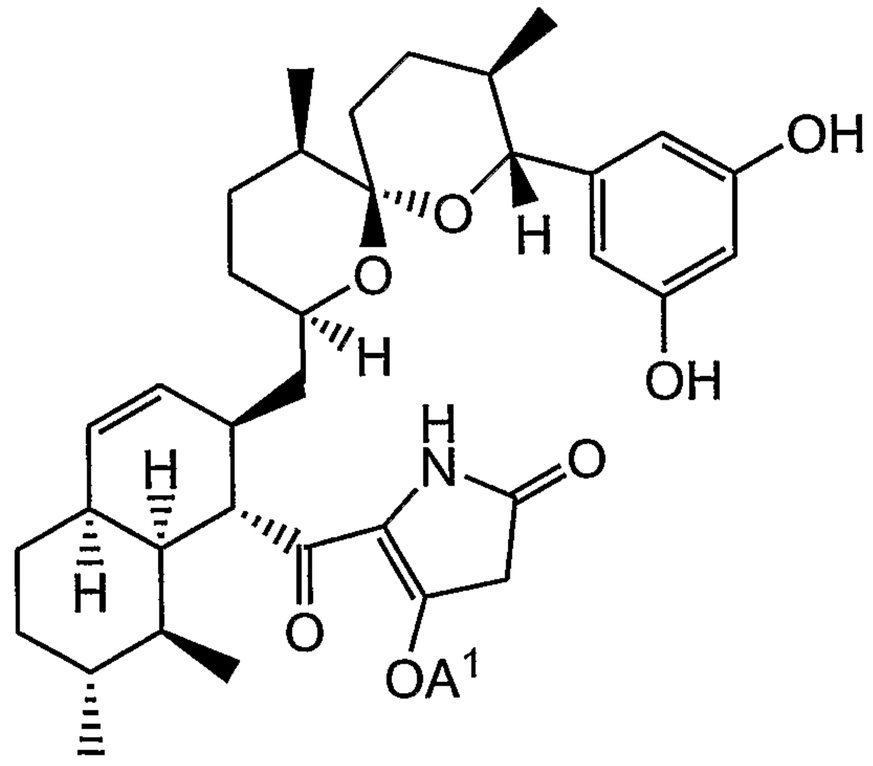
In one aspect, the invention includes phosphonate analogs of spiro ketal compounds derived from fungal cultures and fungus, and their chemically modified derivatives (Neamati, N. (2002) Expert Opinion Therapeutic Patents 12(5):709-724, compound 47, Table 2, p. 714) with the Formula XXV structure:

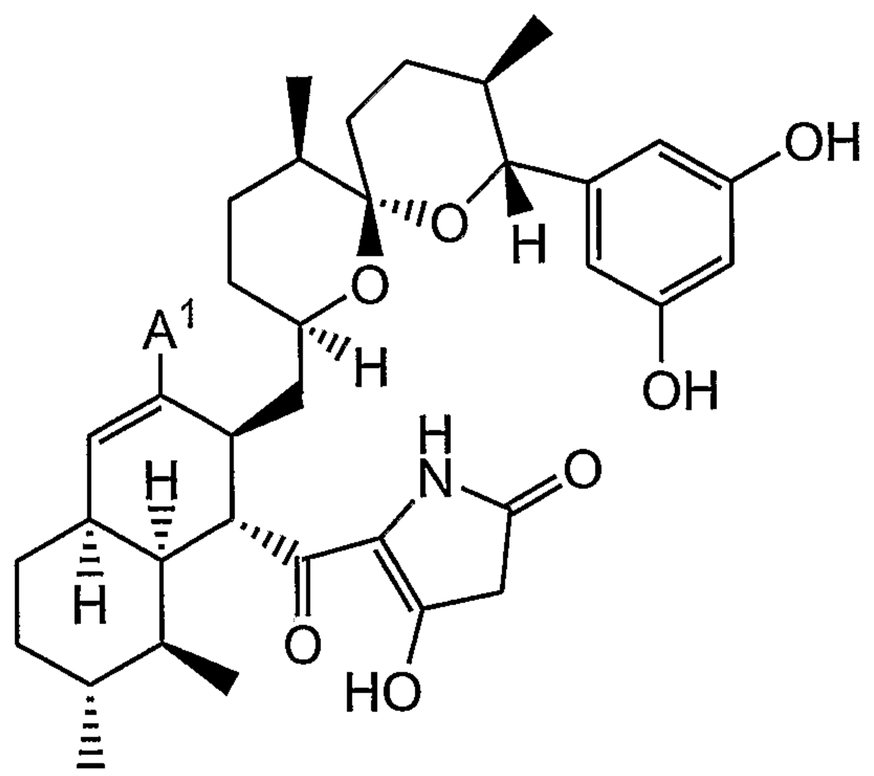


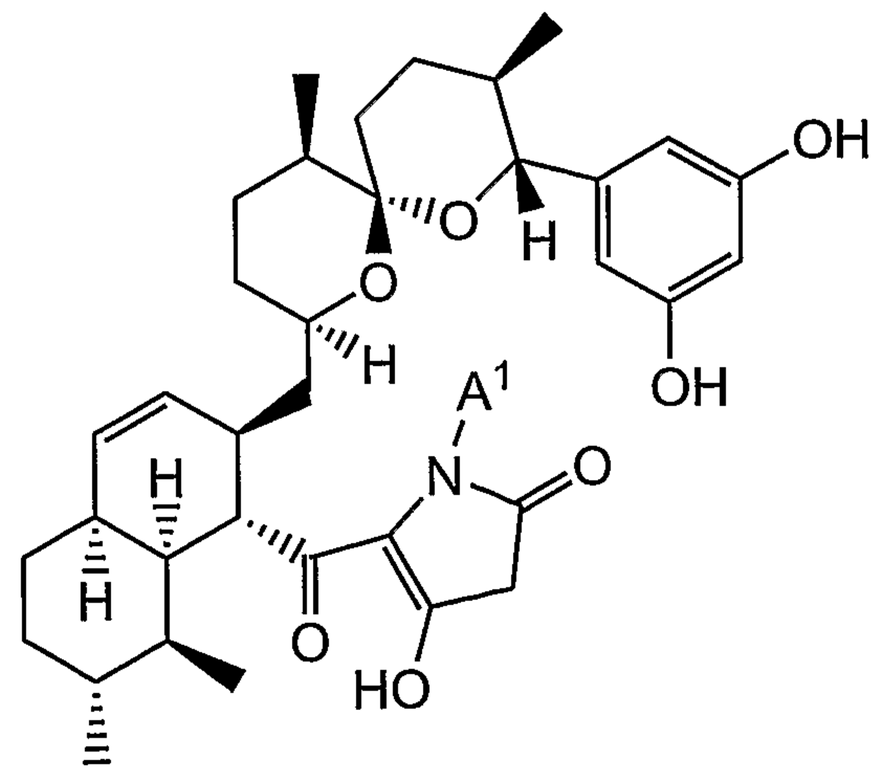
XXV

Embodiments of spiro ketal phosphonate Formula XXV compounds include the structures:



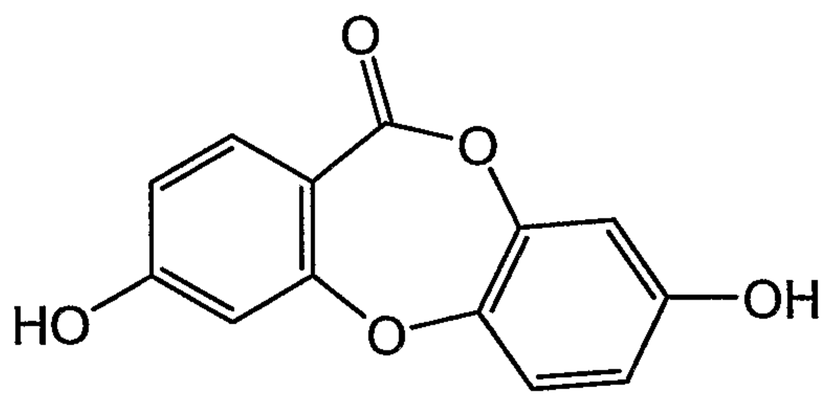






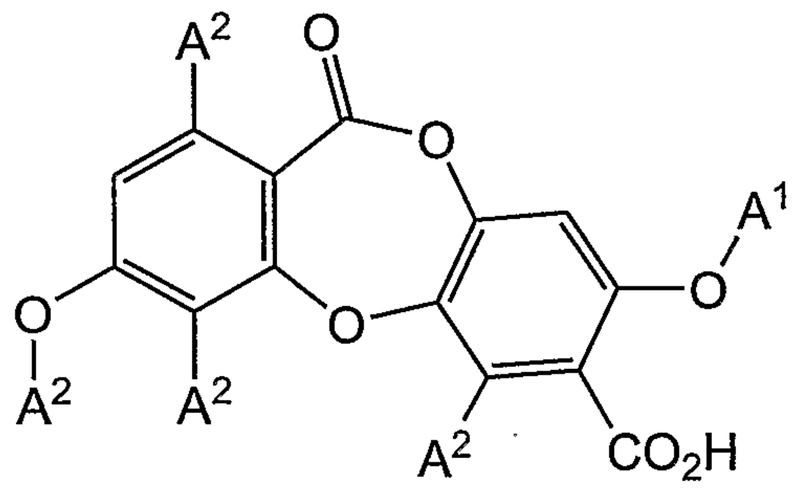
Group XXVI

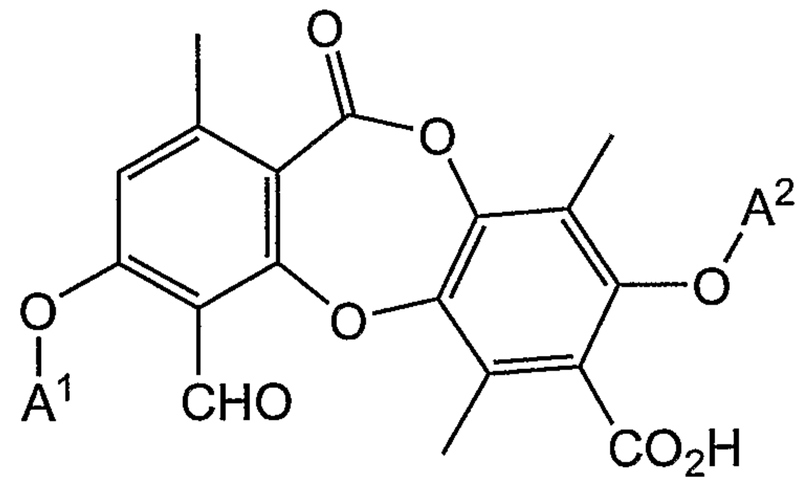
In one aspect, the invention includes phosphonate analogs of aromatic lactone compounds derived from lichen extracts, and their chemically modified derivatives (Neamati et al (1997) *J. Med. Chem.* 40:942-951; Neamati et al (1997) *Antimicrob. Agents Chemother.* 41:385-393). Phosphonate aromatic lactone Formula XXVI compounds include the structures:

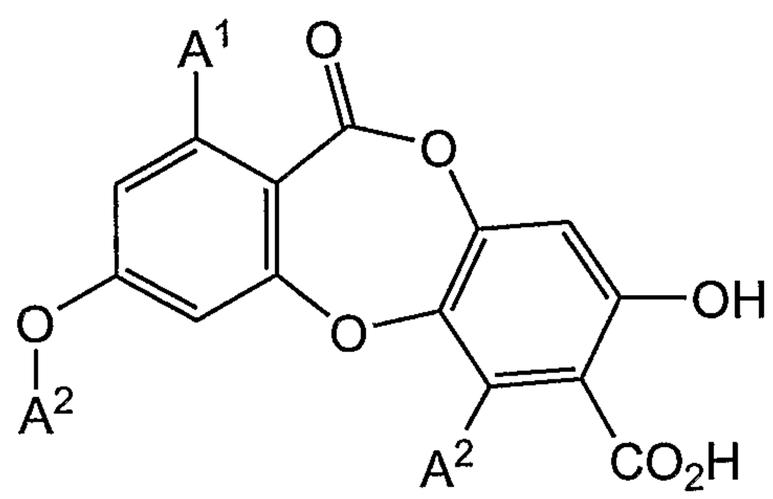


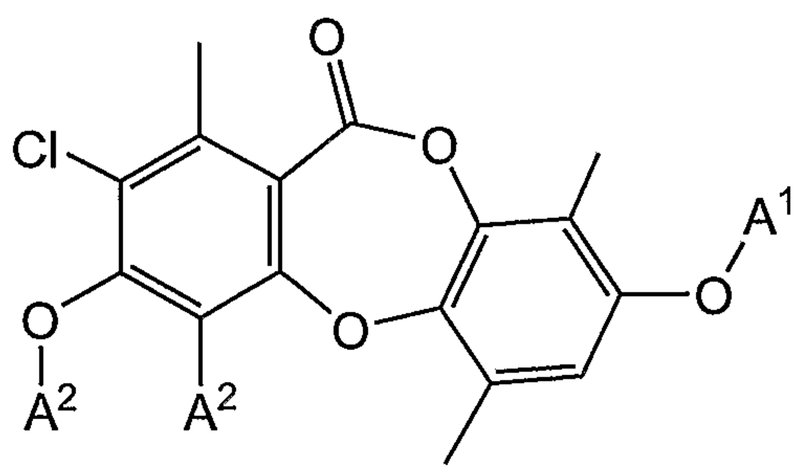
XXVI

Embodiments of phosphonate aromatic lactone Formula XXVI compounds include the structures:





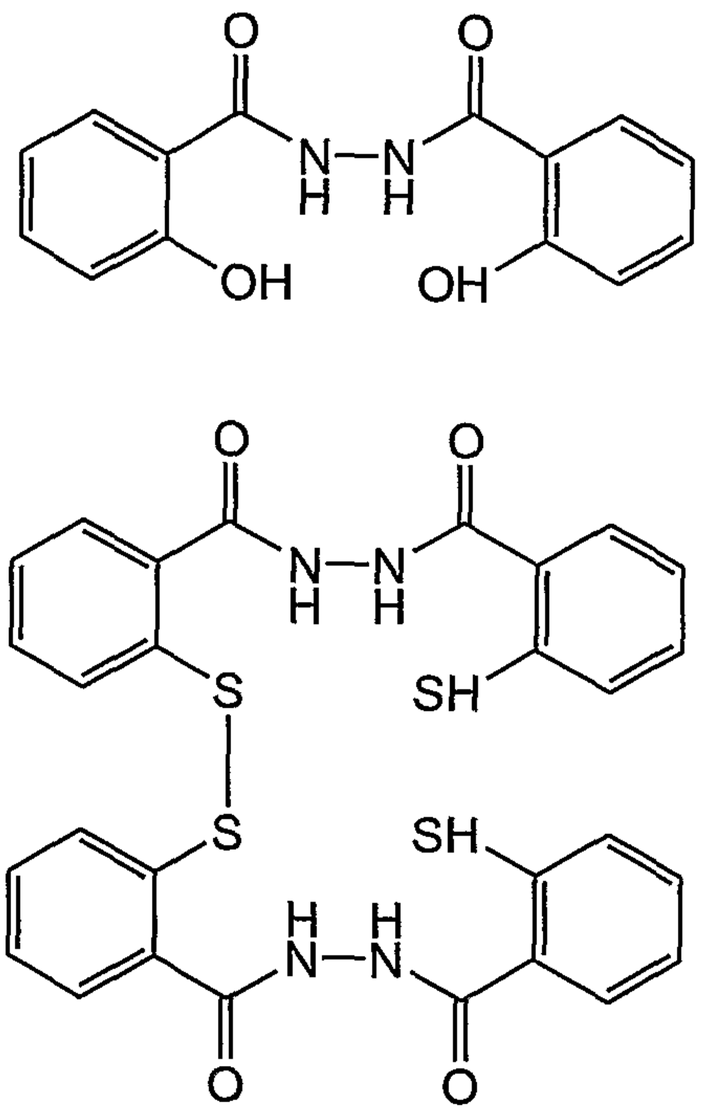


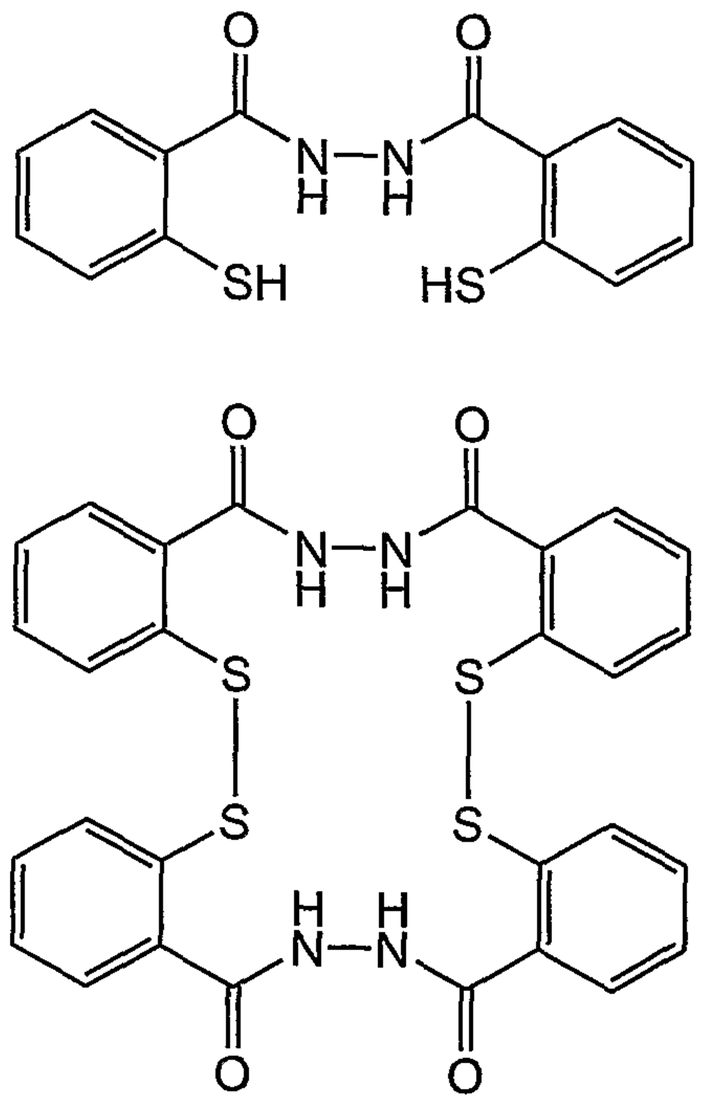


Group XXVII

In one aspect, the invention includes phosphonate analogs of salicylhydrazide and mercaptosalicylhydrazide compounds (Neamati et al (2002) J. Med. Chem. 45(26): 5661-5670; Neamati et al (1998) *J. Med. Chem.* 41:3202-3209; Zhao et al

(1997) *J. Med. Chem.* 40:937-941; WO 00/53577) which have Formula XXVII structures:

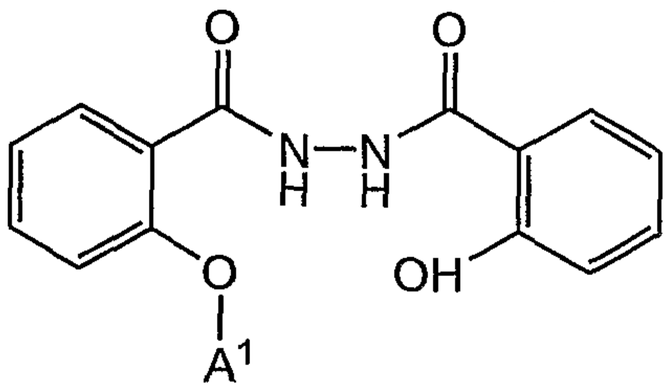


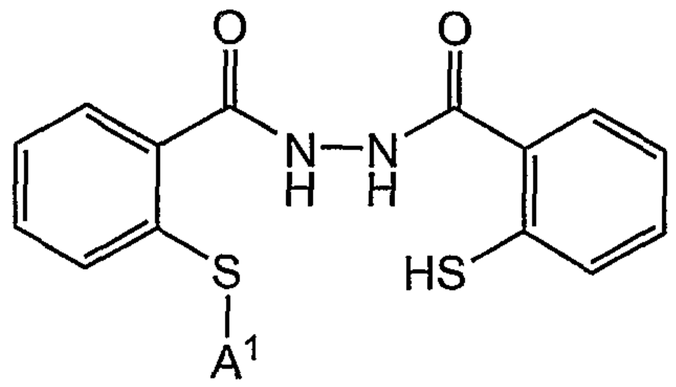


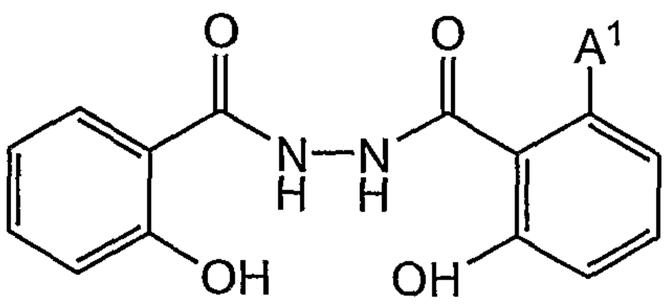
XXVII

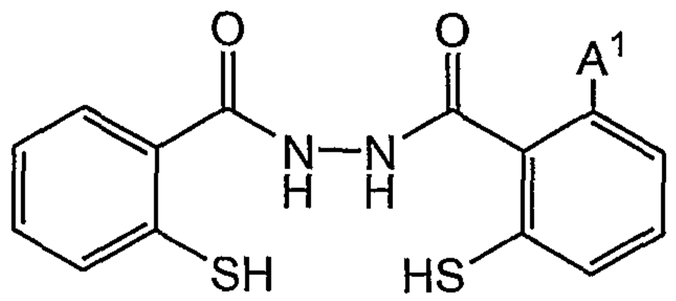
where each of the phenyl rings, N, S, or hydroxyl oxygen atoms in the structures above may be independently substituted with A^0 groups.

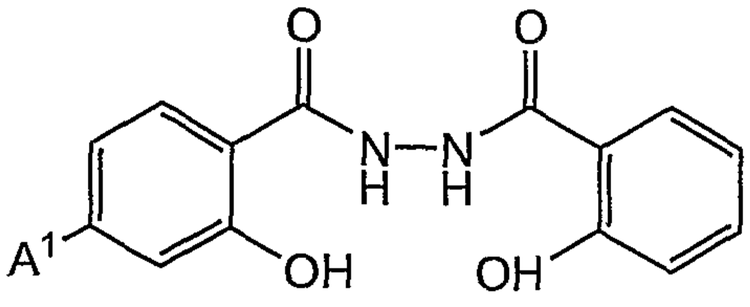
Embodiments of Formula XXVII compounds include the structures:

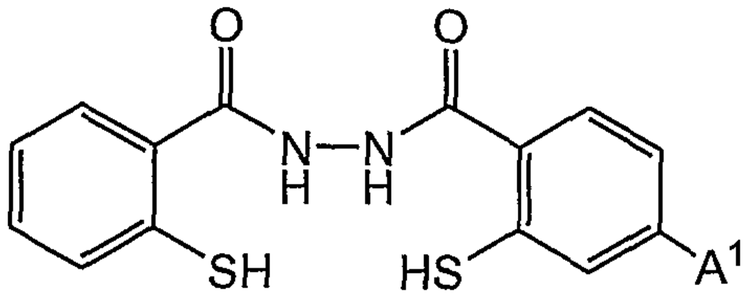




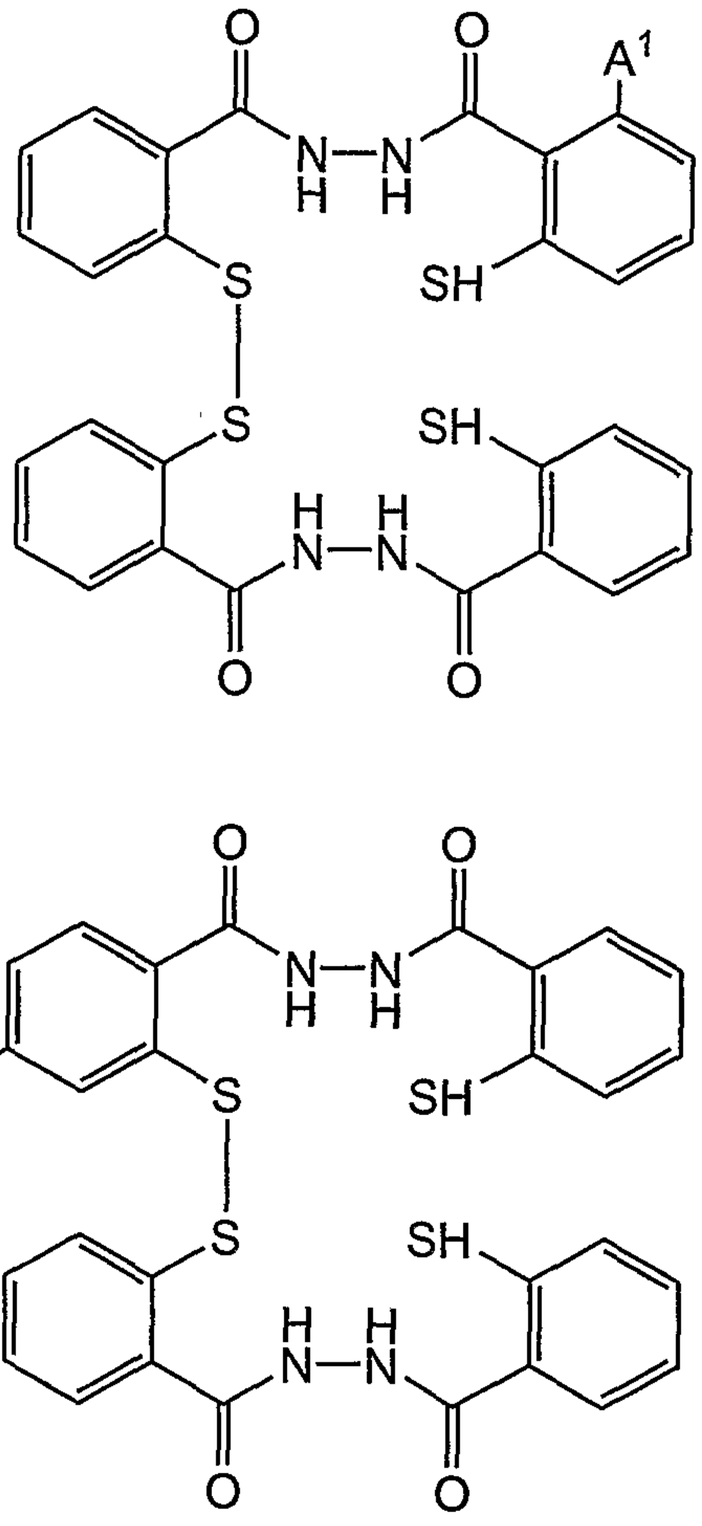


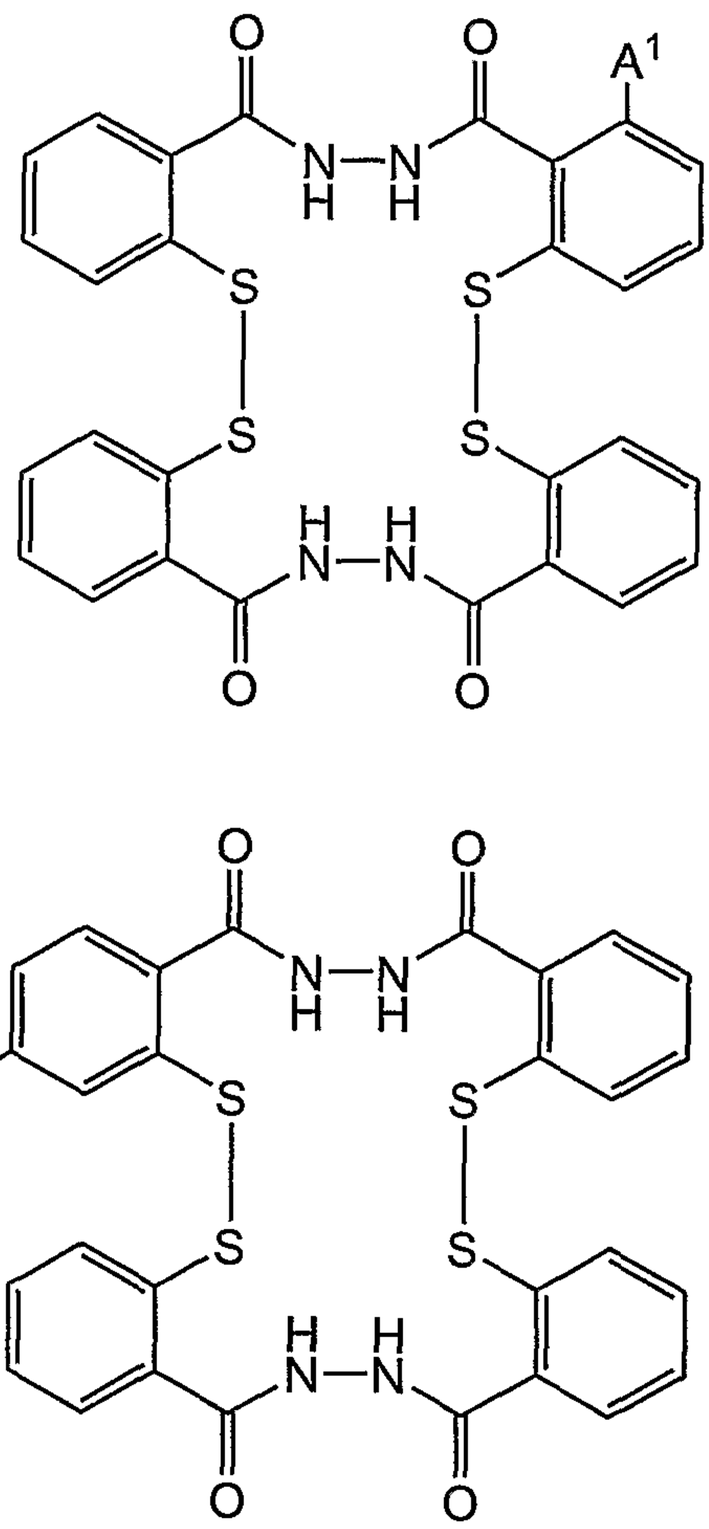


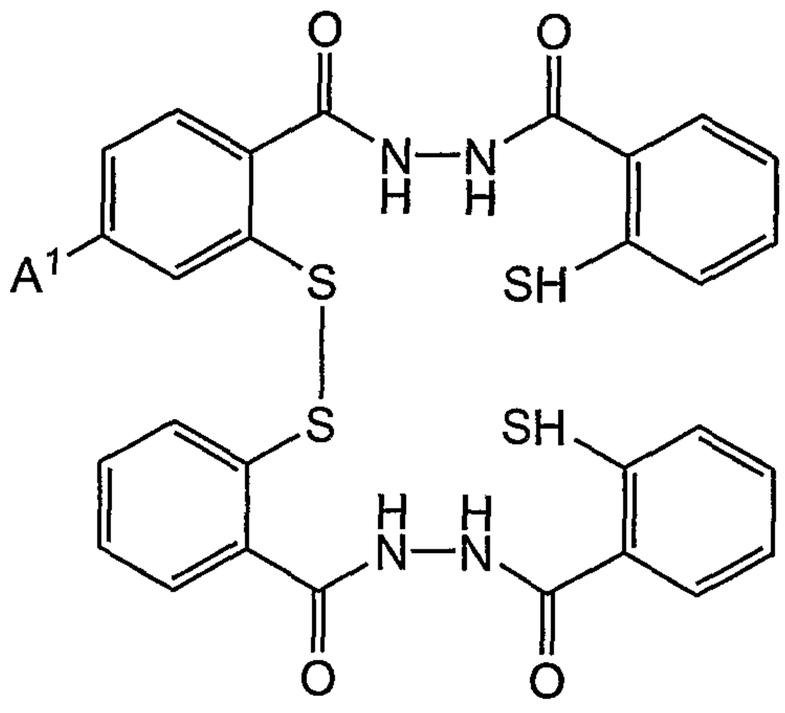


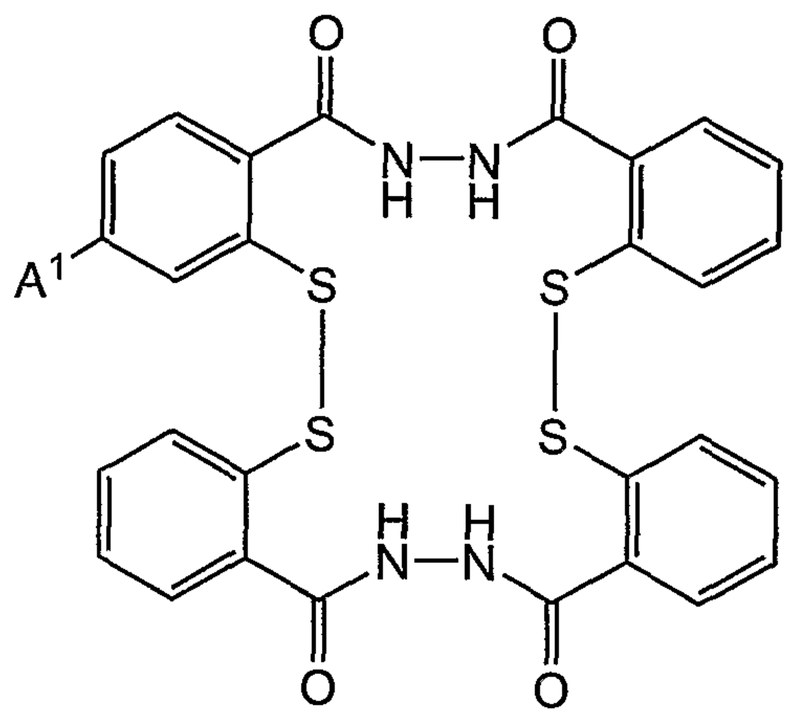


Embodiments of Formula XXVII compounds also include the structures:





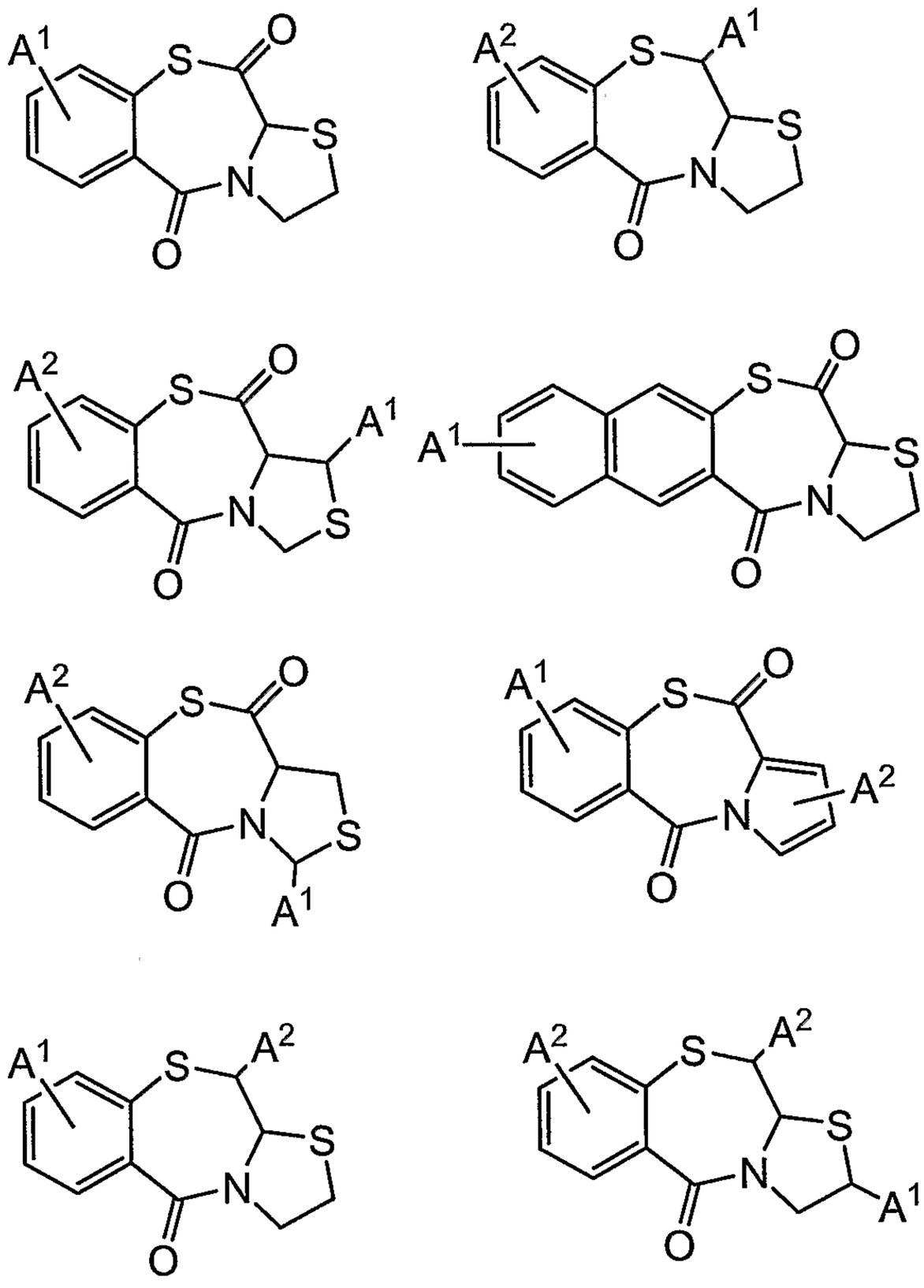




Group XXVIII

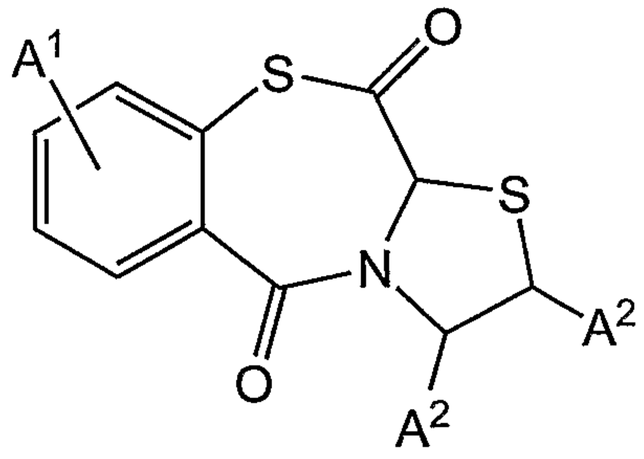
In one aspect, the invention includes phosphonate analogs of thiazolothiazepine compounds (Neamati et al (1999) *J. Med. Chem.* 42:3334-3341; WO 00/68235).

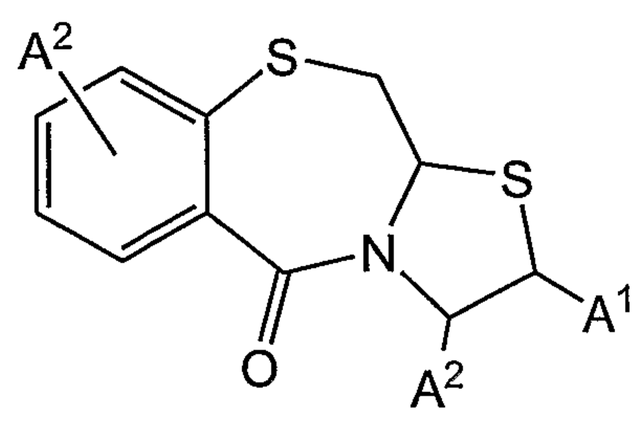
Embodiments of Formula XXVIII thiazolothiazepine phosphonate compounds include the structures:

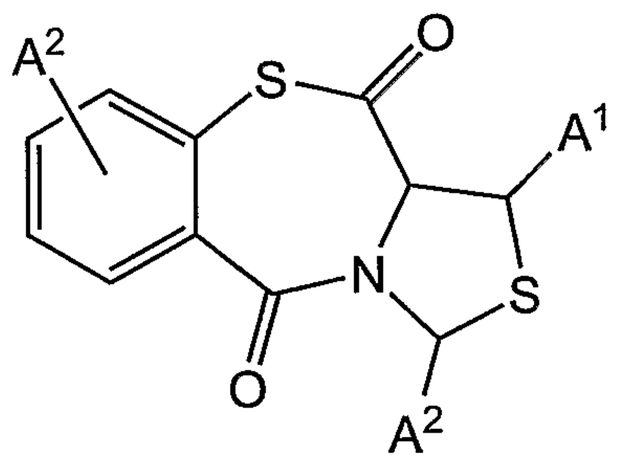


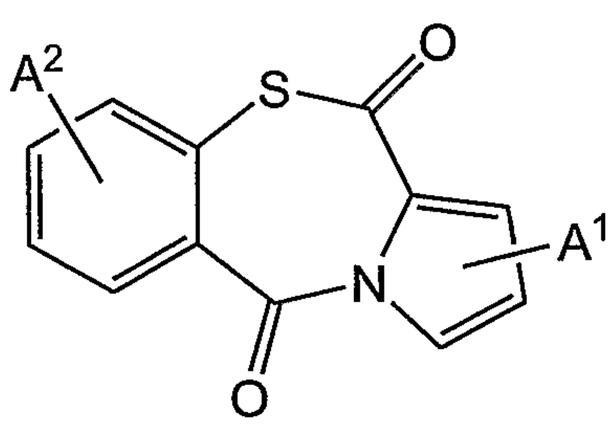
XXVII

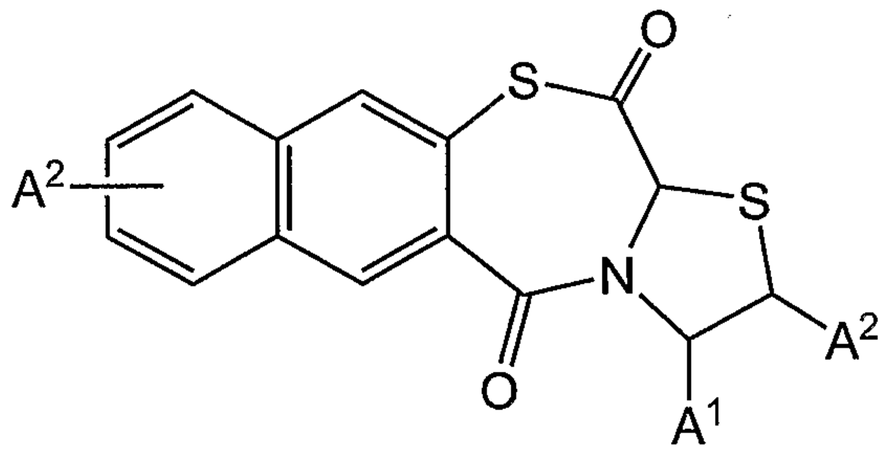
Embodiments of Formula XXVIII thiazolothiazepine phosphonate compounds also include the structures:









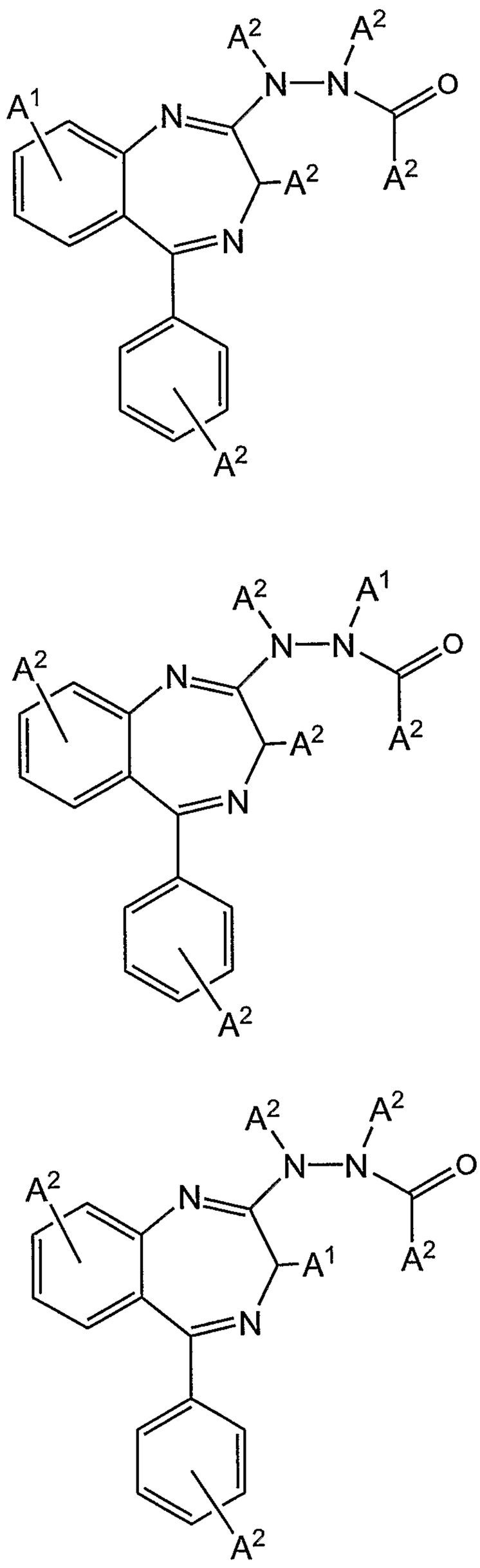


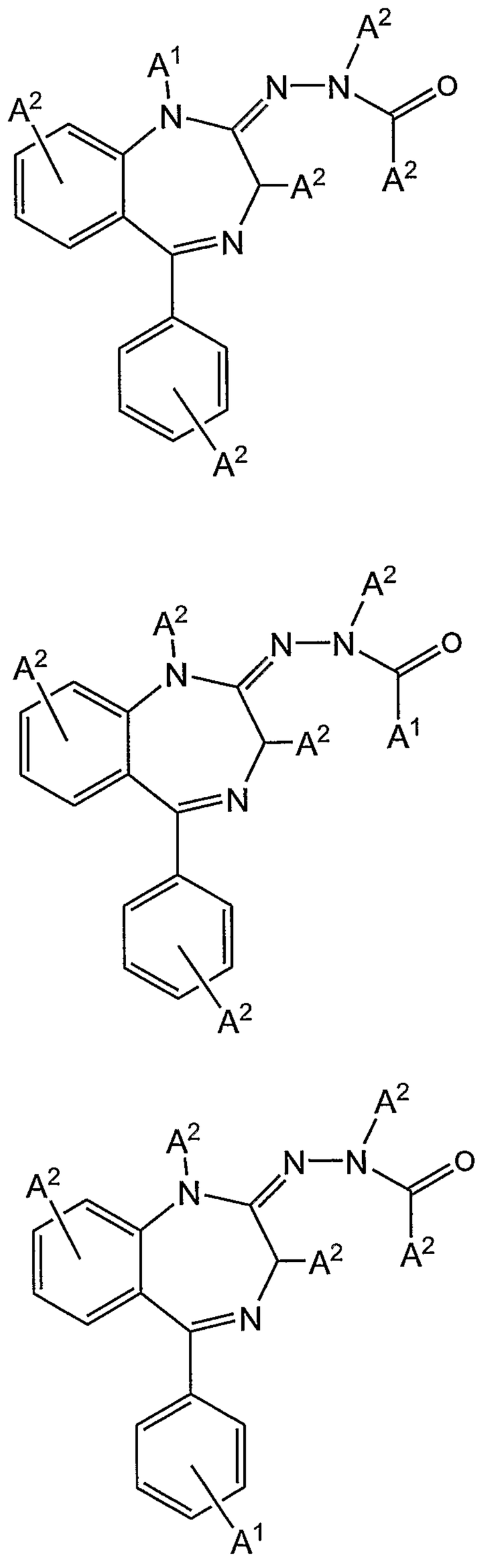
5

Group XXIX

In one aspect, the invention includes phosphonate analogs of benzodiazepine hydrazide compounds (WO 98/18473). Embodiments of Formula XXIX benzodiazepine hydrazide phosphonate compounds include the structures:

10



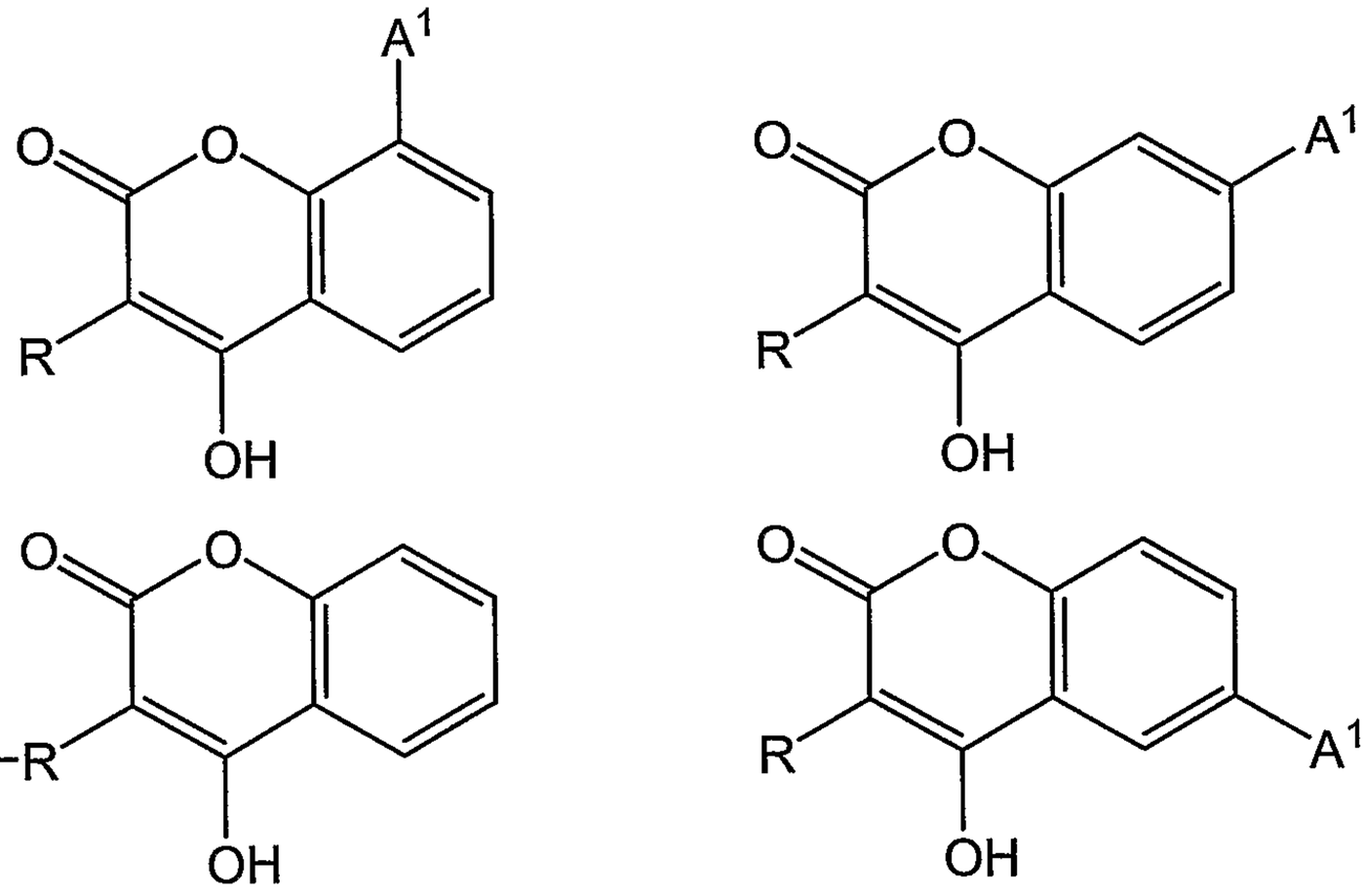


Group XXX

In one aspect, the invention includes phosphonate analogs of coumarin compounds (Mao et al (2002) *Chemical & Pharmaceutical Bulletin* 50(12):1634-1637; Chavda et al (2002) *Indian Journal of Chemistry, Section B: Organic*

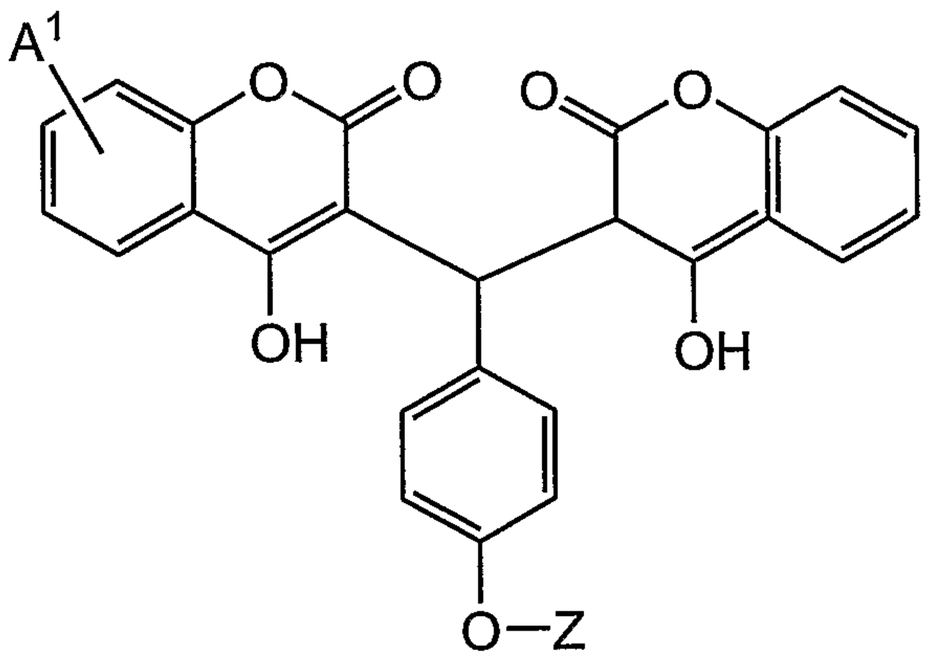
Chemistry Including Medicinal Chemistry 41B(10):2197-2199; Zhao et al (1997) *J. Med. Chem.* 40:242-249; Mazumder et al (1996) *J. Med. Chem.* 39:2472-2481; Hong et al (1997) *J. Med. Chem.* 40-930-936; JP 12178267). Coumarin phosphonate compounds include Lamellarin-type marine natural products (Reddy et al (1999) *J. Med. Chem.* 42(11):1901-1907; Zhang et al (2003) Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003; Ridley et al (2002) *Bioorganic & Medicinal Chemistry* 10(10)3285-3290; Handy et al Abstracts of Papers, 224th ACS National Meeting, Boston, MA, August 18-22, 2002).

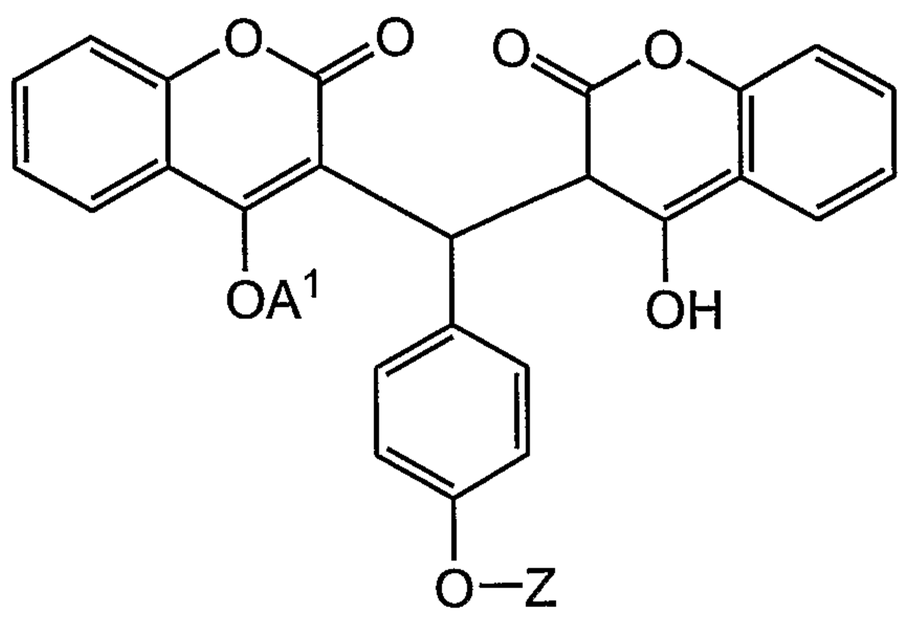
Exemplary phosphonate coumarin Formula XXX compounds include the structures:

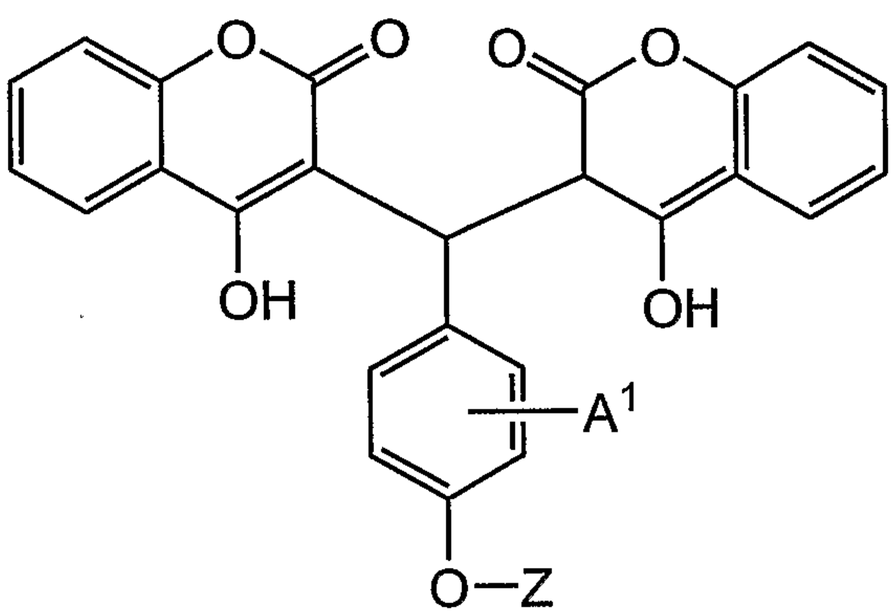


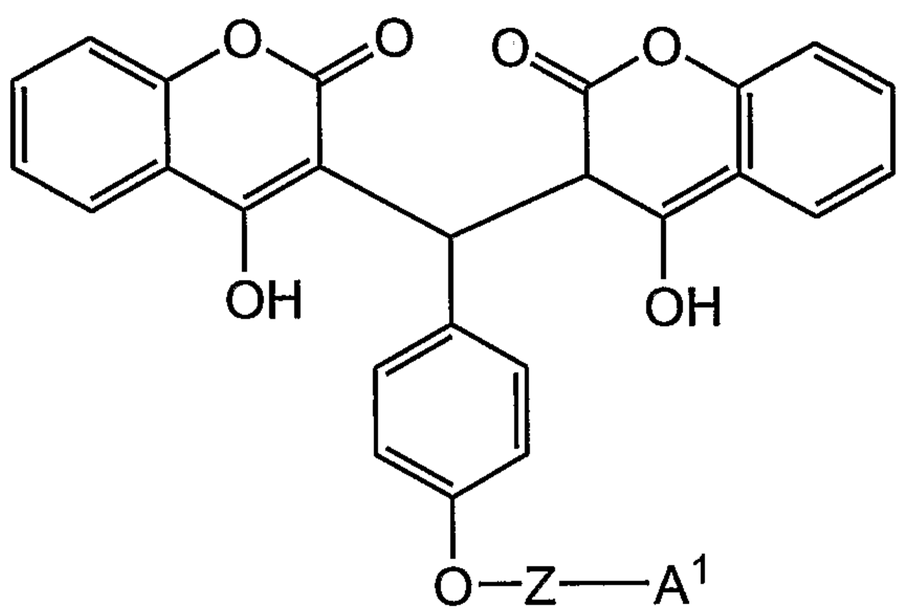
where R is H, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, or C_2–C_{20} substituted heteroaryl.

Exemplary phosphonate coumarin dimer Formula XXX compounds include the structures:



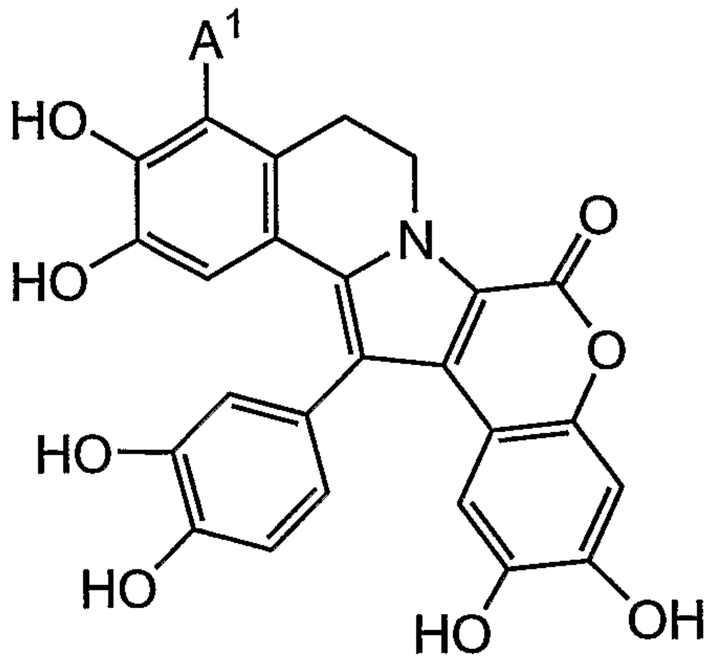


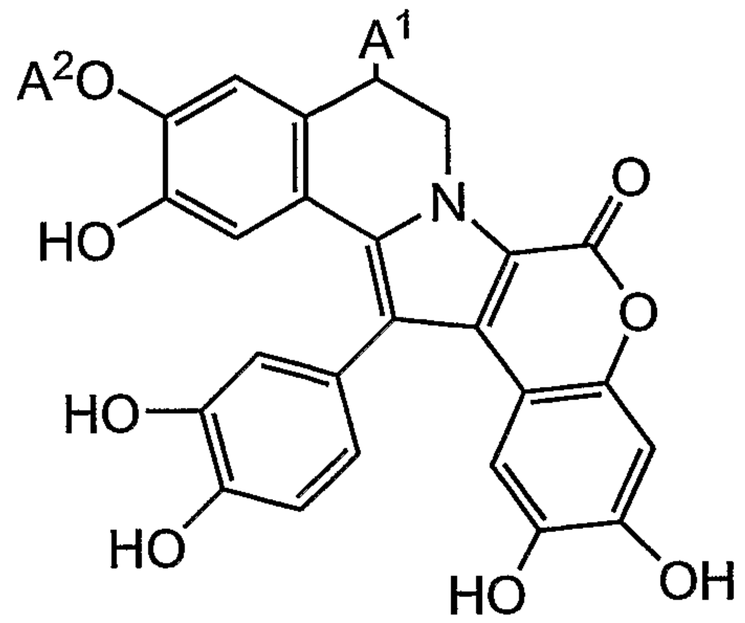


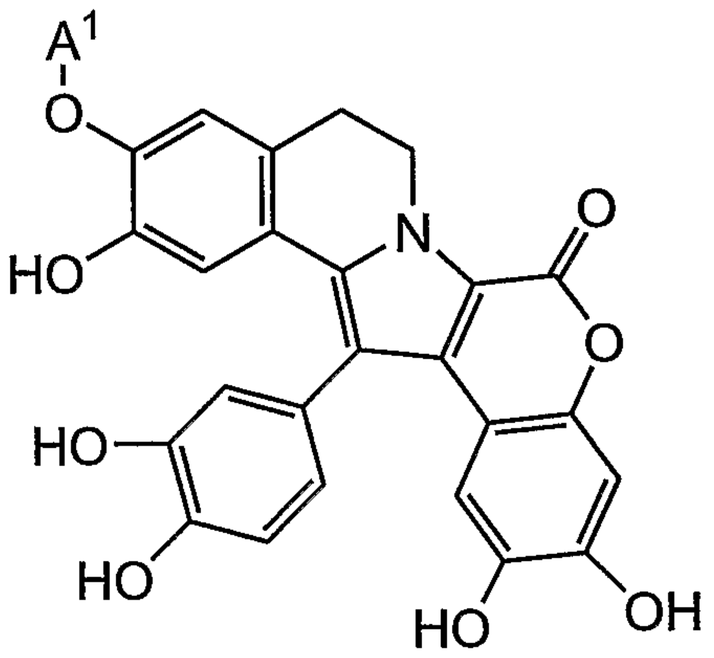


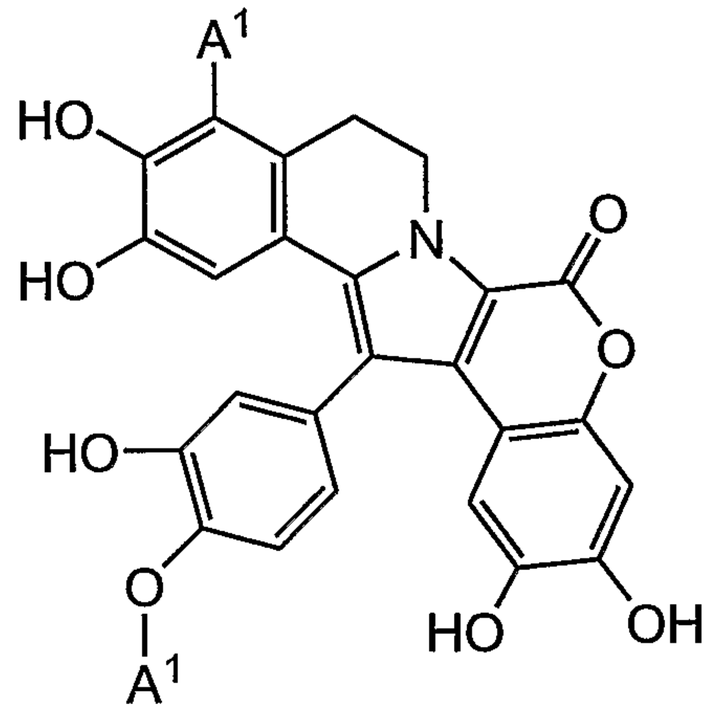
where Z is -C(O)Ar or -SO_2R.

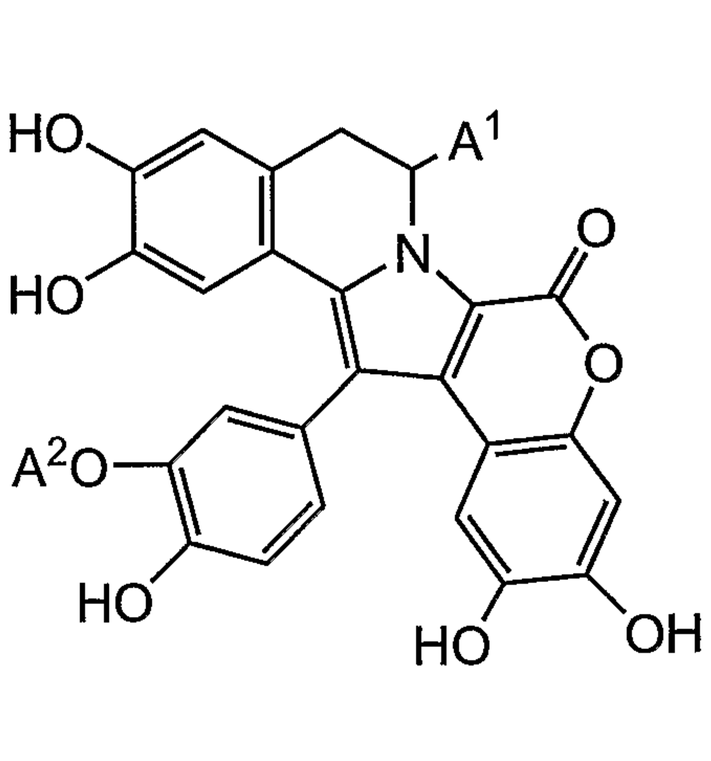
Exemplary phosphonate Lamellarin Formula XXX compounds include the structures:

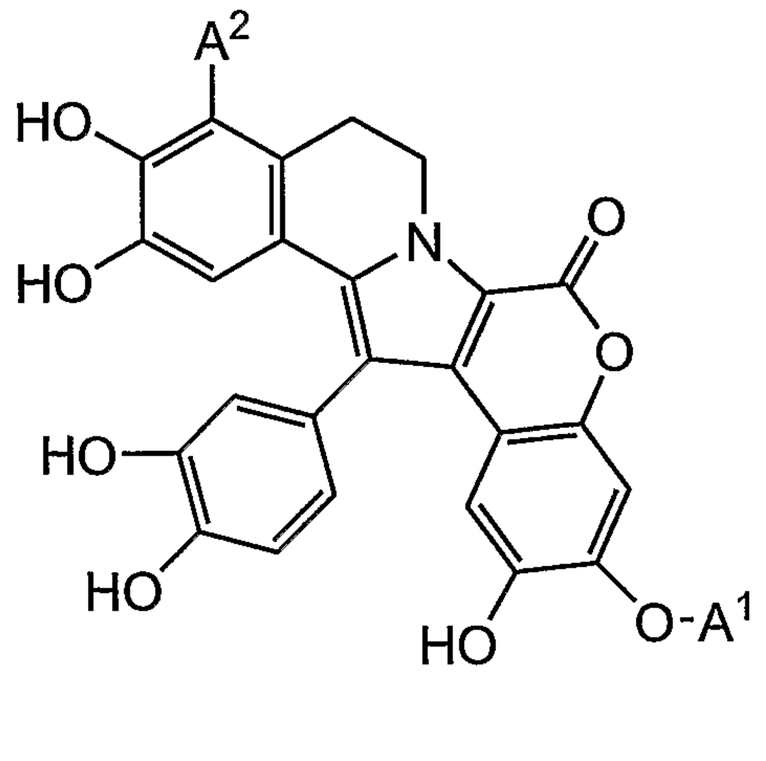








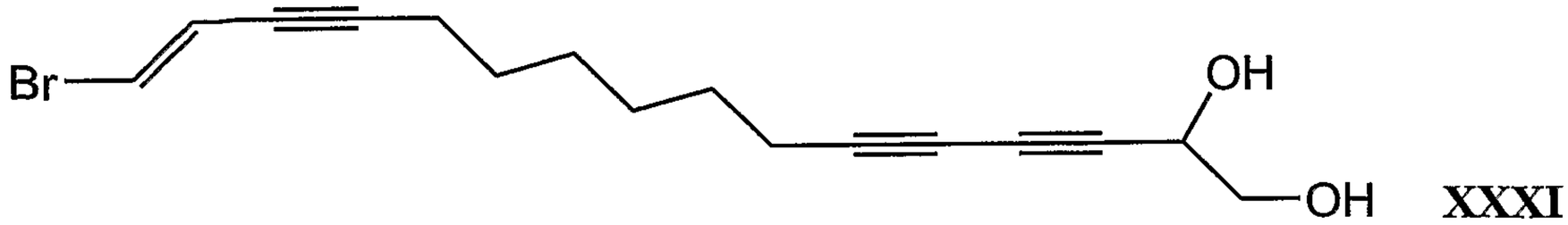




5 Group XXXI

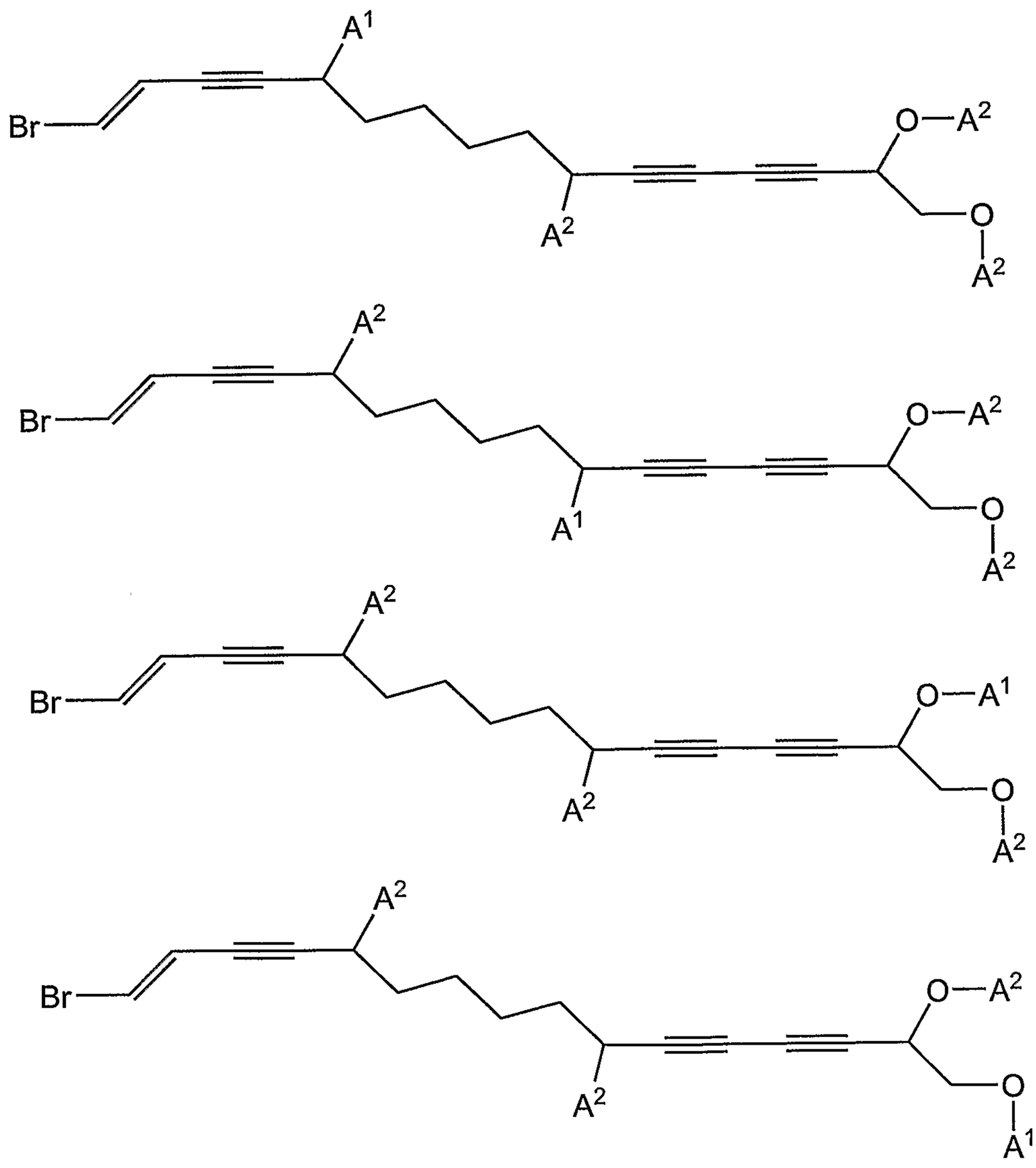
In one aspect, the invention includes phosphonate analogs of brominated polyacetylene marine natural products from sponges such as Diplastrella sp. (Lerch et al (2003) *Journal of Natural Products* 66(5):667-670). Brominated polyacetylene

phosphonate Formula XXXI compounds, including sulfated and sufonated analogs, have the structure:



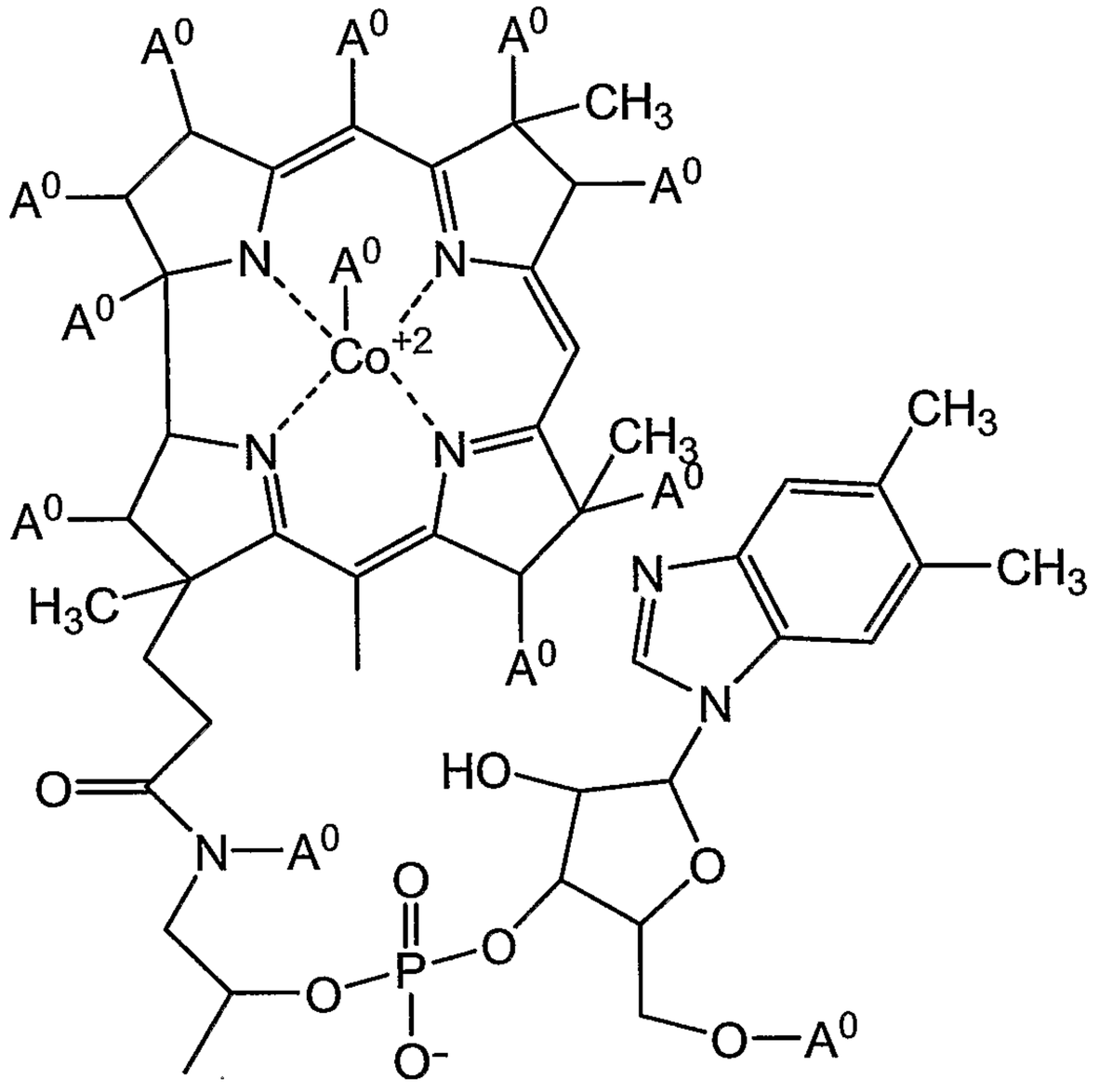
XXXI

Exemplary phosphonate brominated polyacetylene Formula XXXI compounds include the structures:



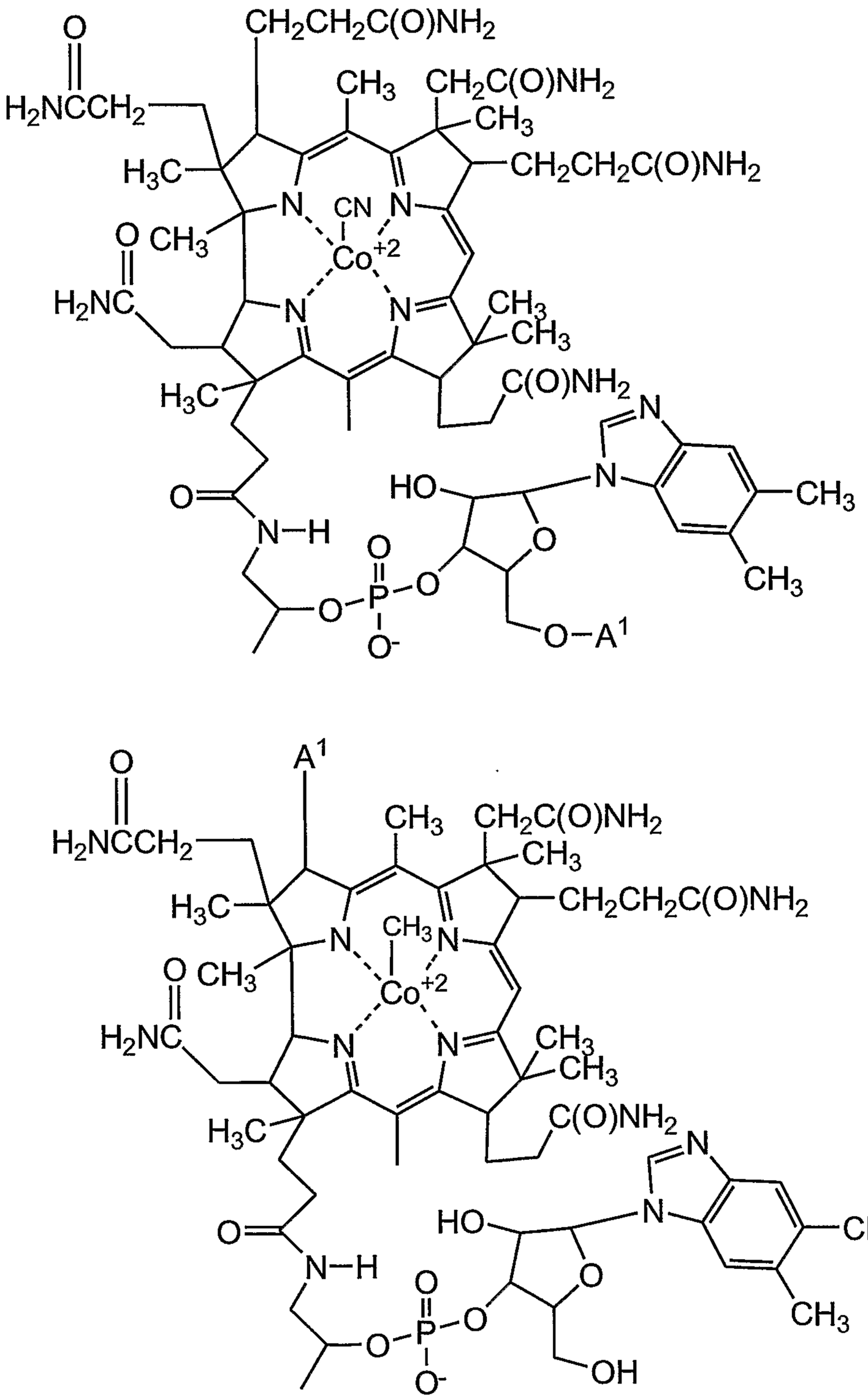
Group XXXII

In one aspect, the invention includes phosphonate analogs of cobalamin (Vitamin B12) compounds (Weinberg et al (1998) *Biochem. Biophys. Res. Commun.* 246:393-397) including structure XXXII.



XXXII

Exemplary phosphonate cobalamin Formula XXXI compounds include the structures:

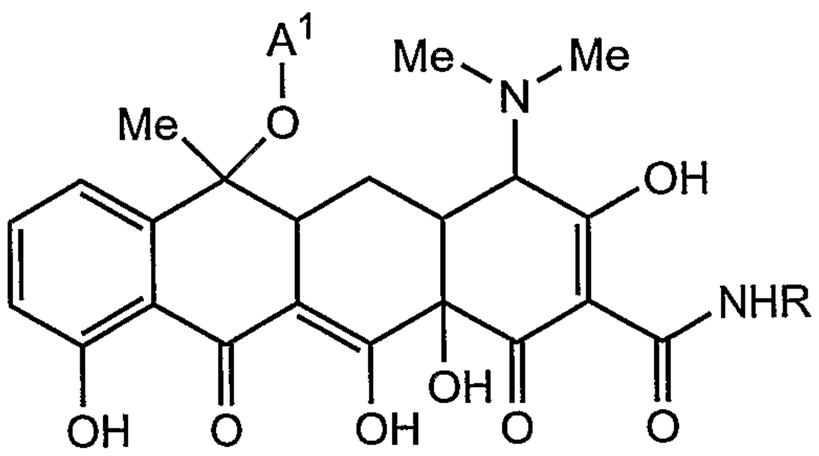


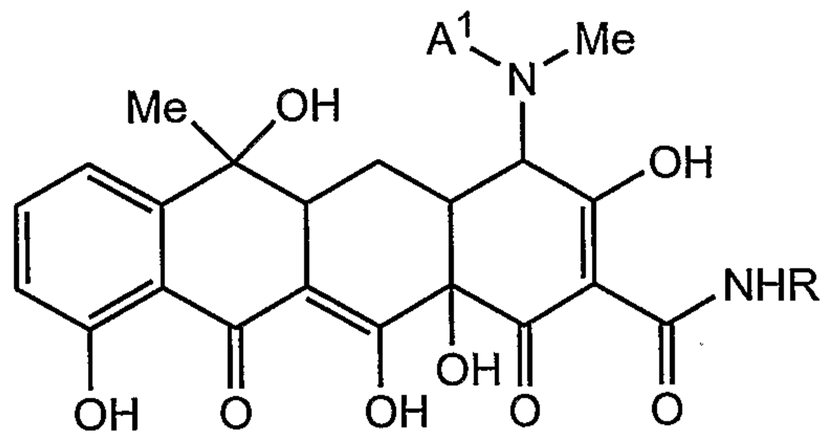
and all phosphonate analogs of cobalt complexes of corrin, cobyrinic acid and corrole ring systems (Merck Index, Eleventh Edition (1989), entry 9921).

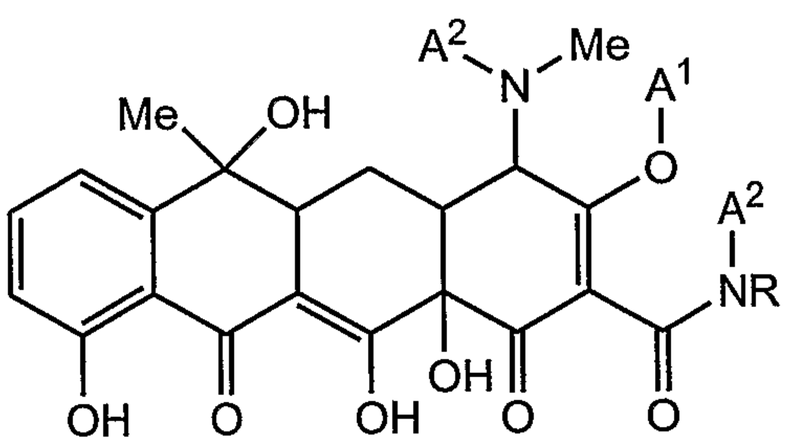
Group XXXIII

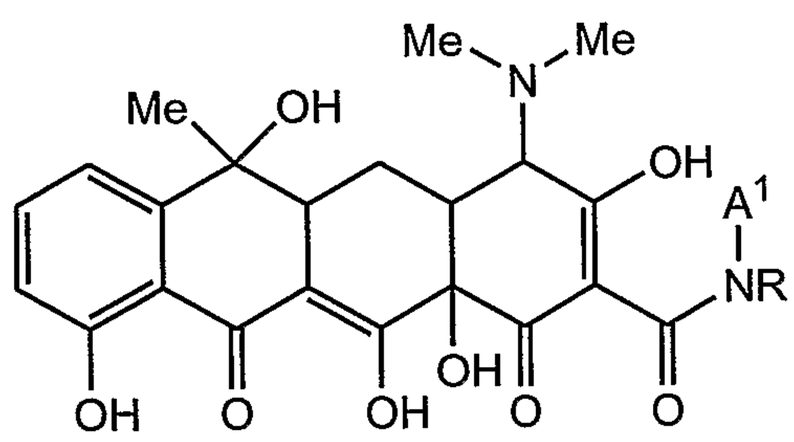
In one aspect, the invention includes phosphonate analogs of hydroxylated aromatic compounds (Burke et al (1995) J. Med. Chem. 38:4171-4178), including: tetracycline compounds (Neamati et al (1997) *Mol. Pharmacol.* 52:1041-1055); anthraquinones and naphthoquinones (Fesen et al (1993) *Proc. Natl. Acad. Sci. USA* 90:2399-2403; Farnet et al (1996) *Proc. Nat. Acad. Sci. USA* 93:9742-9747); and flavones, flavanones, flavanols, and flavanoids (Lee et al (2003) *Hakhak Hoechi* (Korea) 47(1):46-51; Mateeva et al (2002) *Jour. of Heterocyclic Chemistry* 39(6):1251-1258; Li et al (2002) *Tetrahedron Lett.* 43(51):9467-9470; Tewtrakul et al (2992) *Chemical & Pharmaceutical Bulletin* 50(5):630-635; Fesen et al (1994) *Biochem. Pharmacol.* 48:595-608; Ahn et al (2002) *Planta Medica* 68(5):457-459; Lee et al (2003) *Planta Medica* 69(9):859-861) including thalassiolins (Rowley et al (2002) *Bioorganic & Medicinal Chemistry* 10(11):3619-3625); baicalein and baicalin (Ahn ety al (2001) *Molecules and Cells* 12(1):127-130); and benzopyrano-oxopyrimidotetrahydrothiazines (WO 02/051419 A2).

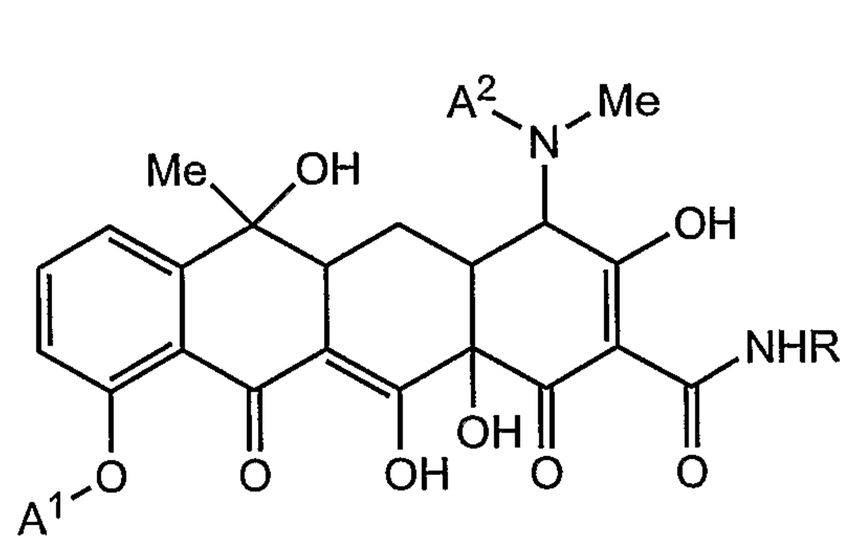
Exemplary embodiments of Formula XXXIII tetracycline phosphonate compounds include:

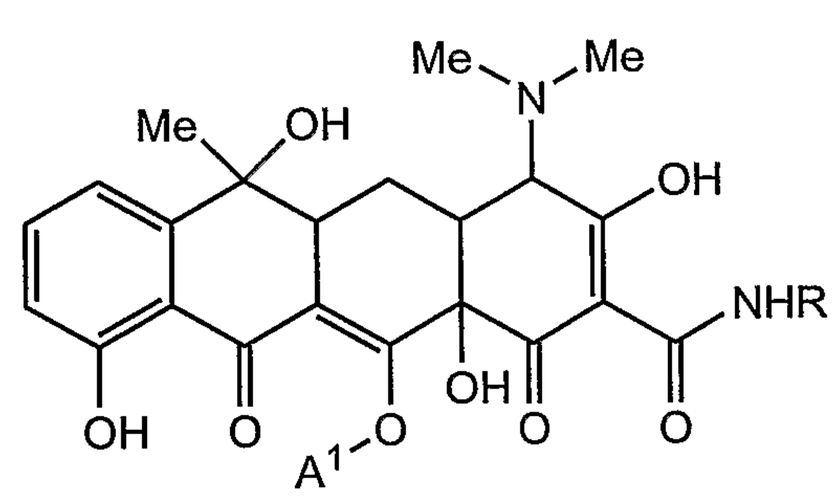




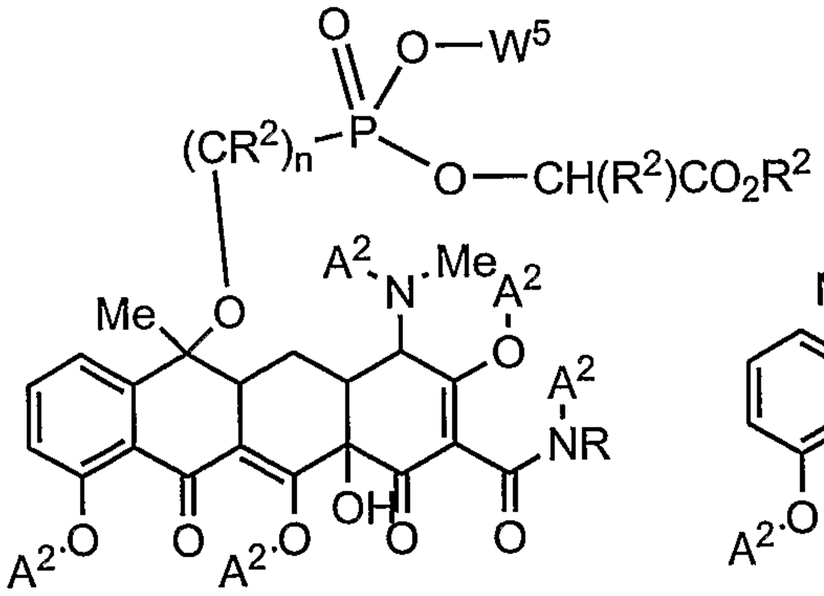


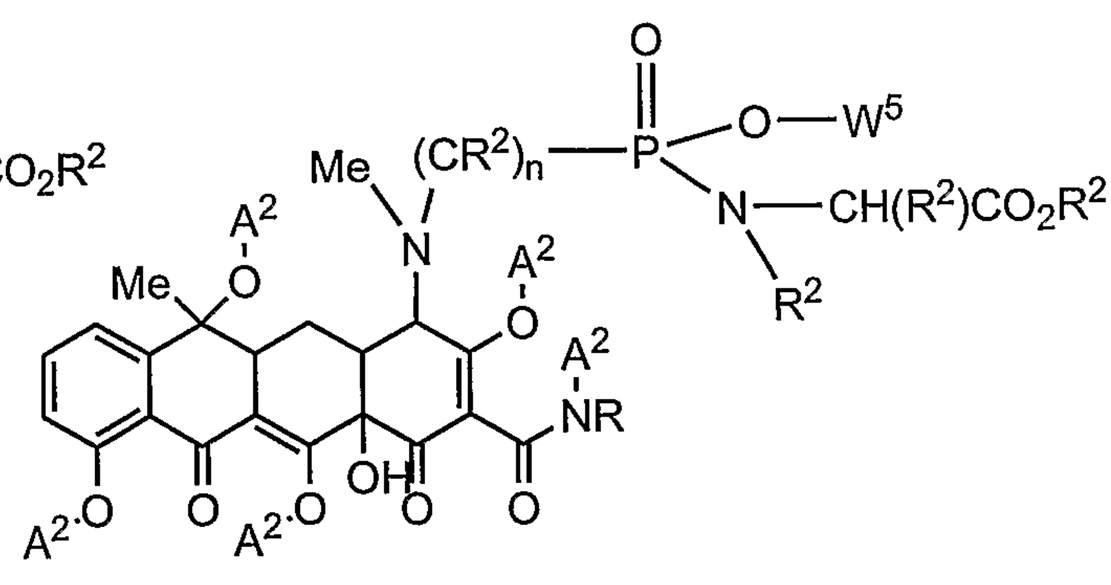


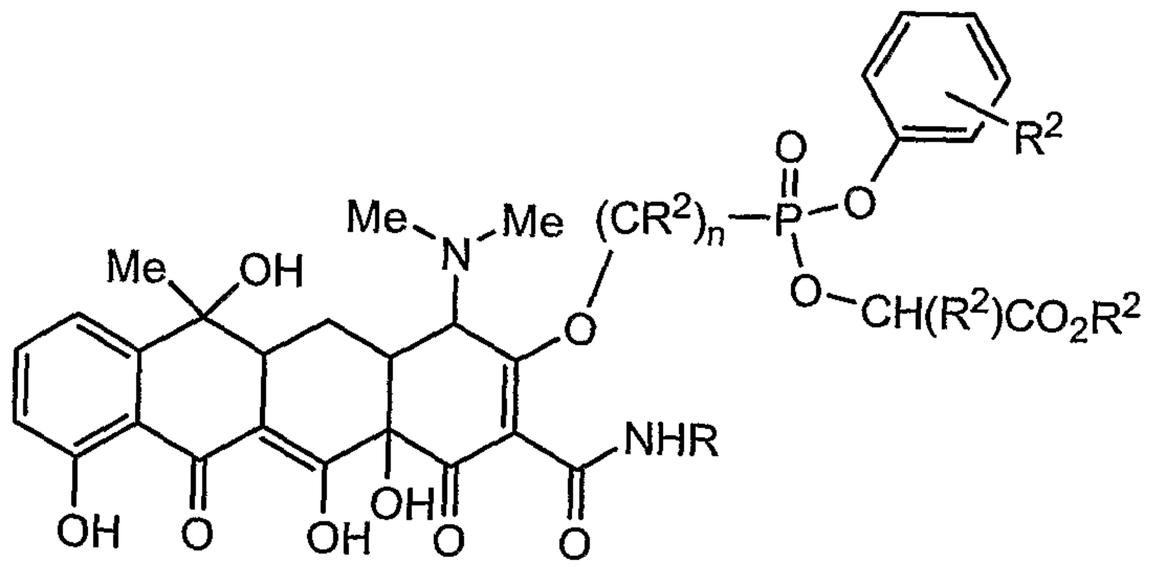


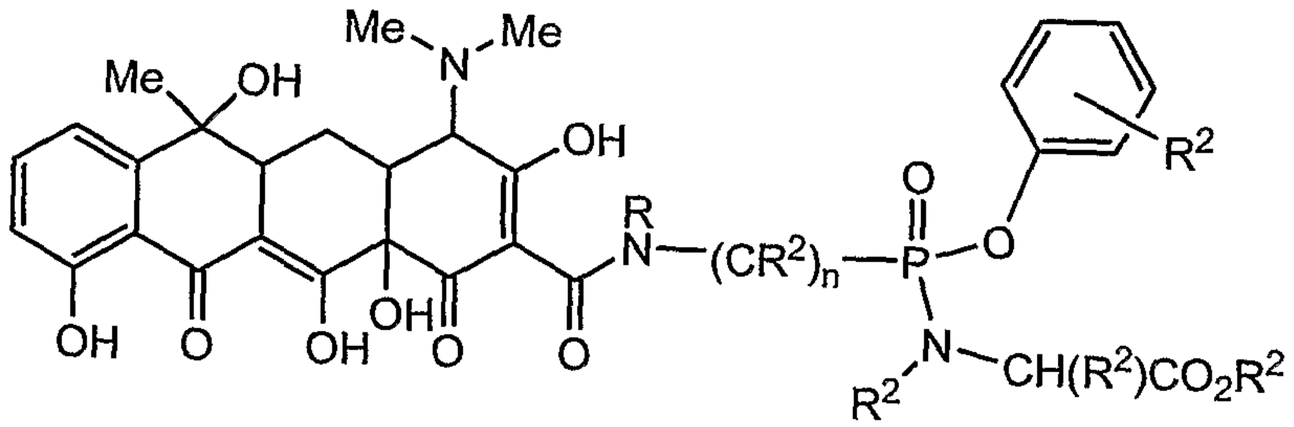


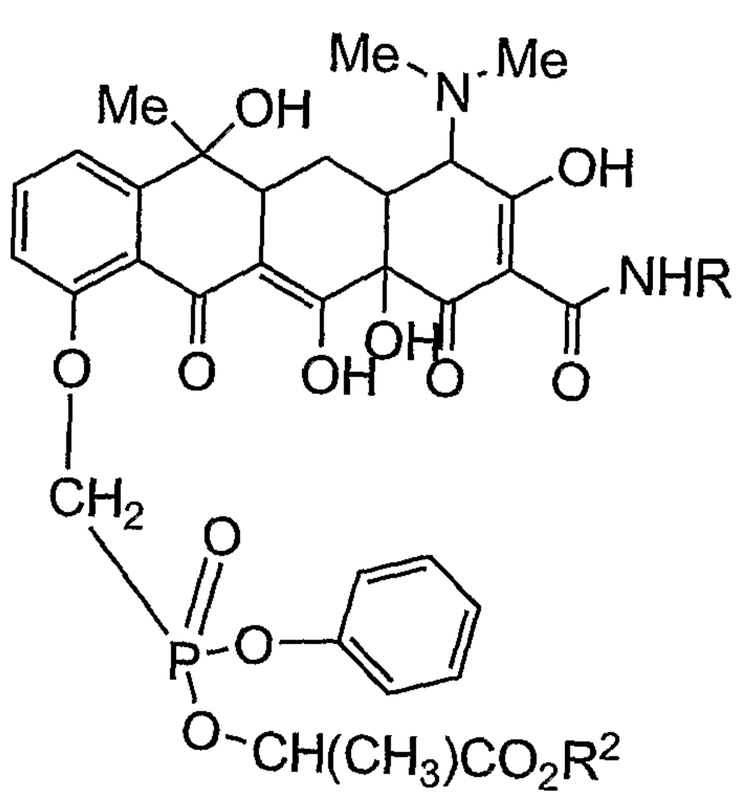
Exemplary embodiments of Formula XXXIII tetracycline phosphonate compounds further include:

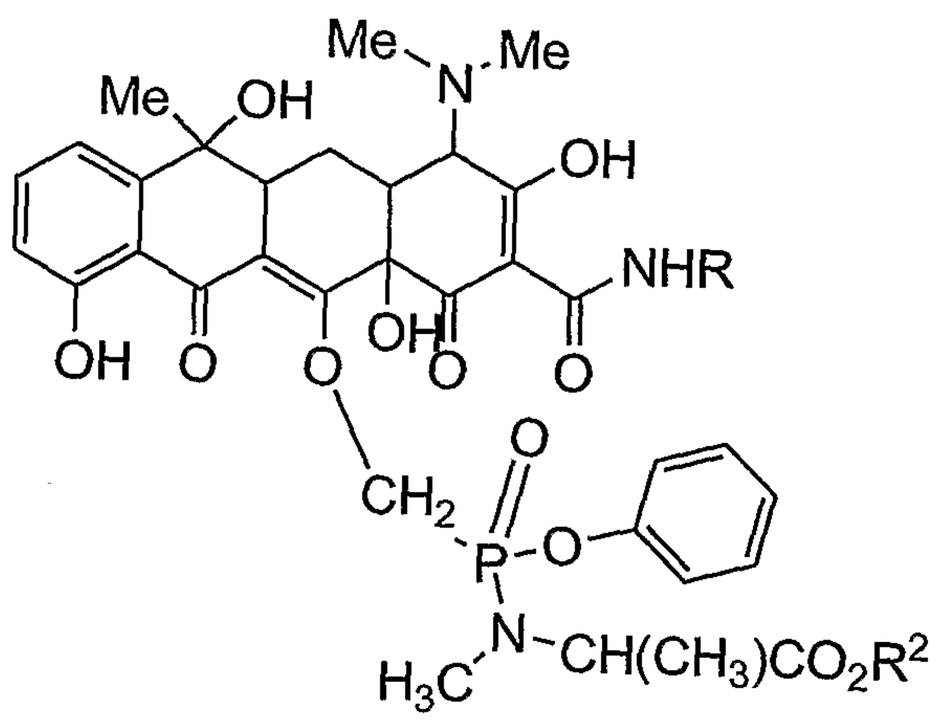




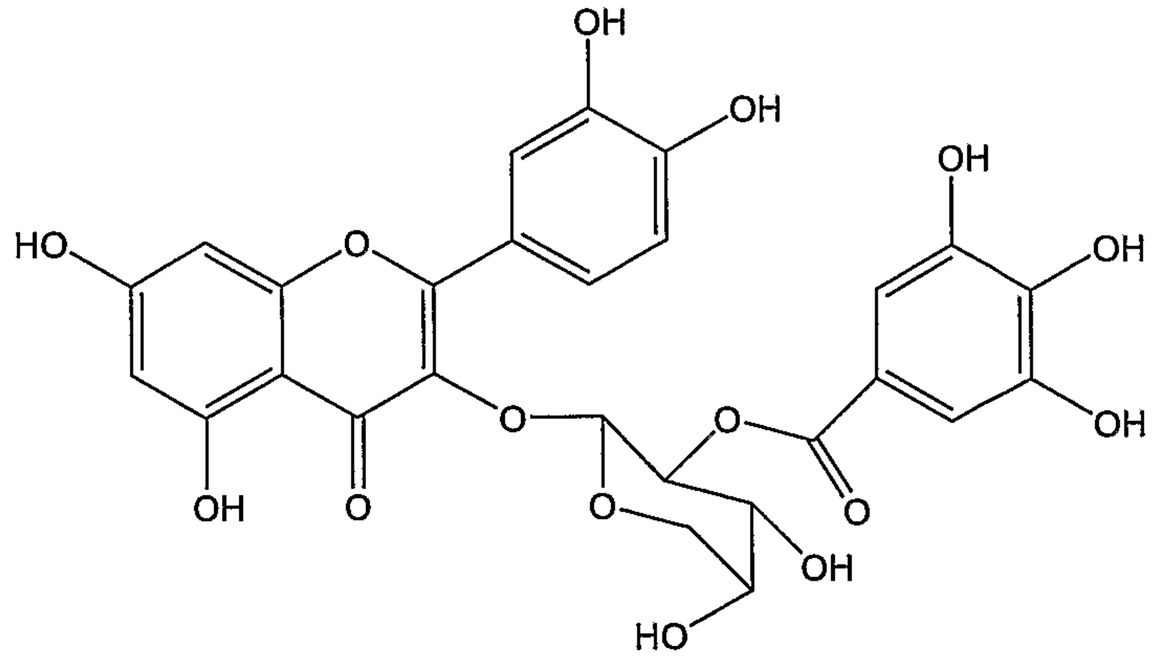




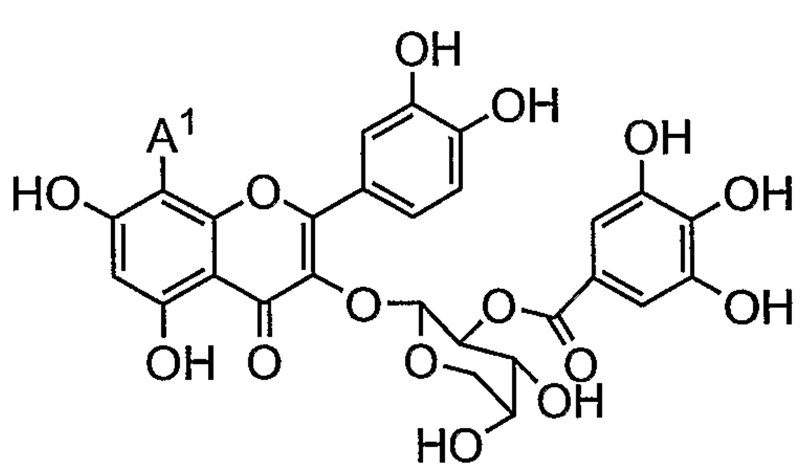


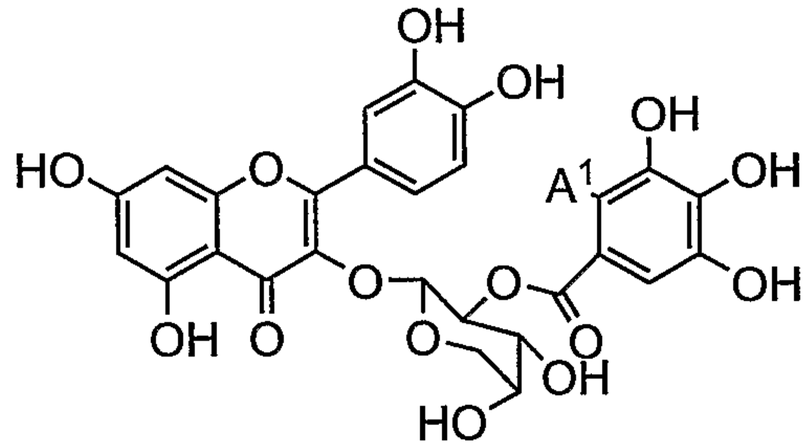


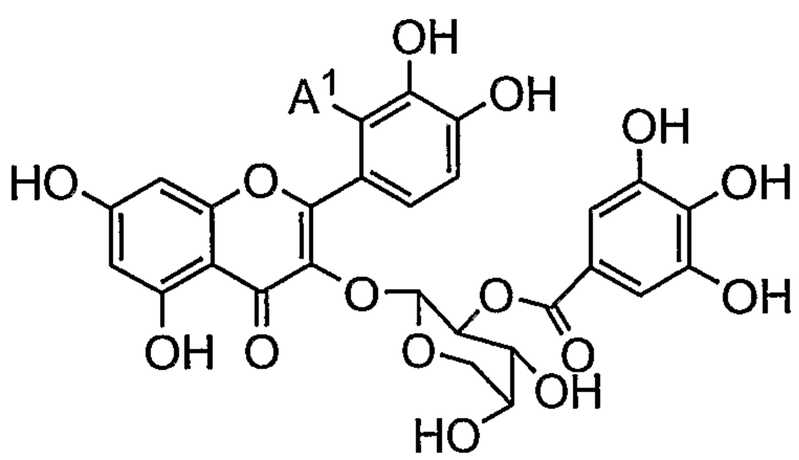
Exemplary embodiments of Formula XXXIII flavanol phosphonate compounds include phosphonate analogs of quercetin 3-O-(2"-galloyl)-α-L-arabinopyranoside such as the structures:

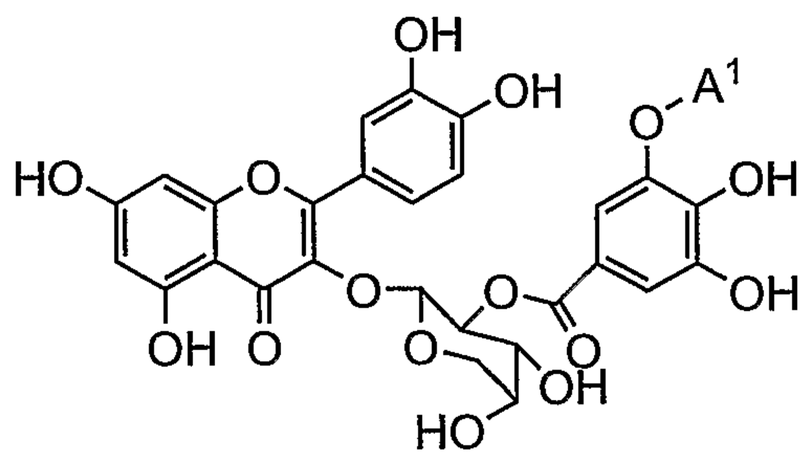


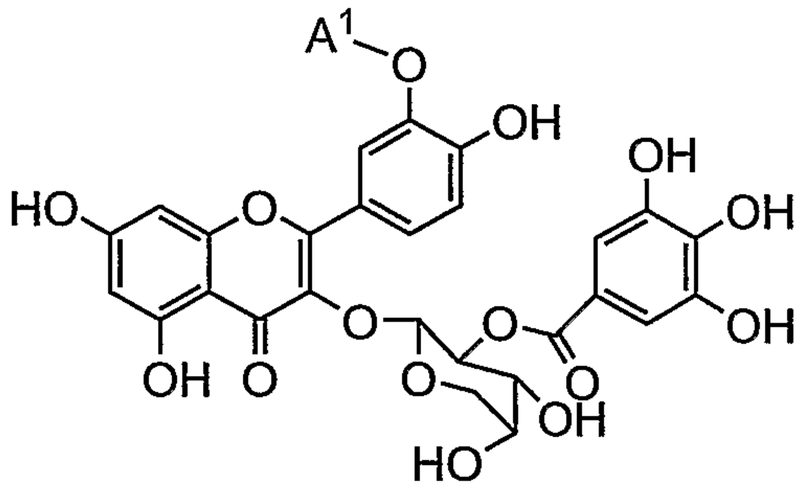
where at least one carbon or hydroxyl oxygen atom is substituted with an A^1 group, and any carbon or hydroxyl oxygen atom may be substituted with an A^2 group, including the exemplary structures:

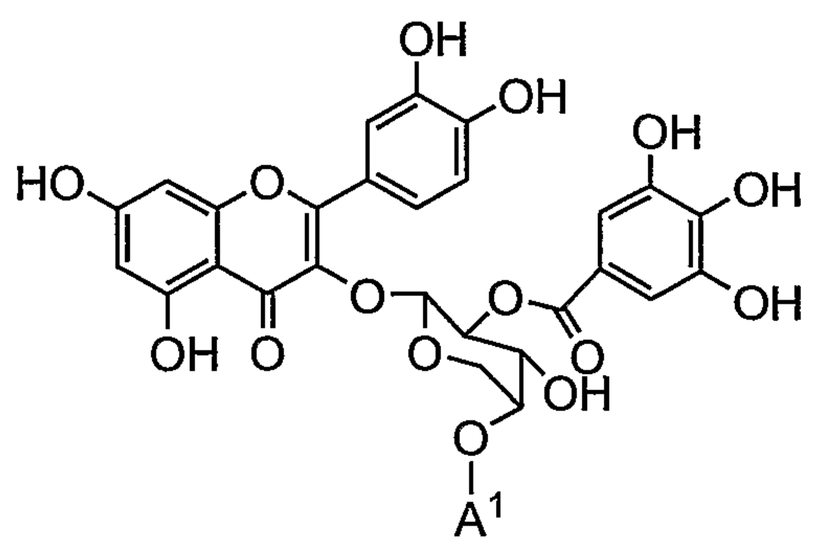


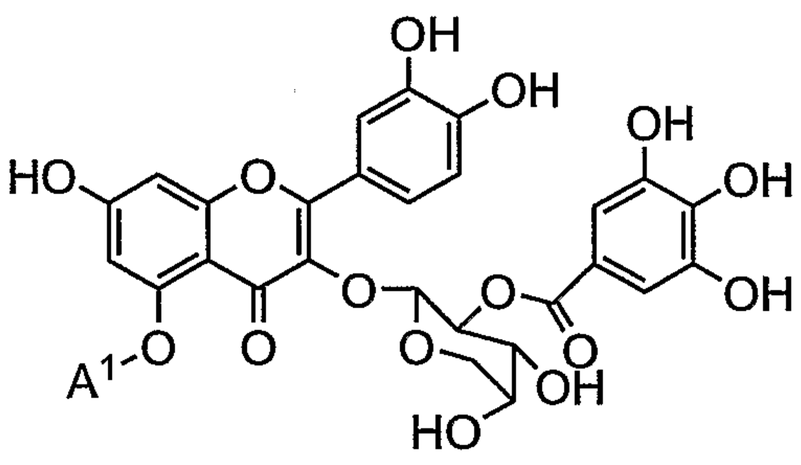


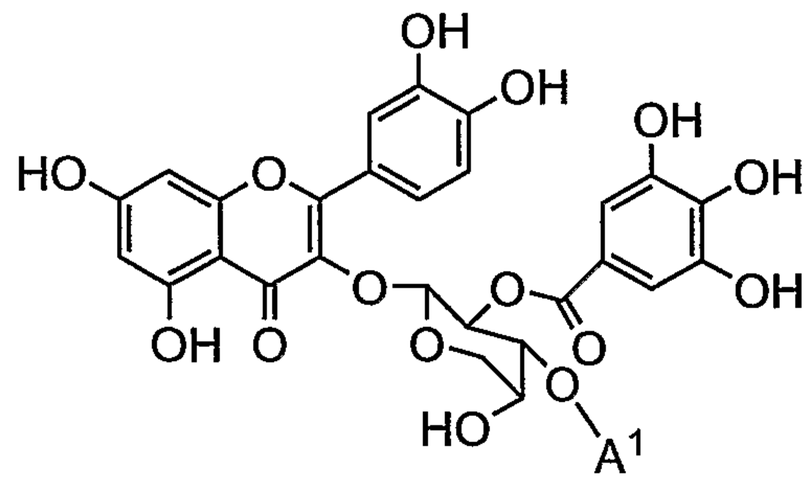




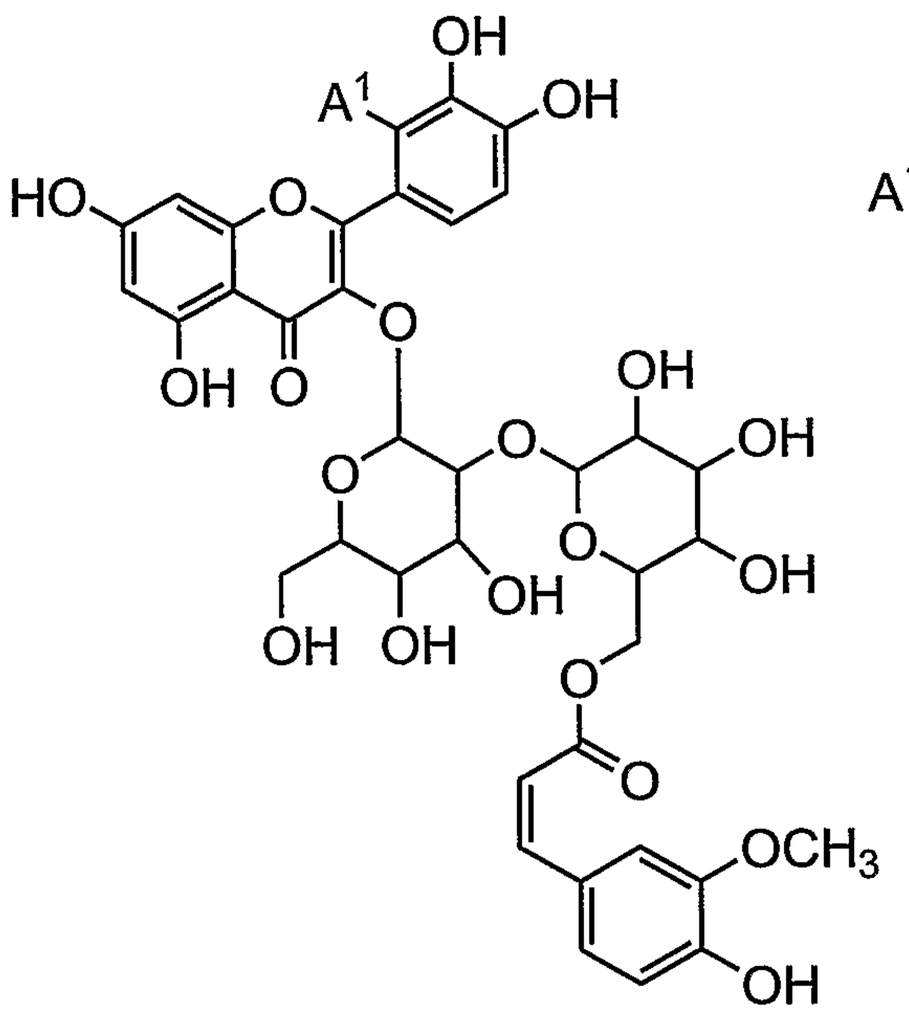

A1
O
OH
HO
O
OH
OH
OH
O
O
O
O
OH
HO

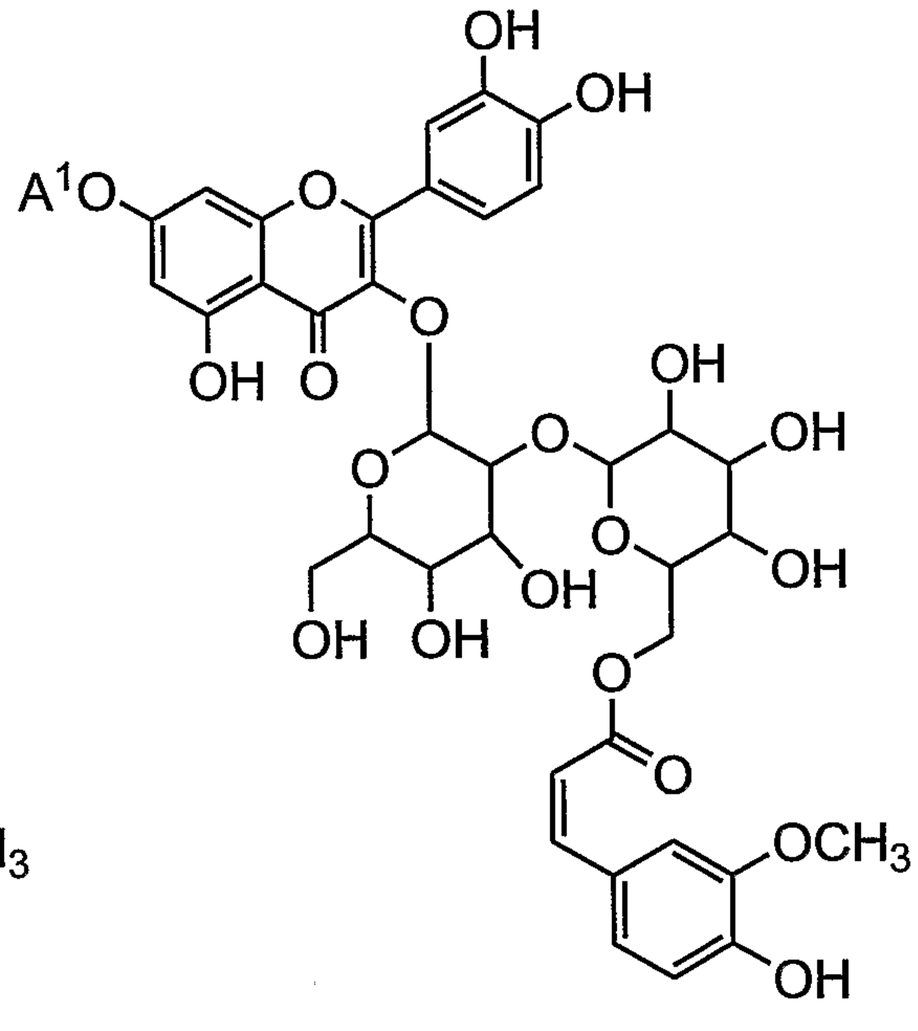

OH
OH
HO
O
OH
OH
OH
O
O
O
O
OH
O
A1


OH
OH
HO
O
OH
OH
OH
O
O
O
O
OH
A1-O
HO

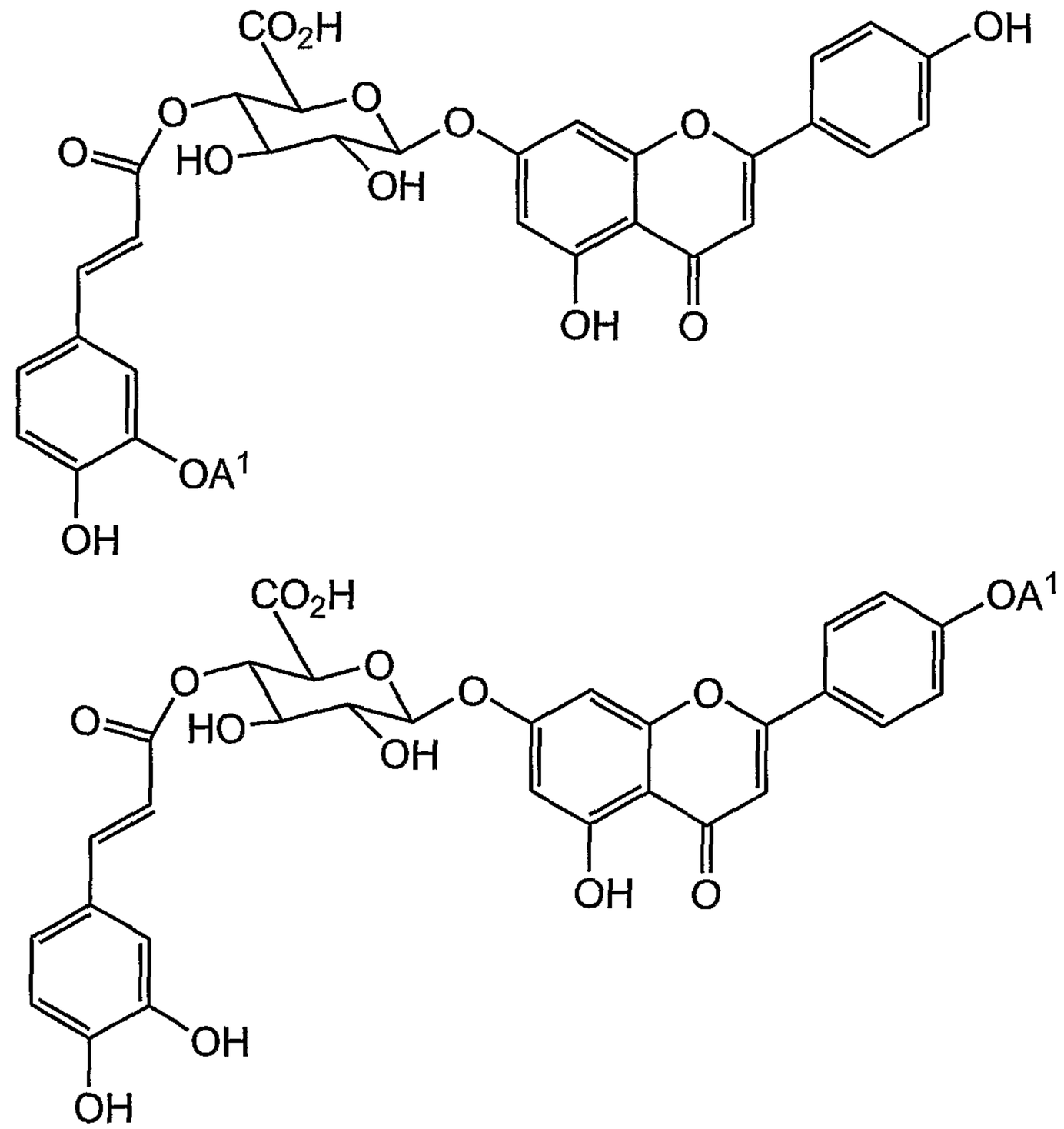

OH
OH
HO
O
OH
OH
OH
O
O
O
O
OH
HO
O
A1

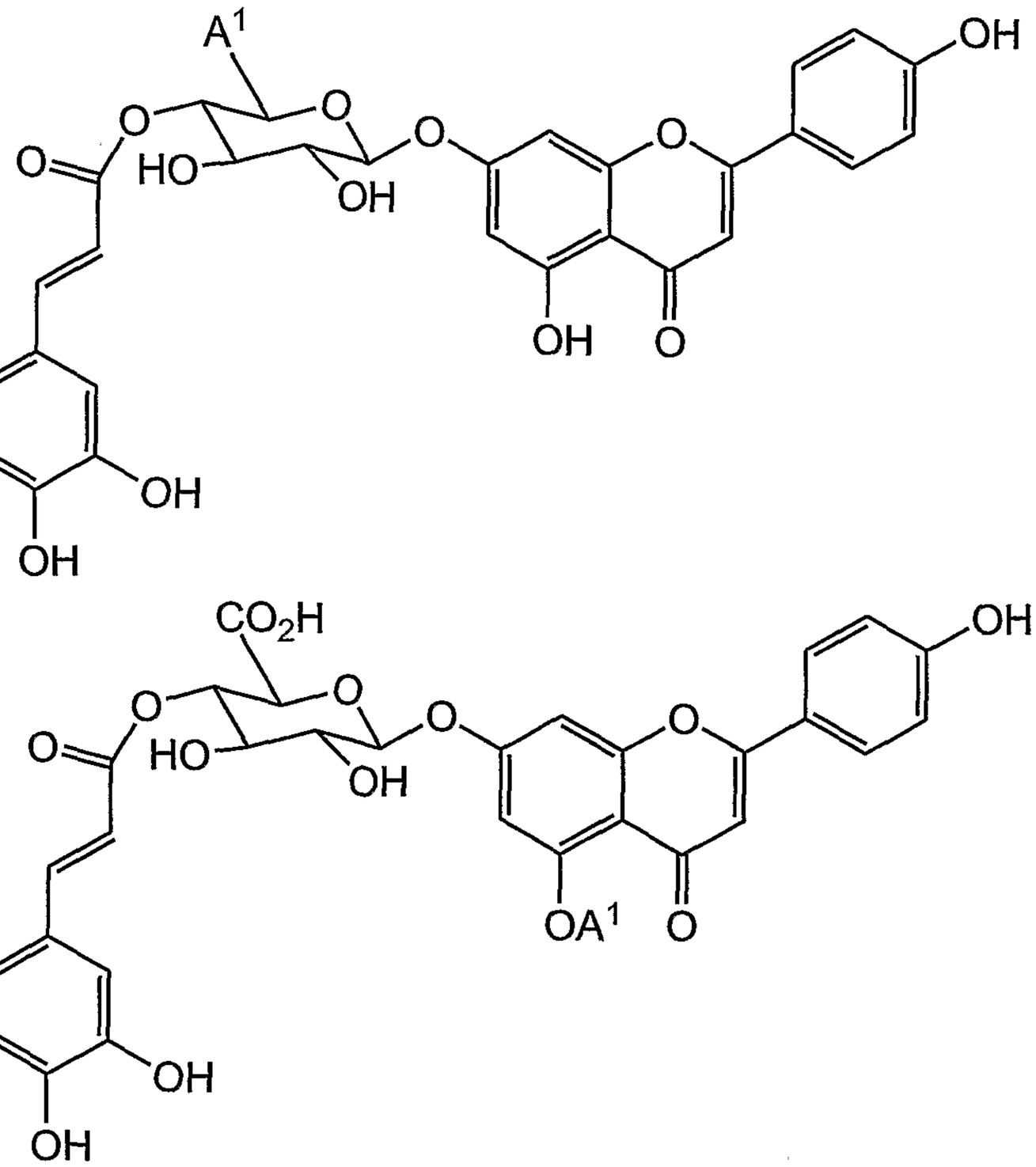
Exemplary Disaccharide catechol phosphonate Formula XXXIII compounds include the structures:





Exemplary flavonoid glucuronide phosphonate Formula XXXIII compounds include the structures:

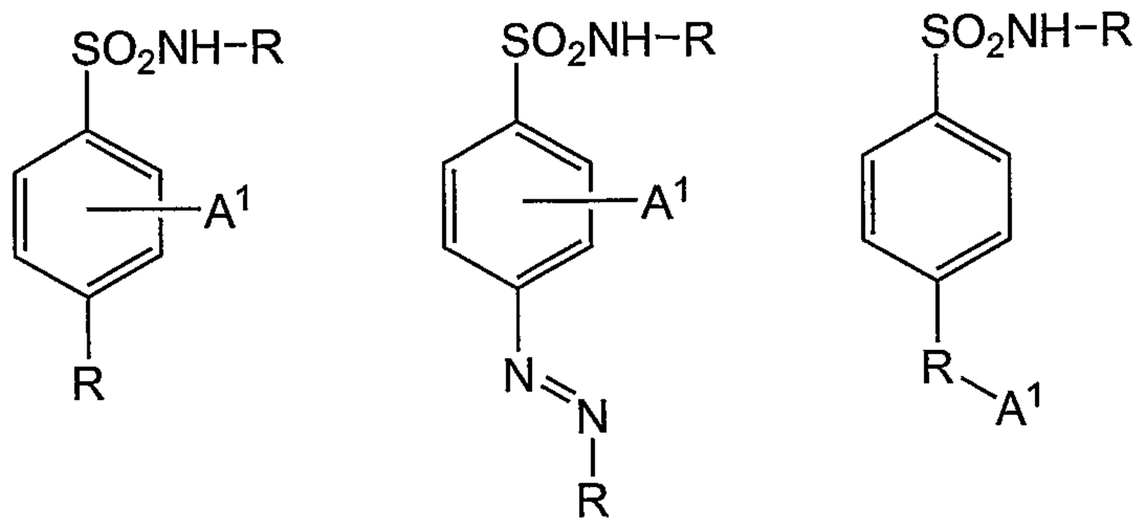


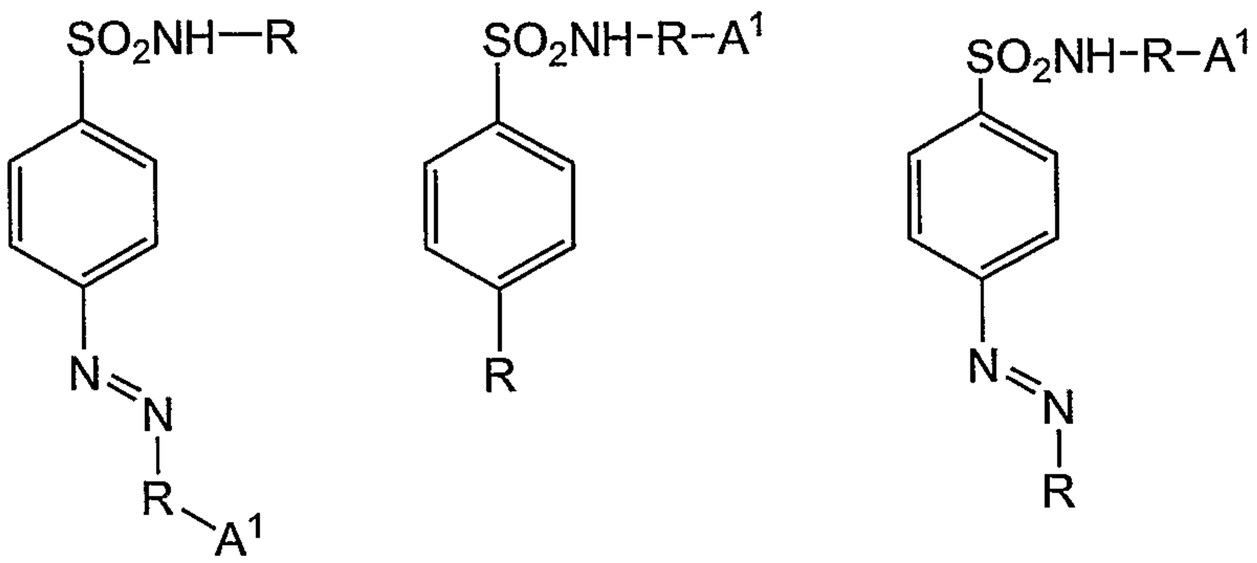


Group XXXIV

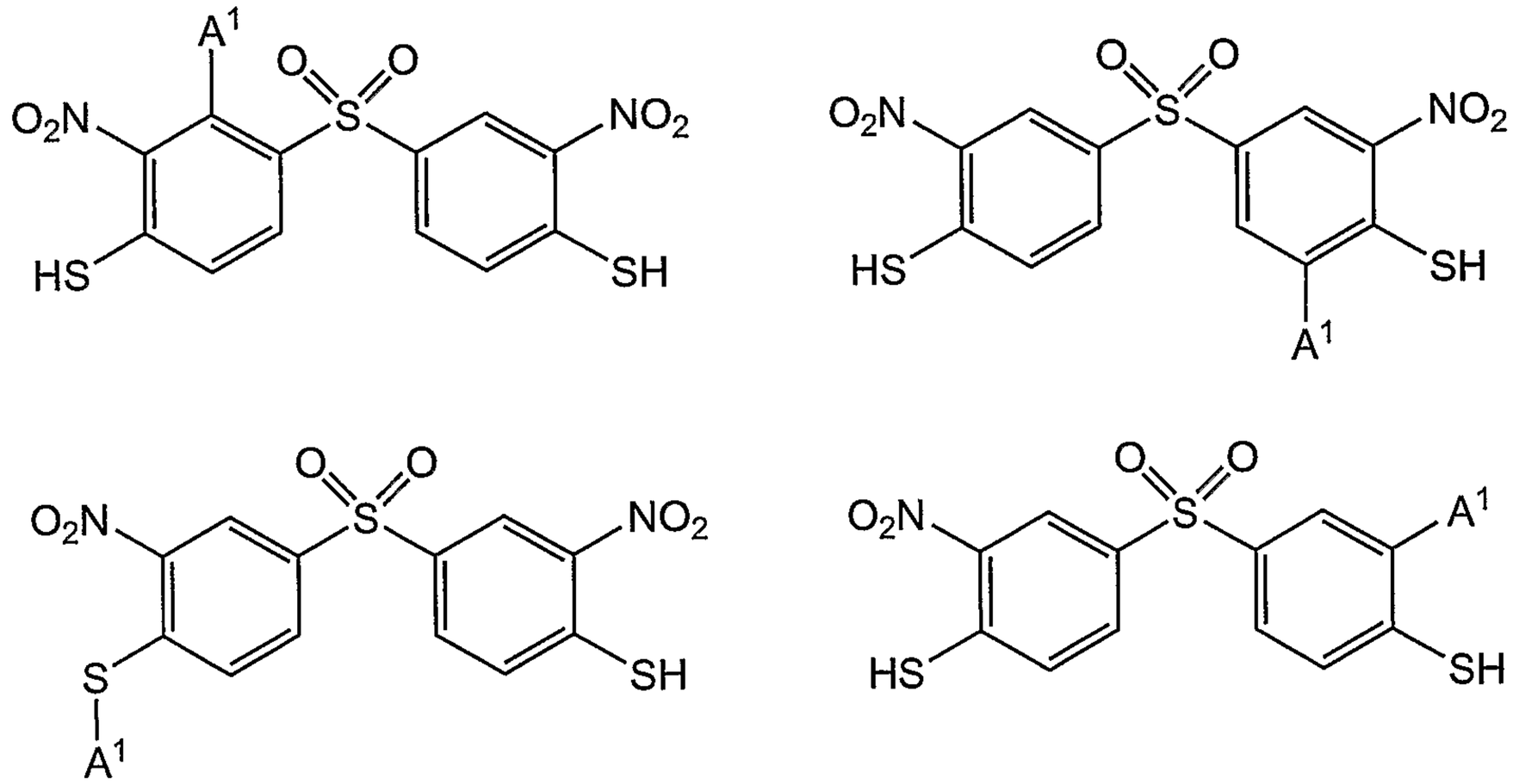
In one aspect, the invention includes phosphonate analogs of various sulfur-containing compounds including phosphonate analogs of: polyanionic sulfonate suramin and dextran sulfate (Billich et al (1992) *Antivir. Chem. Chemothe*r. 3:113-119; Carteau et al (1993) *Arch. Biochem. Biophys*. 305:606-610); diaryl sulfones (Gervay-Hague et al (2003) Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003; Abstract No. 2003:184008; Neamati et al (1997) *Antimicrob. Agents Chemother*. 41:385-393); sulfonamides (Nicklaus et al (1997) *J. Med. Chem*. 40:920-929); aromatic disulfides; and 2-mercaptobenzenesulfonamides (Neamati et al (1997) *Antimicrob. Agents Chemother*. 8:485-495).

Exemplary phosphonate sulfonamide Formula XXXIV compounds include:

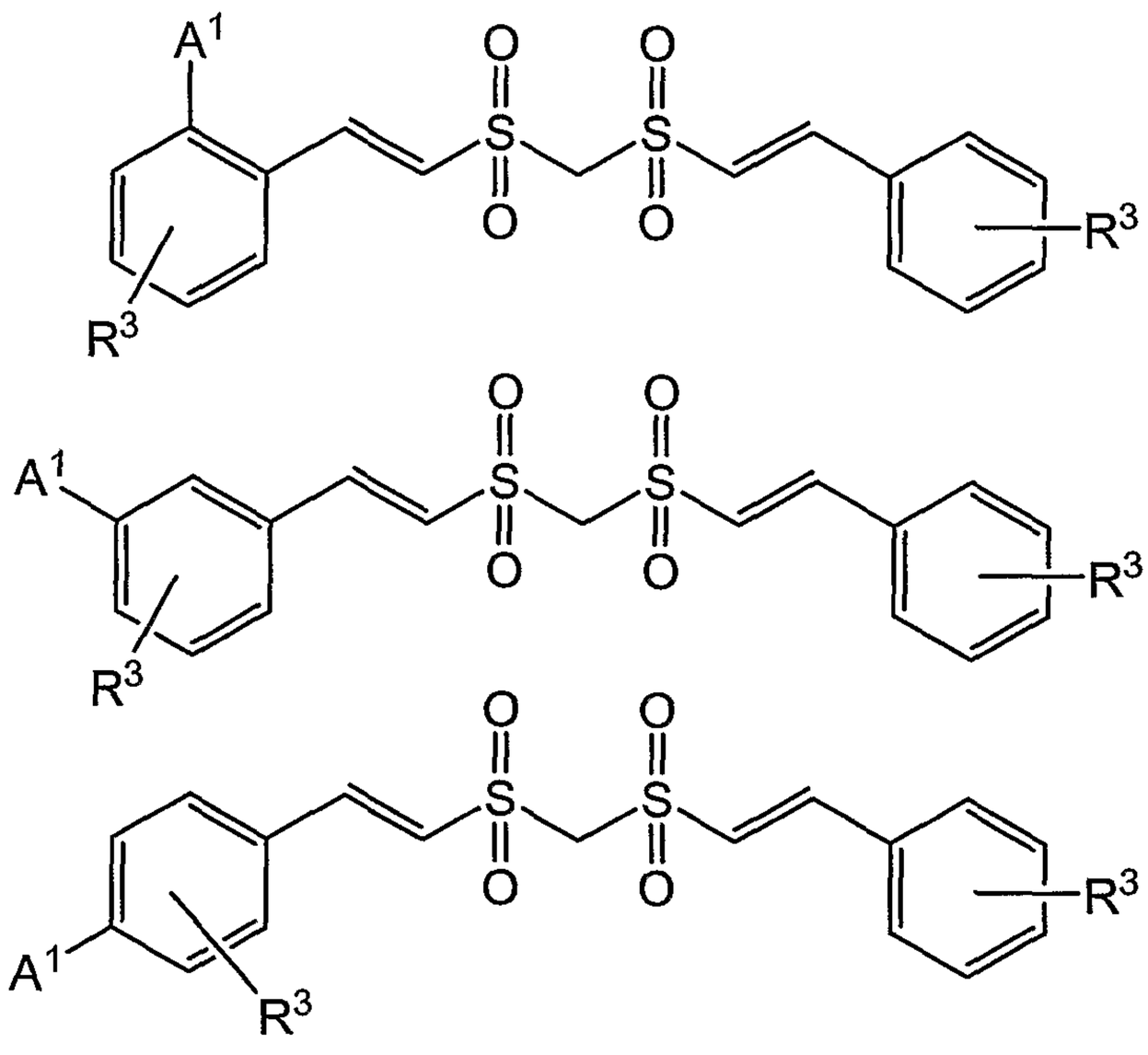




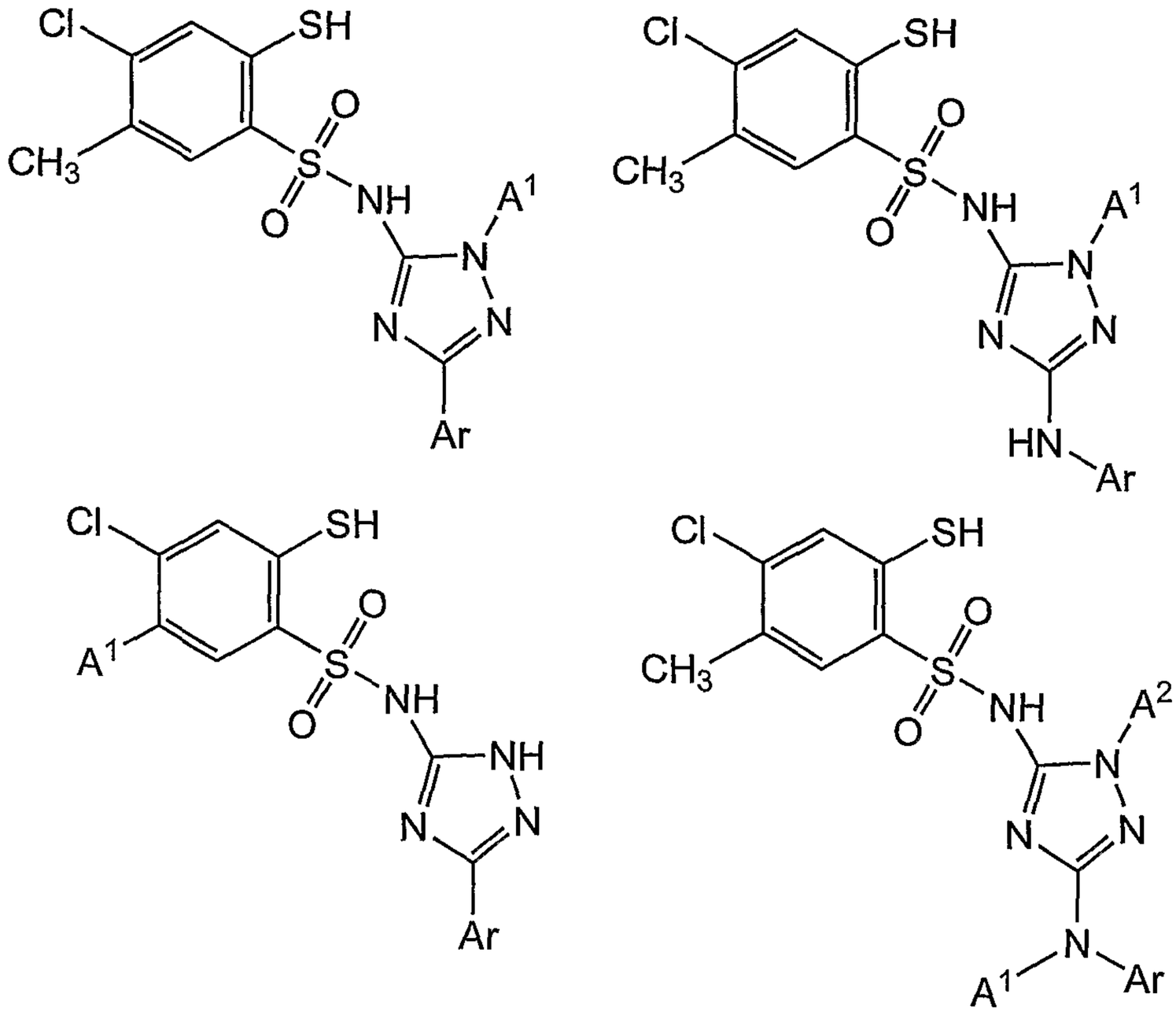
Exemplary diaryl sulfone phosphonate Formula XXXIV compounds include:



Exemplary distyryl disulfone phosphonate Formula XXXIV compounds include:



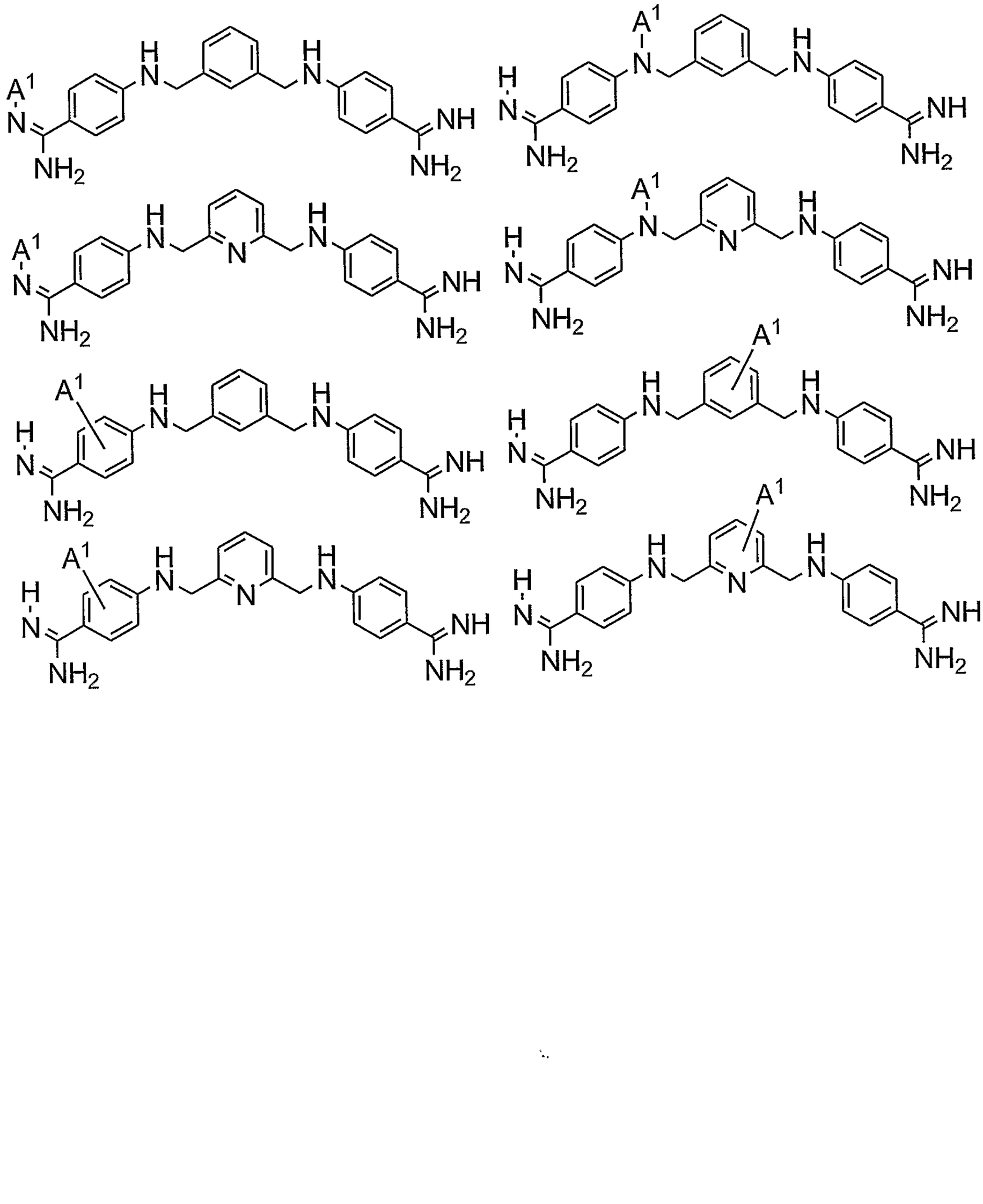
Exemplary 2-mercaptobenzenesulfonamide phosphonate Formula XXXIV compounds include the structures:



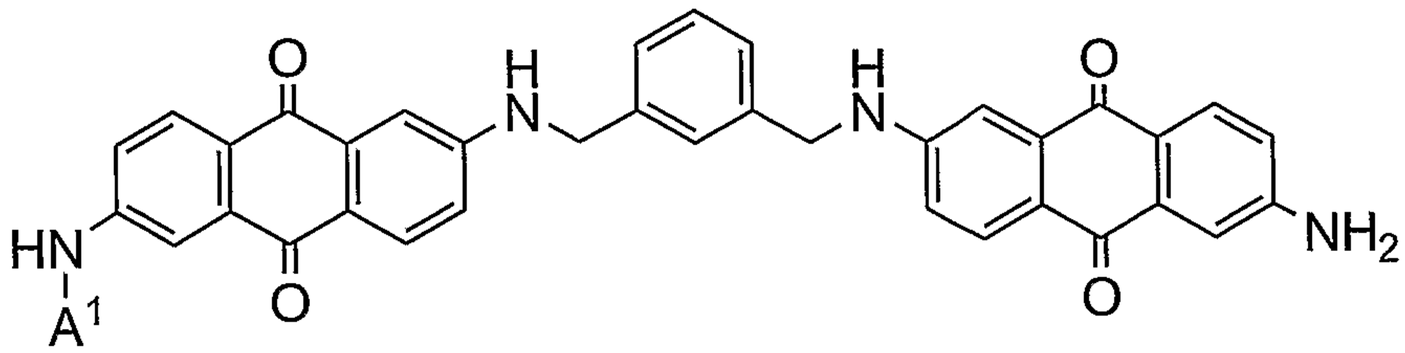
where Ar is carbocycle or heterocycle.

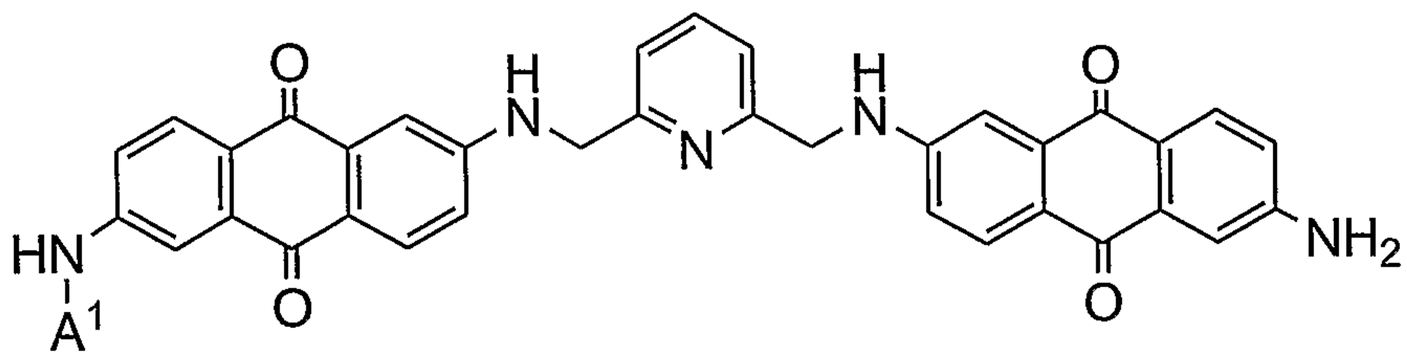
Group XXXV

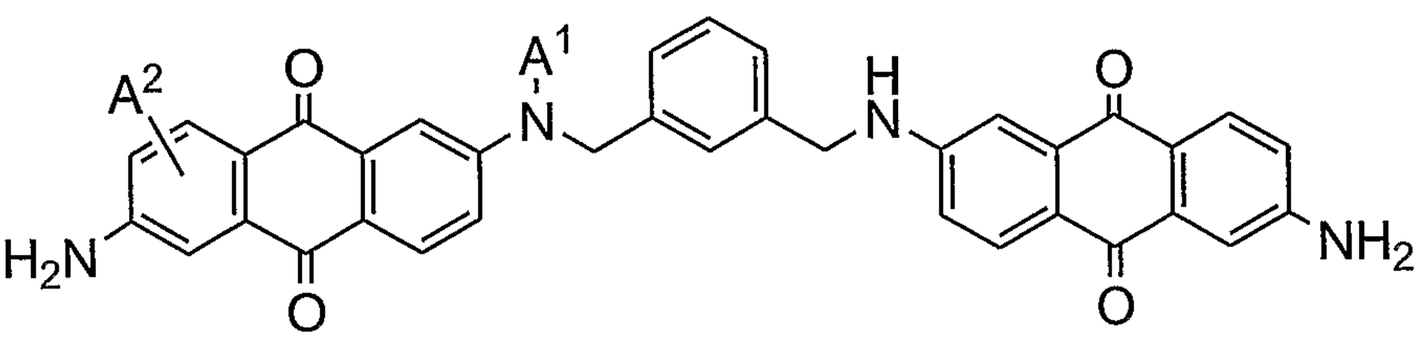
In one aspect, the invention includes phosphonate analogs of symmetrical pentamidine compounds derived from serine protease inhibitors (WO 02/02516). Exemplary embodiments of pentamidine phosphonate Formula XXXV compounds include the structures:

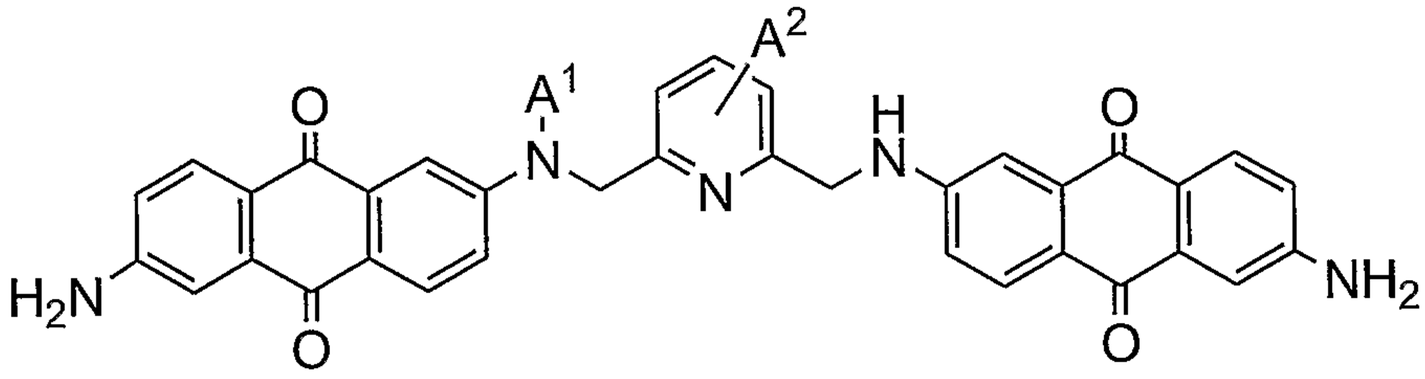


Exemplary embodiments of pentamidine phosphonate Formula XXXV compounds also include the structures:

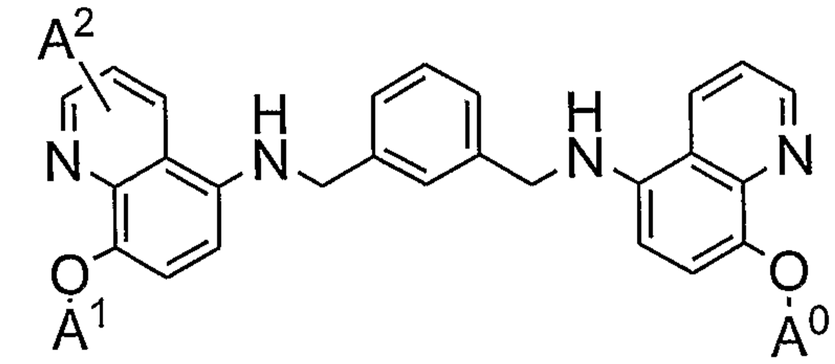


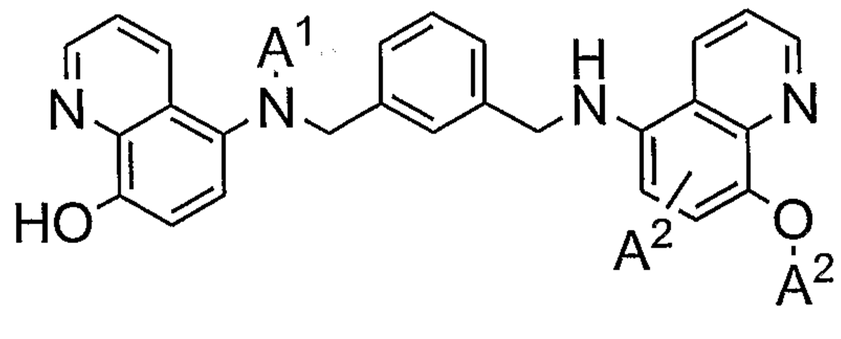


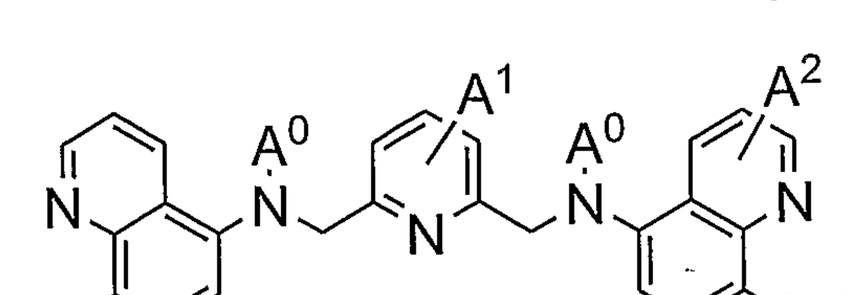


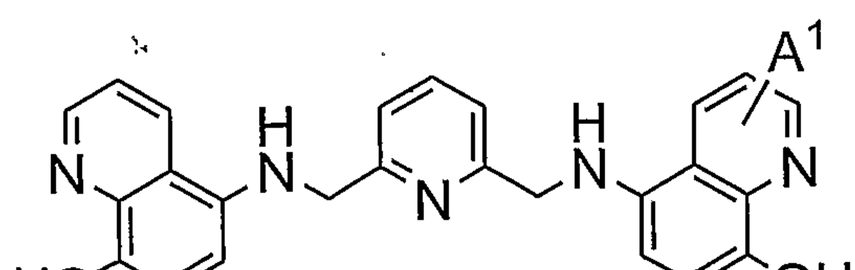


Exemplary embodiments of pentamidine phosphonate Formula XXXV compounds also include the structures:

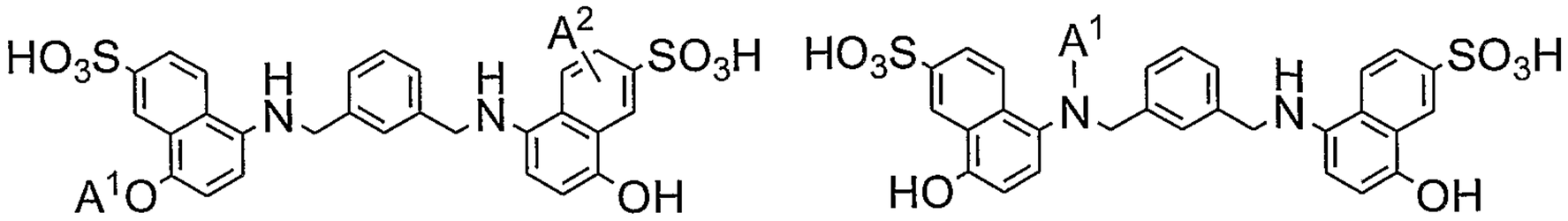


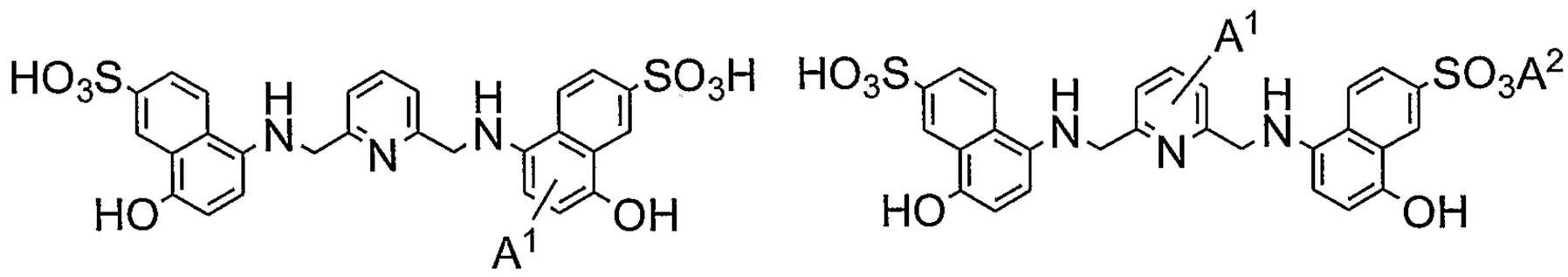






Exemplary embodiments of pentamidine phosphonate Formula XXXV compounds also include the structures:



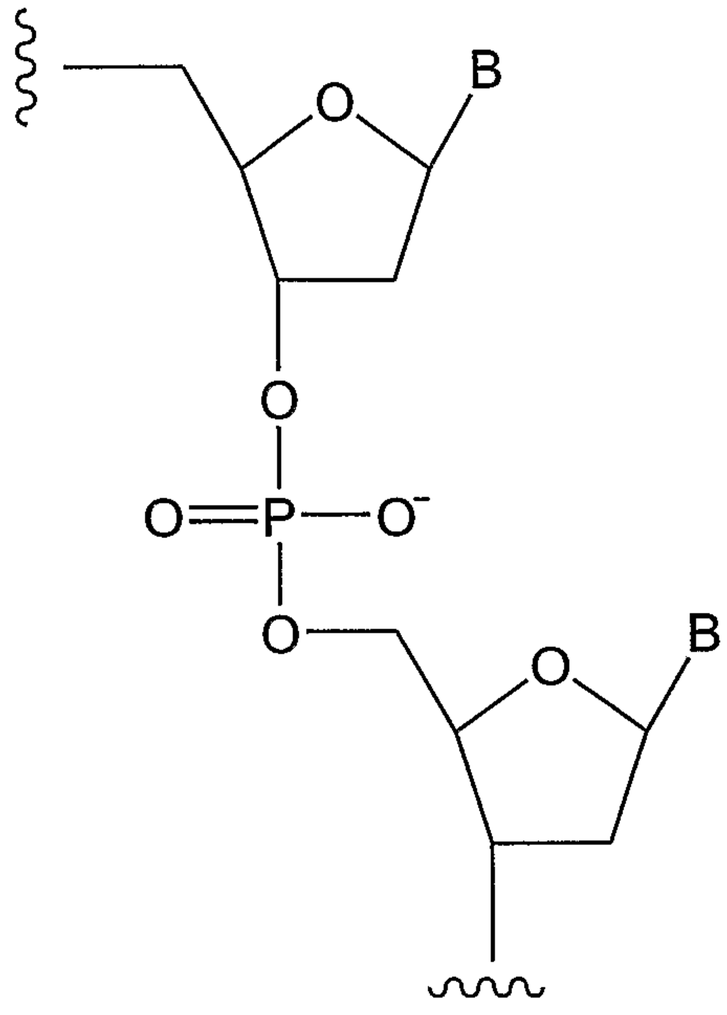


Group XXXVI

In one aspect, the invention includes phosphonate analogs of nucleic acid compounds. Nucleic acid phosphonate compounds include: (a) nucleosides and nucleotides (Zhao et al (1997) *Heterocycles* 45:2277-2282; Drake et al (1998) *Proc. Natl. Acad. Sci. USA* 95:4170-4175; Mazumder et al (1994) *Proc. Natl. Acad. Sci. USA* 91:5771-5775), dinucleotides (Taktakishvili et al (2000) *J. Am. Chem. Soc.* 122(24):5671-5677; Mazumder et al (1997) *Mol. Pharmacol.* 51:567-575) including 5H-pyrano[2,3-d:-6,5-d']dipyrimidines (Pannecouque et al (2002) *Current Biology* 12(14):1169-1177); (b) oligonucleotides (Bischerour et al (2003) *Nucleic Acids Research* 31(10):2694-2702; Risitano et al (2003) *Biochemistry* 42(21):6507-6513; Guenther et al (2002) *Bioorganic & Medicinal Chemistry Letters* 12(16):2233-2236; de Soultrait et al (2002) *Jour. of Mol. Biology* 324(2):195-203; Jing et al (2002) *Biochemistry* 41(17):5397-5403; Jing et al (2000) *J. Biol. Chem.* 275(5):3421-3430; Jing et al (2000) *J. Biol. Chem.* 275(28):21460-21467; Jing et al (2001) *DNA and Cell Biology* 20(8):499-508; Snasel et al (2001) *Eur. J. Biochem.* 268(4):980-986; Mouscadet et al (1994) *J. Biol. Chem.* 269:21635-21638; Mazumder et al (1996) *Biochemistry* 35:13762-13771; Ojwang et al (1995) *Antimicrob. Agents Chemother.* 39:2426-2435; Thomas et al (1997) *Trends Biotechnol.* 15:167-172; Este et al (1998) *Mol. Pharmacol.* 53:340-345; Allen et al (1995) *Virology* 209:327-336; US 6323185; US 5567604); and (c) analogs thereof, with one or more phosphonate groups. Nucleic acid analogs include L and D stereoisomers (Mazumder et al (1996) *Mol. Pharmacol.* 49:621-62); nucleobase analogs (Brodin et al (2002) *Biochemistry* 41(5):1529-1538; Brodin et al (2001) *Nucleosides, Nucleotides & Nucleic Acids* 20(4-7):481-486);

sugar analogs and; internucleotide phosphate analogs (Tramontano et al (1998) *Biochemistry* 37:7237-7243; Zhang et al (1998) *Bioorg. Med. Chem. Lett.* 8:1887-1890; 8).

Embodiments of phosphonate analogs of nucleic acid HIV integrase inhibitor Formula XXXVI compounds include the structure:



XXXVI

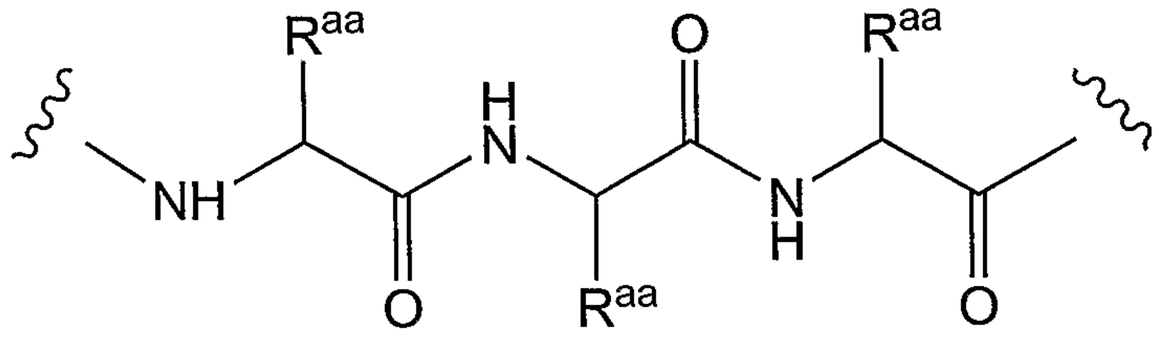
where the wavy lines indicate additional nucleotide units in the molecule and B is a nucleobase. Formula XXXVI compounds may be substituted at any location on the 5' terminus, 3' terminus, internucleotide phosphate linkage, sugar, or nucleobase moieties with a phosphonate group, as described for A^1. Formula XXXVI compounds also include any oligonucleotide analog with a modified internucleotide linkage, a modified sugar, or a modified nucleobase.

Group XXXVII

In one aspect, the invention includes phosphonate analogs of amino acids (WO 02/026697; US 6362165) and peptides and proteins (Maroun et al (2001) *Biochemistry* 40(46):13840-13848; Zhao et al (2003) *Bioorganic & Medicinal Chemistry Letters* 13(6):1175-1177; Marchand et al (2003) *Mol. Pharm.* 64(3):600-609; Krajewski et al (2003) *Bioorganic & Med. Chem. Letters* 13(19):3203-3205; de Soultrait et al (2003) *Current Medicinal Chem.* 10(18):1765-1778; de Soultrait et al (2002) *Jour. Mol. Biology* 318(1):45-58; Sonika et al (2002) *Journ. of Biomolecular Structure & Dynamics* 20(1):31-38; Ng et al (2001) *Life Sciences* 69(19):2217-2223;

Lutzke et al (1995) *Proc. Natl. Acad. Sci USA* 92:11456-11460; Krebs et al (1998) *Eur. J. Biochem.* 253:236-244; Sourgen et al (1996) *Eur. J. Biochem.* 240:765-773; Gulizia et al (1994) *J. Virol.* 68:2021-2025; WO 02/004488), including cyclic peptide (Singh et al (2001) *Jour. Natural Products* 64:874-882; Singh et al (2002) *Organic Letters* 4:1431-1434) and antibody (Strayer et al (2002) *Molecular Therapy* 5(1):33-41; Barsov et al (1996) *J. Virology* 70:4484-4494; US 2003206909 A1; US 2003152913 A1; US 2003206909 A1) phosphonate compounds.

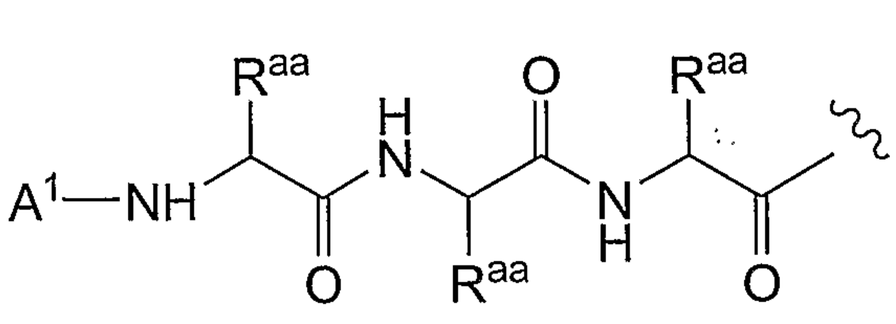
Embodiments of phosphonate analogs of peptide or protein HIV integrase inhibitor Formula XXXVII compounds include the structure:

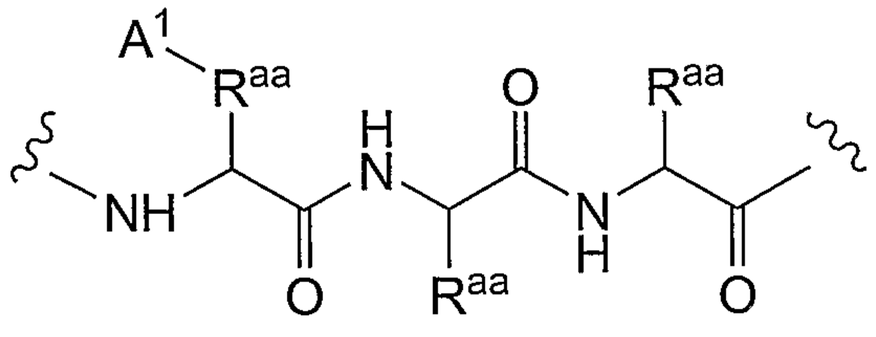


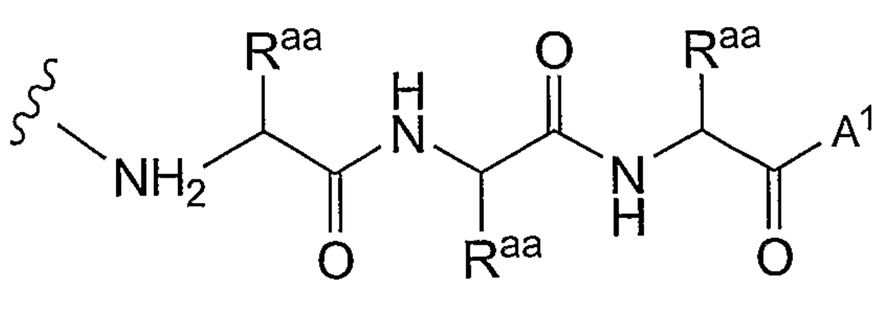
XXXVII

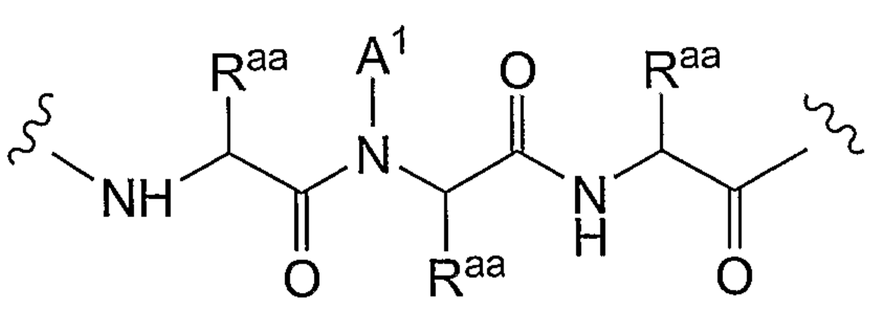
where the wavy lines indicate additional amino acid units in the molecule and R^{aa} is an amino acid side chain. Formula XXXVII compounds may be substituted at any location on the amino terminus, carboxyl terminus, side chain, or amide backbone with a phosphonate group, as described for A^1.

Exemplary phosphonate peptide and protein Formula XXXVII compounds include the substructures:





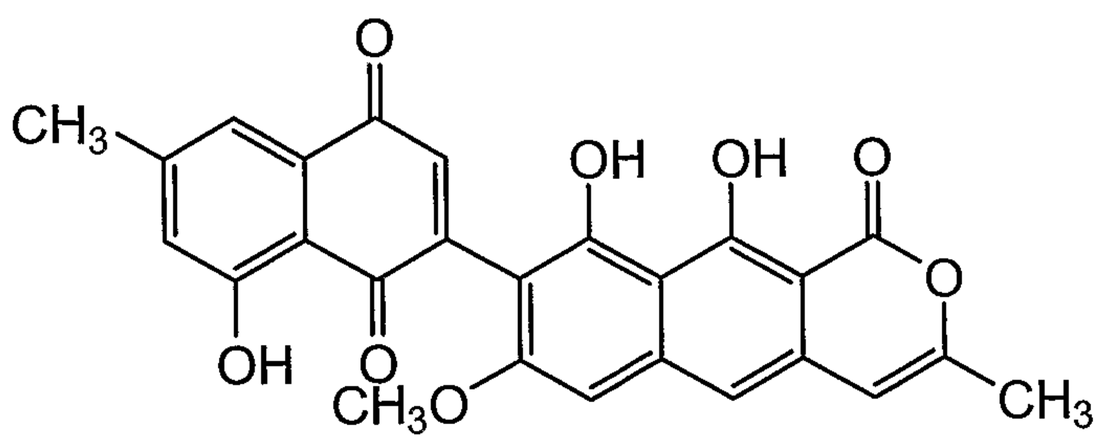




Group XXXVIII

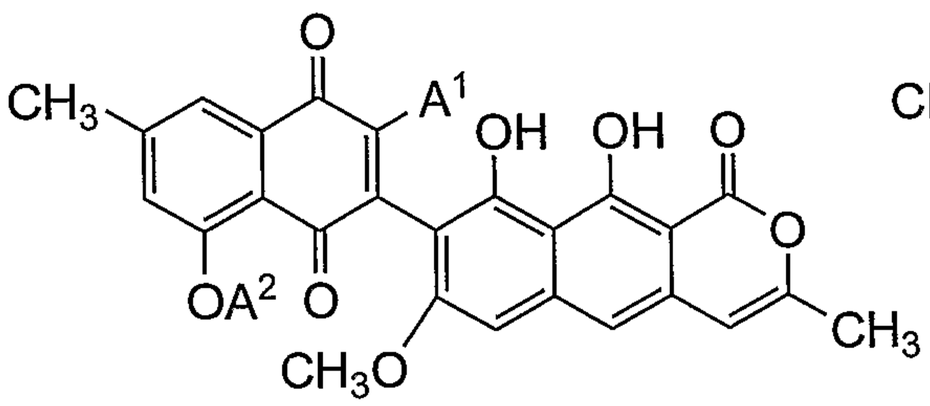
In one aspect, the invention includes phosphonate analogs of polyketide natural products including Xanthoviridicatins isolated from a fermentation broth of an

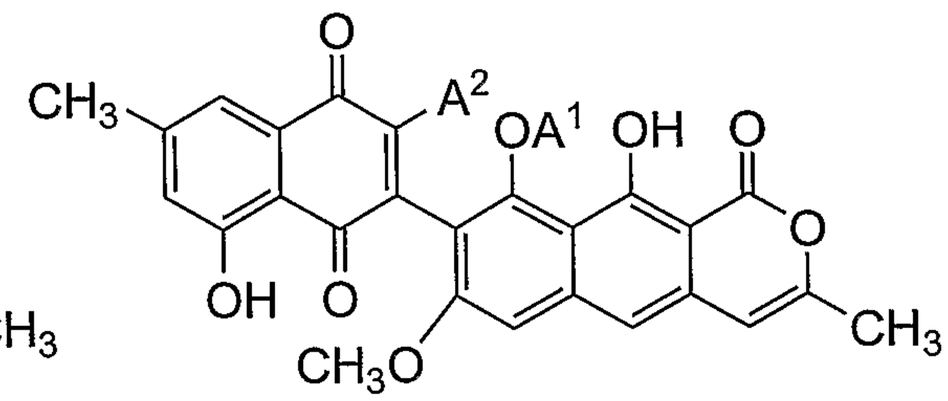
endophytic strain of Penicillium chrysogenum (Singh, et al (2003) *Helvetica Chimica Acta*, 86(10):3380-3385) having the Formula XXXVIII structure:

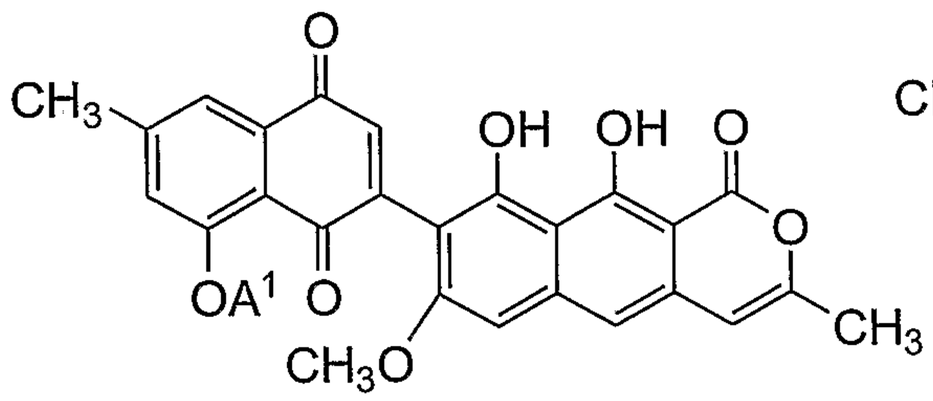


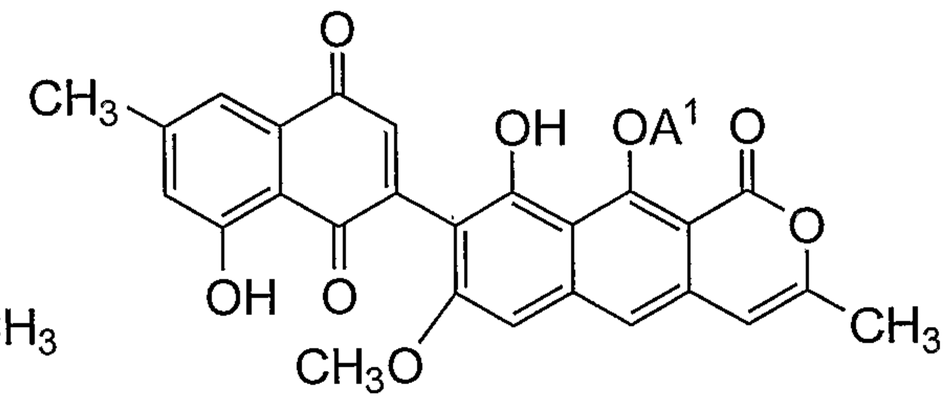
XXXVIII

Exemplary phosphonate polyketide Formula XXXVIII compounds include:





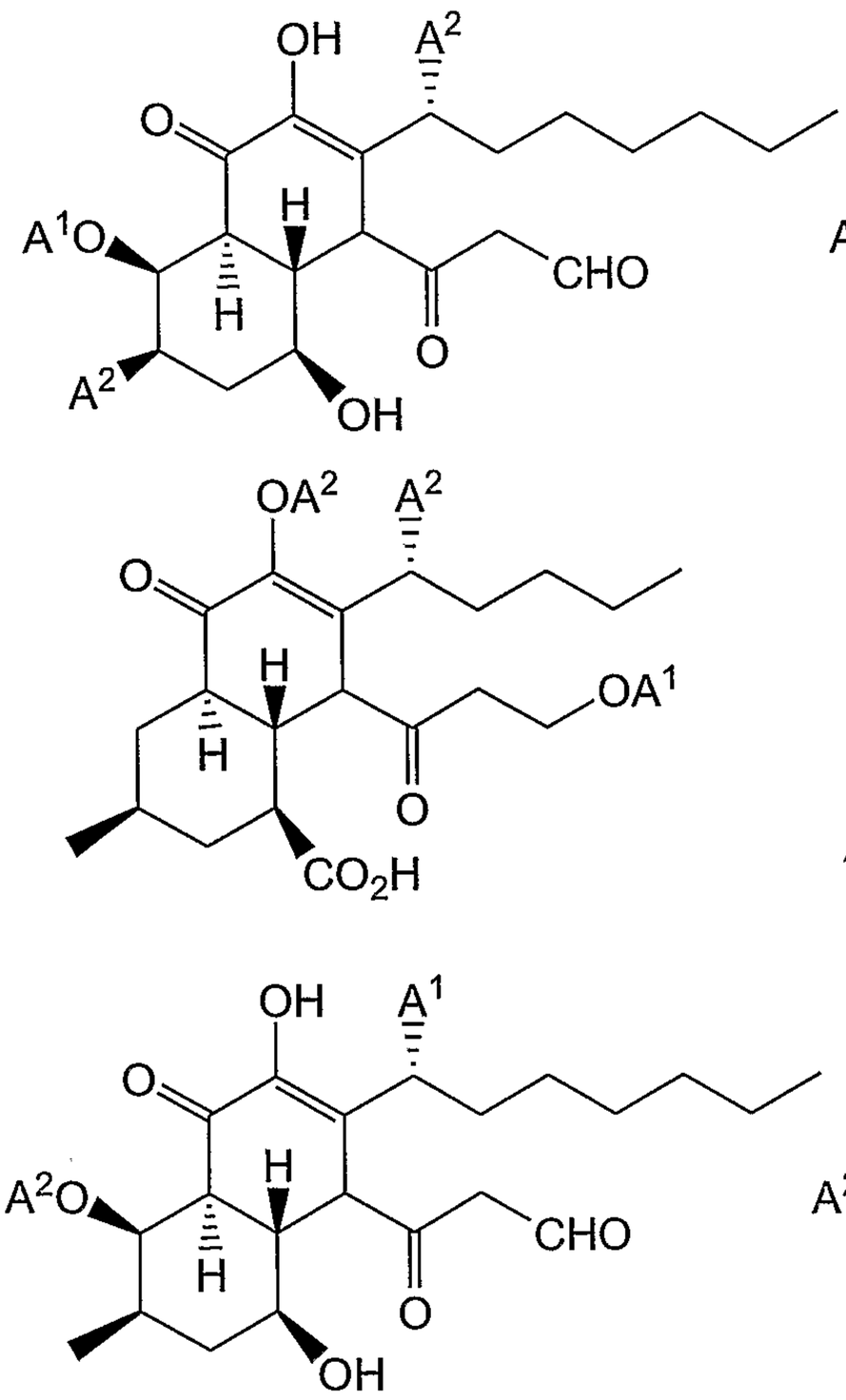


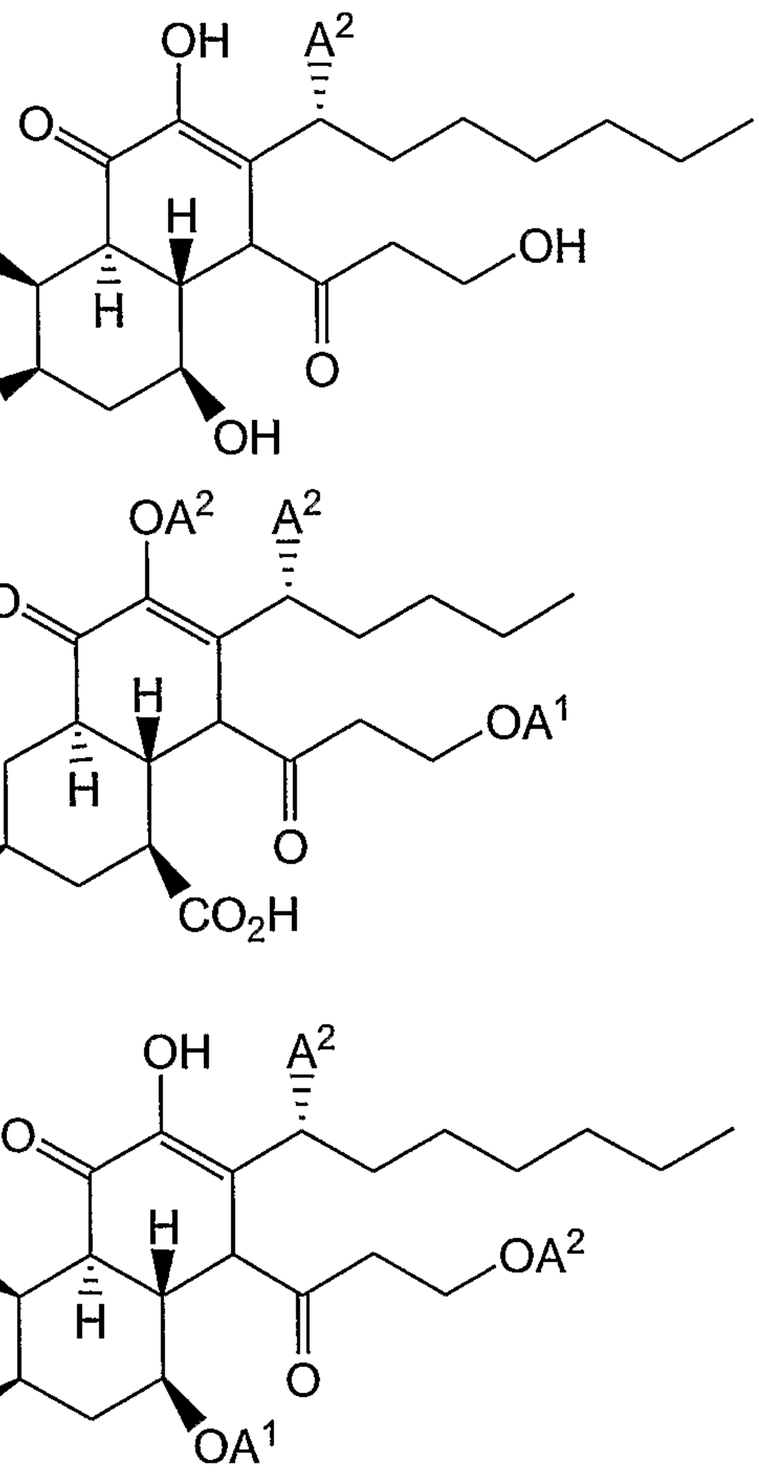


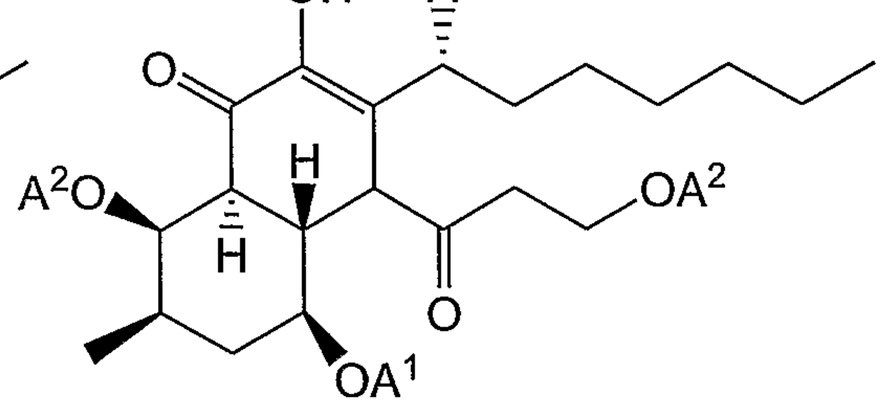
Group XXXIX

In one aspect, the invention includes phosphonate analogs of polyketide natural products including cytosporic acid, australifungin and australifunginol isolated from a fermentation broth of the filamentous fungus *Cytospora* sp. (Jayasuriya et al (2003) *Journal of Natural Products* 66(4):551-553).

Exemplary phosphonate cytosporic australifungin and australifunginol analog Formula XXXIX compounds include:







Protecting Groups

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

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

efficiency. The order of deprotection to yield free, deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

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

A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; "Protecting Groups" (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

<u>Ether- and Ester-forming protecting groups</u>

Ester-forming groups include: (1) phosphonate ester-forming groups, such as phosphonamidate esters, phosphorothioate esters, phosphonate esters, and phosphon-bis-amidates; (2) carboxyl ester-forming groups, and (3) sulphur ester-forming groups, such as sulphonate, sulfate, and sulfinate.

The phosphonate moieties of the compounds of the invention may or may not be prodrug moieties, i.e. they may or may be susceptible to hydrolytic or enzymatic cleavage or modification. Certain phosphonate moieties are stable under most or nearly all metabolic conditions. For example, a dialkylphosphonate, where the alkyl

groups are two or more carbons, may have appreciable stability *in vivo* due to a slow rate of hydrolysis. Within the context of phosphonate prodrug moieties, a large number of structurally-diverse prodrugs have been described for phosphonic acids (Freeman and Ross in Progress in Medicinal Chemistry 34: 112-147 (1997) and are included within the scope of the present invention.

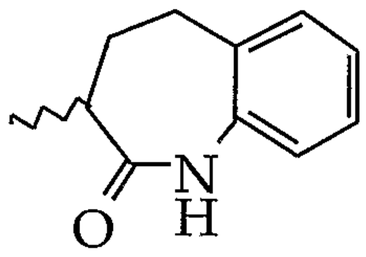
In its ester-forming role, a protecting group typically is bound to any acidic group such as, by way of example and not limitation, a $-CO_2H$ or $-C(S)OH$ group, thereby resulting in $-CO_2R^x$ where R^x is defined herein. Also, R^x for example includes the enumerated ester groups of WO 95/07920.

Examples of protecting groups include:

C_3–C_{12} heterocycle (described above) or aryl. These aromatic groups optionally are polycyclic or monocyclic. Examples include phenyl, spiryl, 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 1-, 2-, 3- and 4-pyridinyl, and 1-, 2-, 4- and 5-pyrimidinyl,

C_3-C_{12} heterocycle or aryl substituted with halo, R^1, R^1-O-C_1-C_{12} alkylene, C_1-C_{12} alkoxy, CN, NO_2, OH, carboxy, carboxyester, thiol, thioester, C_1-C_{12} haloalkyl (1-6 halogen atoms), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl. Such groups include 2-, 3- and 4-alkoxyphenyl (C_1-C_{12} alkyl), 2-, 3- and 4-methoxyphenyl, 2-, 3- and 4-ethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-diethoxyphenyl, 2- and 3-carboethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-5-hydroxyphenyl, 2- and 3-ethoxy-6-hydroxyphenyl, 2-, 3- and 4-O-acetylphenyl, 2-, 3- and 4-dimethylaminophenyl, 2-, 3- and 4-methylmercaptophenyl, 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl and 2-, 3- and 4-chlorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-biscarboxyethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 3,5-difluorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylphenyl), 2-, 3- and 4-cyanophenyl, 2-, 3- and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylbenzyl and 2-, 3- and 4-trichloromethylphenyl and 2-, 3- and 4-trichloromethylphenyl), 4-N-methylpiperidinyl, 3-N-methylpiperidinyl, 1-

ethylpiperazinyl, benzyl, alkylsalicylphenyl (C_1-C_4 alkyl, including 2-, 3- and 4-ethylsalicylphenyl), 2-,3- and 4-acetylphenyl, 1,8-dihydroxynaphthyl (-$C_{10}H_6$-OH) and aryloxy ethyl [C_6-C_9 aryl (including phenoxy ethyl)], 2,2'-dihydroxybiphenyl, 2-, 3- and 4-N,N-dialkylaminophenol, -$C_6H_4CH_2$-$N(CH_3)_2$, trimethoxybenzyl, triethoxybenzyl, 2-alkyl pyridinyl (C_{1-4} alkyl);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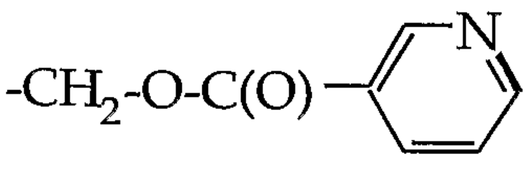
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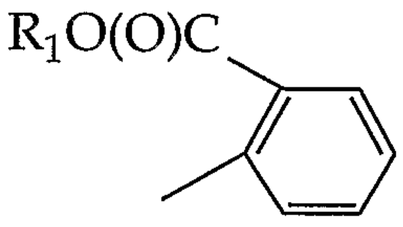
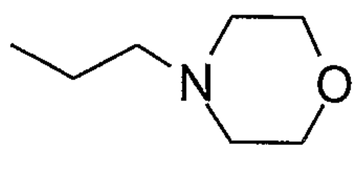

;

C_4 - C_8 esters of 2-carboxyphenyl; and C_1-C_4 alkylene-C_3-C_6 aryl (including benzyl, -CH_2-pyrrolyl, -CH_2-thienyl, -CH_2-imidazolyl, -CH_2-oxazolyl, -CH_2-isoxazolyl, -CH_2-thiazolyl, -CH_2-isothiazolyl, -CH_2-pyrazolyl, -CH_2-pyridinyl and -CH_2-pyrimidinyl) substituted in the aryl moiety by 3 to 5 halogen atoms or 1 to 2 atoms or groups selected from halogen, C_1-C_{12} alkoxy (including methoxy and ethoxy), cyano, nitro, OH, C_1-C_{12} haloalkyl (1 to 6 halogen atoms; including -CH_2CCl_3), C_1-C_{12} alkyl (including methyl and ethyl), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl; alkoxy ethyl [C_1-C_6 alkyl including -CH_2-CH_2-O-CH_3 (methoxy ethyl)]; alkyl substituted by any of the groups set forth above for aryl, in particular OH or by 1 to 3 halo atoms (including -CH_3, -$CH(CH_3)_2$, -$C(CH_3)_3$, -CH_2CH_3, -$(CH_2)_2CH_3$, -$(CH_2)_3CH_3$, -$(CH_2)_4CH_3$, -$(CH_2)_5CH_3$, -CH_2CH_2F, -CH_2CH_2Cl, -CH_2CF_3, and -CH_2CCl_3);


;

-N-2-propylmorpholino, 2,3-dihydro-6-hydroxyindene, sesamol, catechol monoester, -CH_2-C(O)-$N(R^1)_2$, -CH_2-S(O)(R^1), -CH_2-$S(O)_2$(R^1), -CH_2-CH($OC(O)CH_2R^1$)-CH_2($OC(O)CH_2R^1$), cholesteryl, enolpyruvate (HOOC-C(=CH_2)-), glycerol;

a 5 or 6 carbon monosaccharide, disaccharide or oligosaccharide (3 to 9 monosaccharide residues);

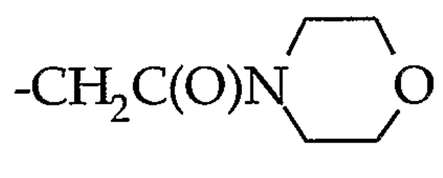
triglycerides such as α-D-β-diglycerides (wherein the fatty acids composing glyceride lipids generally are naturally occurring saturated or unsaturated C_{6-26}, C_{6-18} or C_{6-10} fatty acids such as linoleic, lauric, myristic, palmitic, stearic, oleic, palmitoleic, linolenic and the like fatty acids) linked to acyl of the parental

compounds herein through a glyceryl oxygen of the triglyceride;

phospholipids linked to the carboxyl group through the phosphate of the phospholipid;

phthalidyl (shown in Fig. 1 of Clayton et al., *Antimicrob. Agents Chemo.* (1974) 5(6):670-671;

cyclic carbonates such as (5-R_d-2-oxo-1,3-dioxolen-4-yl) methyl esters (Sakamoto et al., *Chem. Pharm. Bull.* (1984) 32(6)2241-2248) where R_d is R_1, R_4 or aryl; and



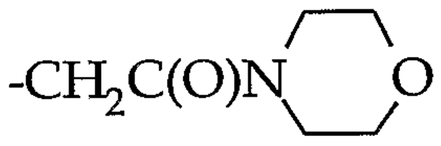
The hydroxyl groups of the compounds of this invention optionally are substituted with one of groups III, IV or V disclosed in WO 94/21604, or with isopropyl.

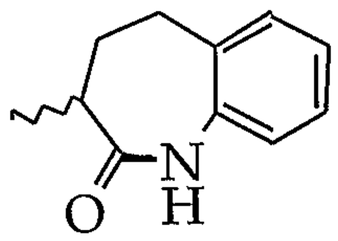
As further embodiments, Table A lists examples of protecting group ester moieties that for example can be bonded via oxygen to -C(O)O- and -P(O)(O-)$_2$ groups. Several amidates also are shown, which are bound directly to -C(O)- or -P(O)$_2$. Esters of structures 1-5, 8-10 and 16, 17, 19-22 are synthesized by reacting the compound herein having a free hydroxyl with the corresponding halide (chloride or acyl chloride and the like) and N ,N-dicyclohexyl-N-morpholine carboxamidine (or another base such as DBU, triethylamine, $CsCO_3$, N,N-dimethylaniline and the like) in DMF (or other solvent such as acetonitrile or N-methylpyrrolidone). When the compound to be protected is a phosphonate, the esters of structures 5-7, 11, 12, 21, and 23-26 are synthesized by reaction of the alcohol or alkoxide salt (or the corresponding amines in the case of compounds such as 13, 14 and 15) with the monochlorophosphonate or dichlorophosphonate (or another activated phosphonate).

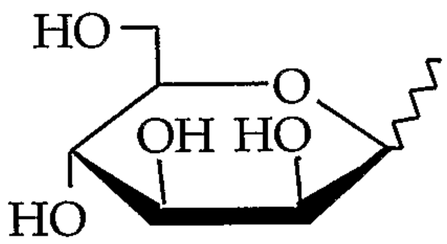
TABLE A

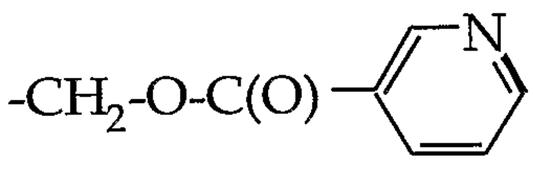
1. -CH_2-C(O)-N(R_1)$_2$ *
2. -CH_2-S(O)(R_1)
3. -CH_2-S(O)$_2$(R_1)
4. -CH_2-O-C(O)-CH_2-C_6H_5
10. -CH_2-O-C(O)-C(CH_3)$_3$
11. -CH_2-CCl_3
12. -C_6H_5
13. -NH-CH_2-C(O)O-CH_2CH_3

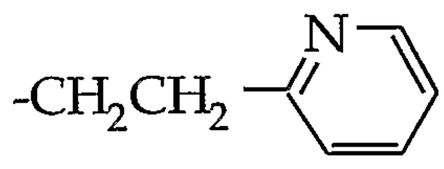
5. 3-cholesteryl
6. 3-pyridyl
7. N-ethylmorpholino
8. $-CH_2-O-C(O)-C_6H_5$
9. $-CH_2-O-C(O)-CH_2CH_3$
14. $-N(CH_3)-CH_2-C(O)O-CH_2CH_3$
15. $-NHR_1$
16. $-CH_2-O-C(O)-C_{10}H_{15}$
17. $-CH_2-O-C(O)-CH(CH_3)_2$
18. $-CH_2-C\#H(OC(O)CH_2R_1)-CH_2(OC(O)CH_2R_1)$*

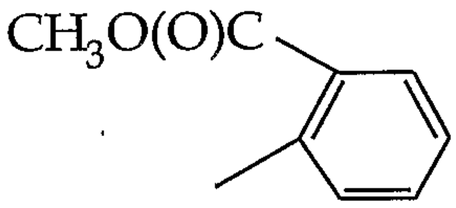
19. 

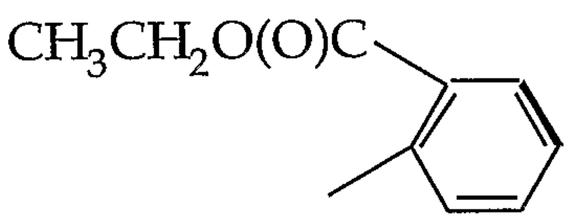
20. 

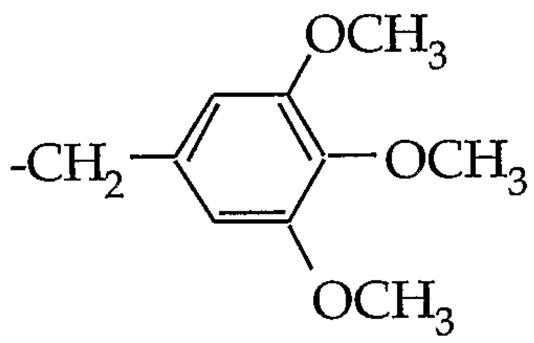
21. 

22. 

23. 

24. 

25. 

26. 

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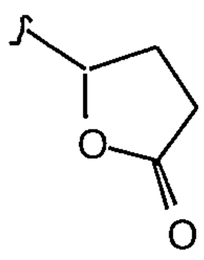
15 # - chiral center is (R), (S) or racemate.

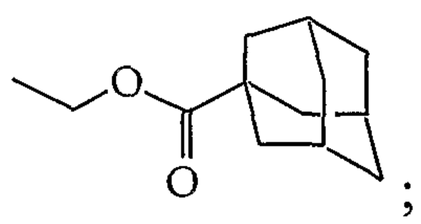
Other esters that are suitable for use herein are described in EP 632048.

Protecting groups also includes "double ester" forming profunctionalities such as $-CH_2OC(O)OCH_3$,



20 $-CH_2SCOCH_3$, $-CH_2OCON(CH_3)2$, or alkyl- or aryl-acyloxyalkyl groups of the structure $-CH(R^1 \text{ or } W^5)O((CO)R^{37})$ or $-CH(R^1 \text{ or } W^5)((CO)OR^{38})$ (linked to oxygen

of the acidic group) wherein R^{37} and R^{38} are alkyl, aryl, or alkylaryl groups (see U.S. patent 4,968,788). Frequently R^{37} and R^{38} are bulky groups such as branched alkyl, ortho-substituted aryl, meta-substituted aryl, or combinations thereof, including normal, secondary, iso- and tertiary alkyls of 1-6 carbon atoms. An example is the pivaloyloxymethyl group. These are of particular use with prodrugs for oral administration. Examples of such useful protecting groups are alkylacyloxymethyl esters and their derivatives, including $-CH(CH_2CH_2OCH_3)OC(O)C(CH_3)_3$,



;

$-CH_2OC(O)C_{10}H_{15}$, $-CH_2OC(O)C(CH_3)_3$, $-CH(CH_2OCH_3)OC(O)C(CH_3)_3$, $-CH(CH(CH_3)_2)OC(O)C(CH_3)_3$, $-CH_2OC(O)CH_2CH(CH_3)_2$, $-CH_2OC(O)C_6H_{11}$, $-CH_2OC(O)C_6H_5$, $-CH_2OC(O)C_{10}H_{15}$, $-CH_2OC(O)CH_2CH_3$, $-CH_2OC(O)CH(CH_3)_2$, $-CH_2OC(O)C(CH_3)_3$ and $-CH_2OC(O)CH_2C_6H_5$.

For prodrug purposes, the ester typically chosen is one heretofore used for antibiotic drugs, in particular the cyclic carbonates, double esters, or the phthalidyl, aryl or alkyl esters.

In some embodiments the protected acidic group is an ester of the acidic group and is the residue of a hydroxyl-containing functionality. In other embodiments, an amino compound is used to protect the acid functionality. The residues of suitable hydroxyl or amino-containing functionalities are set forth above or are found in WO 95/07920. Of particular interest are the residues of amino acids, amino acid esters, polypeptides, or aryl alcohols. Typical amino acid, polypeptide and carboxyl-esterified amino acid residues are described on pages 11-18 and related text of WO 95/07920 as groups L1 or L2. WO 95/07920 expressly teaches the amidates of phosphonic acids, but it will be understood that such amidates are formed with any of the acid groups set forth herein and the amino acid residues set forth in WO 95/07920.

Typical esters for protecting acidic functionalities are also described in WO 95/07920, again understanding that the same esters can be formed with the acidic groups herein as with the phosphonate of the '920 publication. Typical ester groups are defined at least on WO 95/07920 pages 89-93 (under R^{31} or R^{35}), the table on page 105, and pages 21-23 (as R). Of particular interest are esters of unsubstituted

aryl such as phenyl or arylalkyl such benzyl, or hydroxy-, halo-, alkoxy-, carboxy- and/or alkylestercarboxy-substituted aryl or alkylaryl, especially phenyl, ortho-ethoxyphenyl, or C_1-C_4 alkylestercarboxyphenyl (salicylate C_1-C_{12} alkylesters).

The protected acidic groups, particularly when using the esters or amides of WO 95/07920, are useful as prodrugs for oral administration. However, it is not essential that the acidic group be protected in order for the compounds of this invention to be effectively administered by the oral route. When the compounds of the invention having protected groups, in particular amino acid amidates or substituted and unsubstituted aryl esters are administered systemically or orally they are capable of hydrolytic cleavage *in vivo* to yield the free acid.

One or more of the acidic hydroxyls are protected. If more than one acidic hydroxyl is protected then the same or a different protecting group is employed, e.g., the esters may be different or the same, or a mixed amidate and ester may be used.

Typical hydroxy protecting groups described in Greene (pages 14-118) include substituted methyl and alkyl ethers, substituted benzyl ethers, silyl ethers, esters including sulfonic acid esters, and carbonates.

Exemplary hydroxy protecting groups include:

- Ethers (methyl, *t*-butyl, allyl);
- Substituted Methyl Ethers (Methoxymethyl, Methylthiomethyl, *t*-Butylthiomethyl, (Phenyldimethylsilyl)methoxymethyl, Benzyloxymethyl, *p*-Methoxybenzyloxymethyl, (4-Methoxyphenoxy)methyl, Guaiacolmethyl, *t*-Butoxymethyl, 4-Pentenyloxymethyl, Siloxymethyl, 2-Methoxyethoxymethyl, 2,2,2-Trichloroethoxymethyl, Bis(2-chloroethoxy)methyl, 2-(Trimethylsilyl)ethoxymethyl, Tetrahydropyranyl, 3-Bromotetrahydropyranyl, Tetrahydropthiopyranyl, 1-Methoxycyclohexyl, 4-Methoxytetrahydropyranyl, 4-Methoxytetrahydrothiopyranyl, 4-Methoxytetrahydropthiopyranyl *S,S*-Dioxido, 1-[(2-Chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-Dioxan-2-yl, Tetrahydrofuranyl, Tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl));
- Substituted Ethyl Ethers (1-Ethoxyethyl, 1-(2-Chloroethoxy)ethyl, 1-Methyl-1-methoxyethyl, 1-Methyl-1-benzyloxyethyl, 1-Methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-Trichloroethyl, 2-Trimethylsilylethyl, 2-(Phenylselenyl)ethyl,

- *p*-Chlorophenyl, *p*-Methoxyphenyl, 2,4-Dinitrophenyl, Benzyl);
- Substituted Benzyl Ethers (*p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *p*-Halobenzyl, 2,6-Dichlorobenzyl, *p*-Cyanobenzyl, *p*-Phenylbenzyl, 2- and 4-Picolyl, 3-Methyl-2-picolyl *N*-Oxido, Diphenylmethyl, *p,p'*-Dinitrobenzhydryl, 5-Dibenzosuberyl, Triphenylmethyl, α-Naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, Di(*p*-methoxyphenyl)phenylmethyl, Tri(*p*-methoxyphenyl)methyl, 4-(4'-Bromophenacyloxy)phenyldiphenylmethyl, 4,4',4"-Tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4"-Tris(levulinoyloxyphenyl)methyl, 4,4',4"-Tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4',4"-dimethoxyphenyl)methyl, 1,1-Bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-Anthryl, 9-(9-Phenyl)xanthenyl, 9-(9-Phenyl-10-oxo)anthryl, 1,3-Benzodithiolan-2-yl, Benzisothiazolyl *S,S*-Dioxido);
- Silyl Ethers (Trimethylsilyl, Triethylsilyl, Triisopropylsilyl, Dimethylisopropylsilyl, Diethylisopropylsilyl, Dimethylthexylsilyl, *t*-Butyldimethylsilyl, *t*-Butyldiphenylsilyl, Tribenzylsilyl, Tri-*p*-xylylsilyl, Triphenylsilyl, Diphenylmethylsilyl, *t*-Butylmethoxyphenylsilyl);
- Esters (Formate, Benzoylformate, Acetate, Choroacetate, Dichloroacetate, Trichloroacetate, Trifluoroacetate, Methoxyacetate, Triphenylmethoxyacetate, Phenoxyacetate, *p*-Chlorophenoxyacetate, *p*-poly-Phenylacetate, 3-Phenylpropionate, 4-Oxopentanoate (Levulinate), 4,4-(Ethylenedithio)pentanoate, Pivaloate, Adamantoate, Crotonate, 4-Methoxycrotonate, Benzoate, *p*-Phenylbenzoate, 2,4,6-Trimethylbenzoate (Mesitoate));
- Carbonates (Methyl, 9-Fluorenylmethyl, Ethyl, 2,2,2-Trichloroethyl, 2-(Trimethylsilyl)ethyl, 2-(Phenylsulfonyl)ethyl, 2-(Triphenylphosphonio)ethyl, Isobutyl, Vinyl, Allyl, *p*-Nitrophenyl, Benzyl, *p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *S*-Benzyl Thiocarbonate, 4-Ethoxy-1-naphthyl, Methyl Dithiocarbonate);
- Groups With Assisted Cleavage (2-Iodobenzoate, 4-Azidobutyrate, 4-Nitro-4-methylpentanoate, *o*-(Dibromomethyl)benzoate, 2-Formylbenzenesulfonate, 2-(Methylthiomethoxy)ethyl Carbonate, 4-(Methylthiomethoxy)butyrate, 2-(Methylthiomethoxymethyl)benzoate); Miscellaneous Esters (2,6-Dichloro-4-

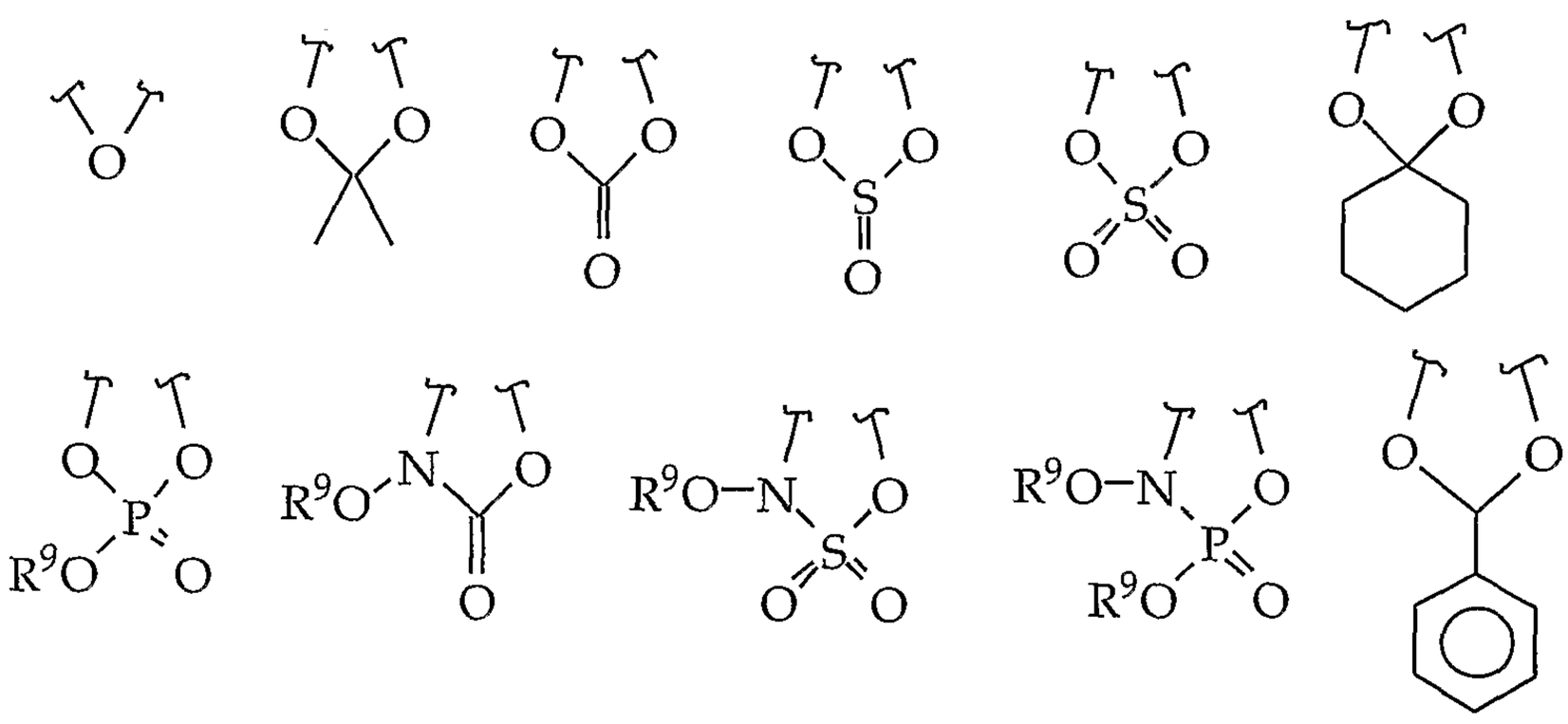
methylphenoxyacetate, 2,6-Dichloro-4-(1,1,3,3 tetramethylbutyl)phenoxyacetate, 2,4-Bis(1,1-dimethylpropyl)phenoxyacetate, Chlorodiphenylacetate, Isobutyrate, Monosuccinate, (*E*)-2-Methyl-2-butenoate (Tigloate), *o*-(Methoxycarbonyl)benzoate, *p*-poly-Benzoate, α-Naphthoate, Nitrate, Alkyl *N,N,N',N'*-Tetramethylphosphorodiamidate, *N*-Phenylcarbamate, Borate, Dimethylphosphinothioyl, 2,4-Dinitrophenylsulfenate); and

- Sulfonates (Sulfate, Methanesulfonate (Mesylate), Benzylsulfonate, Tosylate).

Typical 1,2-diol protecting groups (thus, generally where two OH groups are taken together with the protecting functionality) are described in Greene at pages 118-142 and include Cyclic Acet als and Ket als (Methylene, Ethylidene, 1-*t*-Butylethylidene, 1-Phenylethylidene, (4-Methoxyphenyl)ethylidene, 2,2,2-Trichloroethylidene, Acetonide (Isopropylidene), Cyclopentylidene, Cyclohexylidene, Cycloheptylidene, Benzylidene, *p*-Methoxybenzylidene, 2,4-Dimethoxybenzylidene, 3,4-Dimethoxybenzylidene, 2-Nitrobenzylidene); Cyclic Ortho Esters (Methoxymethylene, Ethoxymethylene, Dimethoxymethylene, 1-Methoxyethylidene, 1-Ethoxyethylidine, 1,2-Dimethoxyethylidene, α-Methoxybenzylidene, 1-(*N,N*-Dimethylamino)ethylidene Derivative, α -(*N,N*-Dimethylamino)benzylidene Derivative, 2-Oxacyclopentylidene); Silyl Derivatives (Di-*t*-butylsilylene Group, 1,3-(1,1,3,3-Tetraisopropyldisiloxanylidene), and Tetra-*t*-butoxydisiloxane-1,3-diylidene), Cyclic Carbonates, Cyclic Boronates, Ethyl Boronate and Phenyl Boronate.

More typically, 1,2-diol protecting groups include those shown in Table B, still more typically, epoxides, acetonides, cyclic ket als and aryl acet als.

Table B



wherein R^9 is C_1-C_6 alkyl.

Amino protecting groups

Another set of protecting groups include any of the typical amino protecting groups described by Greene at pages 315-385.

Exemplary amino protecting groups include:

- Carbamates: (methyl and ethyl, 9-fluorenylmethyl, 9(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, 4-methoxyphenacyl);
- Substituted Ethyl: (2,2,2-trichoroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'- and 4'-pyridyl)ethyl, 2-(*N,N*-dicyclohexylcarboxamido)ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, *N*-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl);
- Groups With Assisted Cleavage: (2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-choro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl);
- Groups Capable of Photolytic Cleavage: (*m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, phenyl(*o*-nitrophenyl)methyl); Urea-Type Derivatives (phenothiazinyl-(10)-carbonyl, *N'*-*p*-toluenesulfonylaminocarbonyl, *N'*-phenylaminothiocarbonyl);
- Miscellaneous Carbamates: (*t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N,N*-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-Iodoethyl, Isobornyl, Isobutyl, Isonicotinyl, *p*-(*p*'-Methoxyphenylazo)benzyl, 1-

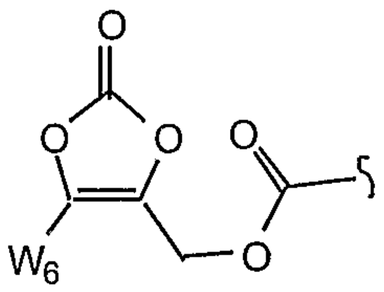
methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(*p*-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium)benzyl, 2,4,6-trimethylbenzyl);

- Amides: (*N*-formyl, *N*-acetyl, *N*-choroacetyl, *N*-trichoroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridylcarboxamide, *N*-benzoylphenylalanyl, *N*-benzoyl, *N*-*p*-phenylbenzoyl);
- Amides With Assisted Cleavage: (*N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N'*-dithiobenzyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxyphenyl)propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, 4,5-diphenyl-3-oxazolin-2-one);
- Cyclic Imide Derivatives: (*N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenylmaleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3-5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridonyl);
- *N*-Alkyl and *N*-Aryl Amines: (*N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), Quaternary Ammonium Salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl, *N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, *N*-2-picolylamine *N'*-oxide);
- Imine Derivatives: (*N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*,(*N'*,*N'*-dimethylaminomethylene, *N*,*N'*-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, *N*-cyclohexylidene);
- Enamine Derivatives: (*N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl));
- *N*-Met al Derivatives (*N*-borane derivatives, *N*-diphenylborinic acid derivatives,

N-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, *N*-copper or *N*-zinc chelate);

- N-N Derivatives: (*N*-nitro, *N*-nitroso, *N*-oxide);
- N-P Derivatives: (*N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, *N*-diphenyl phosphoryl);
- N-Si Derivatives, N-S Derivatives, and N-Sulfenyl Derivatives: (*N*-benzenesulfenyl, *N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl, *N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxybenzenesulfenyl, *N*-triphenylmethylsulfenyl, *N*-3-nitropyridinesulfenyl); and *N*-sulfonyl Derivatives (*N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxybenzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6,-tetramethyl-4-methoxybenzenesulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy-4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*-β-trimethylsilyethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, *N*-phenacylsulfonyl).

More typically, protected amino groups include carbamates and amides, still more typically, $-NHC(O)R^1$ or $-N=CR^1N(R^1)_2$. Another protecting group, also useful as a prodrug for amino or $-NH(R^5)$, is:



See for example Alexander, J. et al (1996) *J. Med. Chem.* 39:480-486.

Amino acid and polypeptide protecting group and conjugates

An amino acid or polypeptide protecting group of a compound of the invention has the structure $R^{15}NHCH(R^{16})C(O)$-, where R^{15} is H, an amino acid or polypeptide residue, or R^5, and R^{16} is defined below.

R^{16} is lower alkyl or lower alkyl (C_1-C_6) substituted with amino, carboxyl,

amide, carboxyl ester, hydroxyl, C_6-C_7 aryl, guanidinyl, imidazolyl, indolyl, sulfhydryl, sulfoxide, and/or alkylphosphate. R^{10} also is taken together with the amino acid α N to form a proline residue (R^{10} = -CH_2)$_3$-). However, R^{10} is generally the side group of a naturally-occurring amino acid such as H, -CH_3, -$CH(CH_3)_2$, -CH_2-$CH(CH_3)_2$, -$CHCH_3$-CH_2-CH_3, -CH_2-C_6H_5, -CH_2CH_2-S-CH_3, -CH_2OH, -$CH(OH)$-CH_3, -CH_2-SH, -CH_2-C_6H_4OH, -CH_2-CO-NH_2, -CH_2-CH_2-CO-NH_2, -CH_2-COOH, -CH_2-CH_2-COOH, -$(CH_2)_4$-NH_2 and -$(CH_2)_3$-NH-$C(NH_2)$-NH_2. R^{10} also includes 1-guanidinoprop-3-yl, benzyl, 4-hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl.

Another set of protecting groups include the residue of an amino-containing compound, in particular an amino acid, a polypeptide, a protecting group, -$NHSO_2R$, NHC(O)R, -$N(R)_2$, NH_2 or -NH(R)(H), whereby for example a carboxylic acid is reacted, i.e. coupled, with the amine to form an amide, as in $C(O)NR_2$. A phosphonic acid may be reacted with the amine to form a phosphonamidate, as in -$P(O)(OR)(NR_2)$.

In general, amino acids have the structure $R^{17}C(O)CH(R^{16})NH$-, where R^{17} is -OH, -OR, an amino acid or a polypeptide residue. Amino acids are low molecular weight compounds, on the order of less than about 1000 MW and which contain at least one amino or imino group and at least one carboxyl group. Generally the amino acids will be found in nature, i.e., can be detected in biological material such as bacteria or other microbes, plants, animals or man. Suitable amino acids typically are alpha amino acids, i.e. compounds characterized by one amino or imino nitrogen atom separated from the carbon atom of one carboxyl group by a single substituted or unsubstituted alpha carbon atom. Of particular interest are hydrophobic residues such as mono-or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. These residues contribute to cell permeability by increasing the partition coefficient of the parental drug. Typically, the residue does not contain a sulfhydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally in plants, animals or microbes, especially proteins thereof. Polypeptides most typically will be substantially composed of such naturally-occurring amino acid residues. These amino acids are glycine, alanine, valine, leucine, isoleucine, serine, threonine,

cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline. Additionally, unnatural amino acids, for example, valanine, phenylglycine and homoarginine are also included. Commonly encountered amino acids that are not gene-encoded may also be used in the present invention. All of the amino acids used in the present invention may be either the D- or L- optical isomer. In addition, other peptidomimetics are also useful in the present invention. For a general review, see Spatola, A. F., in *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, B. Weinstein, eds., Marcel Dekker, New York, p. 267 (1983).

When protecting groups are single amino acid residues or polypeptides, these conjugates may be produced by forming an amide bond between a carboxyl group of the amino acid (or C-terminal amino acid of a polypeptide for example). Generally, only one of any site in the parental molecule is amidated with an amino acid as described herein, although it is within the scope of this invention to introduce amino acids at more than one permitted site. In general, the α-amino or α-carboxyl group of the amino acid or the terminal amino or carboxyl group of a polypeptide are bonded to the parental functionalities, i.e., carboxyl or amino groups in the amino acid side chains generally are not used to form the amide bonds with the parental compound (although these groups may need to be protected during synthesis of the conjugates as described further below).

With respect to the carboxyl-containing side chains of amino acids or polypeptides it will be understood that the carboxyl group optionally will be blocked, e.g. by R^1, esterified with R^5 or amidated. Similarly, the amino side chains R^{16} optionally will be blocked with R^1 or substituted with R^5.

Such ester or amide bonds with side chain amino or carboxyl groups, like the esters or amides with the parental molecule, optionally are hydrolyzable *in vivo* or *in vitro* under acidic (pH <3) or basic (pH >10) conditions. Alternatively, they are substantially stable in the gastrointestinal tract of humans but are hydrolyzed enzymatically in blood or in intracellular environments. The esters or amino acid or polypeptide amidates also are useful as intermediates for the preparation of the parental molecule containing free amino or carboxyl groups. The free acid or base of the parental compound, for example, is readily formed from the esters or amino acid

or polypeptide conjugates of this invention by conventional hydrolysis procedures.

When an amino acid residue contains one or more chiral centers, any of the D, L, meso, threo or erythro (as appropriate) racemates, scalemates or mixtures thereof may be used. In general, if the intermediates are to be hydrolyzed non-enzymatically (as would be the case where the amides are used as chemical intermediates for the free acids or free amines), D isomers are useful. On the other hand, L isomers are more versatile since they can be susceptible to both non-enzymatic and enzymatic hydrolysis, and are more efficiently transported by amino acid or dipeptidyl transport systems in the gastrointestinal tract.

Examples of suitable amino acids whose residues are represented by R^x or R^y include the following:

Glycine;

Aminopolycarboxylic acids, e.g., aspartic acid, β-hydroxyaspartic acid, glutamic acid, β -hydroxyglutamic acid, β-methylaspartic acid, β-methylglutamic acid, β, β-dimethylaspartic acid, γ-hydroxyglutamic acid, β, γ-dihydroxyglutamic acid, β -phenylglutamic acid, γ-methyleneglutamic acid, 3-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid;

Amino acid amides such as glutamine and asparagine;

Polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β -aminoalanine, γ -aminobutyrine, ornithine, citruline, homoarginine, homocitrulline, hydroxylysine, allohydroxylsine and diaminobutyric acid;

Other basic amino acid residues such as histidine;

Diaminodicarboxylic acids such as α, α'-diaminosuccinic acid, α, α'-diaminoglutaric acid, α, α'-diaminoadipic acid, α, α'-diaminopimelic acid, α, α'-diamino- β-hydroxypimelic acid, α, α'-diaminosuberic acid, α, α'-diaminoazelaic acid, and α, α'-diaminosebacic acid;

Imino acids such as proline, hydroxyproline, allohydroxyproline, γ-methylproline, pipecolic acid, 5-hydroxypipecolic acid, and azetidine-2-carboxylic acid;

A mono- or di-alkyl (typically C_1-C_8 branched or normal) amino acid such as alanine, valine, leucine, allylglycine, butyrine, norvaline, norleucine, heptyline, α-methylserine, α-amino-α-methyl-γ-hydroxyvaleric acid, α-amino- α-methyl-δ-

hydroxyvaleric acid, α-amino- α-methyl-ε-hydroxycaproic acid, isovaline, α-methylglutamic acid, α-aminoisobutyric acid, α-aminodiethylacetic acid, α-aminodiisopropylacetic acid, α-aminodi-n-propylacetic acid, α-aminodiisobutylacetic acid, α-aminodi-n-butylacetic acid, α-aminoethylisopropylacetic acid, α-amino-n-propylacetic acid, α-aminodiisoamyacetic acid, α-methylaspartic acid, α-methylglutamic acid, 1-aminocyclopropane-1-carboxylic acid, isoleucine, alloisoleucine, *tert*-leucine, β-methyltryptophan and α-amino- β-ethyl-β-phenylpropionic acid;

β-phenylserinyl;

Aliphatic α-amino-β-hydroxy acids such as serine, β-hydroxyleucine, β-hydroxynorleucine, β -hydroxynorvaline, and α-amino-β-hydroxystearic acid;

α-Amino, α-, γ-, δ- or ε-hydroxy acids such as homoserine, δ -hydroxynorvaline, γ-hydroxynorvaline and ε-hydroxynorleucine residues; canavine and canaline; γ -hydroxyornithine;

2-hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid;

α-Amino-β-thiols such as penicillamine, β-thiolnorvaline or β-thiolbutyrine;

Other sulfur containing amino acid residues including cysteine; homocystine, β-phenylmethionine, methionine, S-allyl-L-cysteine sulfoxide, 2-thiolhistidine, cystathionine, and thiol ethers of cysteine or homocysteine;

Phenylalanine, tryptophan and ring-substituted α-amino acids such as the phenyl- or cyclohexylamino acids α-aminophenylacetic acid, α-aminocyclohexylacetic acid and α-amino-β-cyclohexylpropionic acid; phenylalanine analogues and derivatives comprising aryl, lower alkyl, hydroxy, guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (e.g., tyrosine, methyltyrosine and o-chloro-, p-chloro-, 3,4-dichloro, *o*-, *m*- or *p*-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro-, 2-hydroxy-5-nitro- and p-nitro-phenylalanine); furyl-, thienyl-, pyridyl-, pyrimidinyl-, purinyl- or naphthyl-alanines; and tryptophan analogues and derivatives including kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan;

α-Amino substituted amino acids including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylvaline and N-benzylvaline; and

α-Hydroxy and substituted α -hydroxy amino acids including serine, threonine, allothreonine, phosphoserine and phosphothreonine.

Polypeptides are polymers of amino acids in which a carboxyl group of one amino acid monomer is bonded to an amino or imino group of the next amino acid monomer by an amide bond. Polypeptides include dipeptides, low molecular weight polypeptides (about 1500-5000 MW) and proteins. Proteins optionally contain 3, 5, 10, 50, 75, 100 or more residues, and suitably are substantially sequence-homologous with human, animal, plant or microbial proteins. They include enzymes (e.g., hydrogen peroxidase) as well as immunogens such as KLH, or antibodies or proteins of any type against which one wishes to raise an immune response. The nature and identity of the polypeptide may vary widely.

The polypeptide amidates are useful as immunogens in raising antibodies against either the polypeptide (if it is not immunogenic in the animal to which it is administered) or against the epitopes on the remainder of the compound of this invention.

Antibodies capable of binding to the parental non-peptidyl compound are used to separate the parental compound from mixtures, for example in diagnosis or manufacturing of the parental compound. The conjugates of parental compound and polypeptide generally are more immunogenic than the polypeptides in closely homologous animals, and therefore make the polypeptide more immunogenic for facilitating raising antibodies against it. Accordingly, the polypeptide or protein may not need to be immunogenic in an animal typically used to raise antibodies, e.g., rabbit, mouse, horse, or rat, but the final product conjugate should be immunogenic in at least one of such animals. The polypeptide optionally contains a peptidolytic enzyme cleavage site at the peptide bond between the first and second residues adjacent to the acidic heteroatom. Such cleavage sites are flanked by enzymatic recognition structures, e.g. a particular sequence of residues recognized by a peptidolytic enzyme.

Peptidolytic enzymes for cleaving the polypeptide conjugates of this invention are well known, and in particular include carboxypeptidases. Carboxypeptidases digest polypeptides by removing C-terminal residues, and are specific in many instances for particular C-terminal sequences. Such enzymes and their substrate

requirements in general are well known. For example, a dipeptide (having a given pair of residues and a free carboxyl terminus) is covalently bonded through its α-amino group to the phosphorus or carbon atoms of the compounds herein.

Intracellular Targetting

The known experimental or approved HIV integrase inhibitor drugs which can be derivatized in accord with the present invention must contain at least one functional group capable of bonding to the phosphorus atom in the phosphonate moiety. The phosphonate derivatives of Formulas I-XXXIX may cleave *in vivo* in stages after they have reached the desired site of action, i.e. inside a cell. One mechanism of action inside a cell may entail a first cleavage, e.g. by esterase, to provide a negatively-charged "locked-in" intermediate. Cleavage of a terminal ester grouping in Formulas I-XXXIX thus affords an unstable intermediate which releases a negatively charged "locked in" intermediate.

After passage inside a cell, intracellular enzymatic cleavage or modification of the phosphonate prodrug compound may result in an intracellular accumulation of the cleaved or modified compound by a “trapping” mechanism. The cleaved or modified compound may then be “locked-in” the cell by a significant change in charge, polarity, or other physical property change which decreases the rate at which the cleaved or modified compound can exit the cell, relative to the rate at which it entered as the phosphonate prodrug. Other mechanisms by which a therapeutic effect are achieved may be operative as well. Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphatases.

In selected instances in which the drug is of the nucleoside type, such as is the case of zidovudine and numerous other antiretroviral agents, it is known that the drug is activated *in vivo* by phosphorylation. Such activation may occur in the present system by enzymatic conversion of the "locked-in" intermediate with phosphokinase to the active phosphonate diphosphate and/or by phosphorylation of the drug itself after its release from the "locked-in" intermediate as described above. In either case, the original nucleoside-type drug will be convened, via the derivatives of this invention, to the active phosphorylated species.

From the foregoing, it will be apparent that many structurally different known approved and experimental HIV integrase inhibitor drugs can be derivatized in accord with the present invention. Numerous such drugs are specifically mentioned herein. However, it should be understood that the discussion of drug families and their specific members for derivatization according to this invention is not intended to be exhaustive, but merely illustrative.

As another example, when the selected drug contains multiple reactive hydroxyl functions, a mixture of intermediates and final products may again be obtained. In the unusual case in which all hydroxy groups are approximately equally reactive, there is not expected to be a single, predominant product, as each mono-substituted product will be obtained in approximate by equal amounts, while a lesser amount of multiply-substituted product will also result. Generally speaking, however, one of the hydroxyl groups will be more susceptible to substitution than the other(s), e.g. a primary hydroxyl will be more reactive than a secondary hydroxyl, an unhindered hydroxyl will be more reactive than a hindered one. Consequently, the major product will be a mono-substituted one in which the most reactive hydroxyl has been derivatized while other mono-substituted and multiply-substituted products may be obtained as minor products.

Cellular Accumulation Embodiment

Another embodiment of the invention is directed toward compounds capable of accumulating in human PBMC (peripheral blood mononuclear cells). PBMC refer to blood cells having round lymphocytes and monocytes. Physiologically, PBMC are critical components of the mechanism against infection. PBMC may be isolated from heparinized whole blood of normal healthy donors or buffy coats, by standard density gradient centrifugation and harvested from the interface, washed (e.g. phosphate-buffered saline) and stored in freezing medium. PBMC may be cultured in multi-well plates. At various times of culture, supernatant may be either removed for assessment, or cells may be harvested and analyzed (Smith R. etal (2003) *Blood* 102(7):2532-2540). The compounds of this embodiment may further comprise a phosphonate or phosphonate prodrug. More typically, the phosphonate or phosphonate prodrug has the structure A^3 as described herein.

Optionally, the compounds of this embodiment demonstrate improved intracellular half-life of the compounds or intracellular metabolites of the compounds in human PBMC when compared to analogs of the compounds not having the phosphonate or phosphonate prodrug. Typically, the half-life is improved by at least about 50%, more typically at least in the range 50-100%, still more typically at least about 100%, more typically yet greater than about 100%.

In another embodiment, the intracellular half-life of a metabolite of the compound in human PBMCs is improved when compared to an analog of the compound not having the phosphonate or phosphonate prodrug. In such embodiments, the metabolite may be generated intracellularly, e.g. generated within human PBMC. The metabolite may be a product of the cleavage of a phosphonate prodrug within human PBMCs. The phosphonate prodrug may be cleaved to form a metabolite having at least one negative charge at physiological pH. The phosphonate prodrug may be enzymatically cleaved within human PBMC to form a phosphonate having at least one active hydrogen atom of the form P-OH.

Stereoisomers

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

The compounds of the invention can also exist as tautomeric isomers in certain

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

Salts and Hydrates

The compositions of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na^+, Li^+, K^+, Ca^{+2} and Mg^{+2}. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth met al ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. Monovalent salts are preferred if a water soluble salt is desired.

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

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

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids. Any of the amino acids described above 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 HIV Integrase

Another aspect of the invention relates to methods of inhibiting the activity of HIV integrase comprising the step of treating a sample suspected of containing HIV

with a composition of the invention.

Compositions of the invention may act as inhibitors of HIV integrase, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of HIV integrase having a geometry unique to HIV integrase. Compositions binding HIV integrase may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of HIV integrase. Accordingly, the invention relates to methods of detecting HIV integrase in a sample suspected of containing HIV integrase comprising the steps of: treating a sample suspected of containing HIV integrase 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 HIV integrase 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 an organism which produces HIV integrase, frequently a pathogenic organism such as HIV. Samples can be contained in any medium including water and organic solvent\water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

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

If desired, the activity of HIV integrase after application of the composition can be observed by any method including direct and indirect methods of detecting HIV integrase activity. Quantitative, qualitative, and semiquantitative methods of determining HIV integrase 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.

Organisms that contain HIV integrase include the HIV virus. The compounds of this invention are useful in the treatment or prophylaxis of HIV infections in animals or in man.

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

Screens for HIV integrase Inhibitors.

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

Useful *in vitro* screens have been described in detail and will not be elaborated here. However, the examples describe suitable *in vitro* assays.

Pharmaceutical Formulations

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such

as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers 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.

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

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

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

so as to provide slow or controlled release of the active ingredient therefrom.

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

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

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

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

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes

or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

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

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium

phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

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

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

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

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable

emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

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

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

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

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

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

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

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

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

The formulations are presented in unit-dose or multi-dose containers, for

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

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

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

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

Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

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) or against an active viral infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately

70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Active ingredients of the invention are also used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating viral infections the compositions of the invention are combined with other antivirals such as other protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors or HIV integrase inhibitors.

Routes of Administration

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

Combination Therapy

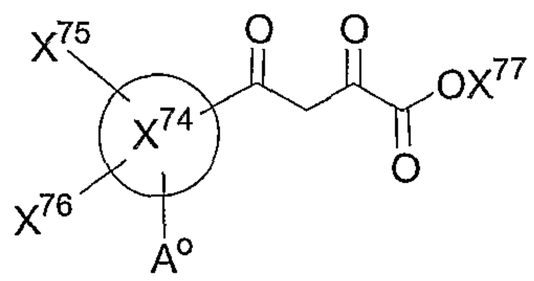
It is also possible to combine any compound of the invention with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to an HIV infected patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. Second and third active ingredients in the combination may have anti-HIV activity. Exemplary active ingredients to be administered in combination with compounds of the invention are protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and HIV integrase inhibitors.

The combination therapy may provide "synergy" and "synergistic", i.e. the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or

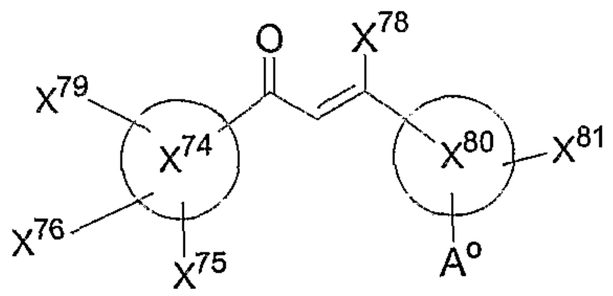
delivered simultaneously in a combined, unit dosage formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g. in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. A synergistic anti-viral effect denotes an antiviral effect which is greater than the predicted purely additive effects of the individual compounds of the combination.

In another embodiment the invention provides an HIV integrase inhibitor compound provided that the compound is not 4-(3-benzyl-phenyl)-2-hydroxy-4-oxo-but-2-enoic acid, 1-[5-(4-fluoro-benzyl)-furan-2-yl]-3-hydroxy-3-(1H-[1,2,4]triazol-3-yl)-propenone, or 5-(1,1-dioxo-116-[1,2]thiazinan-2-yl)-8-hydroxy-quinoline-7-carboxylic acid 4-fluoro-benzylamide.

In another embodiment the invention provides an HIV integrase inhibitor compound provided that the compound is not:



wherein X^{74} (-X^{75}, -X^{76}) is not phenyl substituted with benzyl and X^{77} is not hydrogen; or the compound is not:



wherein X^{74} (-X^{75}, -X^{76} , -X^{79}) is not furan substituted with p-fluorobenzyl, when X^{78} is hydroxy, and X^{80} (-X^{81}) is *1H*-[1,2,4]triazole.

It is also possible to combine a compound of the invention with a second or third active ingredient in a unitary dosage form for simultaneous or sequential administration. When administered sequentially, the combination may be administered in two or three administrations. The second or third active ingredient

may have anti-HIV activity and include protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and integrase inhibitors. Exemplary second or third active ingredients to be administered in combination with a compound of the invention are shown in Table C.

Table C

5,6 dihydro-5-azacytidine

5-aza 2'deoxycytidine

5-azacytidine

5-yl-carbocyclic 2'-deoxyguanosine (BMS200,475)

9 (arabinofuranosyl)guanine; 9-(2' deoxyribofuranosyl)guanine

9-(2'-deoxy 2'fluororibofuranosyl)-2,6-diaminopurine

9-(2'-deoxy 2'fluororibofuranosyl)guanine

9-(2'-deoxyribofuranosyl)-2,6 diaminopurine

9-(arabinofuranosyl)-2,6 diaminopurine

Abacavir, Ziagen®

Acyclovir, ACV; 9-(2-hydroxyethoxylmethyl)guanine

Adefovir dipivoxil, Hepsera®

amdoxivir, DAPD

Amprenavir, Agenerase®

araA; 9-b-D-arabinofuranosyladenine (Vidarabine)

atazanivir sulfate (Reyataz®)

AZT; 3'-azido-2',3'-dideoxythymdine, Zidovudine, (Retrovir®)

BHCG; (.+-.)-(1a,2b,3a)-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanine

BMS200,475; 5-yl-carbocyclic 2'-deoxyguanosine

Buciclovir; (R) 9-(3,4-dihydroxybutyl)guanine

BvaraU; 1-b-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil (Sorivudine)

Calanolide A

Capravirine

CDG; carbocyclic 2'-deoxyguanosine

Cidofovir, HPMPC; (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine

Clevudine, L-FMAU; 2'-Fluoro-5-methyl-β-L-arabino-furanosyluracil

Combivir® (lamivudine/zidovudine)

Cytallene; [1-(4'-hydroxy-1',2'-butadienyl)cytosine]

d4C; 3'-deoxy-2',3'-didehydrocytidine

DAPD; (-)-β-D-2,6-diaminopurine dioxolane

ddA; 2',3'-dideoxyadenosine

ddAPR; 2,6-diaminopurine-2',3'-dideoxyriboside

ddC; 2',3'-dideoxycytidine (Zalcitabine)

ddI; 2',3'-dideoxyinosine, didanosine, (Videx®, Videx® EC)

Delavirdine, Rescriptor®

Didanosine, ddI, Videx®; 2',3'-dideoxyinosine

DXG; dioxolane guanosine

E-5-(2-bromovinyl)-2'-deoxyuridine

Efavirenz, Sustiva®

Emtricitabine; (-)-cis FTC (Emtriva™)

Enfuvirtide (Fuzeon®)

F-ara-A; fluoroarabinosyladenosine (Fludarabine)

FDOC; (-)-β-D-5-fluoro-1-[2-(hydroxymethyl)-1,3-dioxolane]cytosine

FEAU; 2'-deoxy-2'-fluoro-1-β-D-arabinofuranosyl-5-ethyluracil

FIAC; 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine

FIAU; 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouridine

FLG; 2',3'-dideoxy-3'-fluoroguanosine

FLT; 3'-deoxy-3'-fluorothymidine

Fludarabine; F-ara-A; fluoroarabinosyladenosine

FMAU; 2'-Fluoro-5-methyl-b-L-arabino-furanosyluracil

FMdC

Foscarnet; phosphonoformic acid, PFA

FPMPA; 9-(3-fluoro-2-phosphonylmethoxypropyl)adenine

Gancyclovir, GCV; 9-(1,3-dihydroxy-2-propoxymethyl)guanine

GS-7340; 9-[*R*-2-[[(*S*)-[[(*S*)-1-(isopropoxycarbonyl)ethyl]amino]-phenoxyphosphinyl]methoxy]propyl]adenine

HPMPA; (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine

HPMPC; (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (Cidofovir)

Hydroxyurea, Droxia®

Indinavir, Crixivan®

Kaletra® (lopinavir/ritonavir)

Lamivudine, 3TC, Epivir™; (2*R*, 5*S*, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one

L-d4C; L-3'-deoxy-2',3'-didehydrocytidine

L-ddC; L-2',3'-dideoxycytidine

L-Fd4C; L-3'-deoxy-2',3'-didehydro-5-fluorocytidine

L-FddC; L-2',3'-dideoxy-5-fluorocytidine

Lopinavir

Nelfinavir, Viracept®

Nevirapine, Viramune®

Oxetanocin A; 9-(2-deoxy-2-hydroxymethyl-beta-D-erythro-oxetanosyl)adenine

Oxetanocin G; 9-(2-deoxy-2-hydroxymethyl-β-D-erythro-oxetanosyl)guanine

Penciclovir

PMEDAP; 9-(2-phosphonylmethoxyethyl)-2,6-diaminopurine

PMPA, tenofovir; (R)-9-(2-phosphonylmethoxypropyl)adenine

PPA; phosphonoacetic acid

Ribavirin; 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide

Ritonavir, Norvir®

Saquinavir, Invirase®, Fortovase®

Sorivudine, BvaraU; 1-β-D-arabinofuranosyl-E-5-(2-bromovinyl)uracil

Stavudine, d4T, Zerit®; 2',3'-didehydro-3'-deoxythymidine

Tenofovir disoproxil fumarate (TDF, Viread®)

Trifluorothymidine, TFT; Trifluorothymidine

Trizivir® (abacavir sulfate/lamivudine/zidovudine)

Vidarabine, araA; 9-β-D-arabinofuranosyladenine

Zalcitabine, Hivid®, ddC; 2',3'-dideoxycytidine

Zidovudine, AZT, Retrovir®; 3'-azido-2',3'-dideoxythymdine

Zonavir; 5-propynyl-1-arabinosyluracil

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and unobvious 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 HIV integrase inhibitory activity of their own.

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

EXEMPLARY METHODS OF MAKING THE COMPOUNDS OF THE INVENTION.

General aspects of exemplary methods are described below and in the Examples for the making, i.e. preparation, synthesis, of Formula I-XXXIX compounds of the invention. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

The compounds of the invention may be prepared by a variety of synthetic routes and methods known to those skilled in the art. The invention also relates to methods of making the compounds of the invention. The compounds 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 (9 Volume set) Barry M. Trost, Editor-in-Chief, Pergamon Press, New York, 1993.

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

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

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

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

The terms "treated", "treating", "treatment", and the like, 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.

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

Modifications of each of the exemplary schemes above and in the examples (hereafter "exemplary schemes") leads to various analogs of the specific exemplary

materials produce. The above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

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

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

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

A single stereoisomer, e.g. an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Stereochemistry of Carbon Compounds, (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113:(3) 283-302). Racemic mixtures of chiral compounds of the

invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: Drug Stereochemistry, Analytical Methods and Pharmacology, Irving W. Wainer, Ed., Marcel Dekker, Inc., New York (1993).

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

Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the pure or enriched enantiomer. 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 enantiomers or 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 (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.

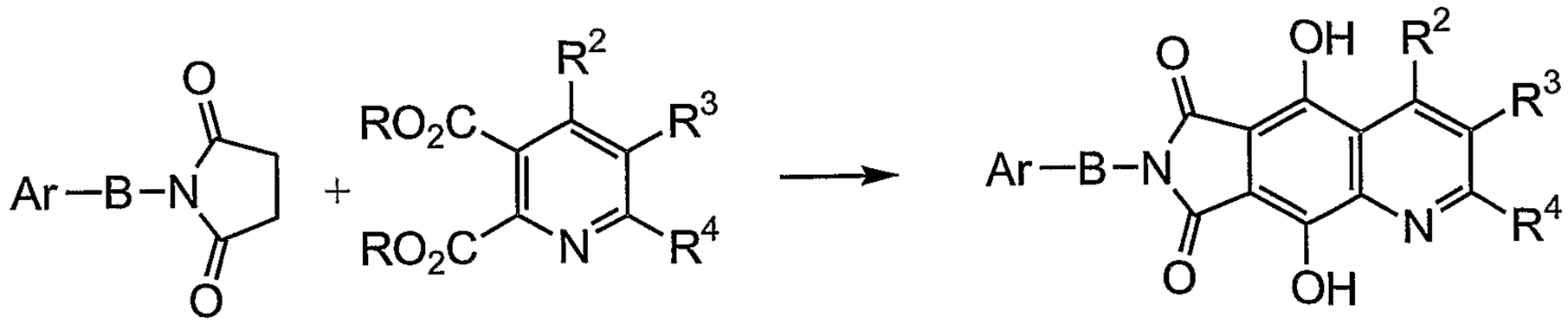
All literature and patent citations above are hereby expressly incorporated by reference at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following Embodiments. It is apparent that certain modifications of the methods and compositions of the following Embodiments can be made within the scope and spirit of the invention.

A number of exemplary methods for the preparation of the compounds, Formulas I-XXXIX, of the invention are provided herein. These methods are intended to illustrate the nature of such preparations and are not intended to limit the scope of applicable methods.

Deliberate use may be made of protecting groups to mask reactive functionality and direct reactions regioselectively (Greene, etal (1991) "Protective Groups in Organic Synthesis", 2nd Ed., John Wiley & Sons). For example, useful protecting groups for the 8-hydroxyl group and other hydroxyl substituents include methyl, MOM (methoxymethyl), trialkylsilyl, benzyl, benzoyl, trityl, and tetrahydropyranyl. Certain aryl positions may be blocked from substitution, such as the 2-position as fluorine.

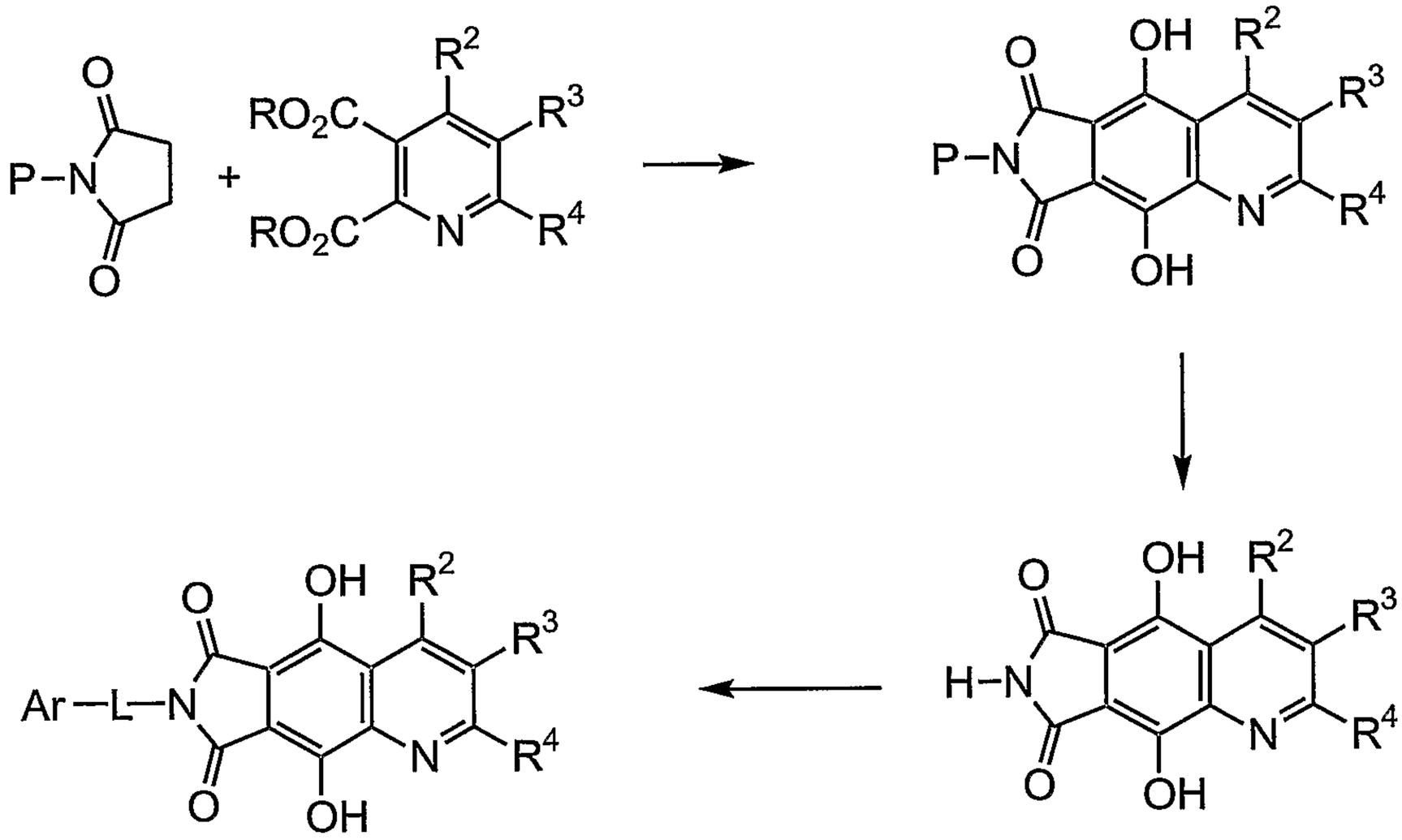
FORMULA I COMPOUNDS

Exemplary methods of synthesis of Formula I compounds are described below in Schemes 1-10 and 15-17. One method of synthesis of Formula I compounds of the invention is cyclization of a succinimide compound with a pyridine dicarboxylate compound to give tricyclic compounds (Murray and Semple, *Synthesis* (1996) 11:80-82; Jones and Jones, *Jour. Chem. Soc., Perkin Transactions I* (1973) 26-32), according to Scheme 1.



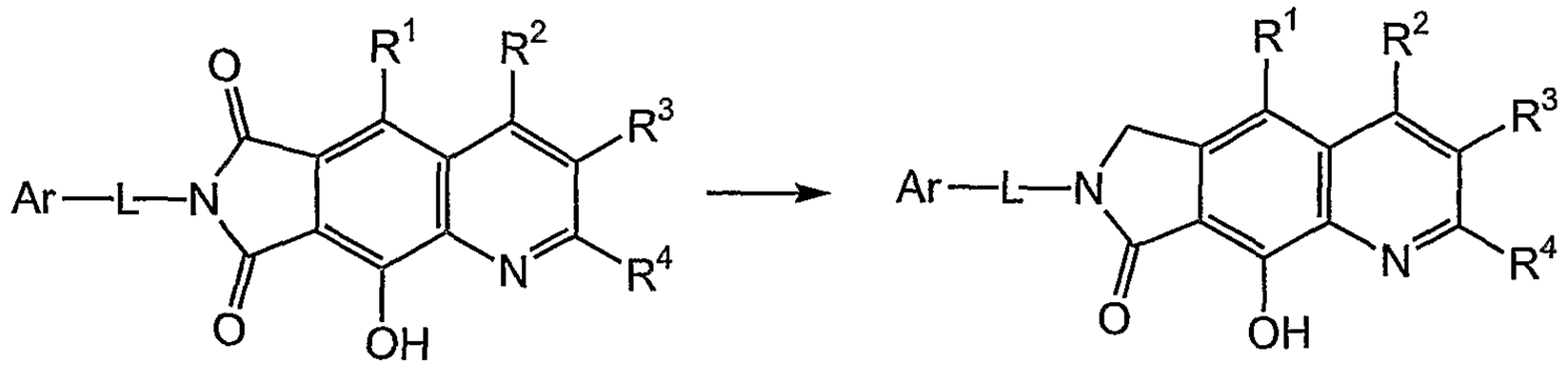
Scheme 1

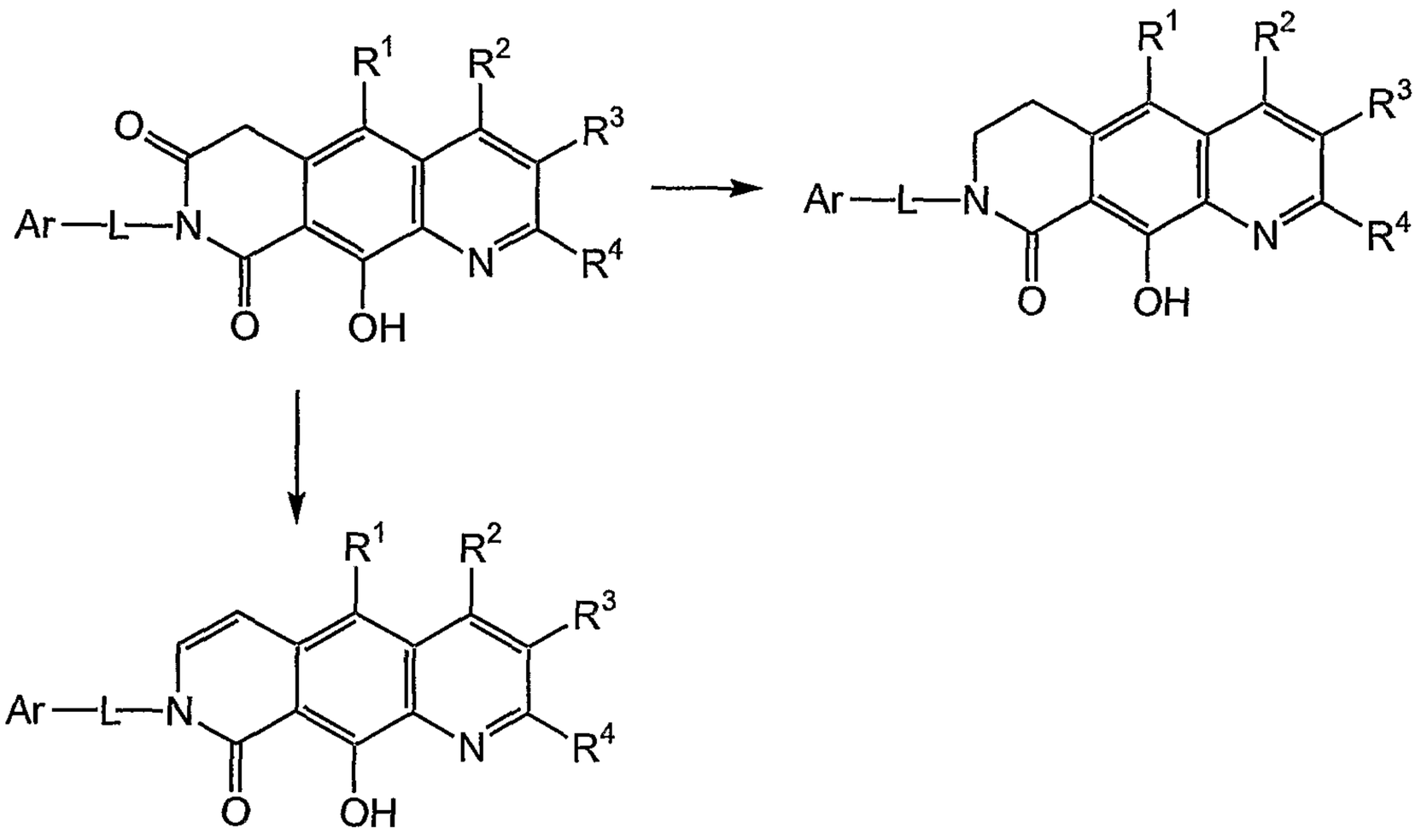
Alternatively, a succinimide with a labile protecting group (P) on the nitrogen may be reacted with a pyridine dicarboxylate compound. P may be an acid-labile protecting group, such as trialkylsilyl. Trialkylsilyl groups may also be removed with fluoride reagents. After P is removed, a variety of Ar-L groups may be covalently attached, according to Scheme 2.



Scheme 2

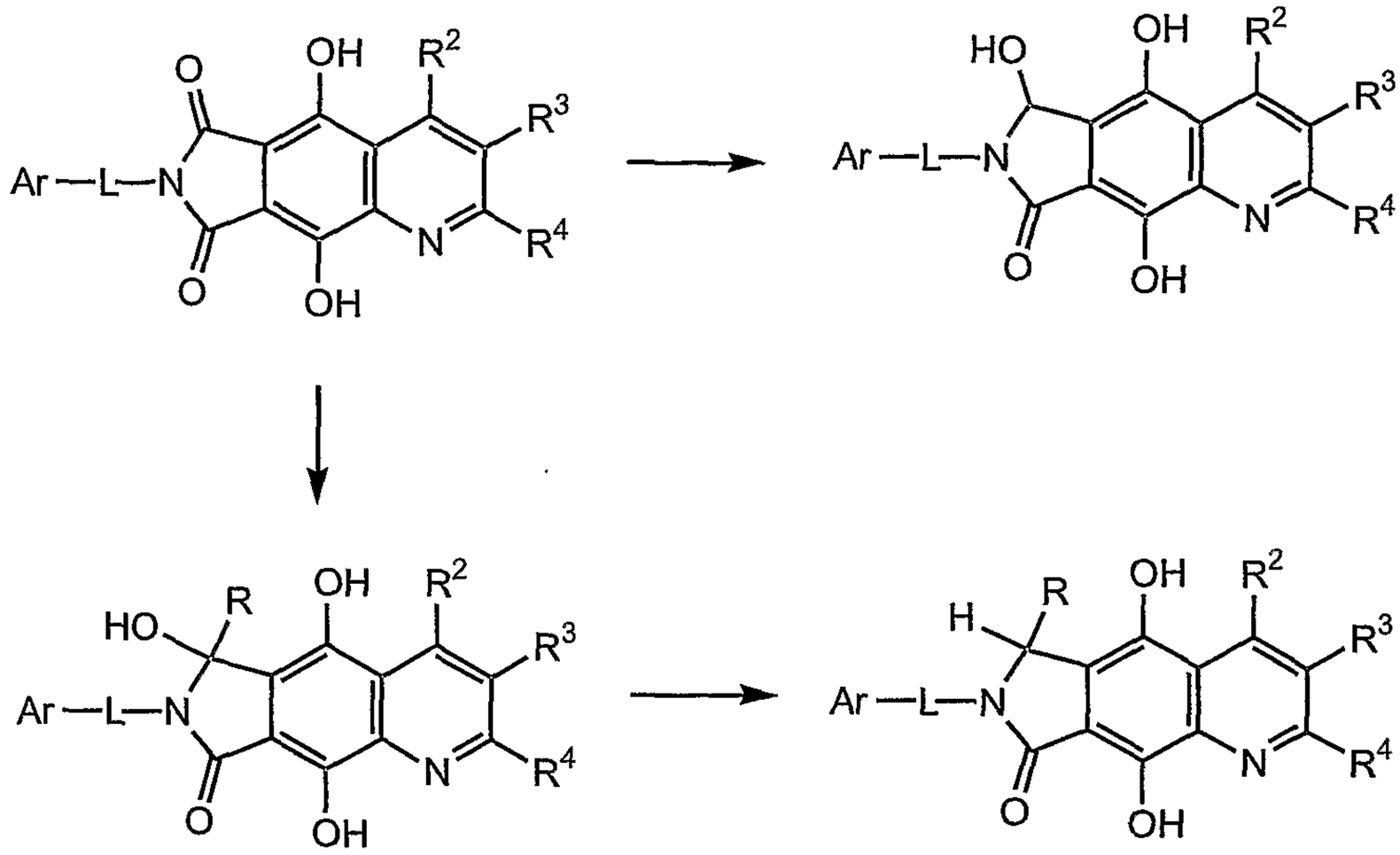
Imide compounds can be reduced with dissolving metal reducing agents, e.g. Zn, or hydride reagents, e.g. $NaBH_4$, to form a lactam. Exemplary regioselective conversions shown in Scheme 3 include:





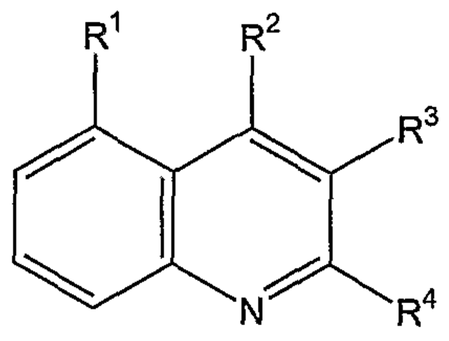
Scheme 3

Imide compounds may also be reduced to the hydroxylactam under mild conditions. Reductions with sodium borohydride and cerium or samarium salts have been shown to proceed with regioselectivity on asymmetric imides (Mase, etal *J. Chem. Soc. Perkin Communication 1* (2002) 707-709), as in Scheme 4, upper. Grignard reagents and acetylenic anions (Chihab-Eddine, etal *Tetrahedron Lett.* (2001) 42:573-576) may also add with regioselectivity to an imide carbonyl to form alkyl-hydroxylactam compounds, as in Scheme 4, lower). The phenolic oxygen groups may be protected and deprotected as necessary to furnish yield reactions.

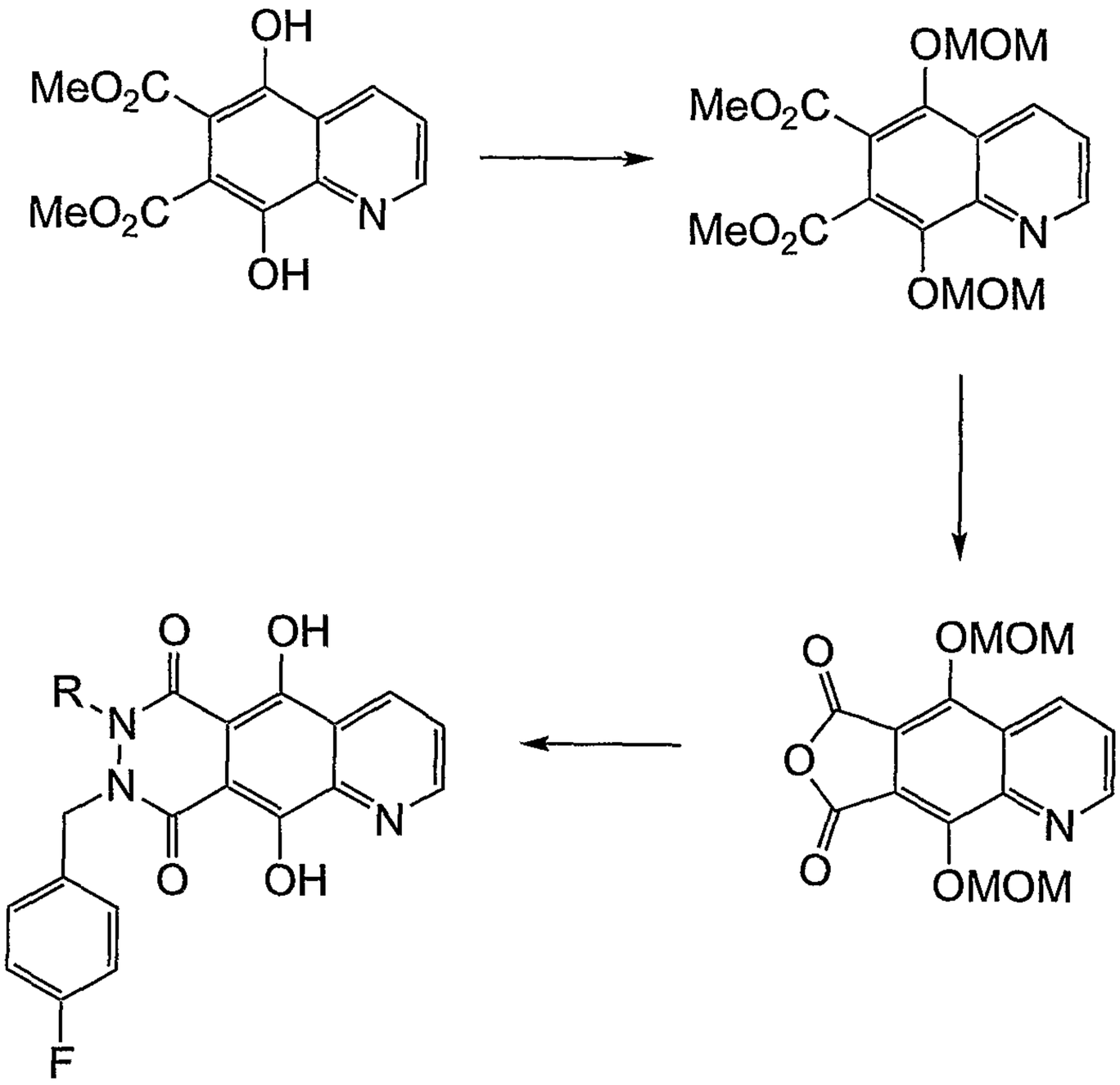


Scheme 4

Another synthetic route to the compounds of the invention proceeds through substituted quinoline intermediates (Clemence, etal U.S. Patent No. 5,324,839; Billhardt-Troughton, etal U.S. Patent No. 5,602,146; Matsumura, *J. Amer. Chem. Soc.* (1935) 57:124-128) having the general formula:

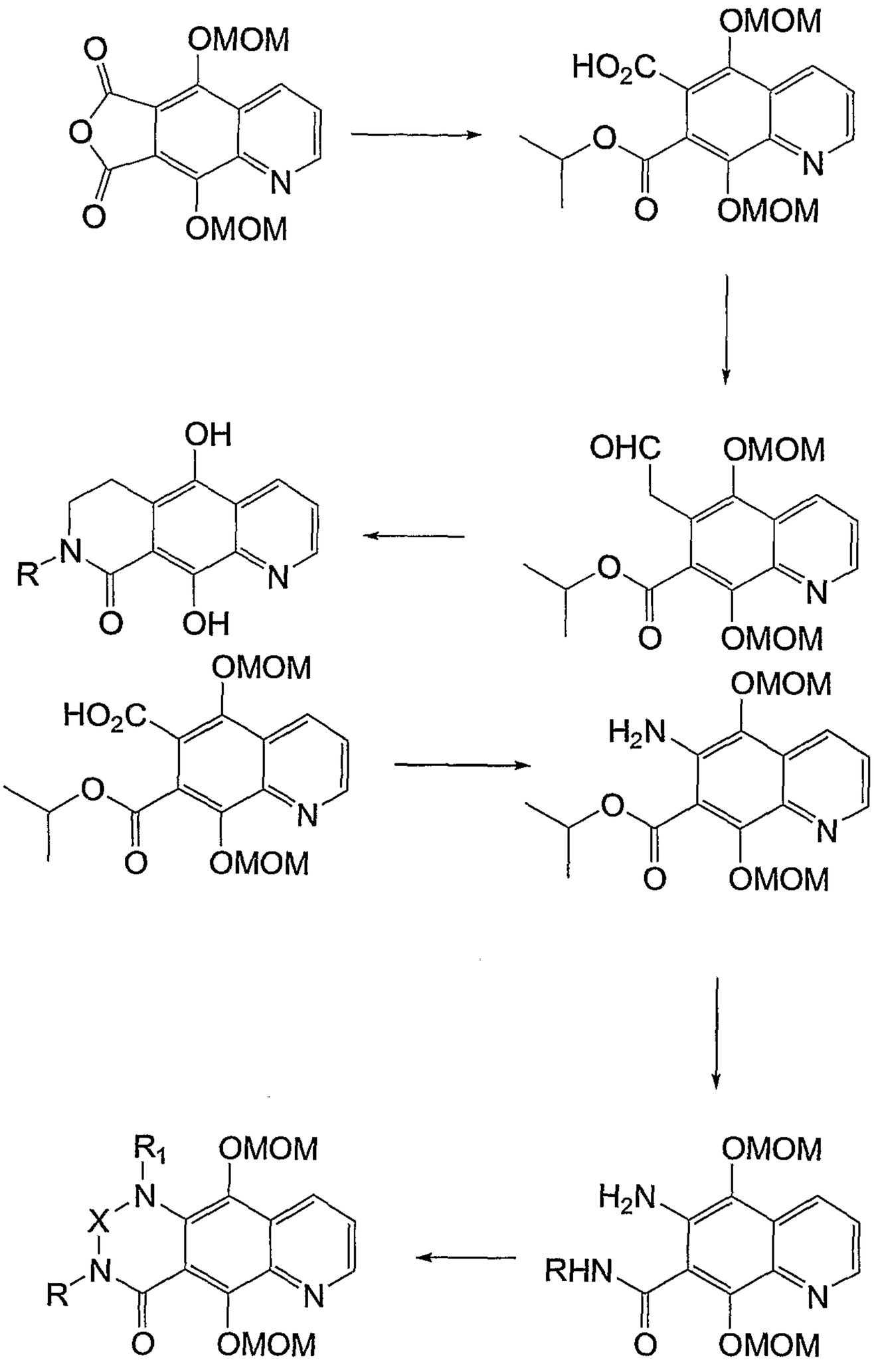


5,8-Dihydroxy quinoline compounds may be elaborated according to Scheme 5:



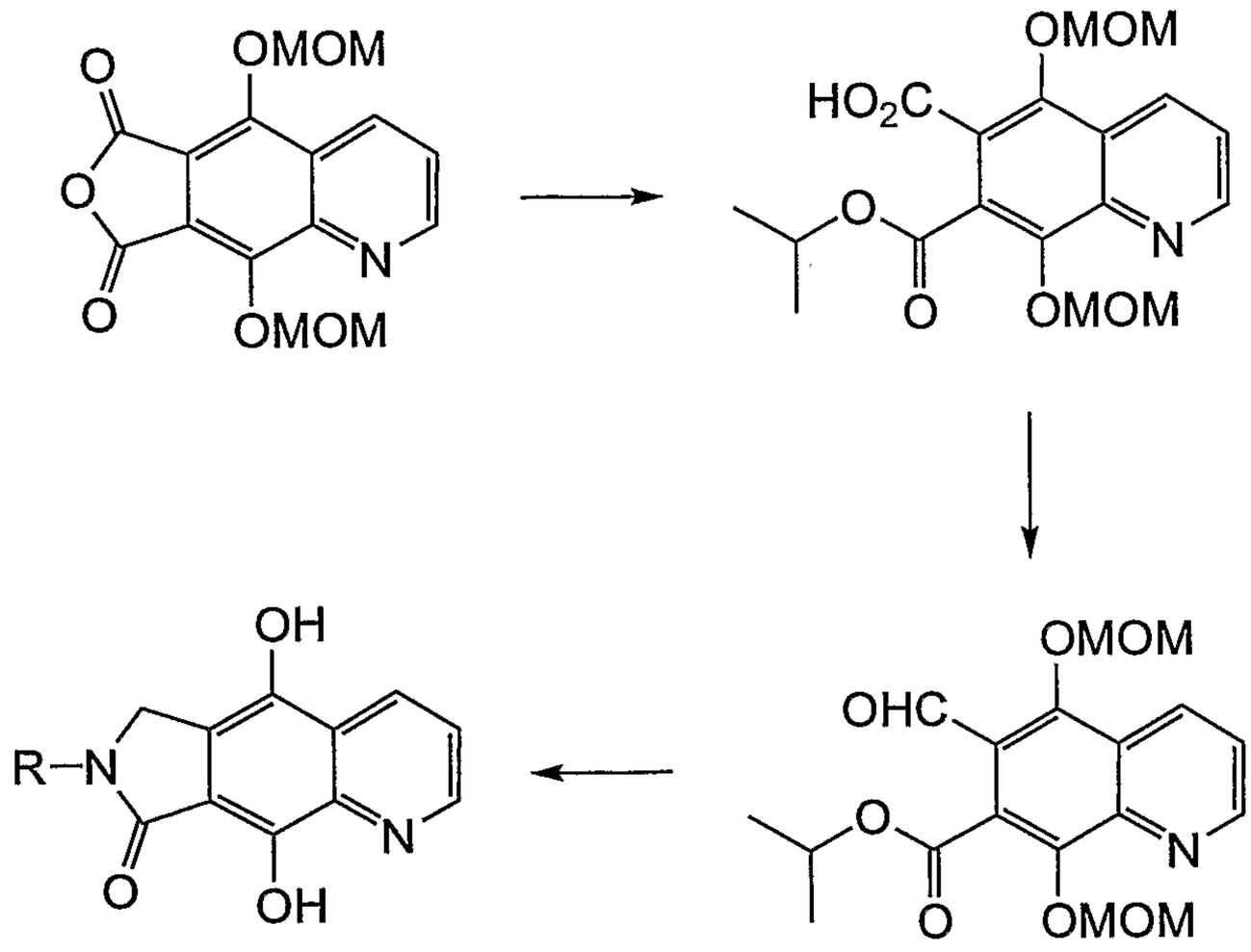
Scheme 5

The cyclic anhydride below may be regioselectively esterified to give the compounds of the invention, for example via the route in Scheme 6



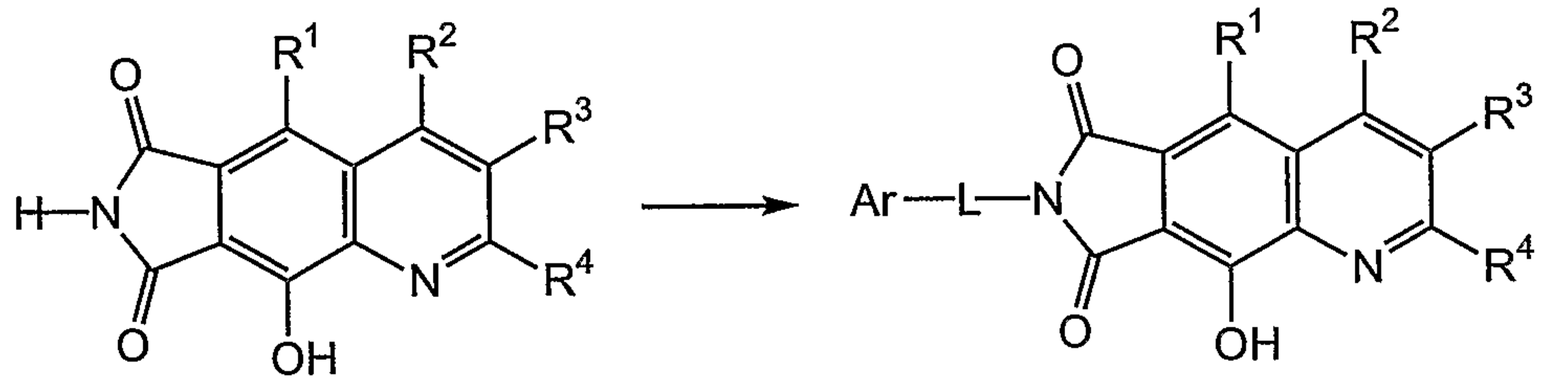
Scheme 6

where MOM is methoxymethyl and X is, for example, C(=O), CRC(=O), C(=O)C(=O), and SO_2. See Ornstein, etal *Jour. Med. Chem.* (1989) 32:827-833. The same chemistry can be applied to the 5-membered lactam synthesis to control the regiochemistry as in Scheme 7:



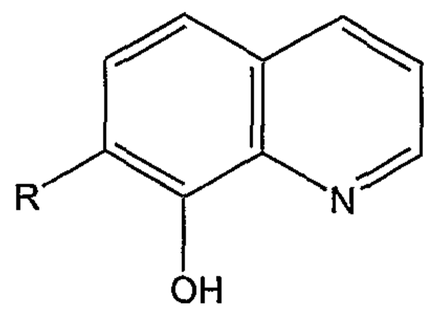
Scheme 7

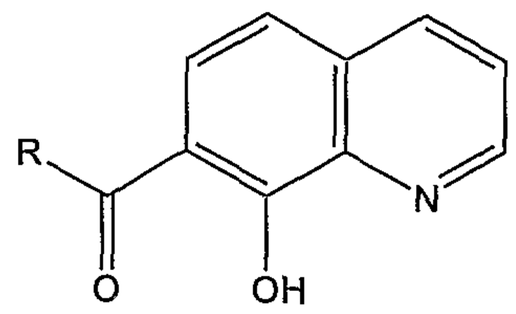
A cyclic imide may be conveniently alkylated, acylated, or otherwise reacted to form a broad array of compounds with Ar–L groups:



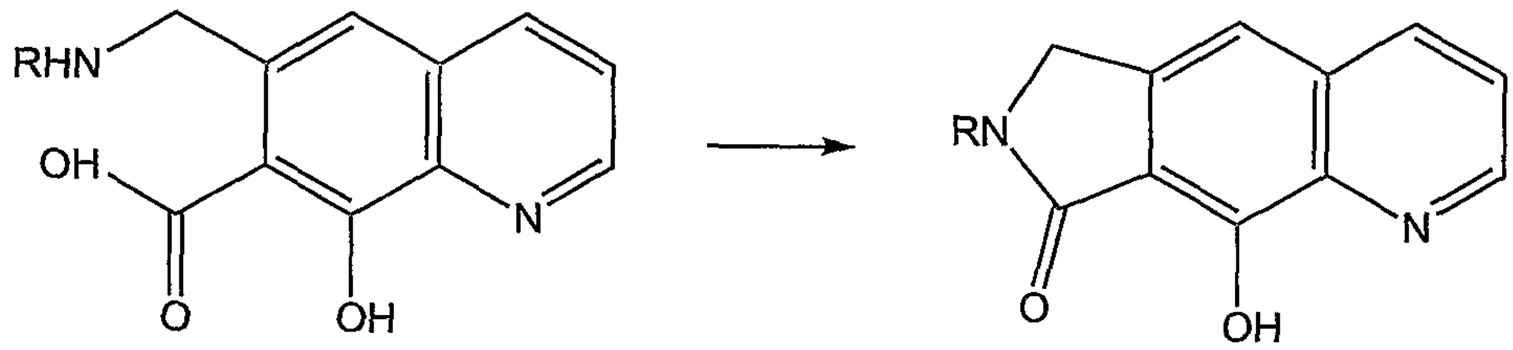
The Ar–L group may be attached as one reactant group, for example as an alkylating reagent like benzyl bromide (Ar = phenyl, L = CH_2) or a sulfonating reagent, like 4-methoxyphenyl sulfonyl chloride (Ar = 4-methoxyphenyl, L = $S(=O)_2$. Alternatively, the Ar–L group may be attached by a multi step process. For example, the imide nitrogen may react with a sulfurizing reagent such as 2,2-dipyridyl disulfide to form an N-sulfide intermediate (Ar = 2-pyridyl, L = S). Such an intermediate may be further elaborated to a variety of Ar–L groups where L is S, S(=O) or $S(=O)_2$.

Another synthetic route to the compounds of the invention proceeds through 7-substituted, 8-quinolinol intermediates (Zhuang, etal WO 02/36734; Vaillancourt, etal U.S. Patent No. 6,310,211; Hodel, U.S. Patent No. 3,113,135) having the general formulas, including aryl substituted compounds:

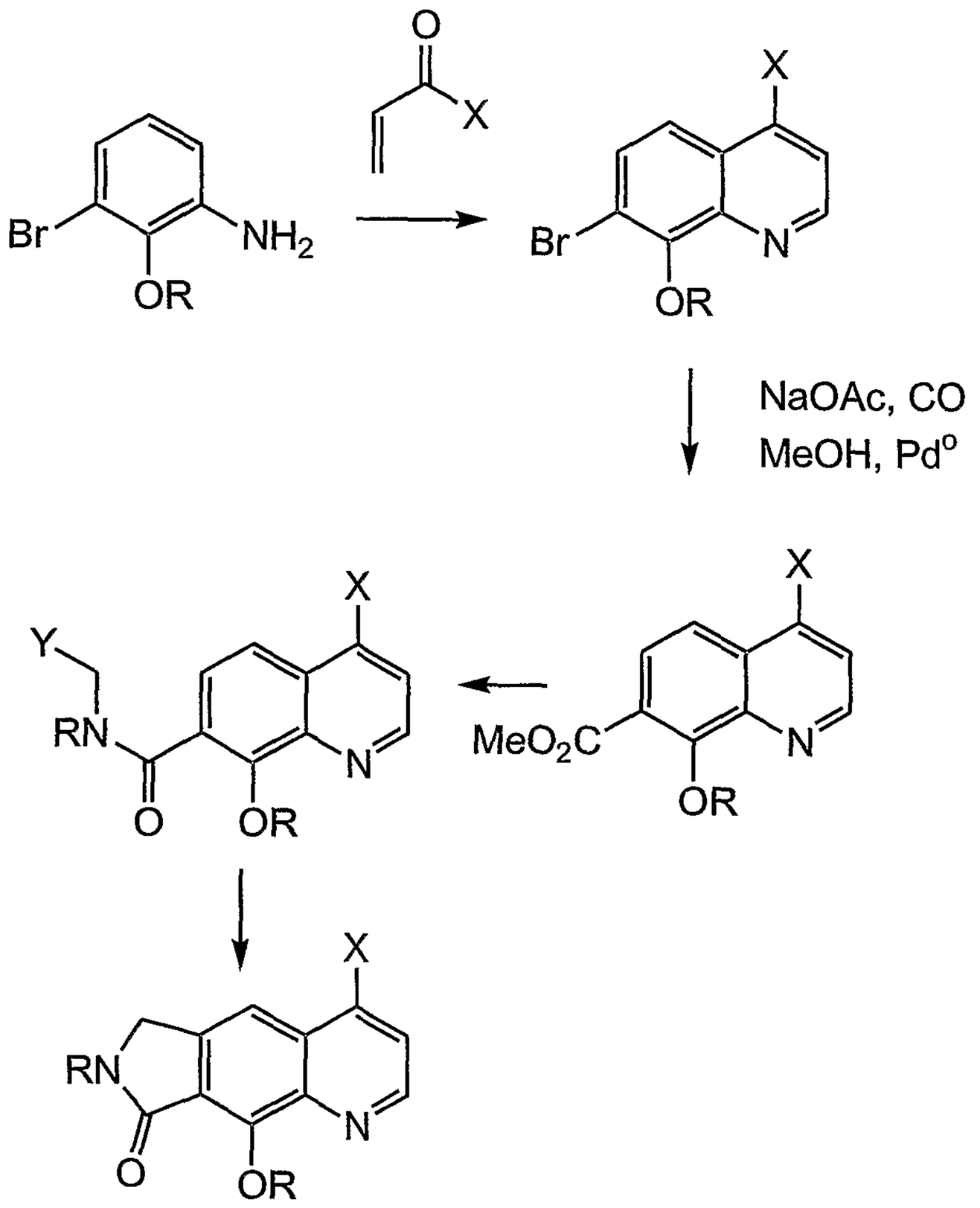




Annulation of the third, 5-7 membered ring can be conducted by appropriate selection of aryl substituents on the quinoline ring system, utilizing known synthetic transformations to give compounds of Formula I. For example, methods for coupling carboxylic acids and other activated acyl groups with amines to form carboxamides are well known in the art (March, J. Advanced Organic Chemistry, 3rd Edition, John Wiley & Sons, 1985, pp. 370-376). An exemplary cyclization includes the following:

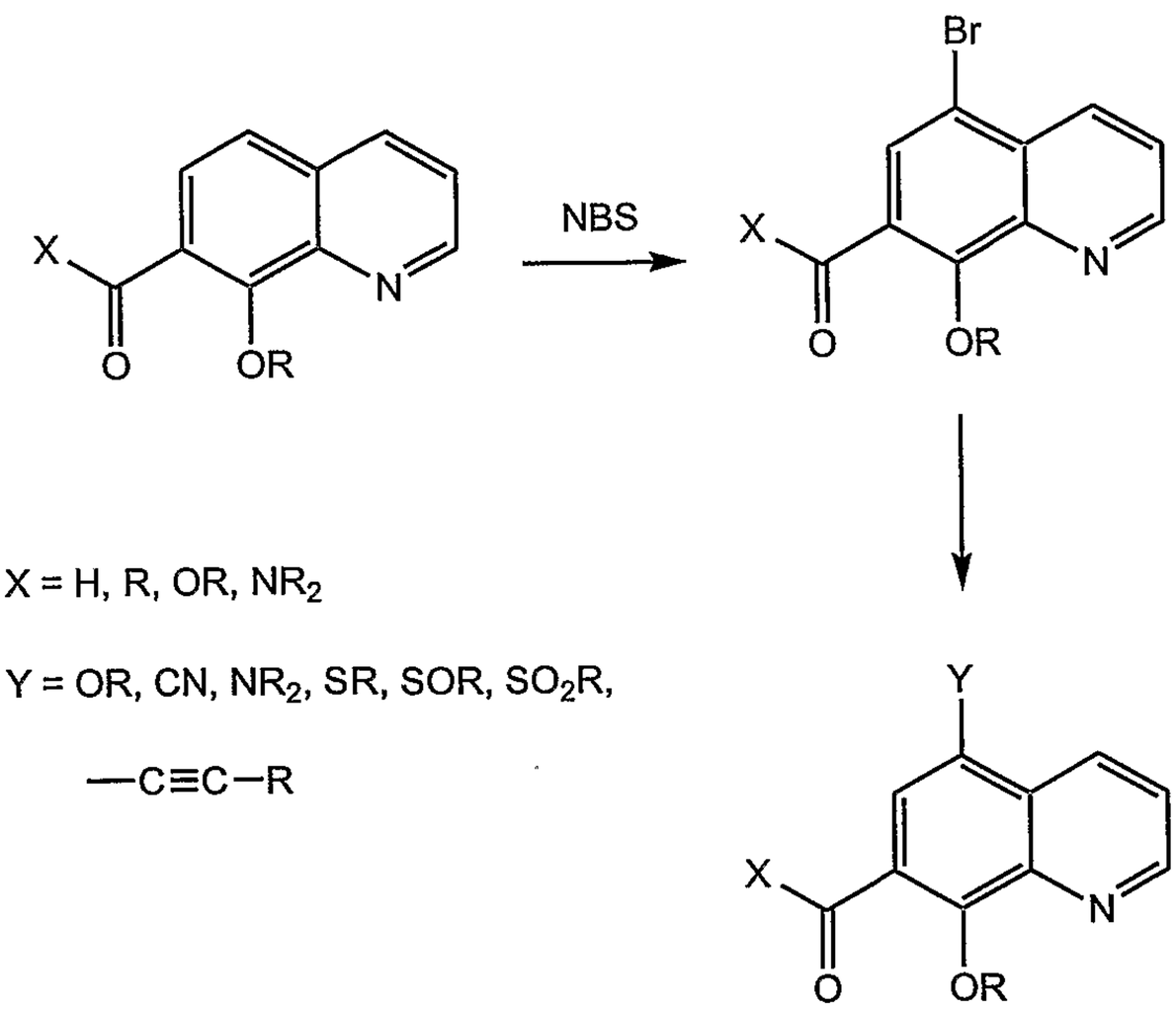


Scheme 8 below shows another synthetic route to compounds of the invention, i.e. Formula I. This route proceeds by cyclization of a 2-O-protected, 3 halo-aniline compound with an α,β-unsaturated carbonyl compound to give a functionalized quinoline. The α,β-unsaturated carbonyl compound may be, for example, an aldehyde (X=H), ketone (X=R), ester (X=OR), amide (X=NR2), acyl halide (X=Cl), or anhydride. Carbonylation via palladium catalysis can give an ester which may be elaborated to the amide functionality and cyclization to form a 5, 6, or 7 membered ring. The R group of phenolic oxygen may be a labile protecting group, e.g. trialkylsilyl or tetrahydropyranyl, which may be removed at a step in the synthetic route, or it may be a substituent which is retained in the putative integrase inhibitor compound.



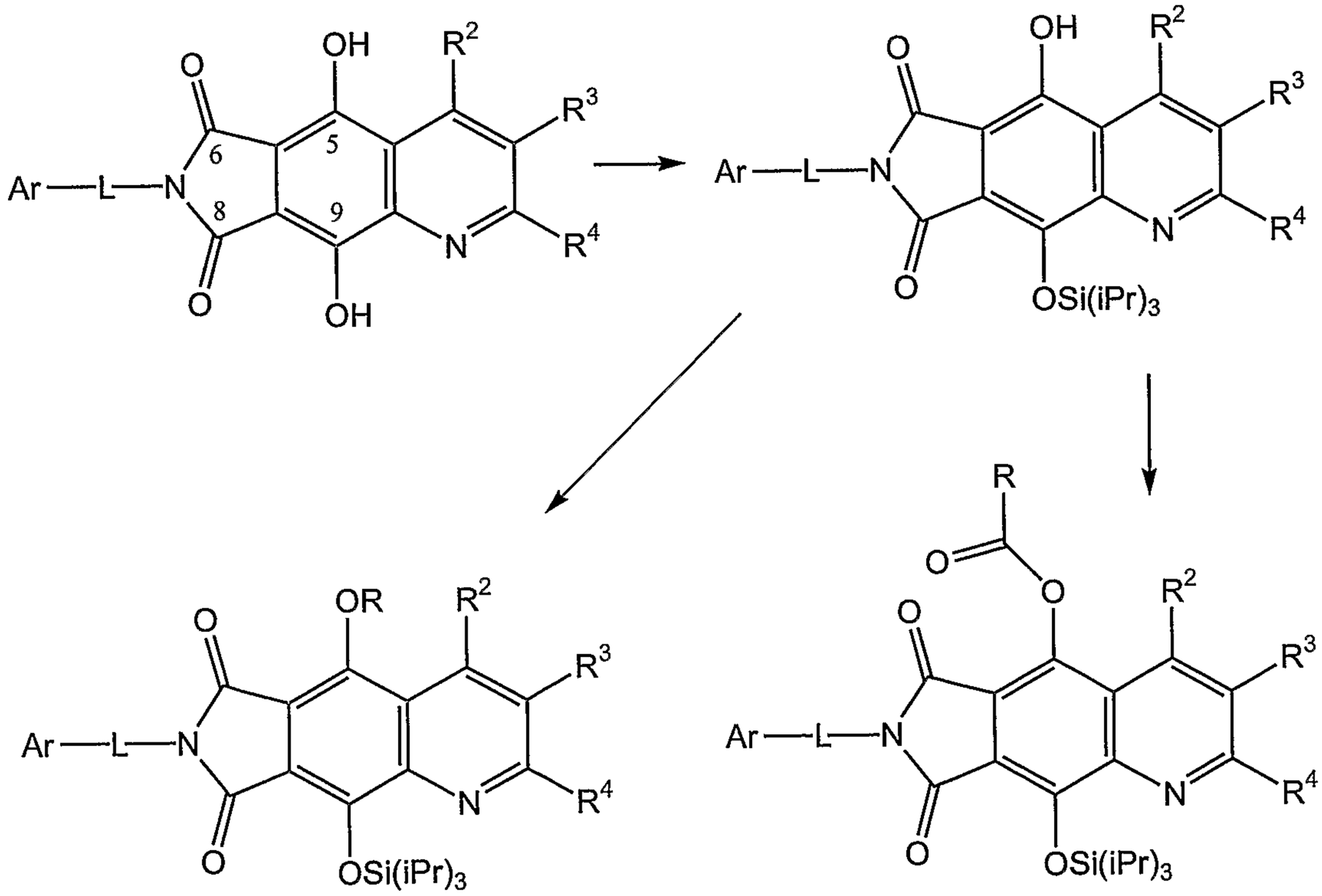
Scheme 8

Halo quinoline intermediates may undergo a flexible array of nucleophilic aromatic substitutions and Suzuki-type reactions, as shown in Scheme 9 below. Suzuki coupling of aryl halide compounds with acetylenic and vinylic palladium complexes are carbon-carbon bond forming reactions under relatively mild conditions. In some instances it may be necessary to block the 2 position to direct reaction at the desired aryl position.



Scheme 9

Formula I compounds with a 5,9-dihydroxy-pyrrolo[3,4-g]quinoline-6,8-dione were prepared by selective protection of the C9 phenol in 5,9-dihydroxy-pyrrolo[3,4-g]quinoline-6,8-dione. The C9 phenol was protected with a TIPS group and the C5 phenol could then be alkylated or acylated (Scheme 10).



Scheme 10

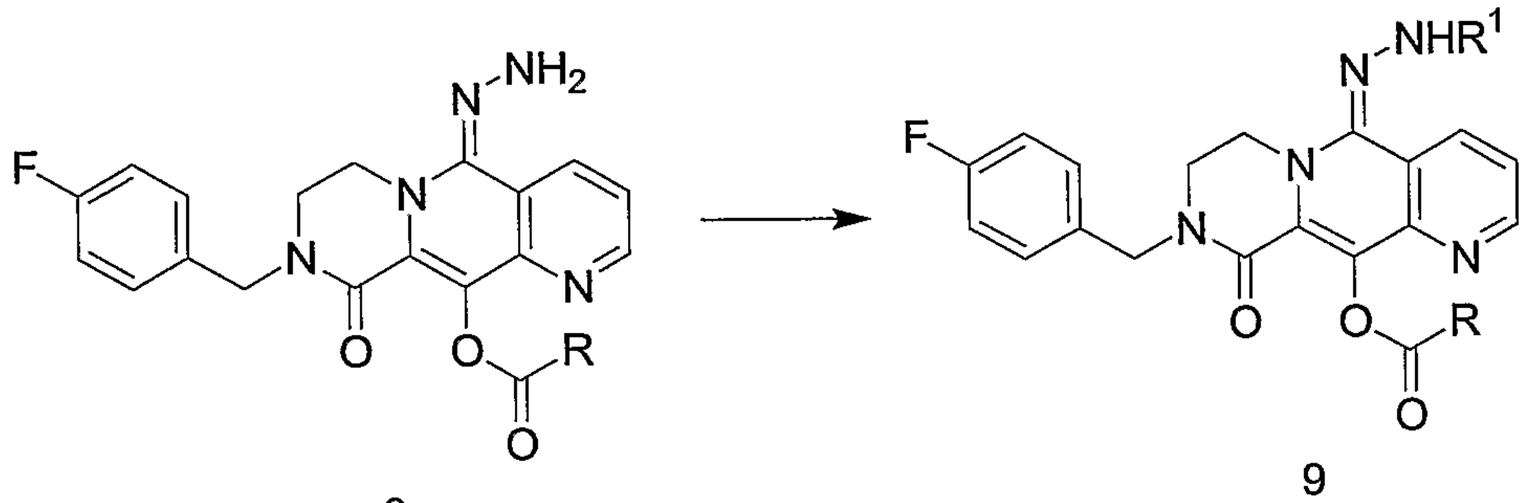
Formula III compounds

Formula III compounds may be prepared by the following methods in Schemes 11-14:

Scheme 11

The acid **1** (WO02/30930, p.173) may be reacted with amine **2** (prepared according to the methods described by T. Morie, et al, Chem. Pharm. Bull., 42 , 1994, 877-882; D. Wenninger, et al, Nucleosides Nucleotides, 16 , 1997, 977-982) by the

method of peptide coupling such as described in WO02/30930, p. 173 to form amide **3**. Bromination with NBS generates compound 4. The phenol is protected with a bulky acyl group such as pivaloyl. Displacement of bromine at C5 of naphthyridine by Bis-boc protected hydrazine is achieved using the method reported by J.B. Arteburn, et al, Org. Lett., 3, 2001, 1351-1354. The silyl protecting group is removed by TBAF (T. Green and P. Wuts, "Protective Groups in Organic Synthesis", p.142, Wiley Science, 1999) and mesylate **7** is formed by reacting the alcohol formed with methanesulfonyl chloride. Treatment of compound **7** with TFA followed by heating hydrazino mesylate in the basic condition affords hydrazono triaza anthracene **8**.



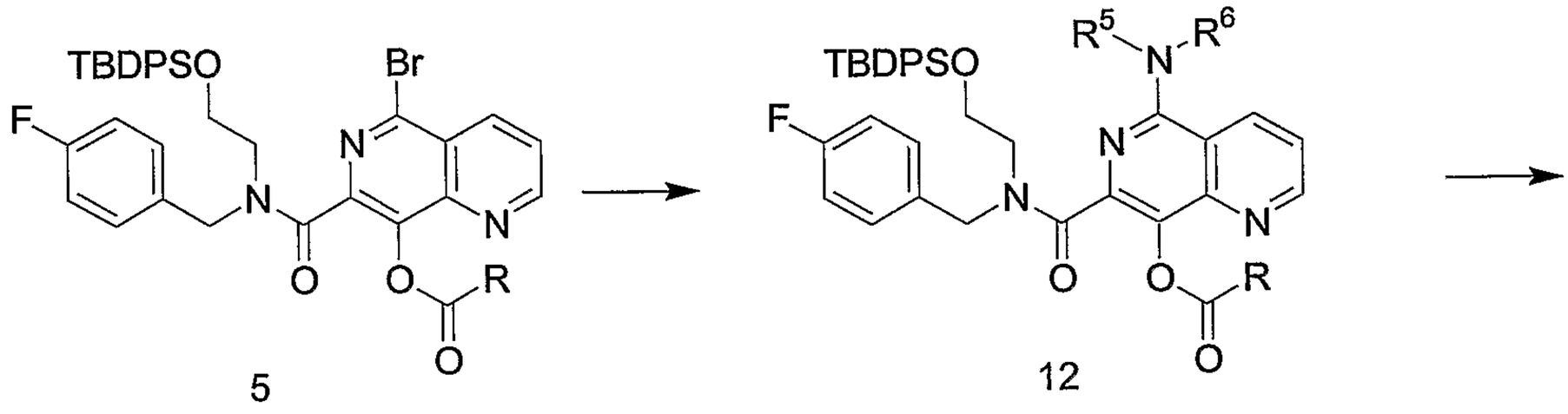
8 9 10 11

Scheme 12

Compound **8** is converted to many different derivatives, e.g. carbazones **9** (R^1 = COR^3) are generated by reaction with acid chlorides or activated carboxylic acids. Carbamates **9** (R^1 = $COOR^3$) are obtained upon reaction of **8** with chloro formates

$ClCOOR^3$. Semicarbazones **9** ($R^1 = CONR^2R^3$) are formed using isocyanates or N,N-dialkyl chloroformaides. Thiosemicarbazones **9** ($R^1 = CSNR^3R^4$) are generated with thioisocyanates. Sulfonyl ureas 9 ($R^1 = SO_2NR^3R^4$) are obtained by reaction of **8** with sulfamoyl chlorides using procedures reported by M.L. Matier, et al, J. Med. Chem., 15, 1972, 538-541. The simple sulfonamides are produced when **8** reacts with sulfonyl chlorides. The ester group in compounds **9** is removed upon saponification to give compound **10**.

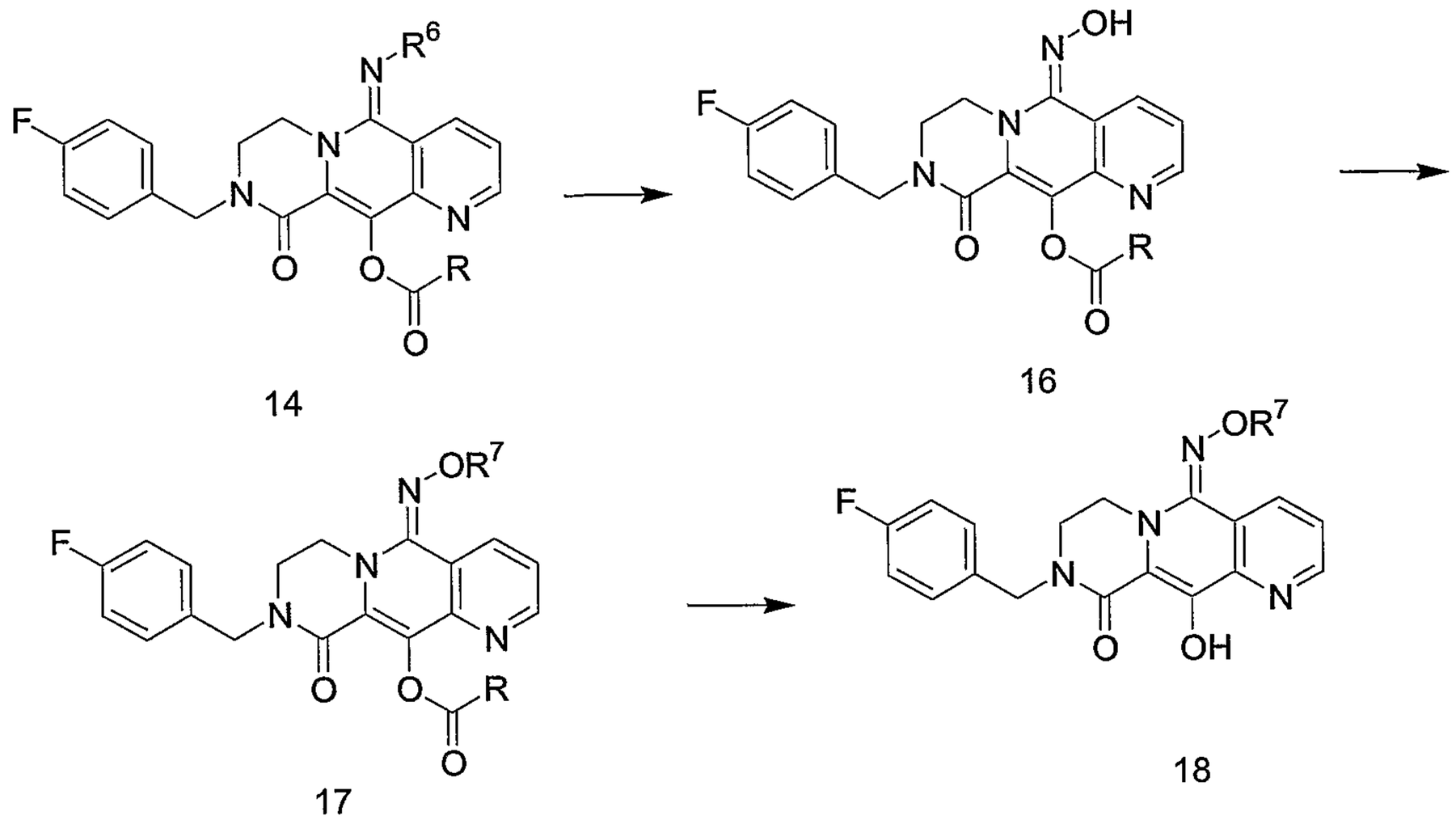
Alternatively, many of hydrazone derivatives **9** are subjected to alkylation followed by saponification to afford compounds **11**.



Scheme 13

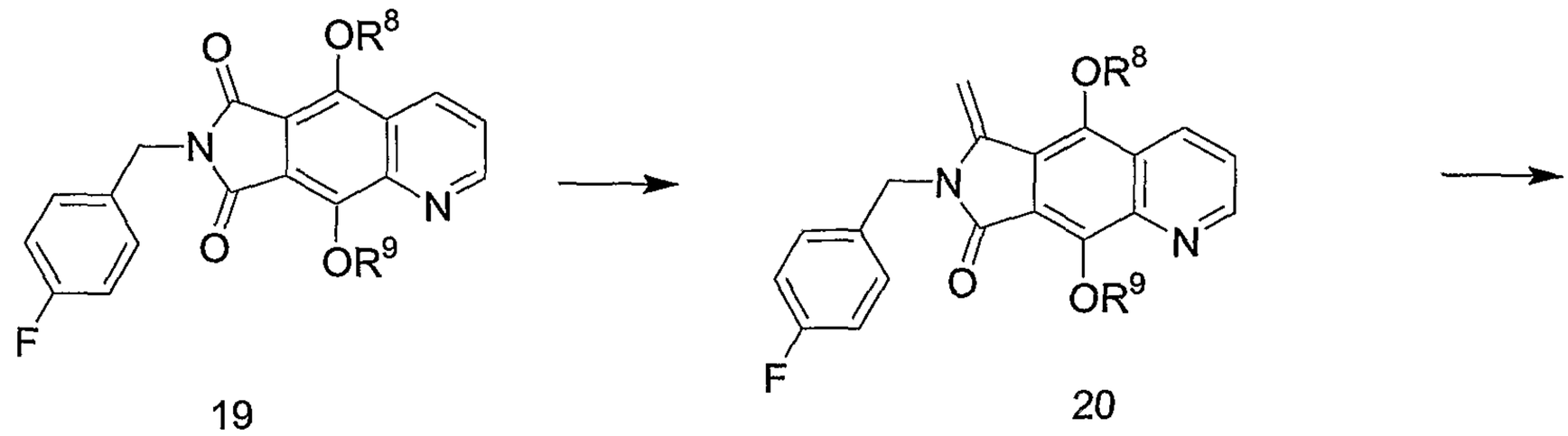
Compound **5** from Scheme 11 is reacted with a substituted hydroxyamine or amine (R^5 = Boc; $R^6 = OR^a$ or alkyl) in a manner similar to that described by L.A., Carpino et al, Org. Lett., 3, 2001, 2793-2795 to give derivative **12**. After transforming the silyl protected hydroxyl in **12** to a leaving group such as the mesylate in **13**,

cyclization is accomplished in the heating condition and the presence of a base to afford compound **14**. Final deprotection by hydrolysis of **14** gives compound **15**.

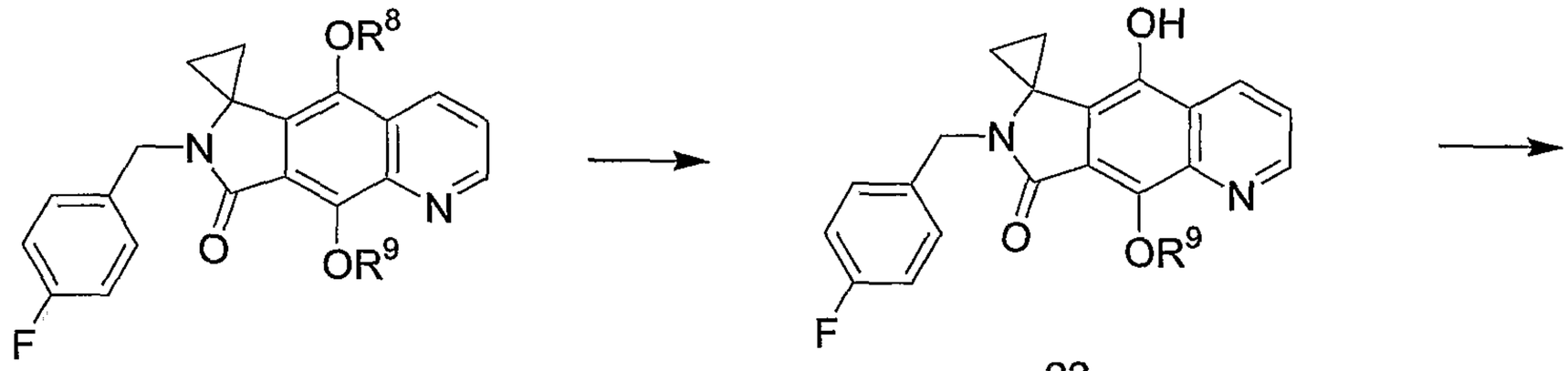


Scheme 14

When R^6 in **14** is OR^a, or where R^a can be removed, oxime **16** is obtained and can be functionalized with many reagents to yield compound **17**. Hydrolysis of ester group affords **18**. For example, when **16** is treated with an alkyl halide (R^7-X) or an alcohol under Mitsunobu condition, an ether **18** is formed. When an isocyanate or thioisocyanate is applied, a carbamate or thiocarbamate **18** (R^7: $C(=O)NHR^8$ or $C(=S)NHR^8$) is generated. An N,N-disubstitued carbamate **18** (R7: $C(=O)NR^2R^3$) is obtained when a chloroformate $ClC(=O)NR^2R^3$ is reacted with **16**. Similarly, treating **16** with a sulfamoyl chlorides affords a sulfamate **18** (R^7: $SO_2NR^1R^2$).



19 20



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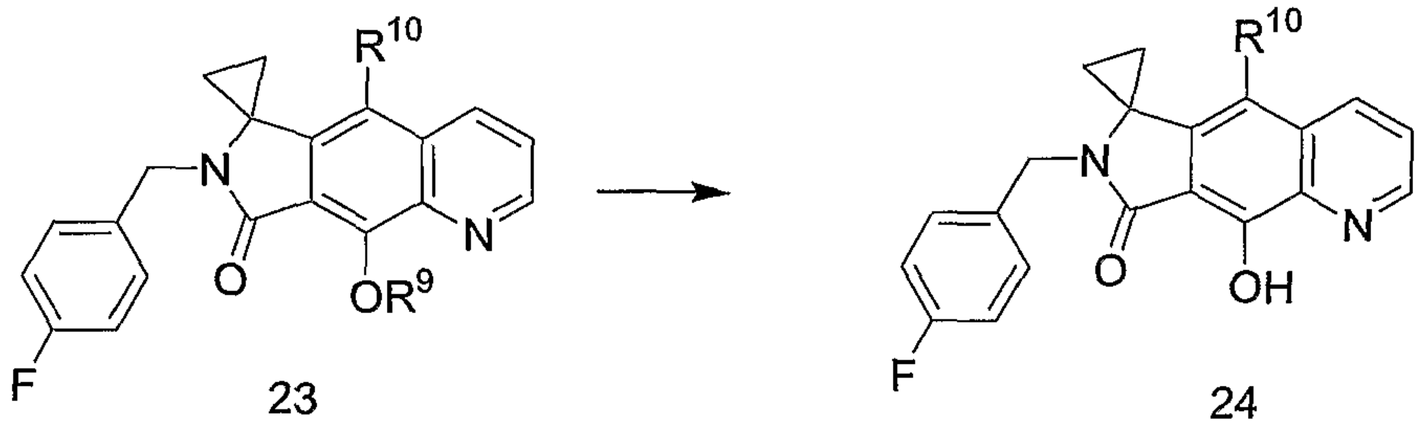
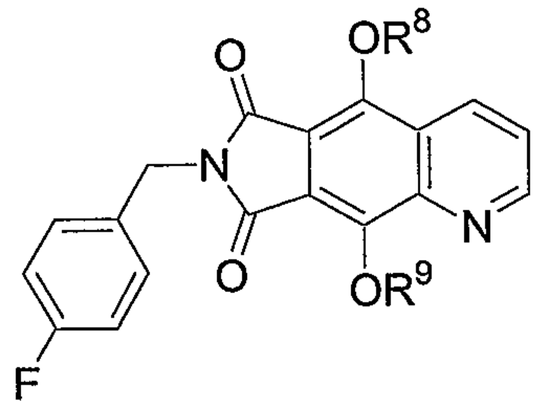


23 24

Scheme 15

Scheme 15 depicts one of the methods to prepare a spiro-cyclopropane-containing lactam fused to quinoline, an embodiment of Formula I. A differentially protected phenol **19** is used where R^8 can be a removable ether group such as trimethylsilyethyl ether and R^9 can be a bulky group such as diphenylmethyl or t-butyl ether. The carbonyl of C6 is converted to an olefin regioselectively by treating **19** with methylmagnesium bromide followed by dehydration of aminal to give **20**. Carbene insertion by Simmons-Smith reaction (for example, Y. Biggs et al, JOC, 57, 1992, 5568-5573) produces cyclopropane **21**. Selective removal of R^8 by TBAF followed by fuctionalization using the methods described in many examples leads to compound **24**.



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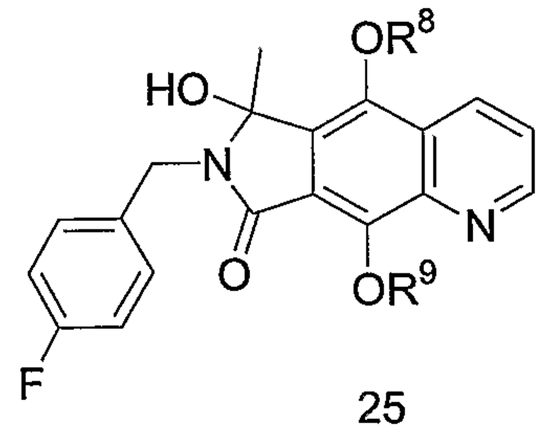

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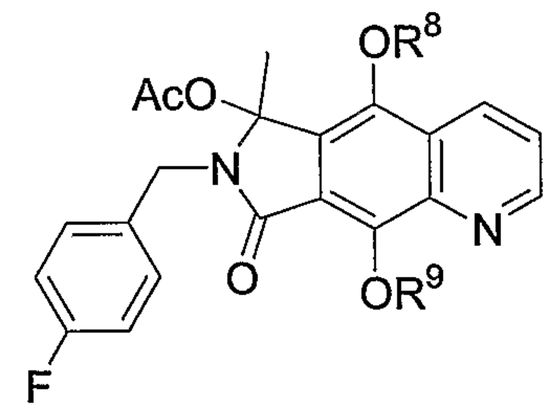

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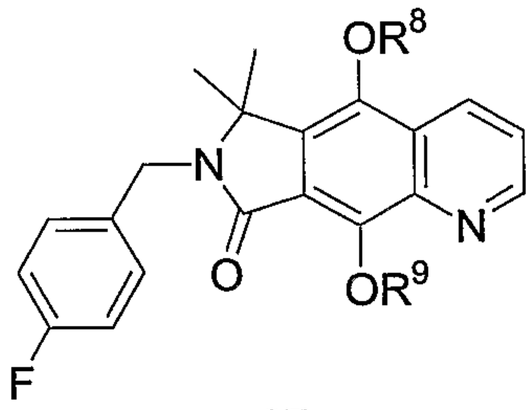

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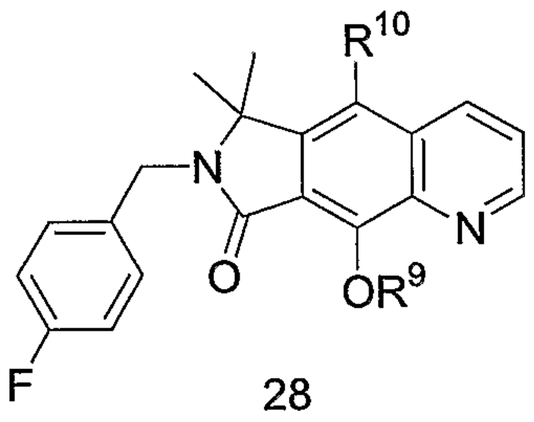

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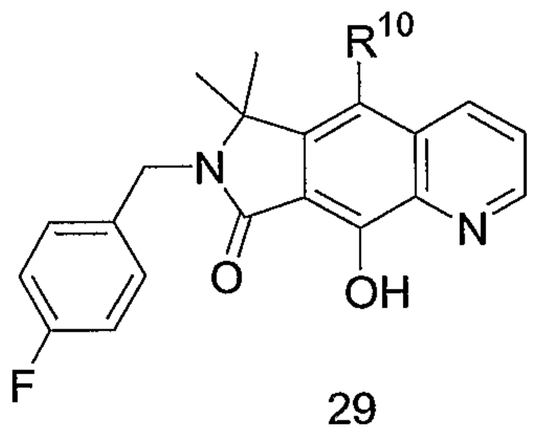

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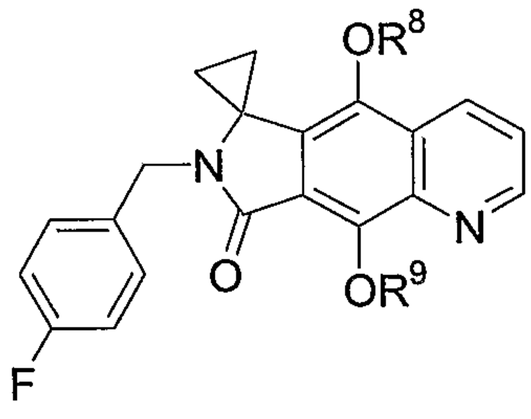
Alternatively:



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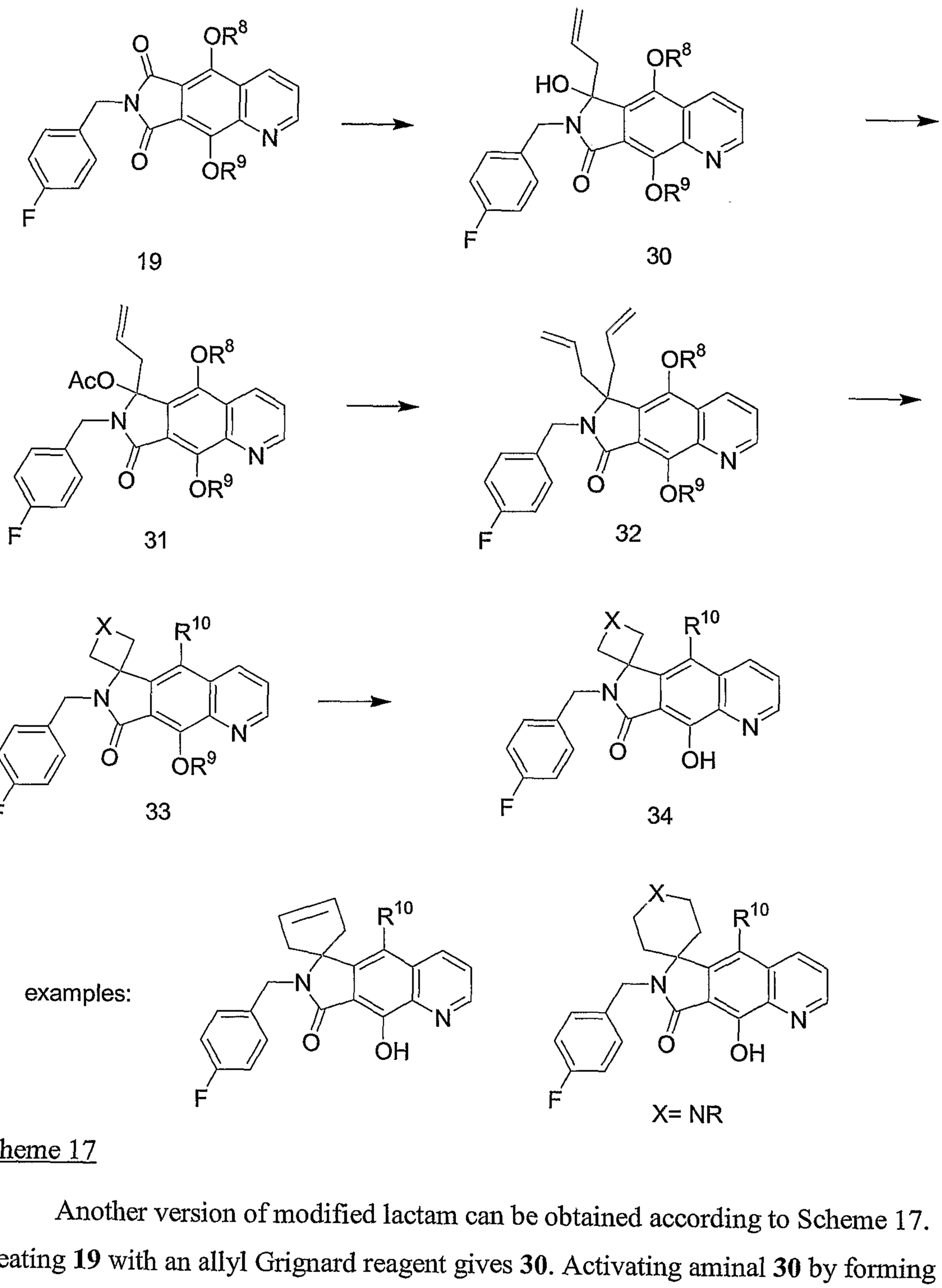
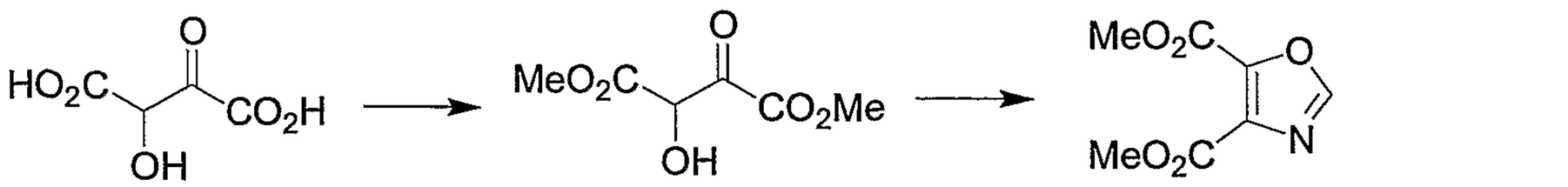
Scheme 16

A dimethyl substituted lactam can be prepared by reacting **19** with a Grignard reagent followed by converting aminal **25** to acetate **26** and treating **26** with Me_3Al/TMSOTf, a method reported by C.U. Kim, et al, Tetrahedron Letters, 35, 1994, 3017-3020, to afford **27**. An alternative method can be used by reducing cyclopropane **21** with PtO_2/H_2 as reported by C.K. Cheung et al, JOC, 54, 1989, 570-573, to give **27**.



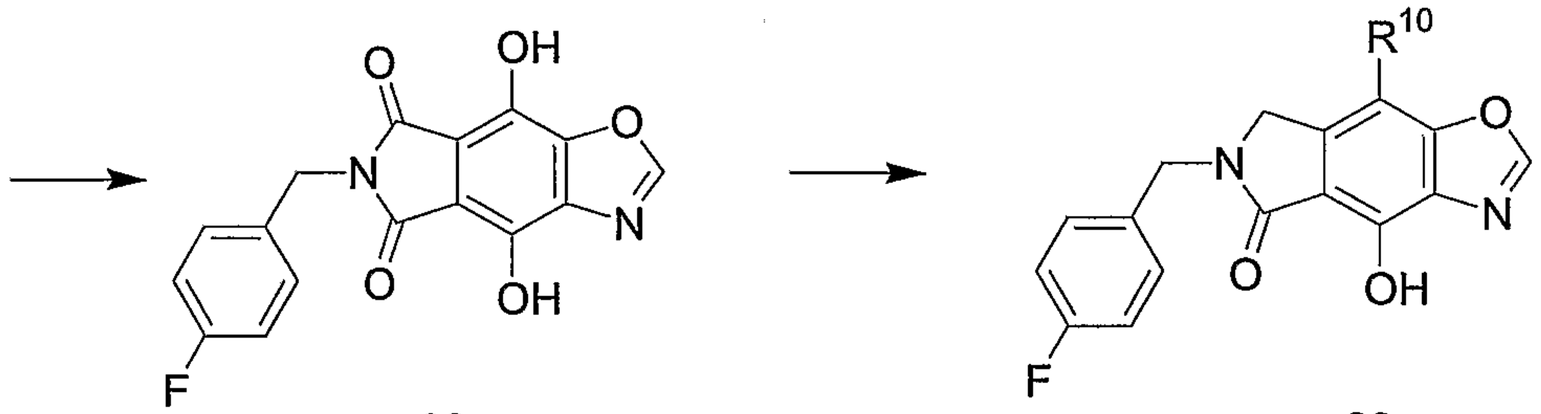
Scheme 17

Another version of modified lactam can be obtained according to Scheme 17. Treating **19** with an allyl Grignard reagent gives **30**. Activating aminal **30** by forming acetate **31** followed by treating **31** with allyl trimethylsilane mediated by a Lewis acid such as TMSOTf affords **32**. Cyclization can be achieved by using Grubb's RCM (ring closure metathesis) method (P. Schwab et al, Angew. Chem. Intl. 34, 1995, 2039). Alternatively, the terminal olefins in **32** can be converted to aldehydes and reductive amination leads to a spiro-piperidine.



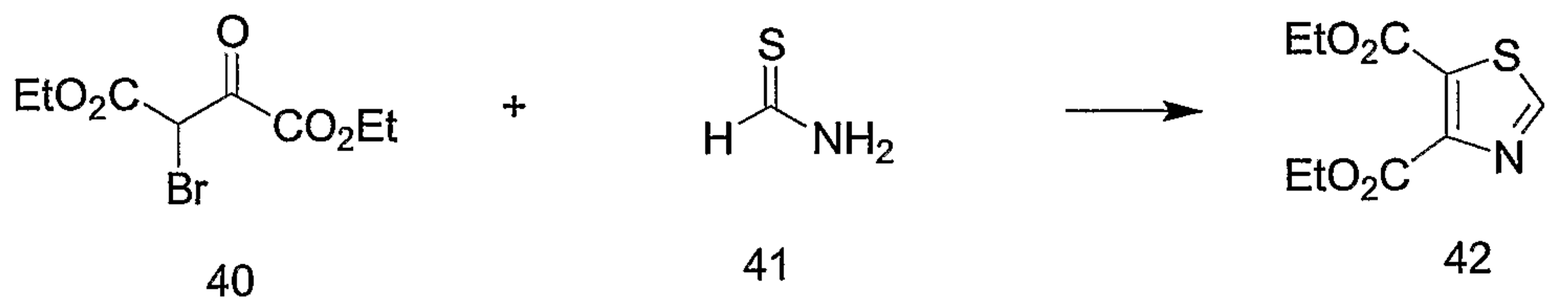
35 36 37

Aldrich JOC, 53, 1968, 4009 Chem. Ber., 97, 1964, 1414-1423



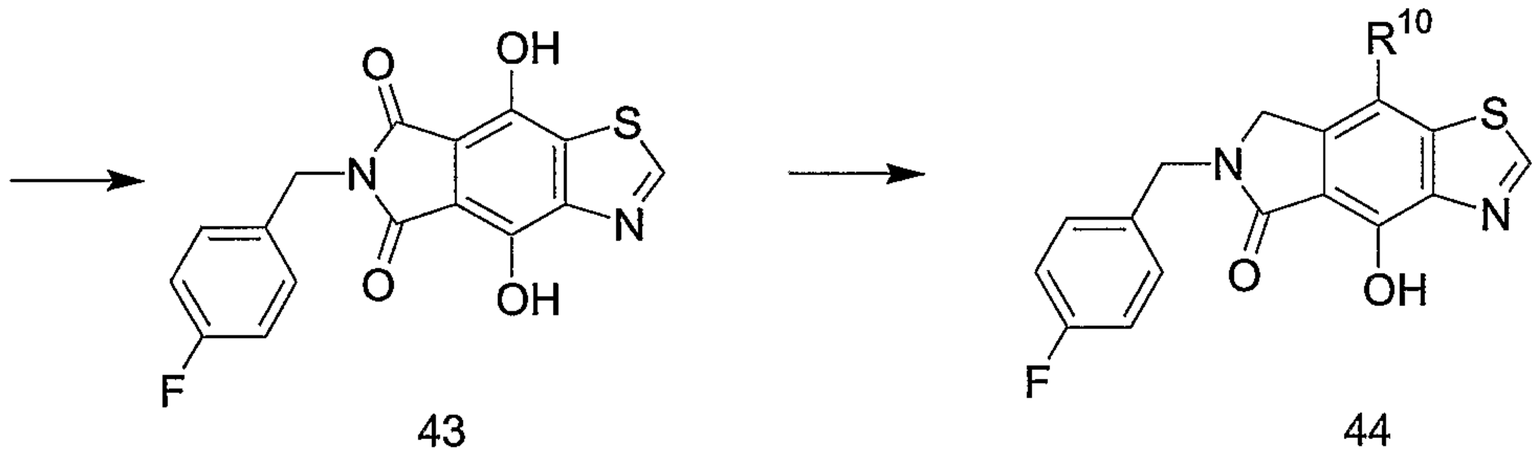
38 39

Scheme 18



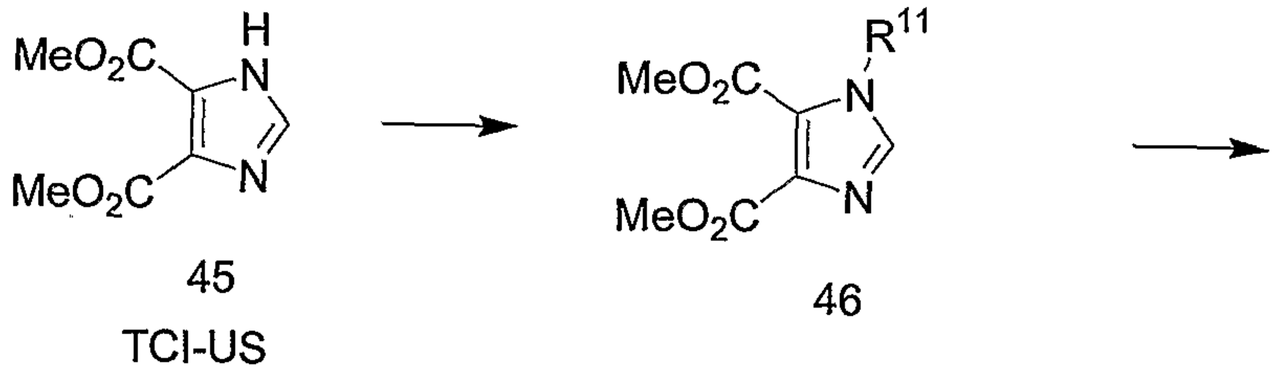
40 41 42

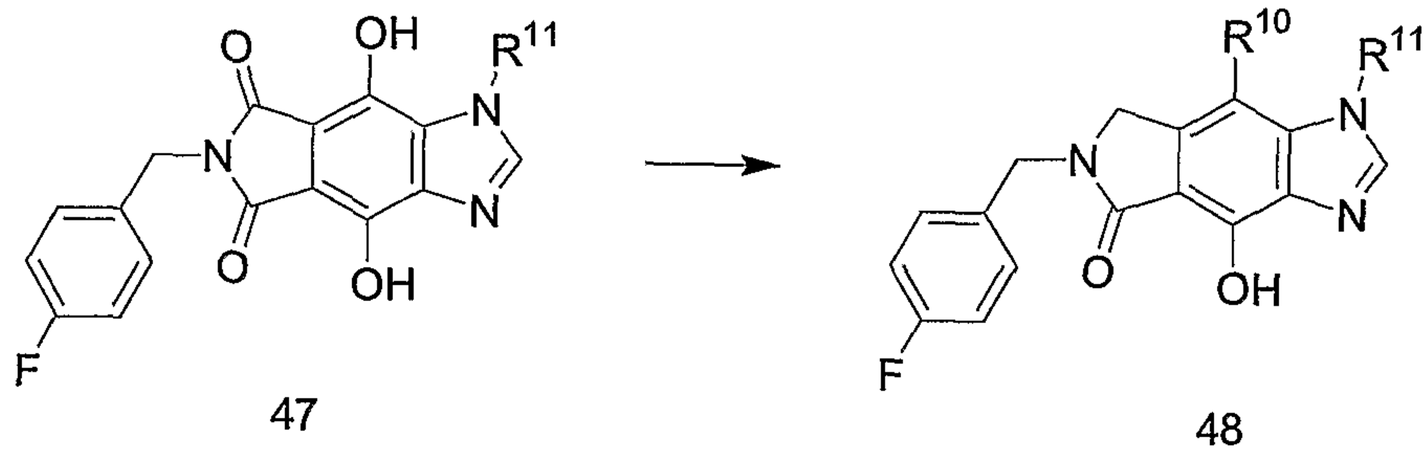
JACS, 72, 1950, 5221 J. Heterocyclic Chem., 1968, 331



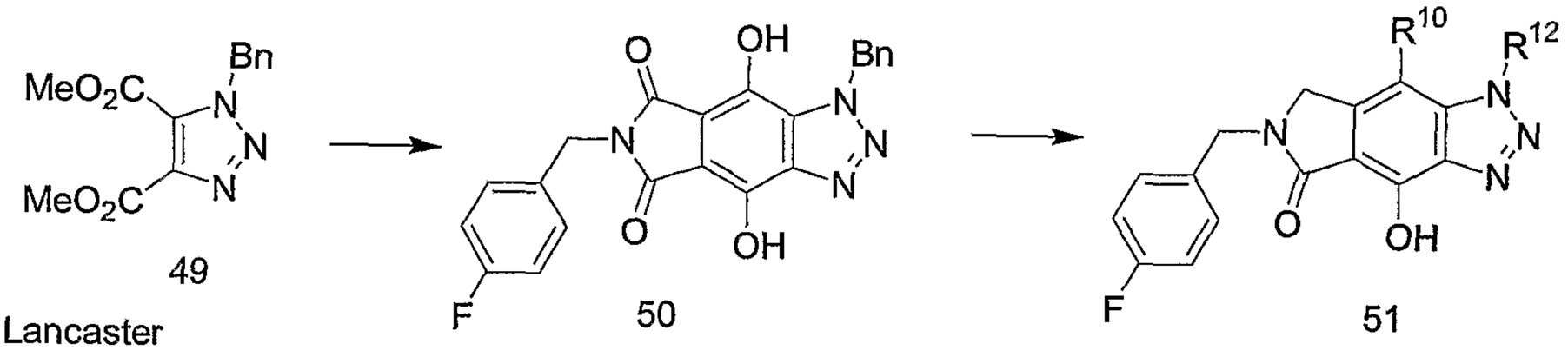
43 44

Scheme 19

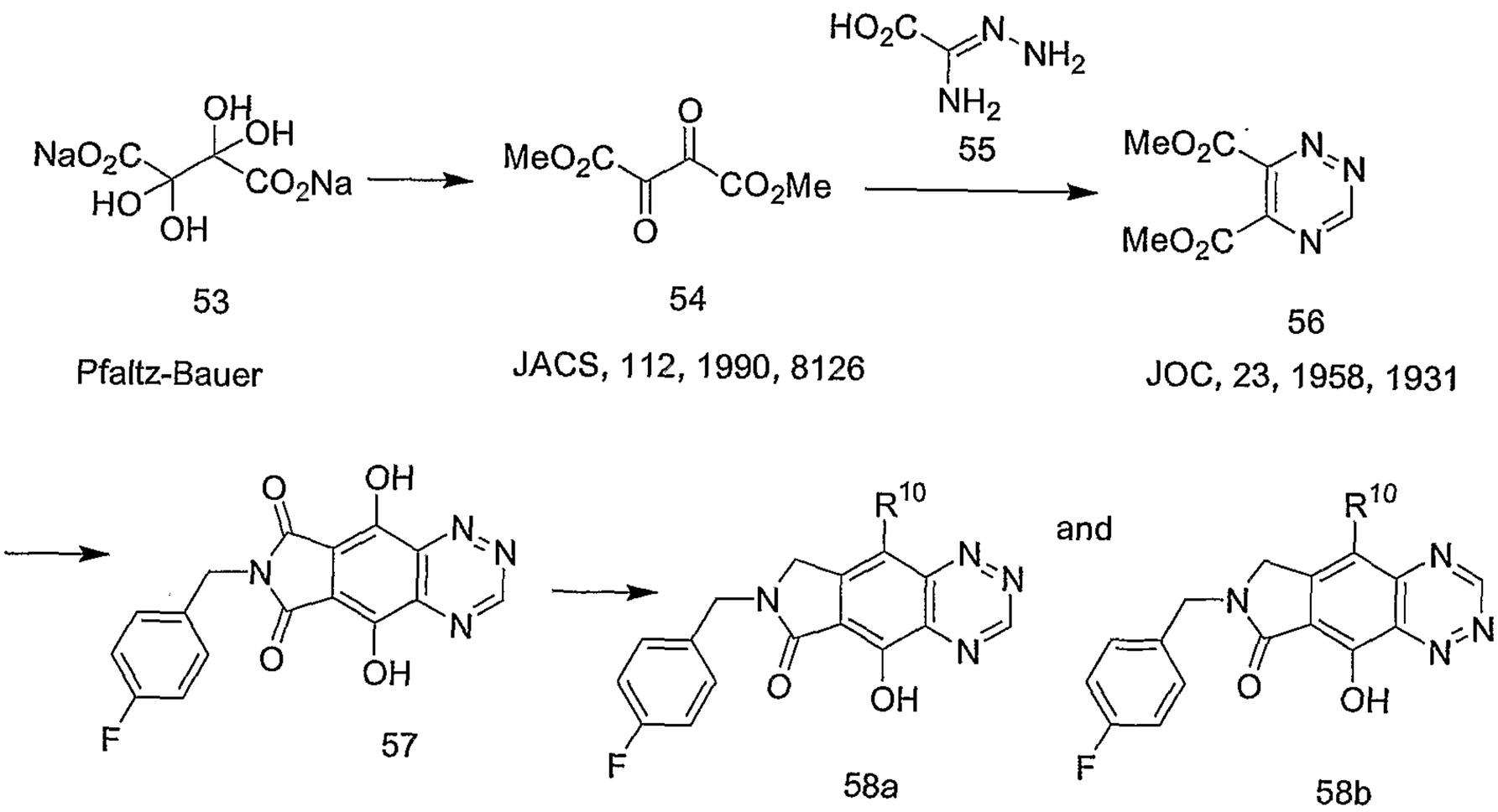




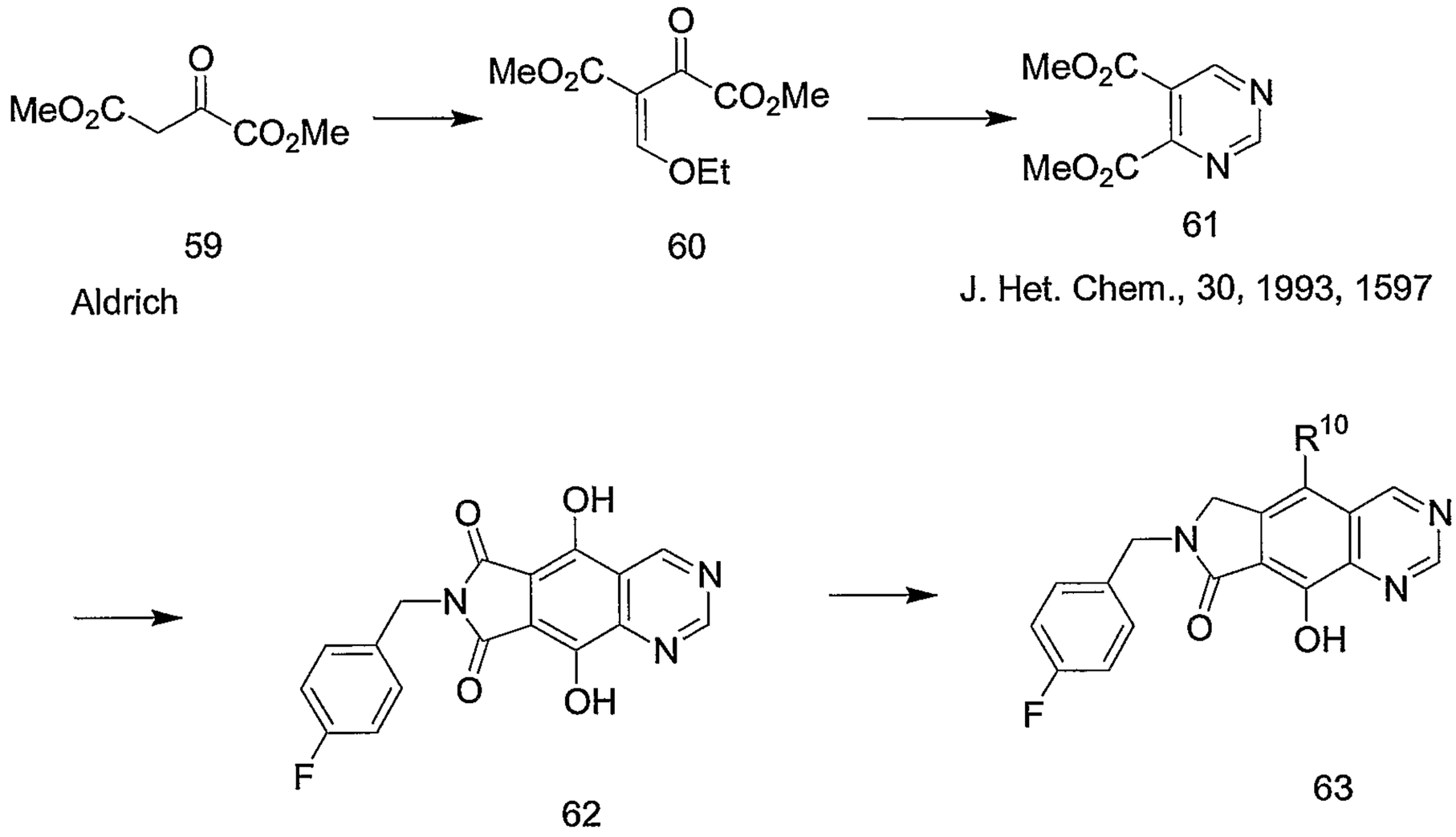
Scheme 20



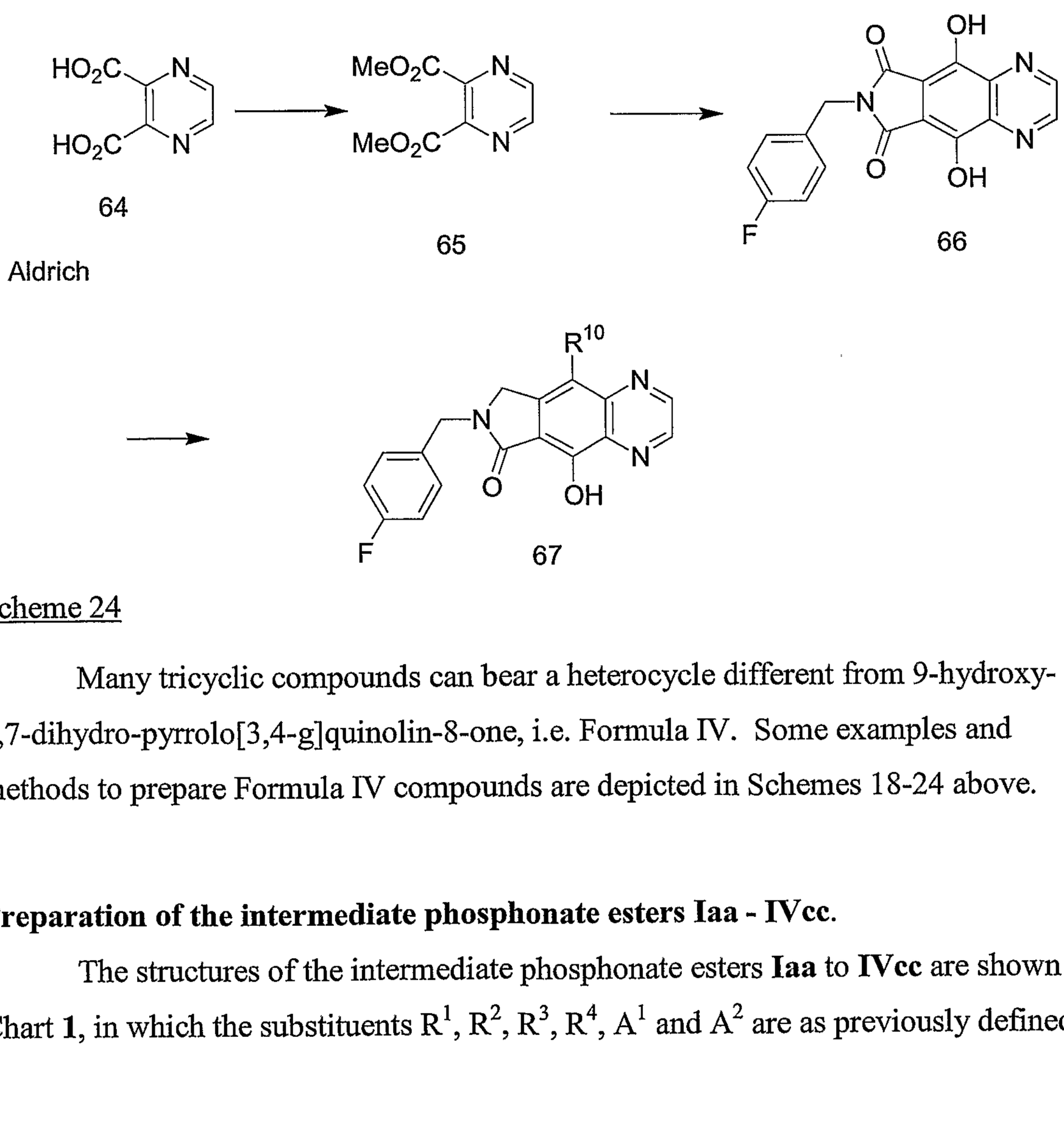
Scheme 21



Scheme 22



Scheme 23



Scheme 24

Many tricyclic compounds can bear a heterocycle different from 9-hydroxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one, i.e. Formula IV. Some examples and methods to prepare Formula IV compounds are depicted in Schemes 18-24 above.

Preparation of the intermediate phosphonate esters Iaa - IVcc.

The structures of the intermediate phosphonate esters **Iaa** to **IVcc** are shown in Chart **1**, in which the substituents R^1, R^2, R^3, R^4, A^1 and A^2 are as previously defined.

The groups A^{1a} and A^{2a} are the same as the groups A^1 and A^2, except that a substituent link-$P(O)(OR^5)_2$ is appended. The substituent R^5 is hydrogen, alkyl, alkenyl, aralkyl, or aryl. Subsequent chemical modifications to the compounds **Iaa** to **Vcc**, as described herein, permit the synthesis of the final compounds of this invention.

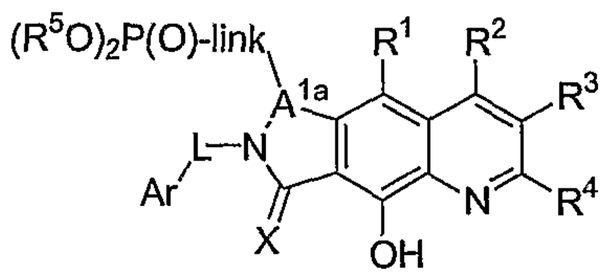
The intermediate compounds **Iaa** to **IVcc** incorporate a phosphonate moiety $(R^5O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Chart **2** illustrates examples of the linking groups present in the structures **Iaa - IVcc**.

Schemes **A1 - A33** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **Iaa - IVcc**, and of the intermediate compounds necessary for their synthesis.

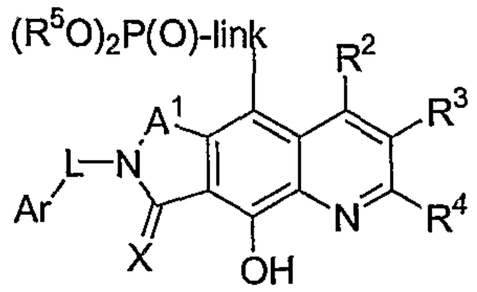
The methods described for the introduction of phosphonate substituents are, with modifications made by one skilled in the art, transferable within the substrates **I - V**. For example, reaction sequences which produce the phosphonates **Iaa** are, with appropriate modifications, applicable to the preparation of the phosphonates **IIaa**, **IIIaa**, or **IVaa**. Methods described below for the attachment of phosphonate groups to reactive substituents such as OH, NH_2, CH_2Br, COOH, CHO etc are applicable to each of the scaffolds **I - V**.

Scheme **A34** illustrates methods for the interconversion of phosphonate diesters, monoesters and acids.

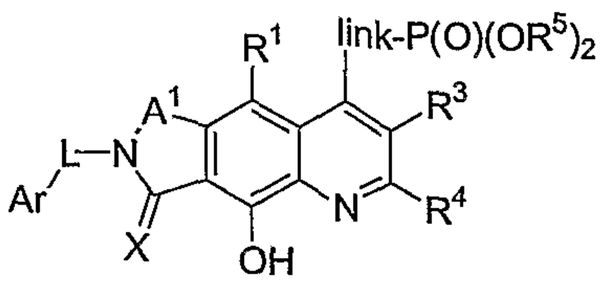
Chart 1. Structures of the phosphonate esters Iaa - IVcc.



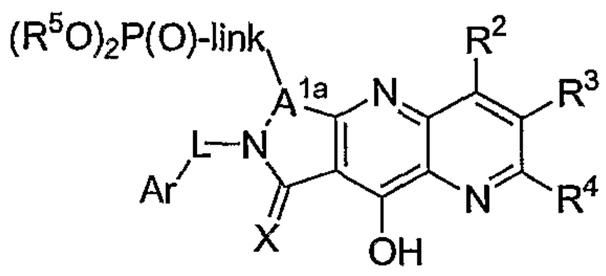
Iaa



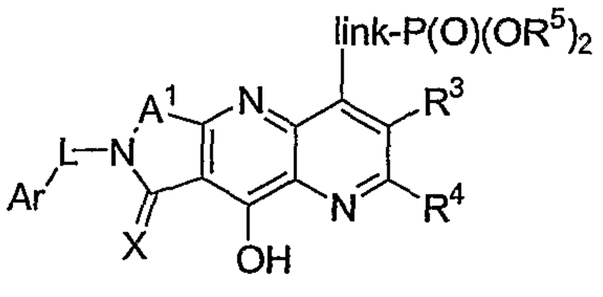
Ibb



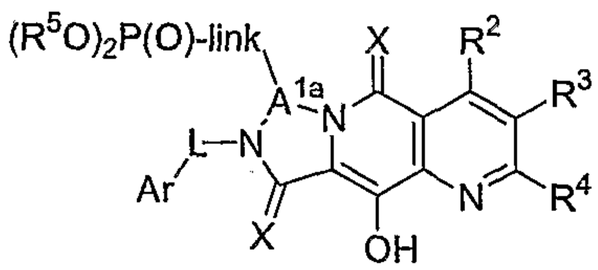
Icc



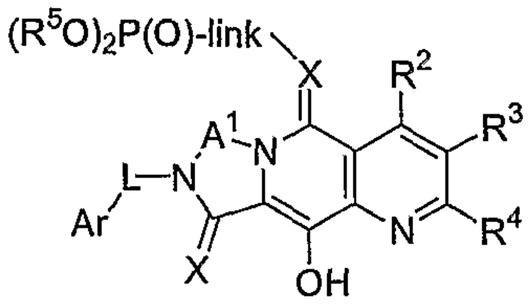
IIaa



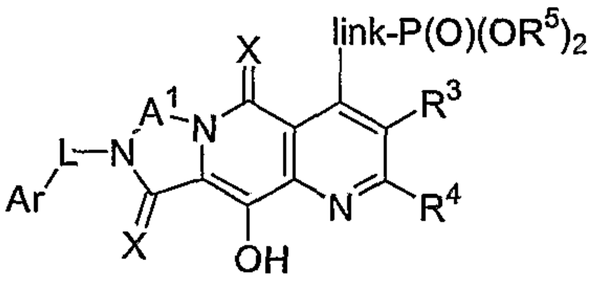
IIcc



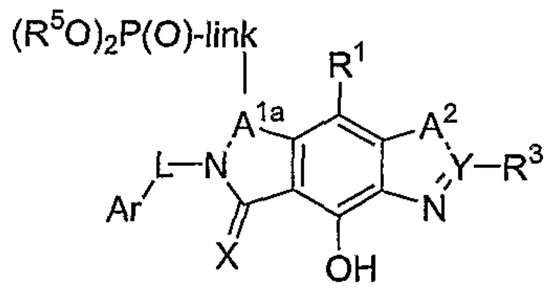
IIIaa



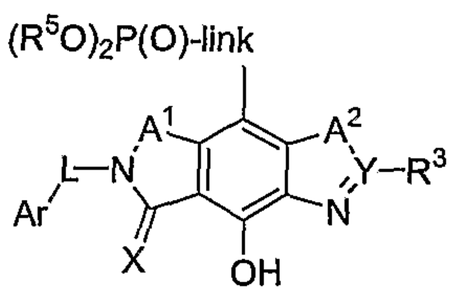
IIIbb



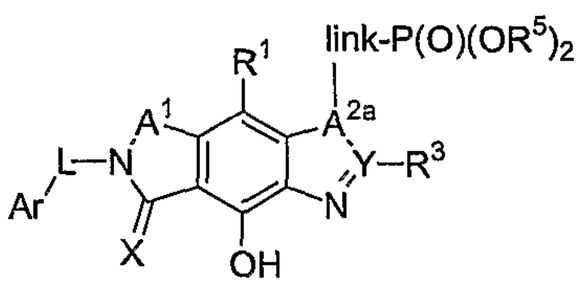
IIIcc



IVaa

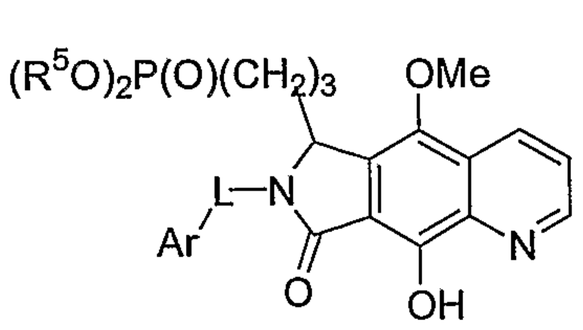


IVbb

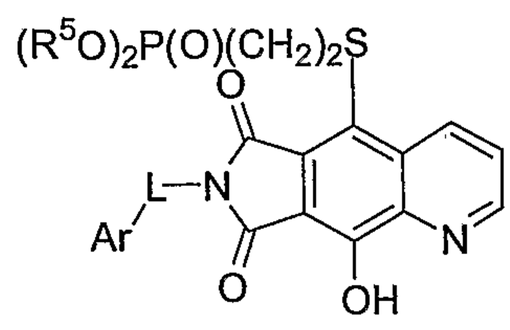


IVcc

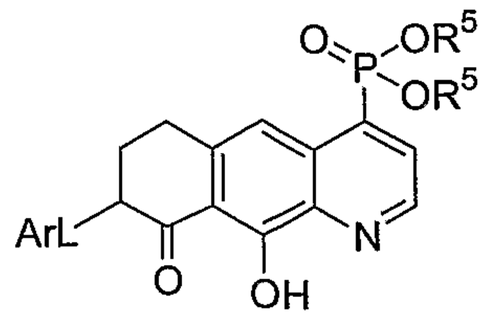
Chart 2 **Examples of phosphonate linkages**



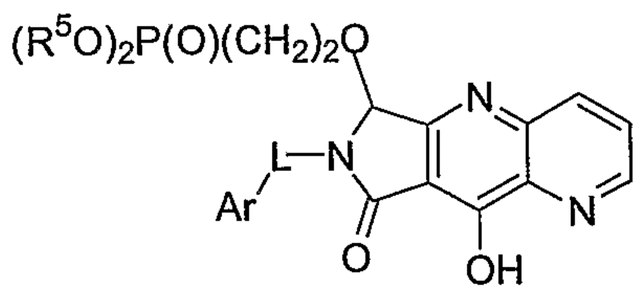
Iaa



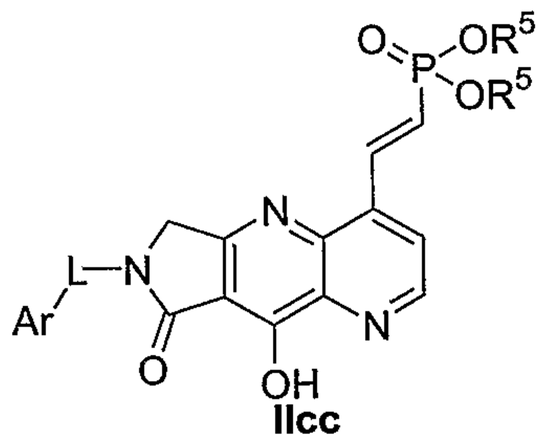
Ibb



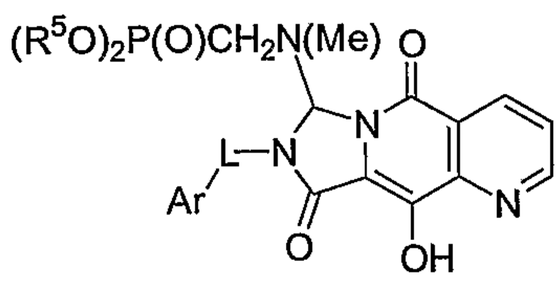
Icc



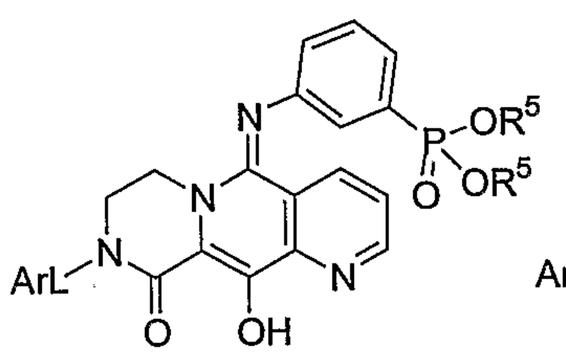
IIaa



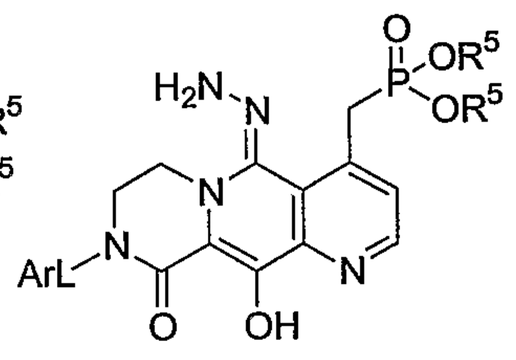
IIcc



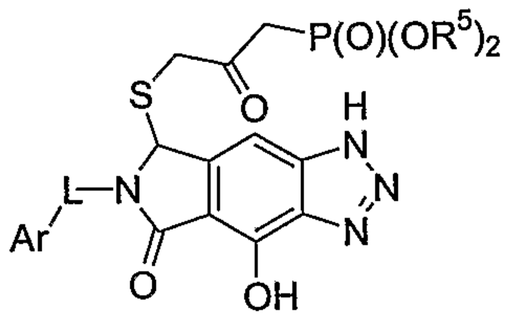
IIIaa



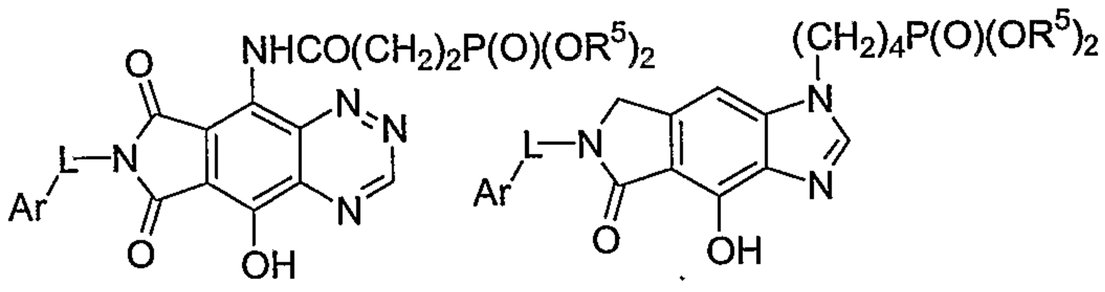
IIIbb



IIIcc



IVaa



IVbb **IVcc**

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which

may be protected are shown in the accompanying schemes as, for example, [OH], [SH], etc.

Preparation of the intermediate phosphonate esters 1aa.

Schemes **A1 - A5** illustrate methods for the preparation of the intermediate phosphonate esters **Iaa**.

As shown in Scheme **A1**, the phenolic hydroxyl substituent present in the tricyclic compound **A1.1** is protected to afford the derivative **A1.2**. The protection of hydroxyl groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10. For example, hydroxyl substituents are protected as trialkylsilyloxy, methoxymethyl, benzyl or tert-butyl ethers. Trialkylsilyl groups are introduced by the reaction of the phenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10ff. The protected product **A1.2** is then reacted, in the presence of a strong base, with a bromoalkyl phosphonate **A1.3**, to give the alkylation product **A1.4**. The reaction is effected in a polar organic solvent such as dimethylformamide, dimethylacetamide, diglyme, tetrahydrofuran and the like, in the presence of a base such as sodium hydride, an alkali metal alkoxide, lithium hexamethyldisilazide, and the like, at from ambient temperature to about 100°, to yield the alkylated product **A1.4**. The phenolic hydroxyl group is then deprotected to afford the phenol **A1.5**. Methods for the deprotection of hydroxyl groups are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10ff.

For example, 7-(4-fluoro-benzyl)-9-hydroxy-5H-1,7-diaza-anthracene-6,8-dione **A1.6** is reacted with one molar equivalent of chlorotriisopropylsilane and imidazole in dimethylformamide at ambient temperature, as described in Tet. Lett., 2865, 1974, to produce 7-(4-fluoro-benzyl)-9-triisopropylsilanyloxy-5H-1,7-diaza-anthracene-6,8-dione **A1.7**. The product is then reacted in dimethylformamide solution at about 60° with one molar equivalent of a dialkyl 2-bromoethyl phosphonate **A1.8** (Aldrich) and lithium hexamethyldisilazide, to yield the alkylated product **A1.9**. The silyl protecting group is then removed by reaction with

tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Org. Chem., 51, 4941, 1986, to give the phenolic product **A1.10**.

Using the above procedures, but employing, in place of the 4-fluorobenzyl-substituted phenol **A1.6**, different phenols **A1.1** and/or different phosphonates **A1.3**, the corresponding products **A1.5** are obtained.

Scheme **A2** illustrates the preparation of phosphonate esters of structure **Iaa** in which the phosphonate group is attached by means of an aryl of heteroaryl ring.

In this procedure, a hydroxy-substituted phthalimide derivative **A2.1** (Formula I) is protected, as described above, to afford the product **A2.2**. This compound is then reacted with a bromoaryl magnesium bromide Grignard reagent **A2.3**, in which the group Ar^1 is an aromatic or heteroaromatic group such as, for example, benzene or thiophene, to afford the alcohol **A2.4**. The regioselective addition of organometallic derivatives to phthalimides is described in Scheme 4. The reaction is performed between approximately equimolar amounts of the reactants in an ethereal solvent such as diethyl ether, tetrahydrofuran and the like, at from -40 °C to ambient temperature, to give the alcohol product **A2.4**. This material is then reacted with a dialkyl phosphite **A2.5** and a palladium catalyst, to give the phosphonate **A2.6**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The reaction is conducted in a hydrocarbon solvent such as benzene, toluene or xylene, at about 100°, in the presence of a palladium (0) catalyst such as tetrakis(triphenylphosphine)palladium(0), and a tertiary base such as triethylamine or diisopropylethylamine. The hydroxyl group is then deprotected to yield the phenolic product **A2.7**. Optionally, the benzylic hydroxyl substituent in the product **A2.7** is removed by means of a reductive procedure, as shown on Scheme 4. Benzylic hydroxyl groups are removed by catalytic hydrogenation, for example by the use of 10% palladium on carbon in the presence of hydrogen or a hydrogen donor, or by means of chemical reduction, for example employing triethylsilane and boron trifluoride etherate.

For example, 7-(3,5-dichloro-benzyl)-5,9-bis-triisopropylsilanyloxy-pyrrolo[3,4-g]quinoline-6,8-dione **A2.9**, prepared by silylation of the corresponding diol, which is reacted with one molar equivalent of 4-bromophenyl magnesium

bromide **A2.10** in ether at 0° to produce the alcohol **A2.11**. The latter compound is then reacted, in toluene solution at reflux, with a dialkyl phosphite **A2.5**, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product **A2.12**. Desilylation, for example by reaction with tetrabutyl ammonium fluoride, gives the diol product **A2.13**. Optionally, the product **A2.12** is reduced, for example by reaction in dichloromethane solution at ambient temperature with ca. four molar equivalents of triethylsilane and boron trifluoride etherate, as described in Example 18 to yield after deprotection the reduced product **A2.14**.

Using the above procedures, but employing, in place of the 3,5-dichlorobenzyl-substituted phenol derivative **A2.9**, different phenol derivatives **A2.1** and/or different bromoaryl Grignard reagents **A2.3**, the corresponding products **A2.7** and **A2.8** are obtained.

Scheme **A3** illustrates the preparation of phosphonate esters of structure **Iaa** in which the phosphonate group is attached by means of an alkylene chain.

In this sequence, a 6-aminoquinoline ester **A3.1**, prepared, for example, from the corresponding carboxylic acid by means of a Curtius rearrangement, (Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p.646) is reacted, under reductive amination conditions, with a dialkyl formylalkyl phosphonate **A3.2**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The product **A3.3** is then converted, by reaction with the amine $ArBNH_2$ **A3.4**, or a derivative thereof, into the amide **A3.5**. The conversion of esters into amides is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 987. The reactants are combined in the presence of a base such as sodium methoxide under azeotropic conditions, or of a dialkyl aluminum or trialkyl

tin derivative of the amine. The use of trimethylaluminum in the conversion of esters to amides is described in J. Med. Chem. Chim. Ther., 34, 1999, 1995, and Syn. Comm., 25, 1401, 1995. The reaction is conducted in an inert solvent such as dichloromethane or toluene. The amide product **A3.5** is then cyclized by reaction with a reagent such as phosgene or a functional equivalent thereof, such as triphosgene or a dialkyl carbonate, or a reagent such as diiodomethane, to give the cyclized product **A3.6** in which D is CO or CH_2. The reaction is conducted in an aprotic solvent such as tetrahydrofuran, in the presence of an inorganic or organic base such as potassium carbonate or diisopropylethylamine.

For example, the amine **A3.7**, prepared by means of a Curtius rearrangement of the corresponding MOM-protected carboxylic acid, is reacted in isopropanol solution with a dialkyl formylmethyl phosphonate **A3.8**, prepared as described in Zh. Obschei. Khim., 1987, 57, 2793, sodium cyanoborohydride and acetic acid, to give the reductive amination product **A3.9**. The product is then reacted with an excess of 3,4-dichlorobenzylamine and sodium methoxide in toluene at reflux, to yield the amide **A3.10**. The latter compound is then reacted with one molar equivalent of triphosgene and N,N-dimethylaminopyridine in dichloromethane, to afford the cyclized product **A3.11**. The MOM protecting groups are then removed, for example by reaction with a catalytic amount of methanolic hydrogen chloride, as described in J. Chem. Soc., Chem. Comm., 298, 1974, to give the dihydroxy product **A3.12**.

Using the above procedures, but employing, in place of the amine **A3.7**, different amines **A3.1**, and/or different aldehydes **A3.2**, and/or different amines **A3.4**, the corresponding products **A3.6** are obtained.

Scheme **A4** illustrates the preparation of phosphonate esters of structure **Iaa** in which the phosphonate group is attached by means of an alkylene chain or an aryl, heteroaryl or aralkyl group and a heteroatom O, S or N. In this sequence, a tricyclic aminal **A4.1** is reacted in the presence of an acid catalyst with a hydroxy, mercapto or amino-substituted dialkyl phosphonate **A4.2** in which X is O, S, NH or N-alkyl, and R is alkyl, alkenyl, aryl, heteroaryl or aralkyl. The reaction is effected at ambient temperature in an inert solvent such as dichloromethane, in the presence of an acid such as p-toluenesulfonic acid or trifluoroacetic acid and an excess of the reagent **A4.2**. The hydroxyl group is then deprotected to yield the phenolic product **A4.4**.

For example, 7-(4-fluoro-benzyl)-6-hydroxy-5-methoxy-9-triisopropylsilanyloxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **A4.5** (Example 20, Scheme 15) is reacted at ambient temperature in dichloromethane solution with a dialkyl 2-mercaptoethyl phosphonate **A4.6** (Zh. Obschei. Khim., 1973, 43, 2364) and trifluoroacetic acid to give the thioether product **A4.7**, which upon deprotection with tetrabutylammonium fluoride yields the phenol **A4.8**.

As a further example, 6-hydroxy-5-methoxy-7-(4-trifluoromethyl-benzyl)-9-triisopropylsilanyloxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **A4.9**, prepared analogously to the 4-fluoro analog **A4.5**, is reacted, under the same conditions, with a dialkyl 3-mercaptophenyl phosphonate **A4.10** to give the thioether **A4.11** which upon deprotection affords the phenol **A4.12**. The phosphonate reagent **A4.10** is obtained by palladium (0) catalyzed coupling reaction, as described in Scheme **A2**, between a dialkyl phosphite and an S-protected derivative of 3-bromothiophenol, for example the S-trityl derivative, followed by removal of the sulfur protecting group. Protection and deprotection of thiols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277.

Using the above procedures, but employing, in place of the alcohols **A4.5** and **A4.9**, different alcohols **A4.1**, and/or different alcohols, thiols or amines **A4.2**, the corresponding products **A4.4** are obtained.

Scheme **A5** illustrates the preparation of phosphonate esters of structure **Iaa** in which the phosphonate group is attached to a 7-membered ring by means of an alkylene or arylmethylene chain. In this sequence, a suitable protected quinoline acid ester **A5.1** is subjected to a Curtius rearrangement, as described in Scheme **A3** to yield the amine **A5.2**. The product is then reductively aminated, as described in Scheme **A3**, with a phosphonate aldehyde **A5.3**, in which the group R is an alkyl group or an aryl group, to give the amine product **A5.4**. This material is then coupled with the glycine derivative **A5.5** to yield the amide **A5.6**. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in

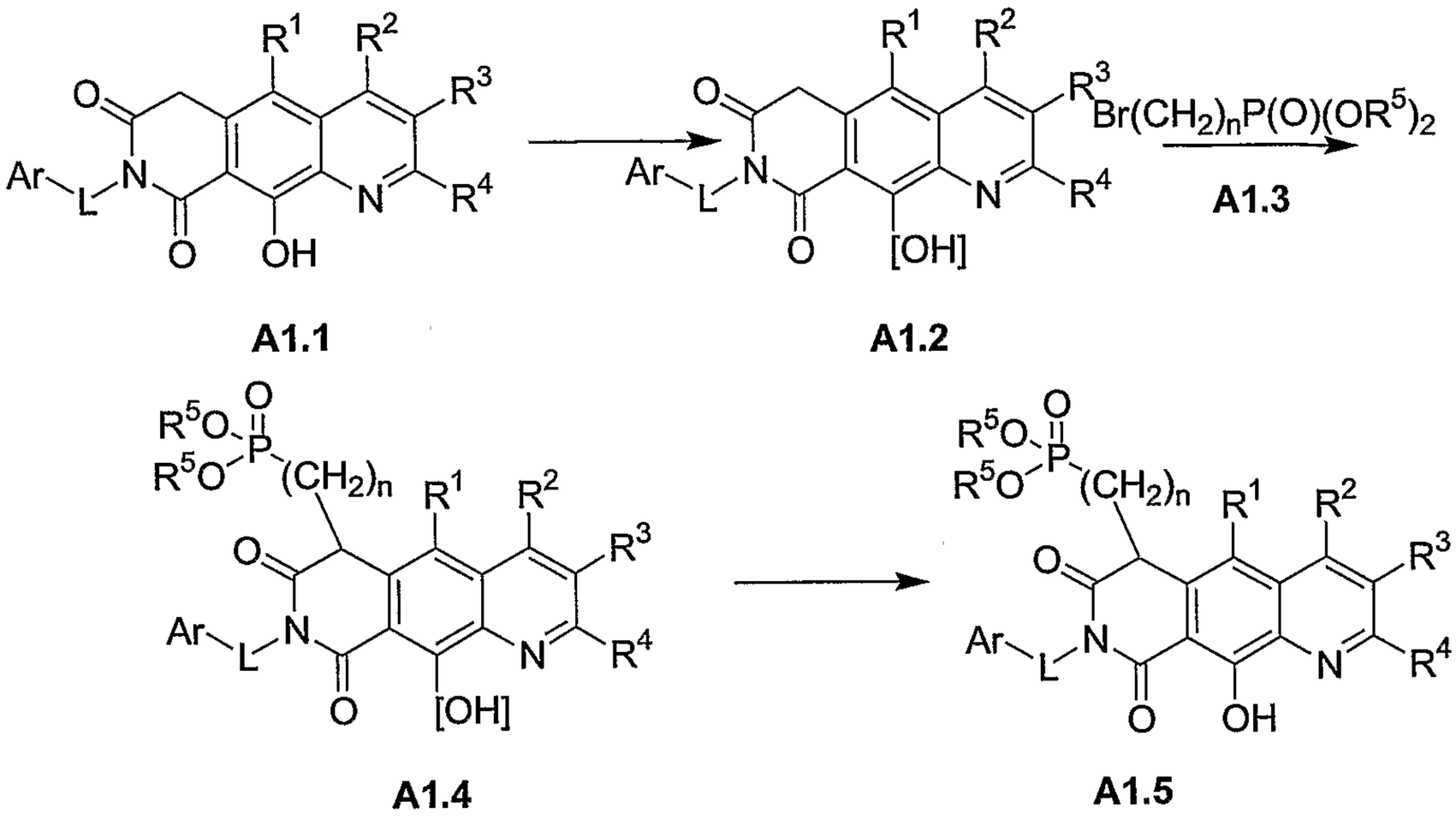
the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide. Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide. The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide. The product **A5.6** is then cyclized, for example by heating at reflux temperature in toluene in the presence of a basic catalyst such as sodium methoxide, or by reaction with trimethylaluminum, as described in Syn. Comm., 25, 1401, 1995, to afford after deprotection of the hydroxyl groups, the diazepindione derivative **A5.7**.

For example, the MOM-protected amine **A3.7** is reductively aminated by reaction with a dialkyl phosphonoacetaldehyde **A5.8** (Aurora) and sodium triacetoxyborohydride, to produce the amine **A5.9**. The product is then coupled in dimethylformamide solution, in the presence of dicyclohexyl carbodiimide, with (4-fluoro-benzylamino)-acetic acid **A5.10**, to give the amide **A5.11**. This material is converted, by reaction with trimethylaluminum in dichloromethane, as described above, into the diazepin derivative **A5.12**. Removal of the MOM protecting groups, as previously described, then affords the phenolic product **A5.13**.

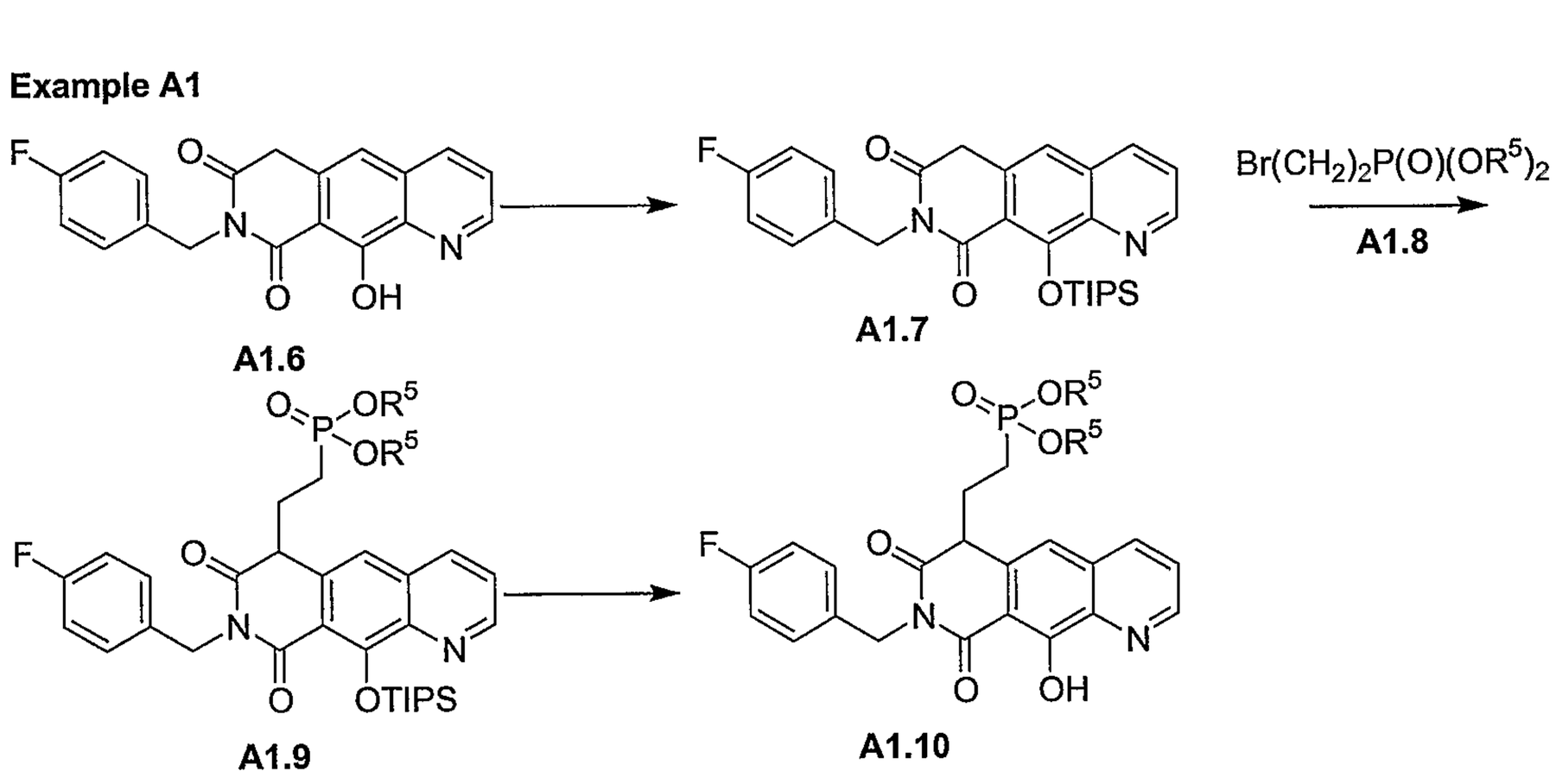
Using the above procedures, but employing, in place of the amine **A3.7**, different amines **A5.2**, and/or different aldehydes **A5.3**, and/or different carboxylic acids **A5.5**, the corresponding products **A5.7** are obtained.

Scheme A1. Phosphonates Iaa.

Method

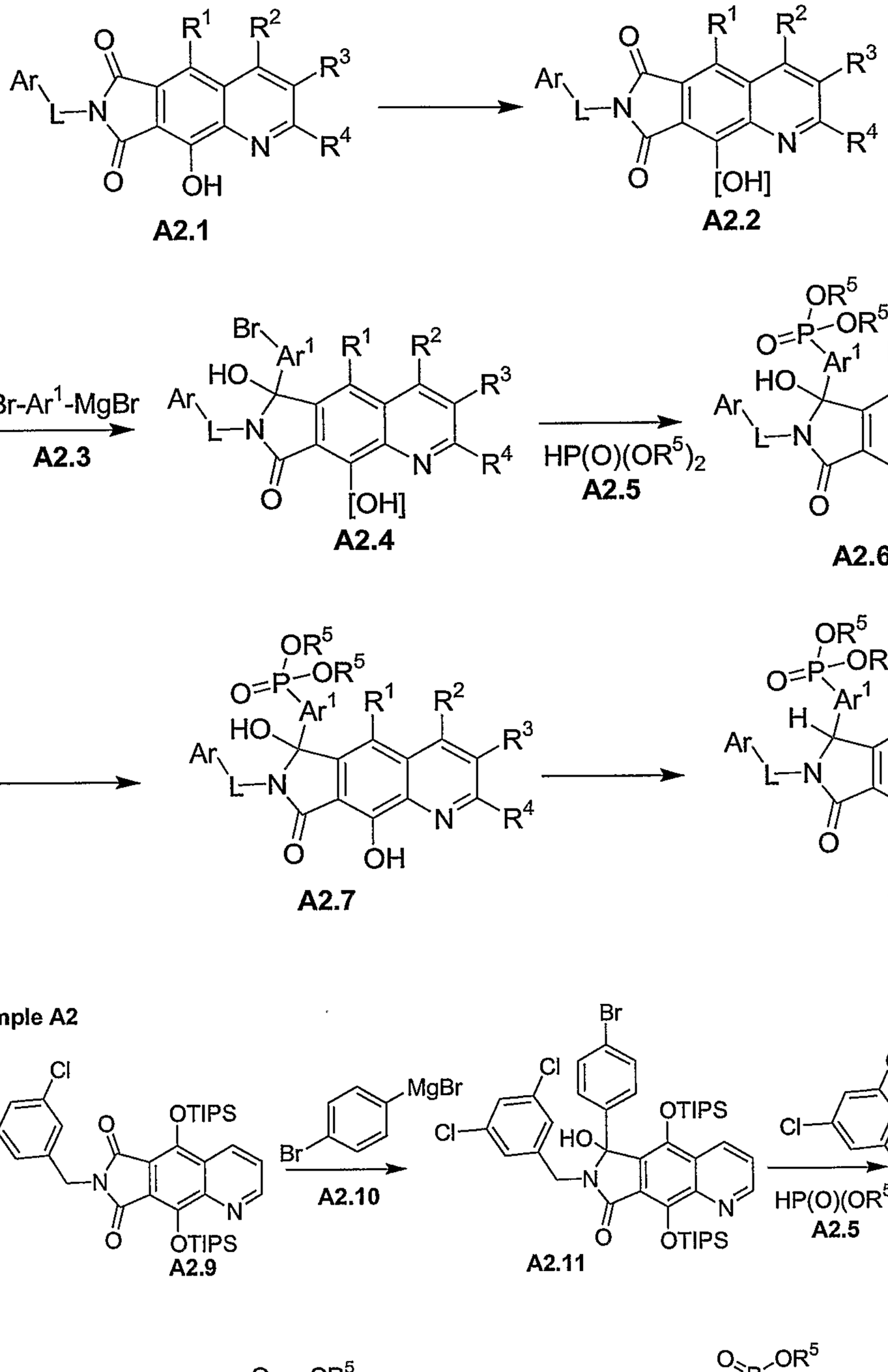


Example A1

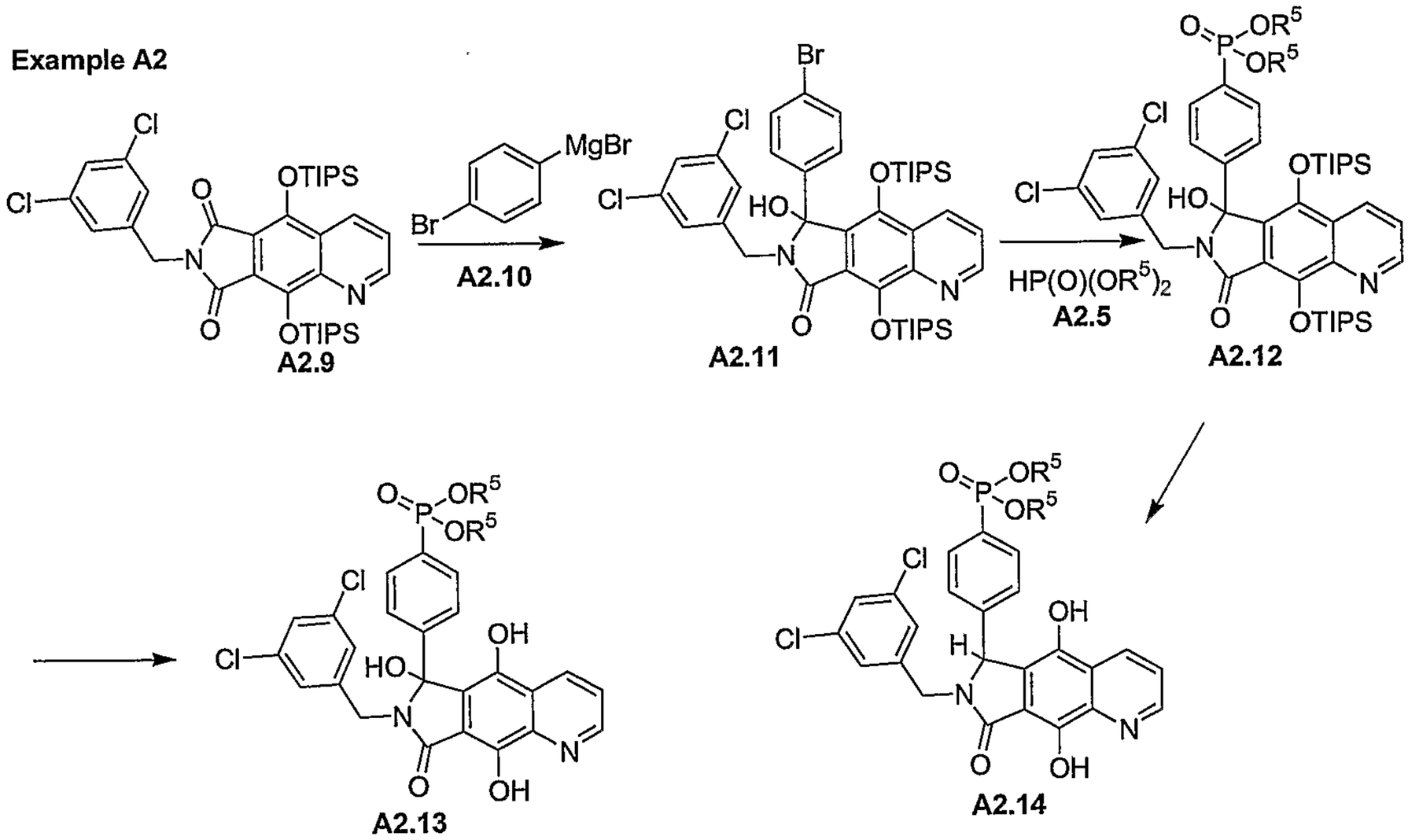


Scheme A2. Phosphonates Iaa.

Method

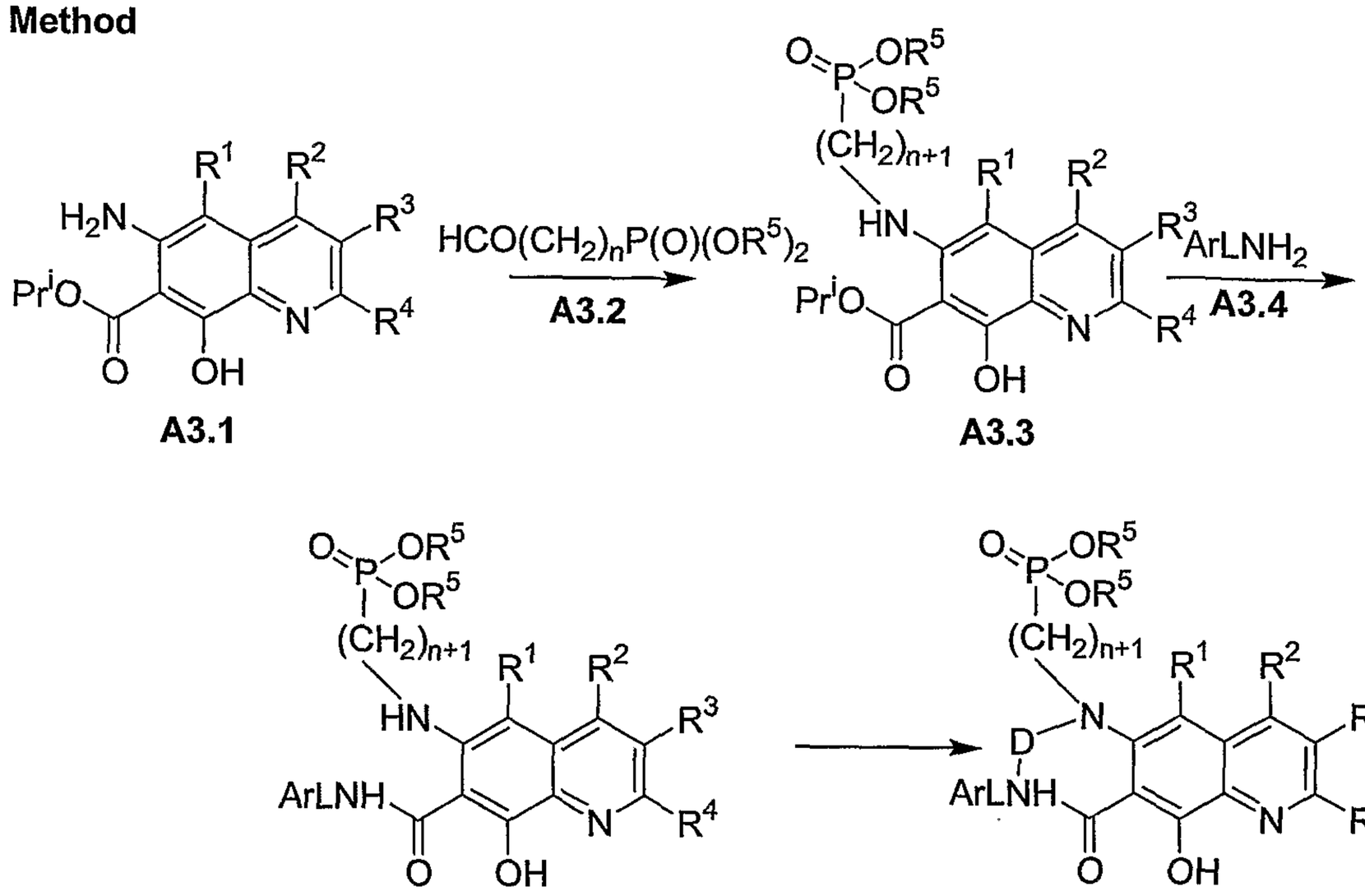


Example A2

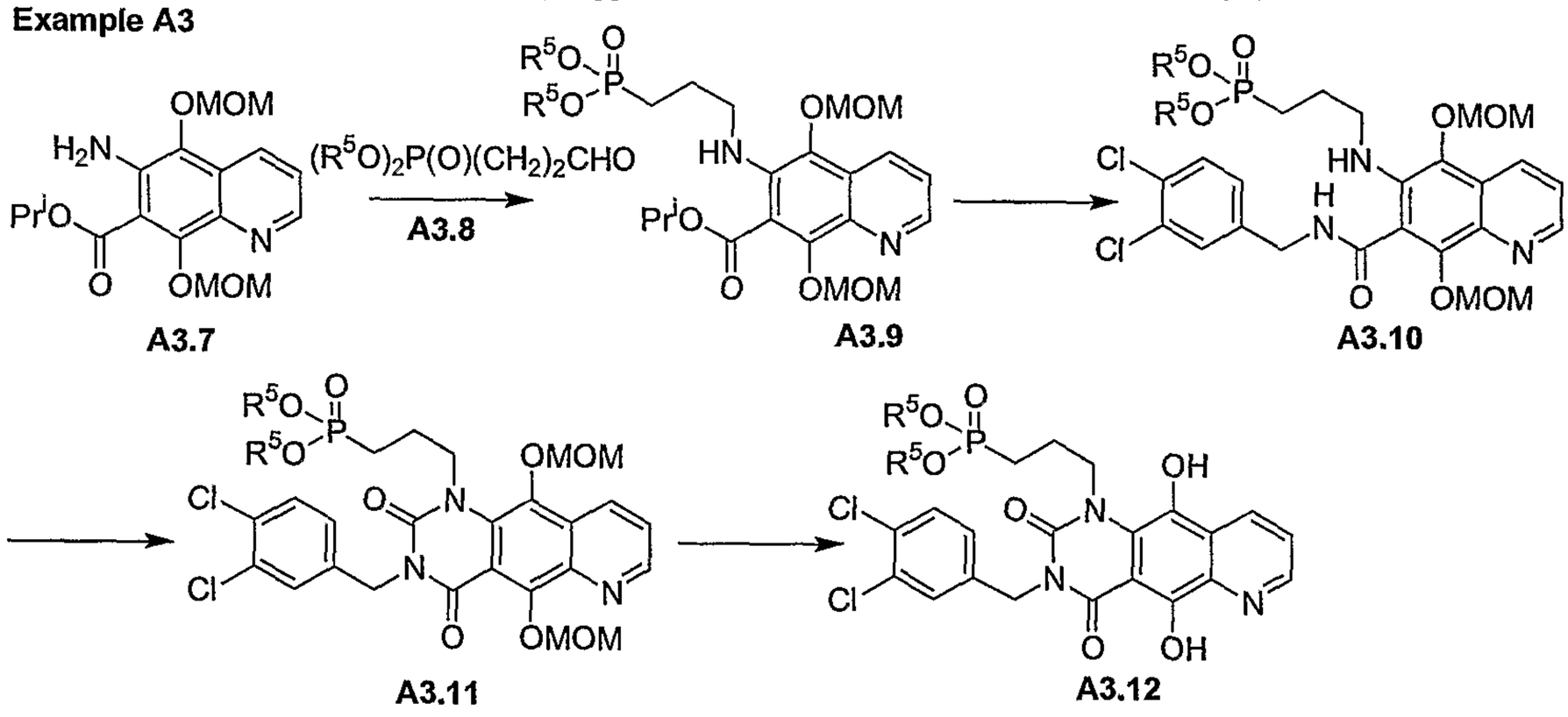


Scheme A3. Phosphonates Iaa.

Method

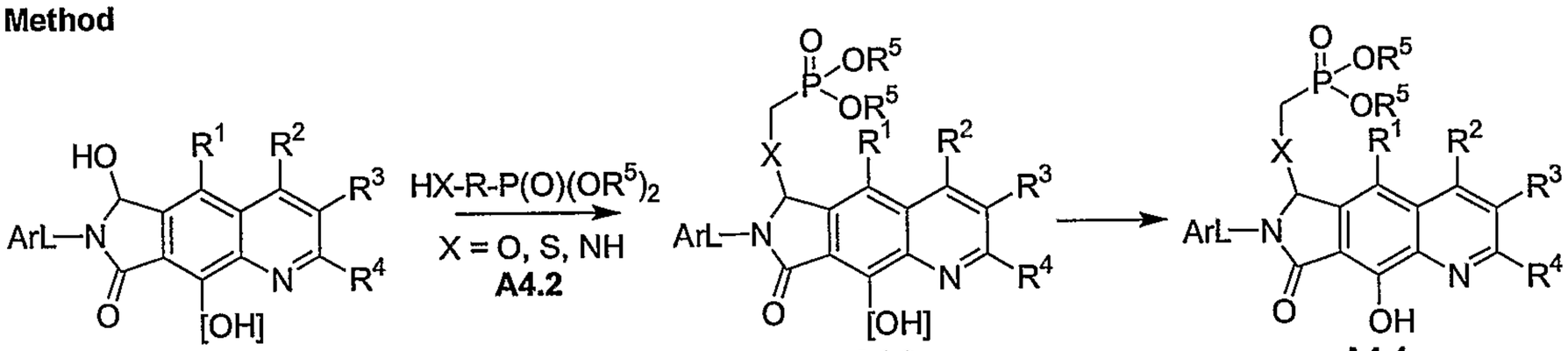


Example A3



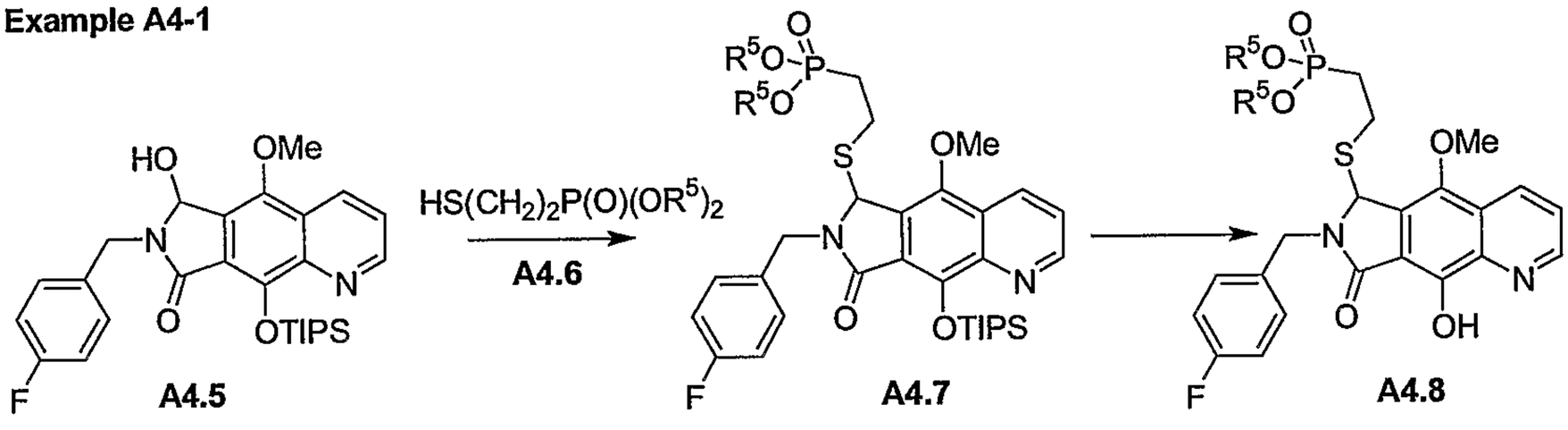
Scheme A4. Phosphonates Iaa.

Method



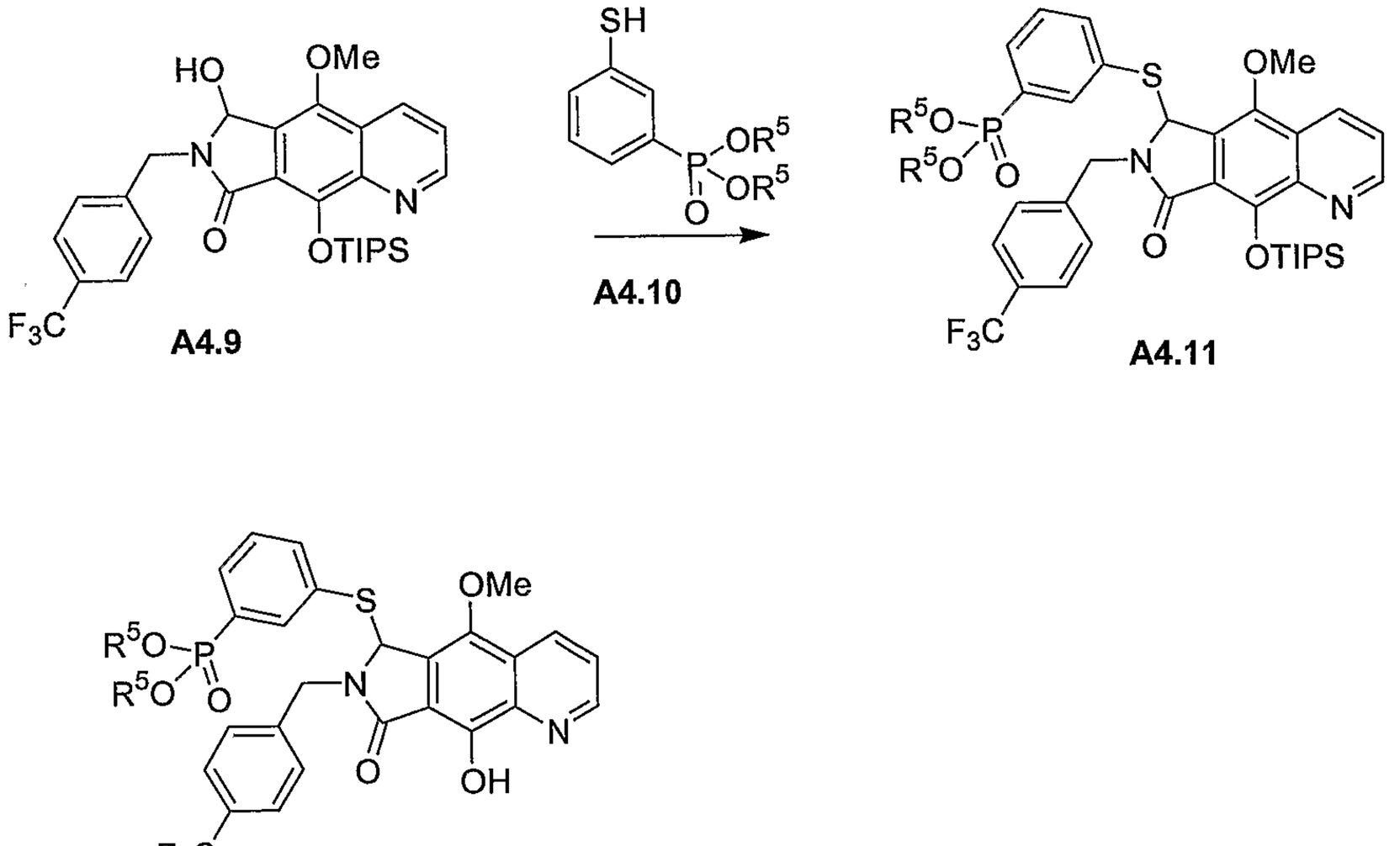
A4.1 **A4.2** **A4.3** **A4.4**

Example A4-1



A4.5 **A4.6** **A4.7** **A4.8**

Example A4-2

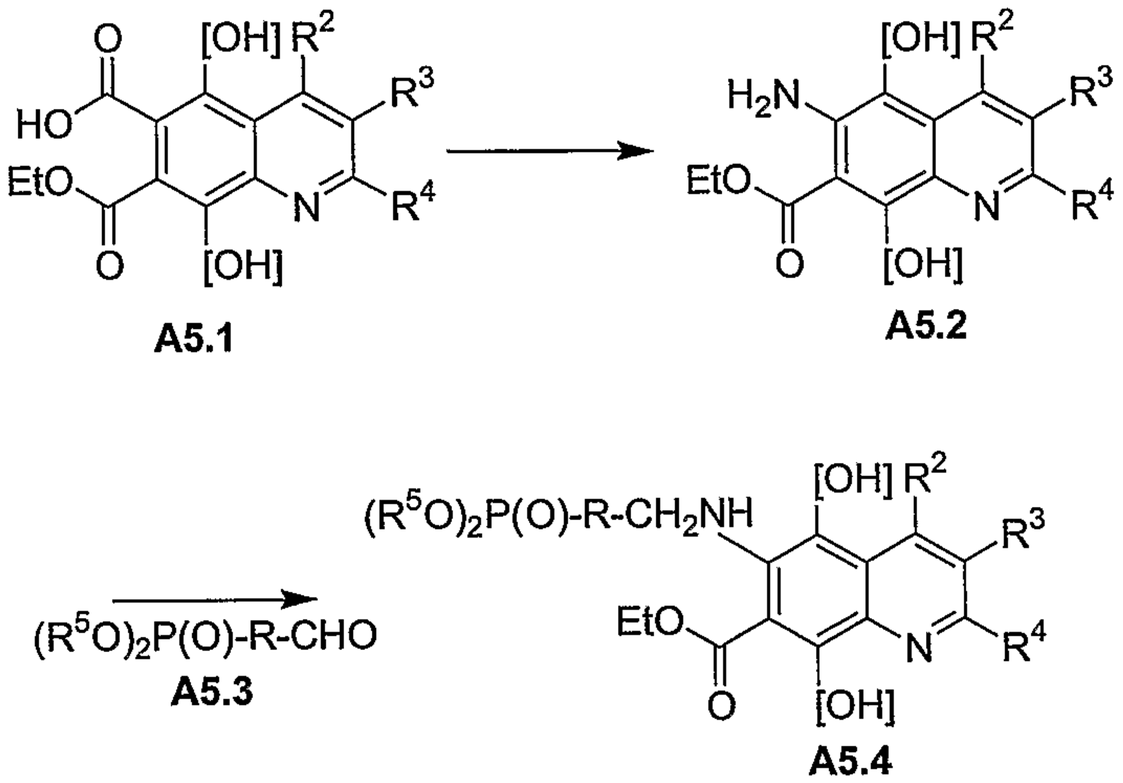


A4.9 **A4.10** **A4.11**

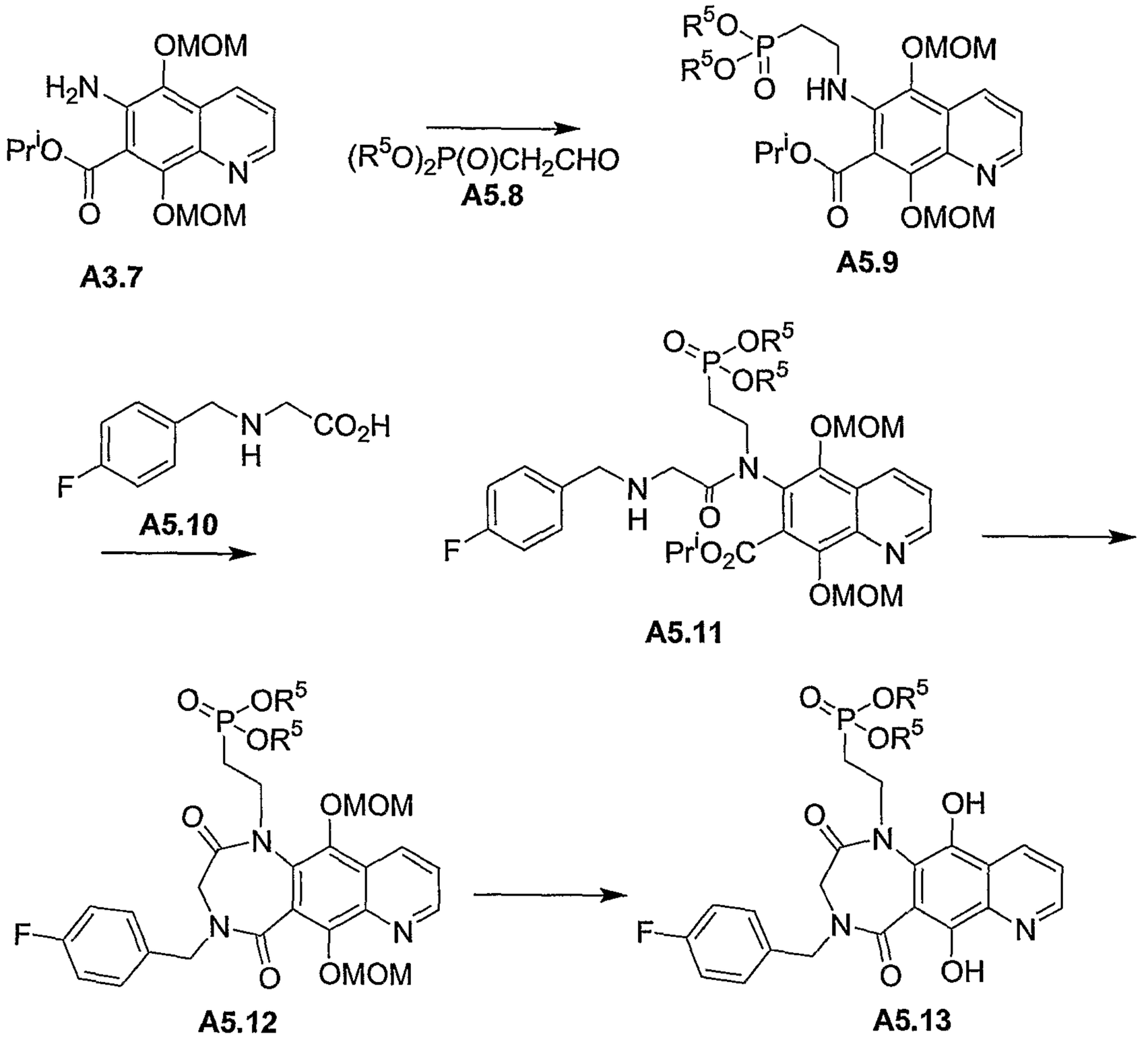
A4.12

Scheme A5. Phosphonates Iaa.

Method



Example A5



Preparation of the intermediate phosphonate esters Ibb.

Schemes **A6 - A16** illustrate methods for the preparation of the phosphonate esters of general structure **Ibb**.

Scheme **A6** depicts two methods for the preparation of phosphonate esters in which the phosphonate group is linked by means of a saturated or unsaturated alkylene chain, or alkylene chains incorporating carbocyclic, aryl or heteroaryl rings. In this procedure, a mono-protected phenol **A6.1**, for example, is reacted either with a bromo-substituted alkyl phosphonate **A6.2**, in which the group R is alkylene, cycloalkyl, alkenyl, aralkyl, heterarylalkyl and the like, or with an analogous hydroxyl-substituted dialkyl phosphonate **A6.3**. The reaction between the phenol and the bromo compound **A6.2** is conducted in a polar organic solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, to afford the

ether product **A6.4**. Alternatively, the ether compounds **A6.4** are obtained by means of a Mitsonobu reaction between the phenol **A6.1** and the hydroxy compound **A6.3**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4 and in Org. React., 1992, 42, 335. The phenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656. Deprotection of the phenolic hydroxyl group then affords the phenol **A6.5**.

For example, 7-(4-fluoro-benzyl)-5-hydroxy-9-triethylsilanyloxy-pyrrolo[3,4-g]quinoline-6,8-dione **A6.6**, (Example 12, Scheme 11) is reacted at ambient temperature in dimethoxyethane solution with one molar equivalent of a dialkyl 4-bromo-2-butenylphosphonate **A6.7** (J. Med. Chem., 1992, 35, 1371) and potassium carbonate, to yield the ether product **A6.8**, which upon deprotection with tetrabutylammonium fluoride gives the phenol **A6.9**.

As a further example, 7-[2-(4-fluoro-phenyl)-ethyl]-5-hydroxy-9-triethylsilanyloxy-pyrrolo[3,4-g]quinoline-6,8-dione **A6.10** prepared by analogous procedures to those shown is reacted in tetrahydrofuran solution with a dialkyl 3-hydroxypropyl phosphonate **A6.11** (Acros), diethyl azodicarboxylate and triphenylphosphine, to afford the ether product **A6.12** which upon deprotection gives the phenol **A6.13**.

Using the above procedures, but employing, in place of the phenols **A6.6** and **A6.10**, the phenols **A6.1**, and/or different bromides **A6.2**, or alcohols **A6.**3, the corresponding products **A6.5** are obtained.

Scheme **A7** illustrates the preparation of phosphonate esters of structure **Ibb** in which the phosphonate is linked by means of an aryl or a heteroaryl group.

In this procedure, a mono-protected phenol **A7.1** (Formula I) is converted into the triflate **A7.2** by reaction, in an inert solvent such as dichloromethane, with trifluoromethanesulfonyl chloride or anhydride, or with trimethylsilyl triflate and triethylsilane, in each case in the presence of a tertiary base such as triethylamine. The

triflate is then coupled with a bromo-substituted arylboronate **A7.3**, in which the group Ar^1 is an aromatic or heteroaromatic moiety, to afford the coupled product **A7.4**. The Suzuki coupling of aryl triflates and aryl boronic acids is described in Palladium Reagents and Catalysts by J. Tsuji, Wiley 1995, p 218. The reactants are combined in an inert solvent such as toluene or dioxan, in the presence of a palladium (0) catalyst such as tetrakis(triphenylphosphine)palladium and a base such as sodium bicarbonate. The coupled product **A7.4** is then reacted, as described previously (Scheme **A2**) with a dialkyl phosphite **A7.5**, to give the phosphonate ester **A7.6**, which upon deprotection yields the phenol **A7.7**.

For example, trifluoro-methanesulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **A7.8** (Example 46) is reacted in dioxan solution at 70° with one molar equivalent of 3-bromophenyl boronic acid **A7.9** (Maybridge), sodium bicarbonate and a catalytic amount of tri-(o-tolyl)phosphine, to produce the coupled compound **A7.10**. This material is then reacted, as described in Scheme **A2**, with a dialkyl phosphite and a palladium (0) catalyst, to give the phosphonate product **A7.10**. Removal of the benzhydryl protecting group, for example by treatment with trifluoroacetic acid and anisole in dichloromethane, as described in Tet. Lett., 25, 3909, 1984, then affords the phenol **A7.11**.

Using the above procedures, but employing, in place of the phenol **A7.8**, the phenol **A7.1**, and/or different boronic acids **A7.3**, the corresponding products **A7.7** are obtained.

Scheme **A8** illustrates the preparation of phosphonate esters of structure **Ibb** in which the phosphonate group is linked by means of an oxygen, sulfur or nitrogen and an aliphatic or aromatic moiety.

In this method, a monoprotected phenol **A8.1** (Formula I) is converted into the corresponding triflate **A8.2**, as described above (Scheme **A7**). The product is then subjected to a nucleophilic displacement reaction with various alcohols, thiols or amines **A8.3**, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety, to afford after deprotection the ether, thioether or amine products **A8.4**. The displacement reaction is performed in an inert

solvent such as dichloroethane or dioxan, at from ambient temperature to about 80°, in the presence of a tertiary organic base such as N-methyl morpholine and the like.

For example, trifluoro-methanesulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **A8.5** (Example 56) is reacted in dioxan at 50° with one molar equivalent of a dialkyl methylaminomethyl phosphonate **A8.6** and diisopropylethylamine, to give the amine product **A8.7**. Deprotection then affords the phenol **A8.8**.

Using the above procedures, but employing, in place of the triflate **A8.5**, different triflates **A8.2**, and/or different alcohols, thiols or amines **A8.3**, the corresponding products **A8.4** are obtained.

Scheme **A9** depicts the preparation of phosphonate esters of structure **Ibb** in which the phosphonate group is attached by means of an methylamino group and a carbon link R, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety. The compounds are obtained by means of a reductive alkylation reaction, as described above (Scheme **A3**) between the aldehyde **A9.1**, prepared by the method shown in Example 49, and a dialkyl aminoalkyl or aryl phosphonate **A9.2**. The amination product **A9.3** is then deprotected to give the phenol **A9.3**.

For example, 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbaldehyde **A9.5** (Example 49) is reacted with a dialkyl aminopropyl phosphonate **A9.6** (Acros), sodium cyanoborohydride and acetic acid in isopropanol to yield the amination product **A9.7**, which is deprotected to produce the phenol **A9.8**.

Using the above procedures, but employing, in place of the aldehyde **A9.5**, different aldehydes **A9.1**, and/or different amines **A9.2**, the corresponding products **A9.4** are obtained.

Scheme **A10** depicts the preparation of phosphonate esters of structure **Ibb** in which the phosphonate group is attached by means of an amide linkage and a carbon link R, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety. In this sequence, the aldehyde **A10.1**, prepared, for example, as shown in Example 49 is oxidized to the corresponding carboxylic acid **A10.2**. The conversion of an aldehyde to the corresponding carboxylic acid is

described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 838. The reaction is effected by the use of various oxidizing agents such as, for example, potassium permanganate, ruthenium tetroxide, silver oxide or sodium chlorite. The carboxylic acid is then coupled, as described in Scheme **A5**, with an amine **A10.3** to afford the amide, which upon deprotection gives the phenolic amide **A10.4**.

For example, 9-benzhydryloxy-7-(4-chloro-benzyl)-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbaldehyde **A10.5**, prepared using the methods described in Example 49, is treated with silver oxide in acetonitrile, as described in Tet. Lett., 5685, 1968, to produce the corresponding carboxylic acid 9-benzhydryloxy-7-(4-chloro-benzyl)-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid **A10.6**. This material is then coupled, in dimethylformamide solution, with one molar equivalent of a dialkyl aminoethyl phosphonate **A10.7** (Aurora) and dicyclohexyl carbodiimide, to afford the amide, which upon deprotection gives the phenolic product **A10.8**.

Using the above procedures, but employing, in place of the aldehyde **A10.5**, different aldehydes **A10.1**, and/or different amines **A10.3**, the corresponding products **A10.4** are obtained.

Scheme **A11** depicts the preparation of phosphonate esters of structure **Ibb** in which the phosphonate group is attached by means of a methylene group. In this procedure, a hydroxymethyl-substituted O-protected phenol **A11.1**, prepared by the method shown in Example 50, is converted into the corresponding bromomethyl derivative **A11.2**. The conversion of alcohols into the corresponding bromides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 356ff. For example, benzyl alcohols can be transformed into the bromo compounds by reaction with bromine and triphenyl phosphite, or by reaction with trimethylsilyl chloride and lithium bromide, or with carbon tetrabromide and triphenylphosphine, as described in J. Am. Chem. Soc., 92, 2139, 1970. The resultant bromomethyl compound **A11.2** is treated with a trialkyl phosphite **A11.3** in an Arbuzov reaction. The preparation of phosphonates by means of the Arbuzov reaction is described in Handb. Organophosphorus Chem., 1992, 115-72. The bromo compound is heated with an excess of the phosphite at from about 80°-130° to

produce the phosphonate product, which upon deprotection affords the phenolic phosphonate **A11.4**.

For example, 9-benzhydryloxy-5-hydroxymethyl-7-(4-methoxy-benzyl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **A11.5** prepared by the method shown in Example 50, is reacted in dichloromethane with one molar equivalent of carbon tetrabromide and triphenylphosphine to produce 9-benzhydryloxy-5-bromomethyl-7-(4-methoxy-benzyl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **A11.6**. The product is then heated at 120° with an excess of a trialkyl phosphite **A11.3**. The resulting phosphonate is then deprotected to afford the phenolic product **A11.7**.

Using the above procedures, but employing, in place of the alcohol **A11.5**, different alcohols **A11.1**, and/or different phosphites **A11.3**, the corresponding products **A11.4** are obtained.

Scheme **A12** depicts the preparation of phosphonate esters of structure **Ibb** in which the phosphonate group is attached by means of a methyleneoxy and a variable alkyl moiety. In this procedure, a protected hydroxymethyl-substituted tricyclic phenol **A12.1** prepared according to the procedure of Example 50, is alkylated with a dialkyl bromo-substituted phosphonate **A12.2**, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety. The alcohol is reacted with one molar equivalent of the bromo compound in a polar aprotic organic solvent such as dimethylacetamide, dioxan and the like, in the presence of a strong base such as sodium hydride, lithium hexamethyldisilazide, or potassium *tert.*-butoxide. The thus-obtained ether **A12.3** is then deprotected to give the phenol **A12.4**.

For example, 9-benzhydryloxy-7-(4-fluoro-benzyl)-5-hydroxymethyl-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **A12.5** (Example 50) is treated in dimethylformamide solution at ambient temperature with one molar equivalent of lithium hexamethyldisilazide, followed by one molar equivalent of a dialkyl 4-(bromomethyl)benzyl phosphonate **A12.6** (Tet., 1998, 54, 9341) to yield the alkylated product **A12.7**. Deprotection then gives the phenol **A12.8**.

Using the above procedures, but employing, in place of the alcohol **A12.5**, different alcohols **A12.1**, and/or different bromo compounds **A12.2**, the corresponding products **A12.4** are obtained.

Scheme **A13** depicts the preparation of phosphonate esters of structure **Ibb** in which the phosphonate group is attached by means of an aryl or heteroaryl ethenyl or ethyl linkage. In this procedure, a vinyl-substituted OH-protected phenol **A13.1**, prepared by the method shown in Example 59, is coupled in a palladium-catalyzed Heck reaction with a dibromo-substituted aromatic or heteroaromatic reagent **A13.2**, in which the group Ar^1 is an aromatic or heteroaromatic ring. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. The coupled product **A13.3** is then reacted, as described in Scheme **A7**, with a dialkyl phosphite **A13.4** and a palladium catalyst, to afford, after deprotection of the phenolic hydroxyl, the ethenyl phosphonate ester **A13.5**. Catalytic or chemical reduction of the product then yields the saturated analog **A13.6**. The reduction reaction is effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5, or catalytically, for example by the use of a palladium on carbon catalyst in the presence of hydrogen or a hydrogen donor.

For example, 9-benzhydryloxy-7-(4-fluoro-benzyl)-5-vinyl-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **A13.7** (Example 59) is reacted in dimethylformamide with 2,5-dibromothiophene **A13.8** and a catalytic amount of palladium (II) acetate and triethylamine, to give the coupled product **A13.9**. This material is then coupled with a dialkyl phosphite, as described above, to afford after deprotection of the phenol, the ethenylthienyl phosphonate **A13.10**. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product **A13.11**.

Using the above procedures, but employing, in place of the vinyl-substituted compound **A13.7**, different analogs **A13.1**, and/or different dibromo compounds **A13.2**, the corresponding products **A13.5** are obtained.

Scheme **A14** depicts the preparation of phosphonate esters of structure **Ibb** in which the phosphonate group is attached by means of an alkoxy chain incorporating an amide linkage. In this procedure, a mono-protected phenol **A14.1** (Example 6) is alkylated with a methyl bromoalkyl carboxylate **A14.2**. The alkylation reaction is conducted under similar conditions to those described in Scheme **A6**, to afford the ester ether **A14.3**. Hydrolysis of the ester group then gives the carboxylic acid **A14.4**. Hydrolysis methods for converting esters into carboxylic acids are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p 981. The methods include the use of enzymes such as pig liver esterase, and chemical methods such as the use of alkali metal hydroxides in aqueous organic solvent mixtures, for example lithium hydroxide in an aqueous organic solvent.

The resultant carboxylic acid is then coupled, as described in Scheme **A10**, with a dialkyl amino-substituted phosphonate **A14.5**, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety, to produce the amide **A14.6**. Deprotection then yields the phenol **A14.7**.

For example, 5-hydroxy-9-methoxymethoxy-7-(4-methyl-benzyl)-pyrrolo[3,4-g]quinoline-6,8-dione **A14.8**, prepared, for example, by the method shown in Example 6 is reacted in dimethylformamide solution with methyl bromoacetate **A14.9** and cesium carbonate, to give the ether **A14.10**. The ester group is then hydrolyzed by reaction with one molar equivalent of lithium hydroxide in aqueous glyme, to produce the carboxylic acid **A14.11**. The carboxylic acid is then coupled in dimethylformamide solution in the presence of diisopropyl carbodiimide with a dialkyl 2-aminoethyl phosphonate **A14.12**, (J. Org. Chem., 2000, 65, 676) to form the amide **A14.13**. Deprotection, for example by the use of 50% aqueous acetic acid containing a catalytic amount of sulfuric acid, as described in J. Am. Chem. Soc., 55, 3040, 1933, then affords the phenol **A14.14**.

Using the above procedures, but employing, in place of the phenol **A14.8**, different phenols **A14.1**, and/or different bromoesters **A14.2**, and/or different amines **A14.5**, the corresponding products **A14.7** are obtained.

Scheme **A15** depicts the preparation of phosphonate esters of structure **Ibb** in which the phosphonate group is attached by means of an alkylene chain incorporating an amide linkage. In this procedure, the malonic ester derivative of a protected phenol

A15.1, prepared, for example, by the methods shown in Example 86, is hydrolyzed and decarboxylated to give the corresponding acetic acid derivative **A15.2**. Hydrolysis and decarboxylation of malonic esters is described, for example, in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 15. The ester hydrolysis is effected under conventional basic conditions, and decarboxylation occurs after acidification either spontaneously or under mild heating. The resultant acetic acid derivative is then coupled, as described previously, with a dialkyl amino-substituted phosphonate **A15.3**, to give the amide product which upon deprotection affords the phenol **A15.4**.

For example, 2-[9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl]-malonic acid dimethyl ester **A15.5** (Example 86) is reacted at ambient temperature with two molar equivalents of lithium hydroxide in aqueous dimethoxyethane, and the reaction mixture is then acidified to pH 4.0 and heated at reflux to effect decarboxylation and production of the acetic acid derivative **A15.6**. The carboxylic acid is then coupled in acetonitrile solution in the presence of a water-soluble carbodiimide with a dialkyl 4-aminophenyl phosphonate **A15.7** (Epsilon) to yield after deprotection the phenolic amide **A15.8**.

Using the above procedures, but employing, in place of the malonic ester **A15.5**, different malonic esters **A15.1**, and/or different amines **A15.3**, the corresponding products **A15.4** are obtained.

Scheme **A16** depicts the preparation of phosphonate esters of structure **Ibb** in which the phosphonate group is attached by means of an alkoxy chain and the nucleus incorporates a benzazepin moiety. In this procedure, a quinoline monoester **A16.1** is decarboxylated to afford the ester **A16.2**. Decarboxylation of carboxylic acids is described in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 676 and in Advanced Organic Chemistry, By J. Marsh, McGraw Hill, 1968, p. 435. The carboxylic acid is decarboxylated thermally in the presence of copper powder and quinoline, or by conversion to an ester with N-hydroxyphthalimide or N-hydroxythiopyridine, followed by photolysis in the presence of a hydrogen donor. The decarboxylated product **A16.2** is then converted into the allyl ether **A16.3** by reaction with allyl bromide in a polar solvent such as dimethylformamide in the presence of a base such h as triethylamine or potassium

carbonate. The allyl ester is then subjected to a thermal Claisen rearrangement to afford the allyl-substituted phenol **A16.4**. The Claisen rearrangement of allyl aryl ethers is described in Advanced Organic Chemistry, By J. Marsh, McGraw Hill, 1968, p. 830 and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 394. The reaction is conducted in a high-boiling solvent or without solvent at ca. 200°. The free phenolic hydroxyl group is then protected to yield the doubly protected product **A16.5**. The latter compound is then subjected to a hydroboration procedure to afford the alcohol **A16.6**. Hydroboration of alkenes is described, for example, in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 226. The olefin is reacted with diborane or a substituted borane such as 9-BBN or catechyl borane, and the resulting borane is oxidized, for example with hydrogen peroxide, oxygen, sodium peroxycarbonate or a tertiary amine oxide. The resultant alcohol **A16.6** is then converted into the substituted amine **A16.7**. The conversion is effected in two stages. In the first step, the alcohol is converted into a leaving group such as mesylate, tosylate or bromide by reaction with, for example, methanesulfonyl chloride, p-toluenesulfonyl chloride or triphenylphosphine/carbon tetrabromide. In the second step, the activated intermediate is reacted in a polar solvent such as N-methylpyrrolidinone or acetonitrile with the amine $ArBNH_2$ to give the product **A16.7**. The aminoester is then cyclized to yield the azepin derivative **A16.8**. The cyclization reaction is performed under similar conditions to those described above (Scheme **A5**). For example, the aminoester is heated in xylene at reflux temperature in the presence of a catalytic amount of sodium isopropoxide. The doubly protected azepin derivative **A16.8** is then selectively deprotected to give the phenol **A16.9**. The procedure for the selective deprotection is dependent on the nature of the protecting groups. For example, if the phenol **A16.1** is protected as the benzhydryl derivative, the phenol **A16.4** is protected as, for example, the TIPS derivative. Deprotection of the azepin **A16.8** is then effected by treatment with tetrabutylammonium fluoride in tetrahydrofuran. The phenol **A16.9** is then reacted with a dialkyl hydroxy-substituted phosphonate **A16.10**, in which the group R is an alkylene or alkenyl chain, optionally incorporating an aryl or heteroaryl group. The reaction is performed under the conditions of the Mitsonobu reaction, as

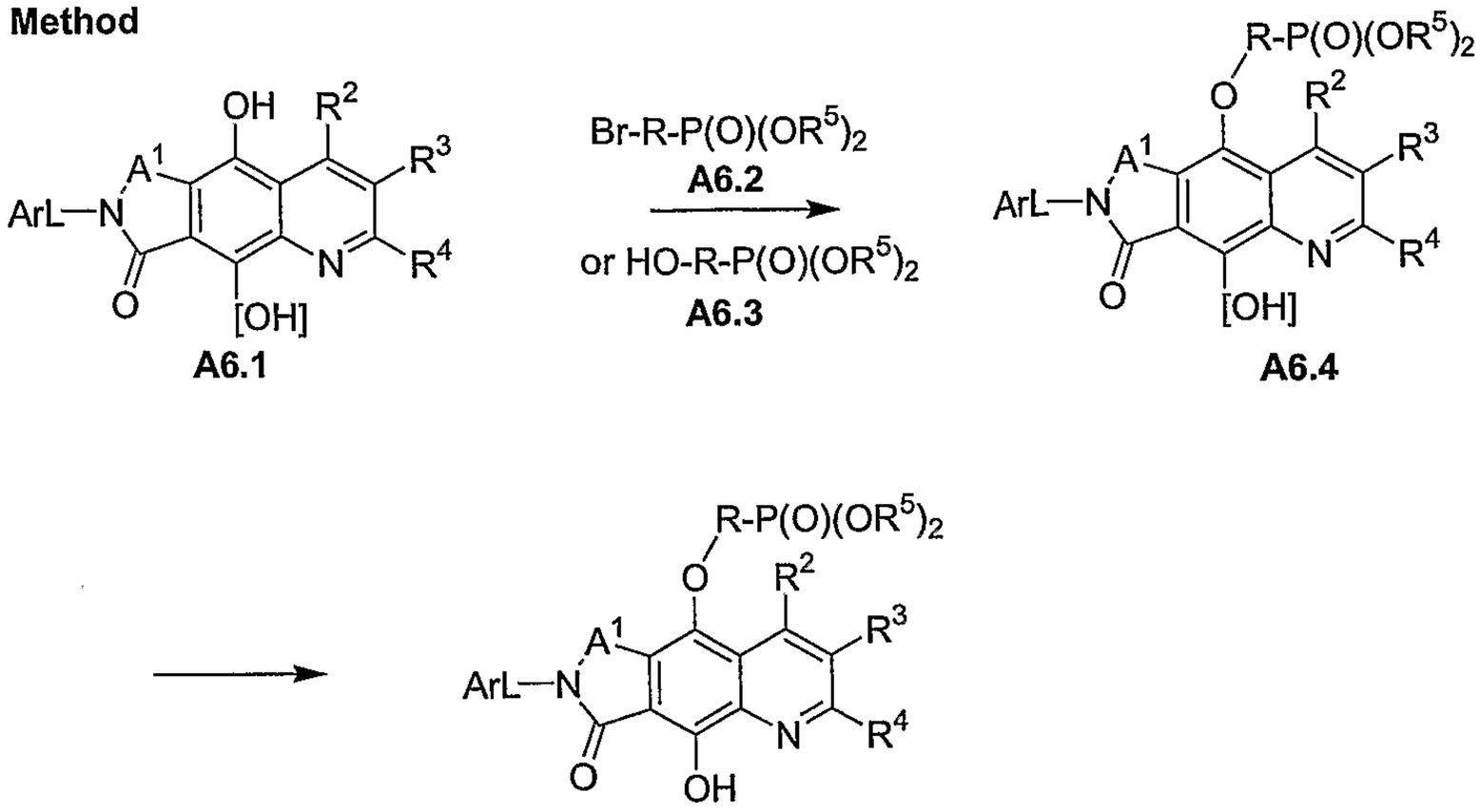
described in Scheme **A6**. The resultant ether is then deprotected to afford the phenol **A16.11**.

For example, 8-benzhydryloxy-7-methyl-quinolin-5-ol **A16.12** prepared as described above from the corresponding carboxyester is converted, via allylation, rearrangement and hydroboration/oxidation, as described above, into 3-(8-benzhydryloxy-7-methyl-5-triisopropylsilanyloxy-quinolin-6-yl)-propan-1-ol **A16.13**. The latter compound is then converted into an activated derivative which is reacted, as described above, with 3-chloro-4-fluorobenzylamine **A16.14** to yield [3-(8-benzhydryloxy-7-methyl-5-triisopropylsilanyloxy-quinolin-6-yl)-propyl]-(3-chloro-4-fluoro-benzyl)-amine **A16.15**. Cyclization of the product, for example by reaction with trimethylaluminum, employing the conditions described above, affords 11-benzhydryloxy-9-(3-chloro-4-fluoro-benzyl)-5-triisopropylsilanyloxy-6,7,8,9-tetrahydro-1,9-diaza-cyclohepta[b]naphthalen-10-one **A16.16**. The compound is deprotected by reaction with tetrabutylammonium fluoride, to produce 11-benzhydryloxy-9-(3-chloro-4-fluoro-benzyl)-5-hydroxy-6,7,8,9-tetrahydro-1,9-diaza-cyclohepta[b]naphthalen-10-one **A16.17**. The product is then reacted with a dialkyl hydroxyethyl phosphonate **A16.18**, diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran to give after deprotection the phenolic ether **A16.19**.

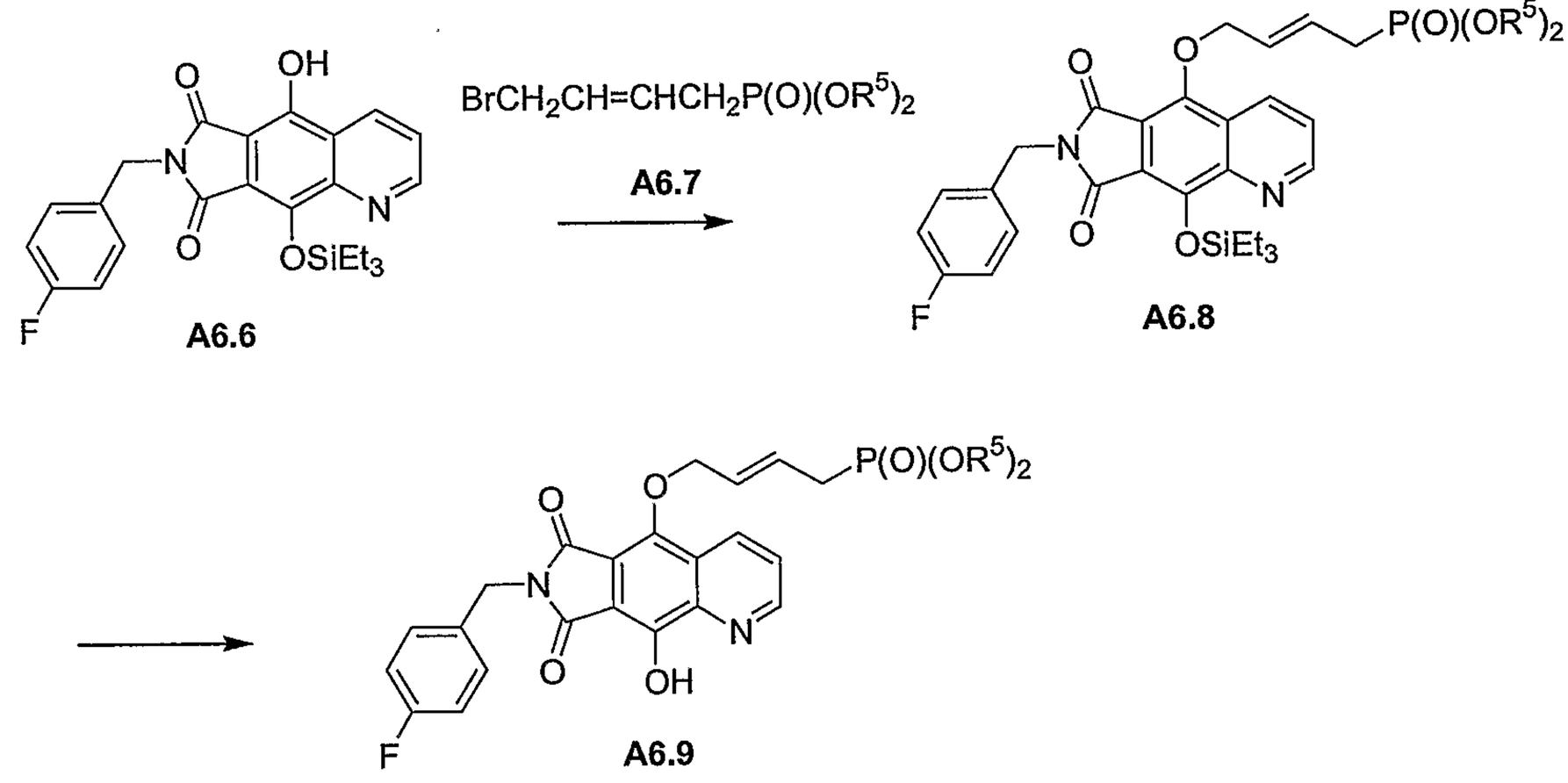
Using the above procedures, but employing, in place of the phenol **A16.12**, different phenols **A16.2**, and/or different hydroxyesters **A16.10**, and/or different amines $ArBNH_2$, the corresponding products **A16.11** are obtained.

Scheme A6. Phosphonates Ibb.

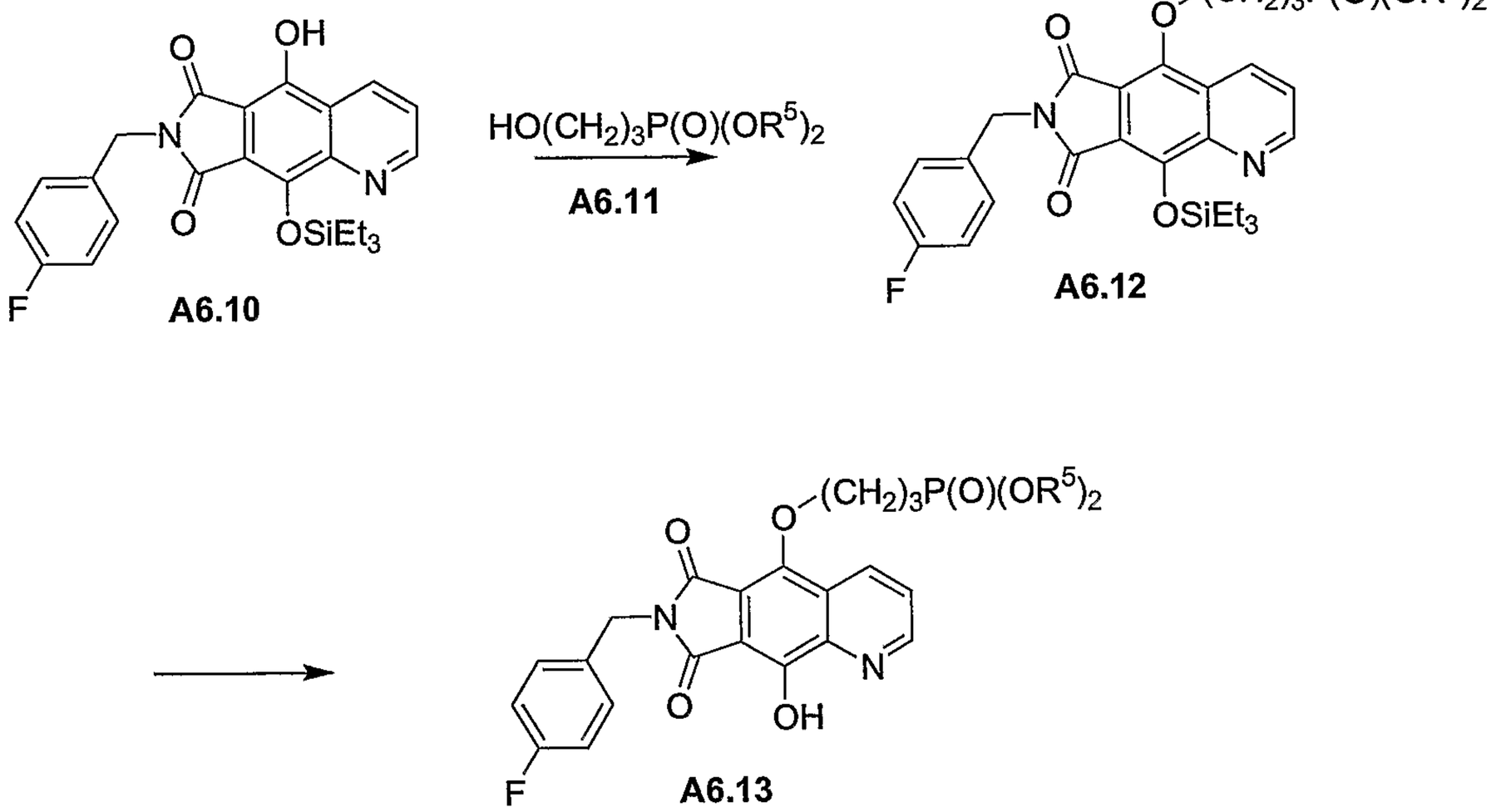
Method



Example A6-1

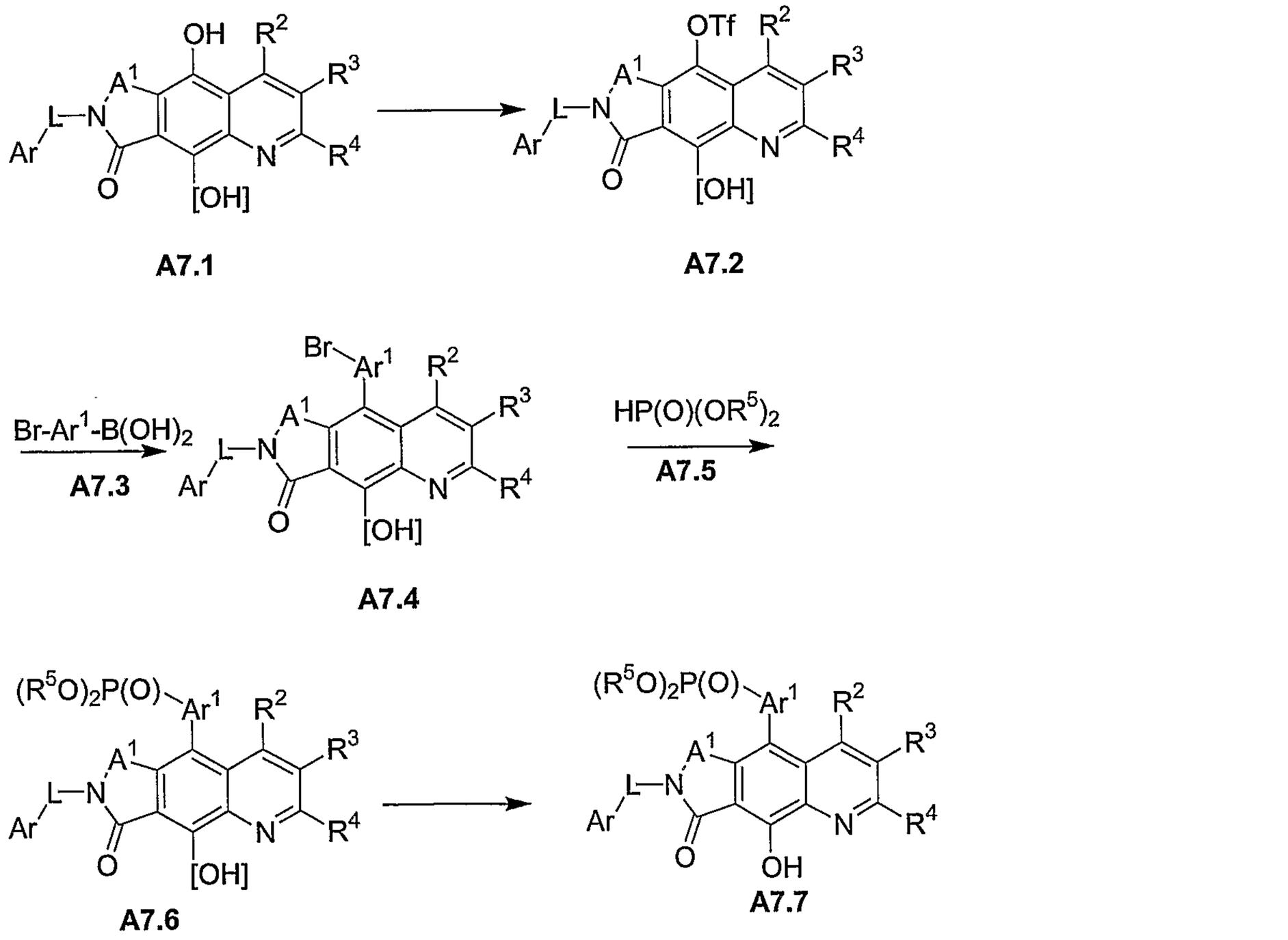


Example A6-2

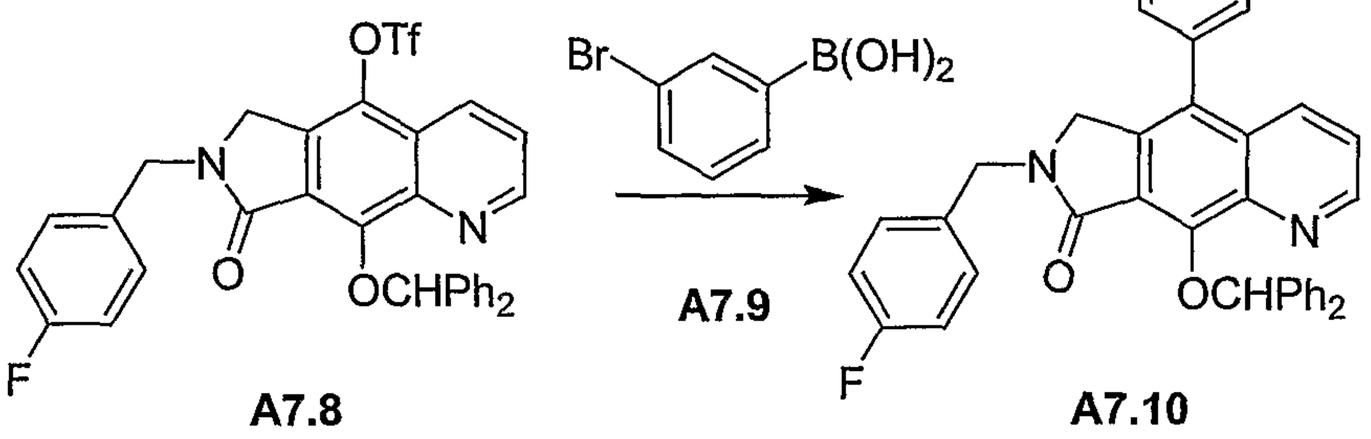


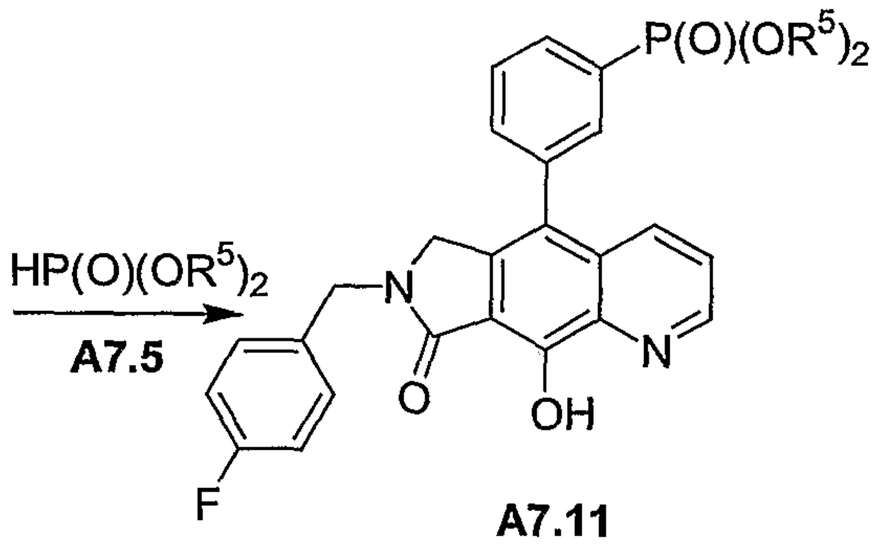
Scheme A7. Phosphonates Ibb.

Method



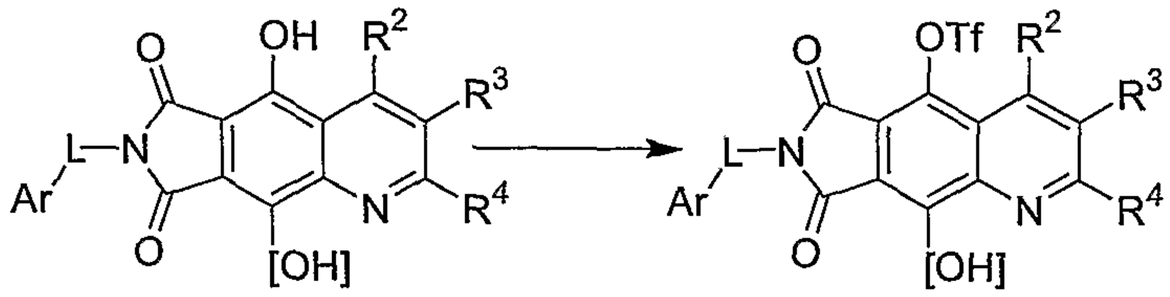
Example A7


OTf
N
O
OCHPh2
F
A7.8
Br
B(OH)2
A7.9
Br
N
O
OCHPh2
F
A7.10

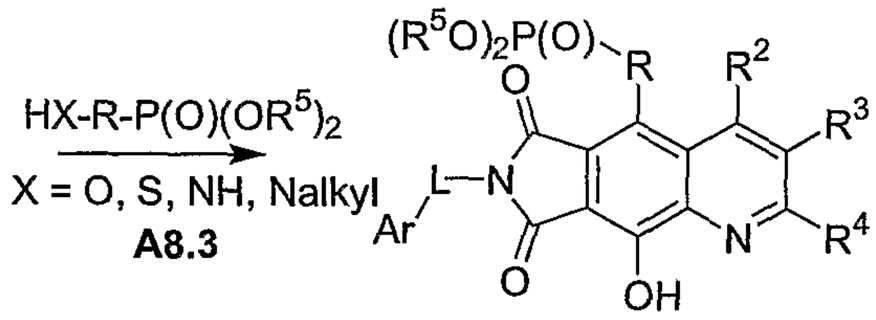

P(O)(OR5)2
HP(O)(OR5)2
A7.5
N
O
OH
N
F
A7.11

Scheme A8. Phosphonates Ibb.

Method

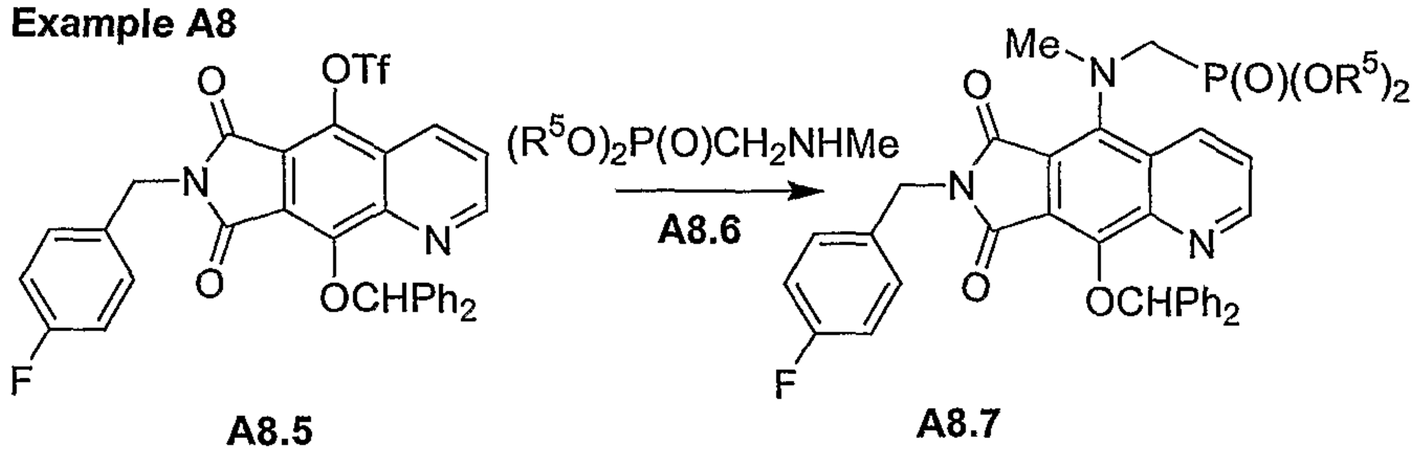


A8.1 **A8.2**

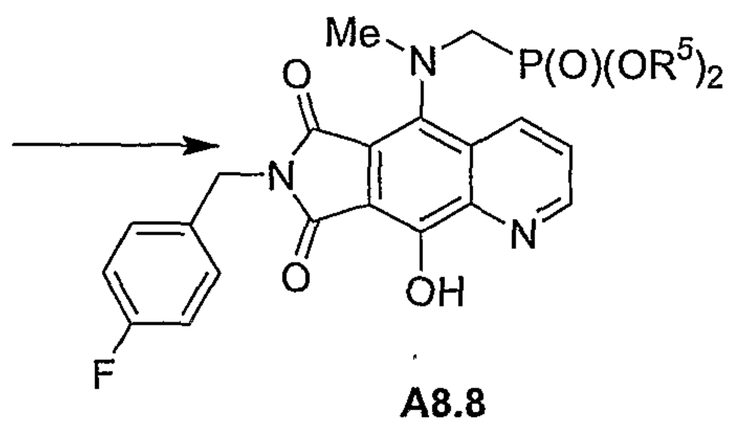


A8.3 **A8.4**

Example A8



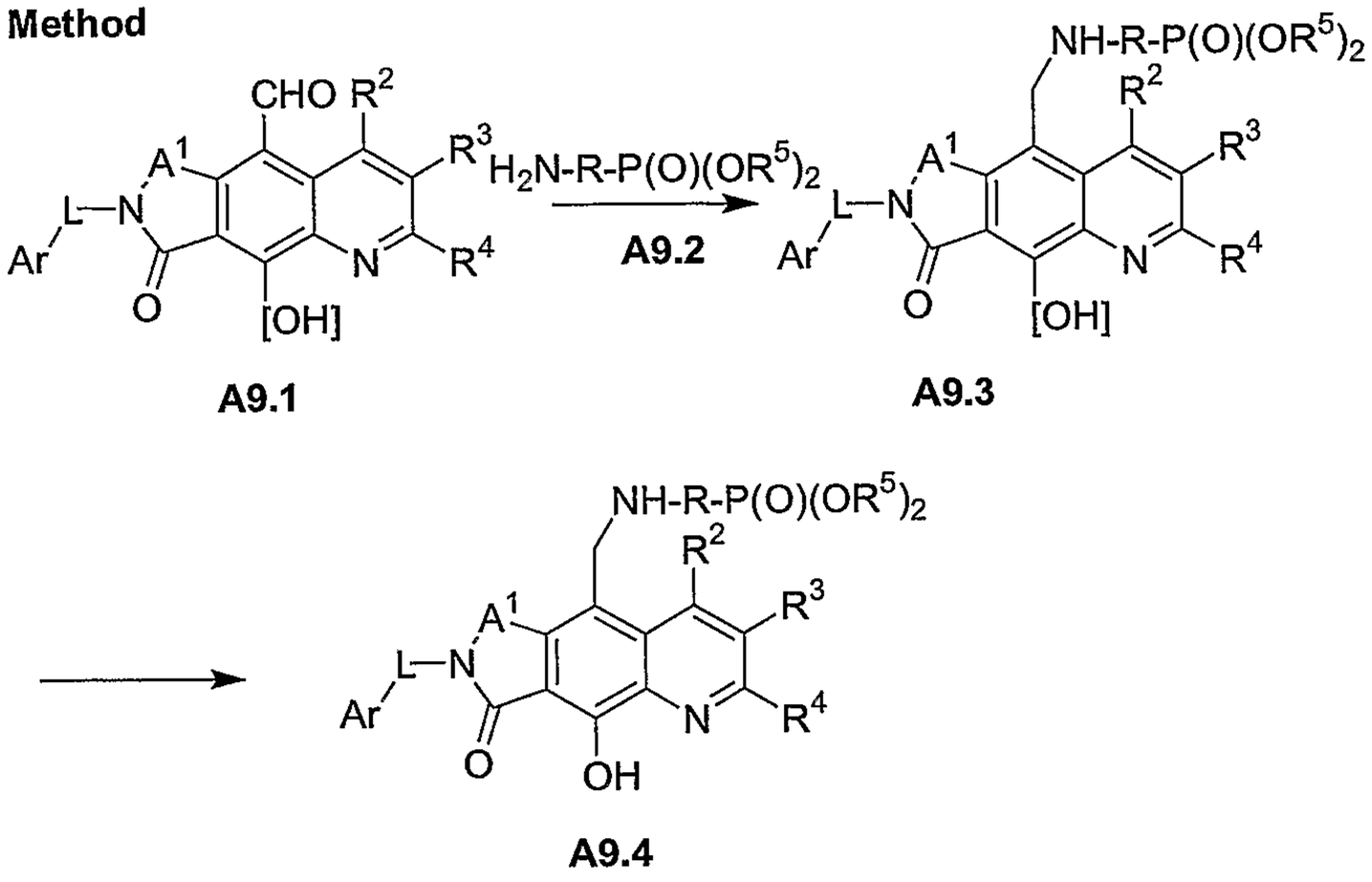
A8.5 **A8.6** **A8.7**



A8.8

Scheme A9. Phosphonates Ibb.

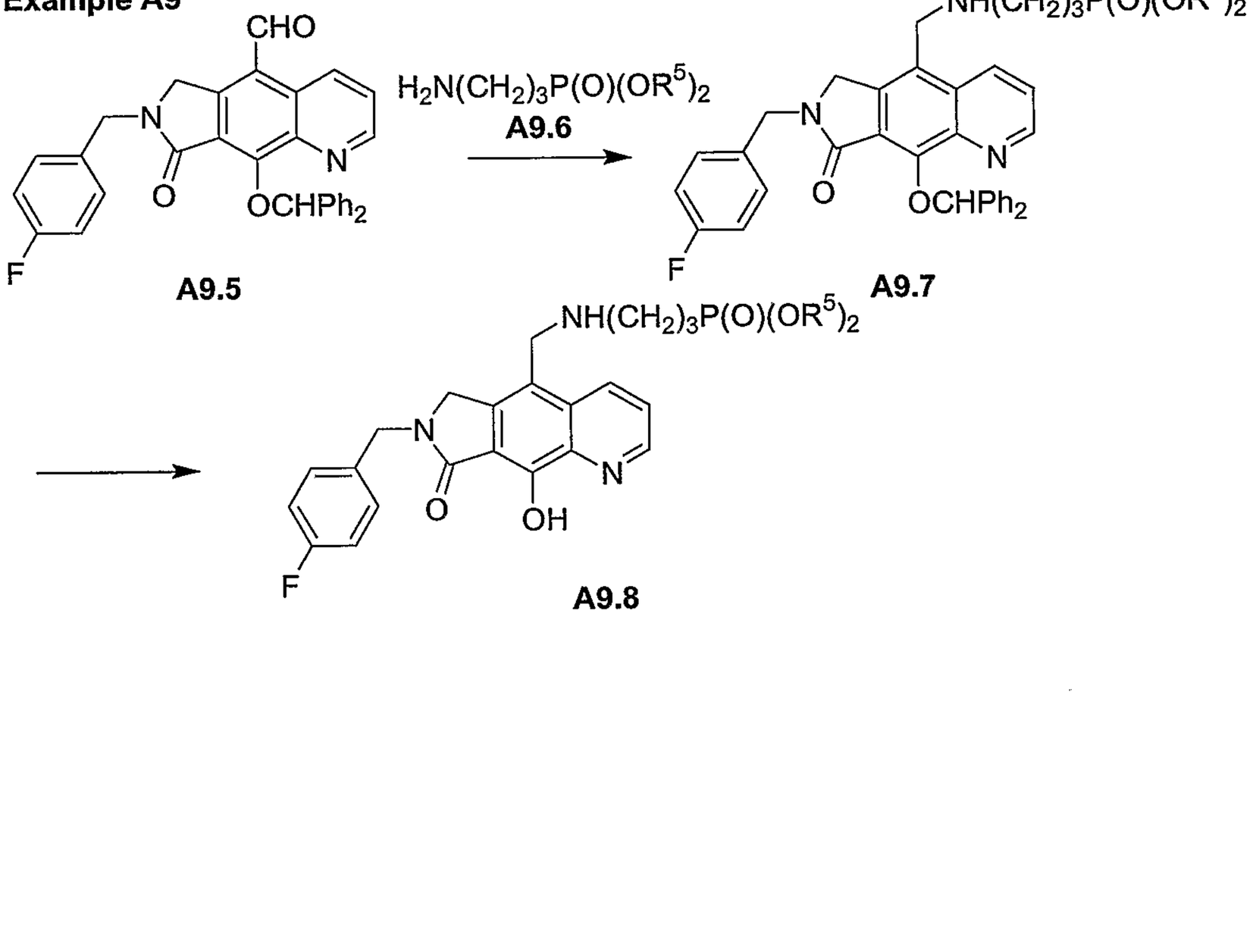
Method



A9.1 **A9.3**

A9.4

Example A9

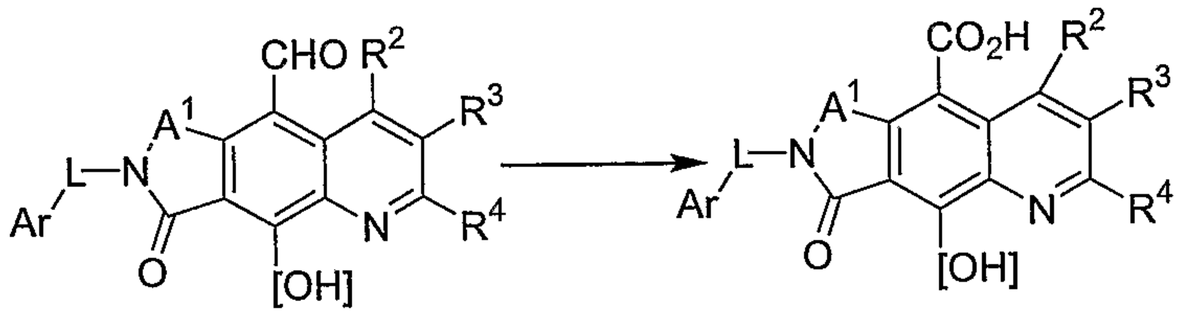


A9.5 **A9.7**

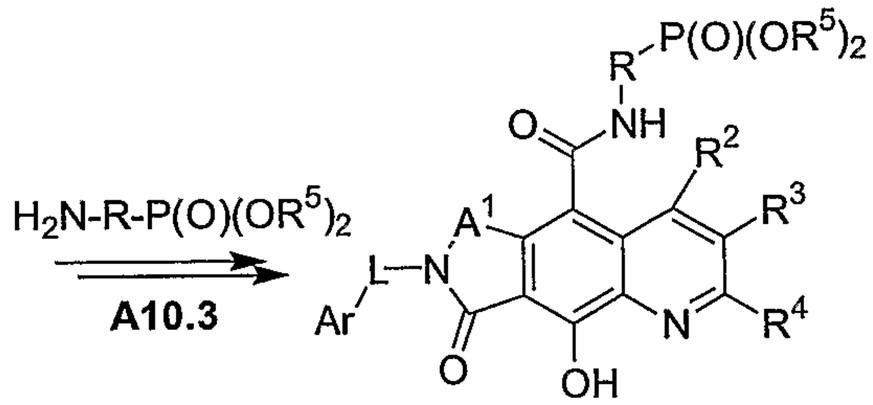
A9.8

Scheme A10. Phosphonates Ibb.

Method

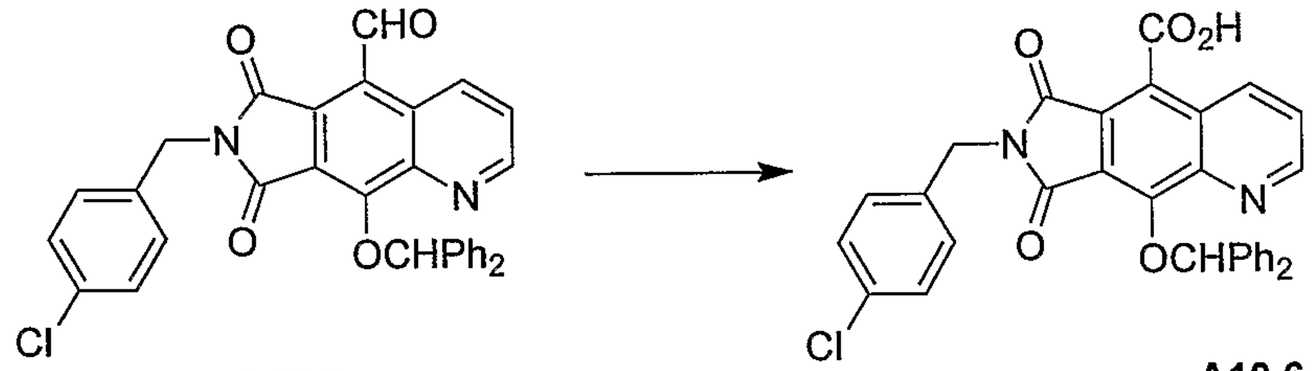


A10.1 **A10.2**

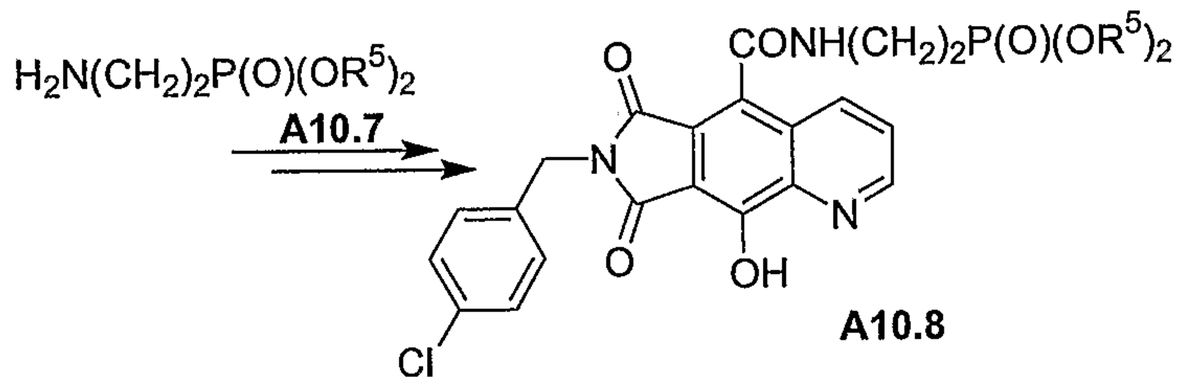


A10.4

Example A10



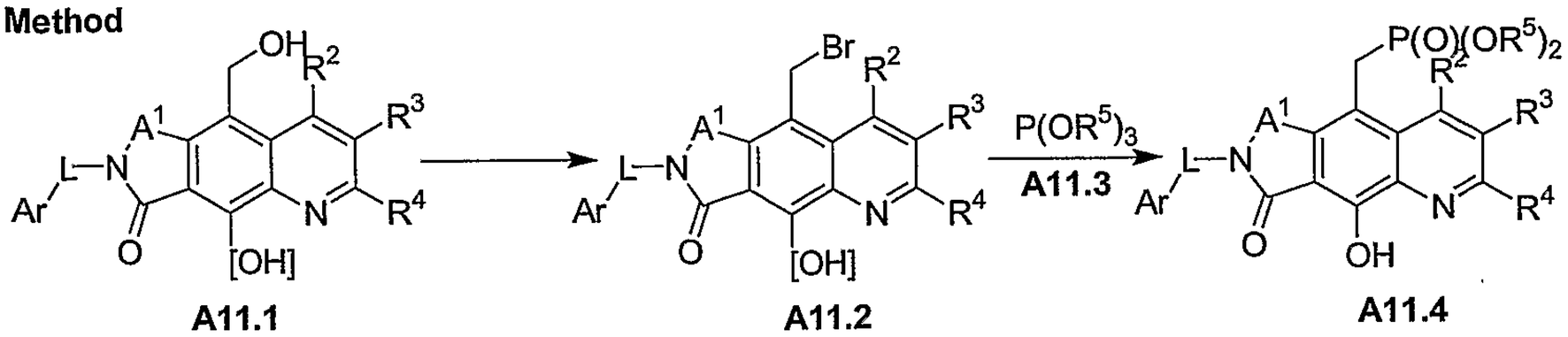
A10.5 **A10.6**



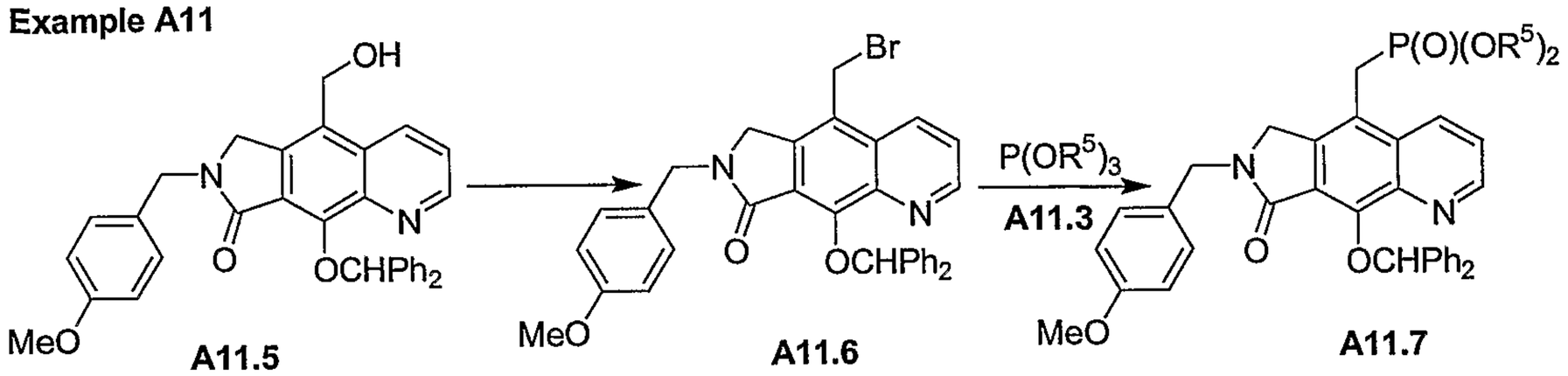
A10.8

Scheme A11. Phosphonates Ibb.

Method

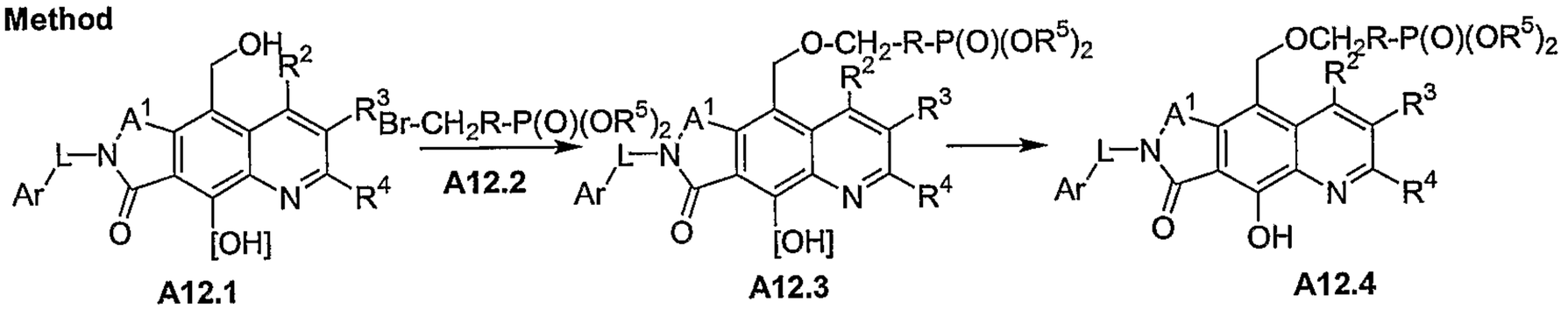


Example A11

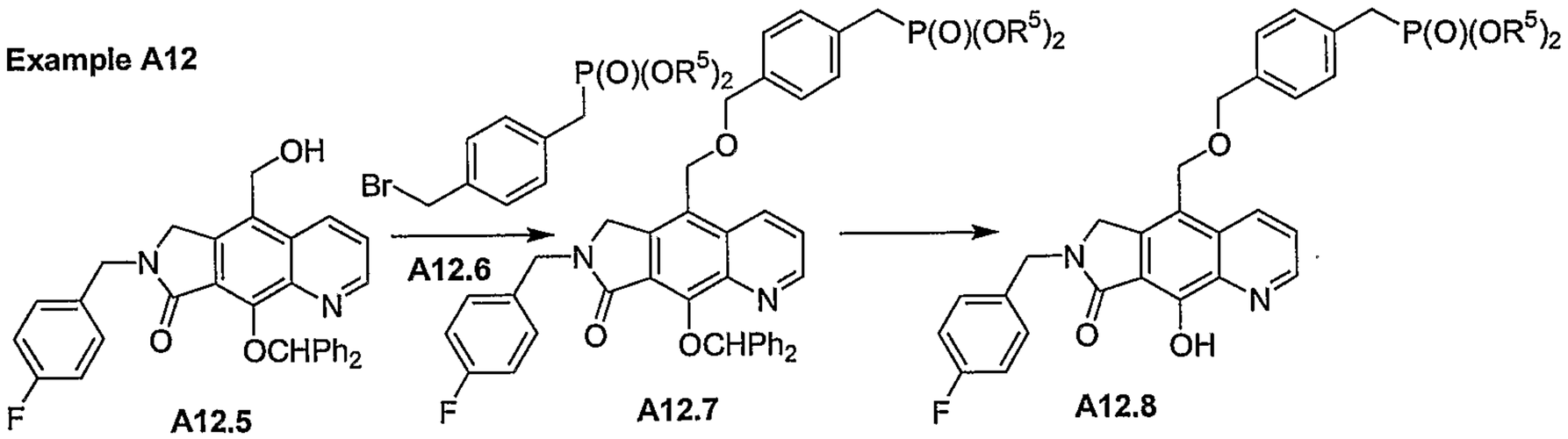


Scheme A12. Phosphonates Ibb.

Method

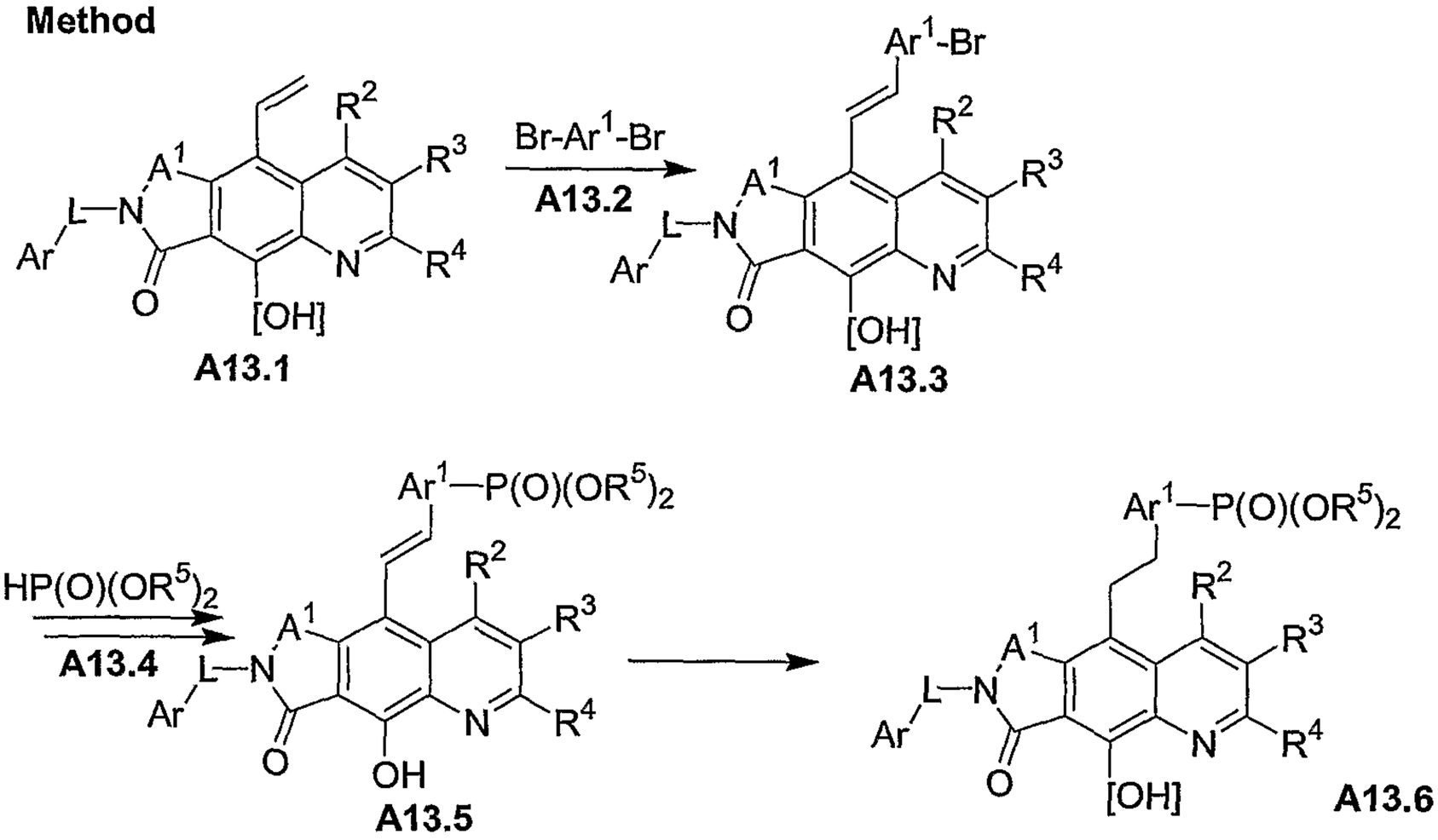


Example A12

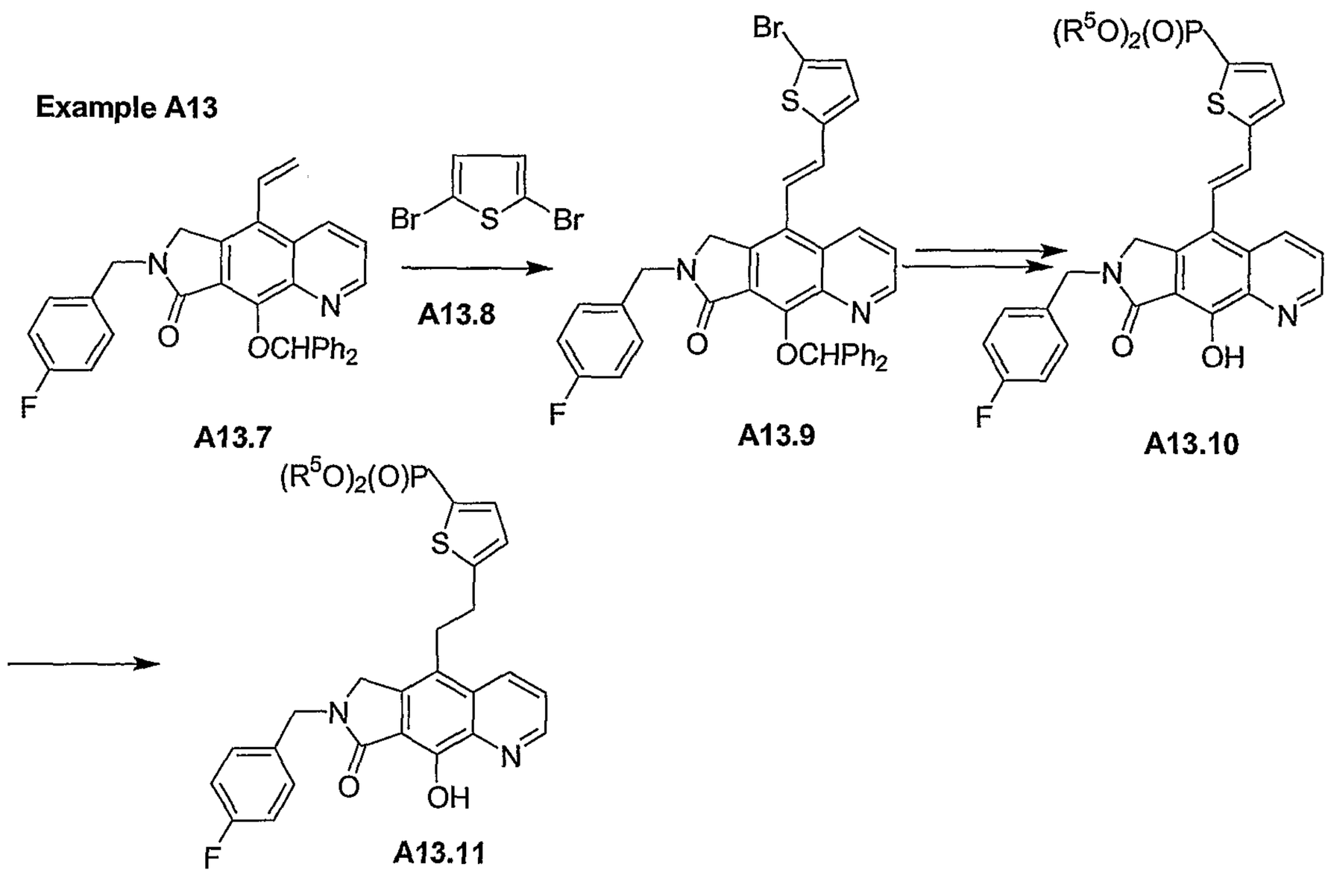


Scheme A13. Phosphonates Ibb.

Method

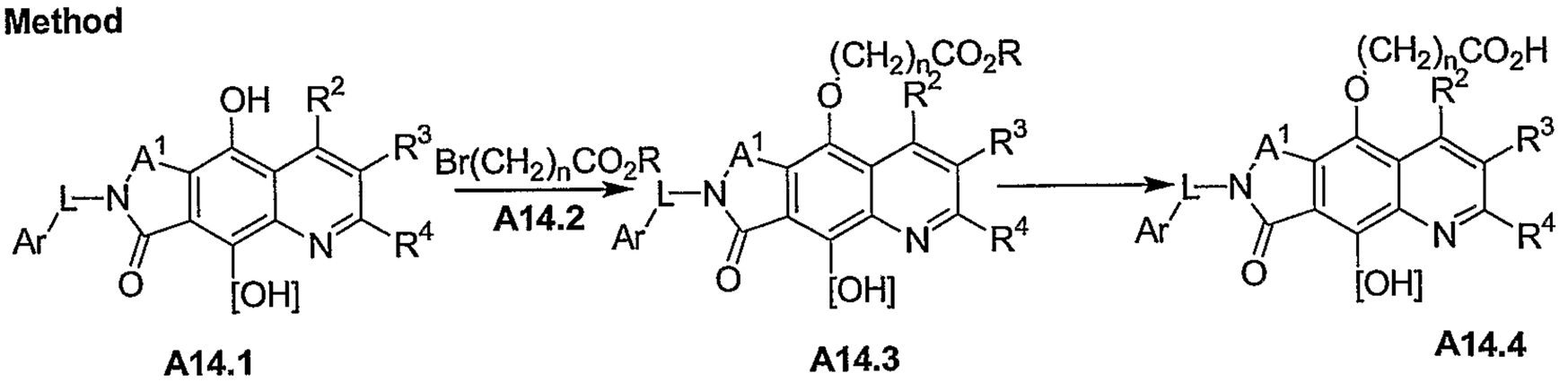


Example A13

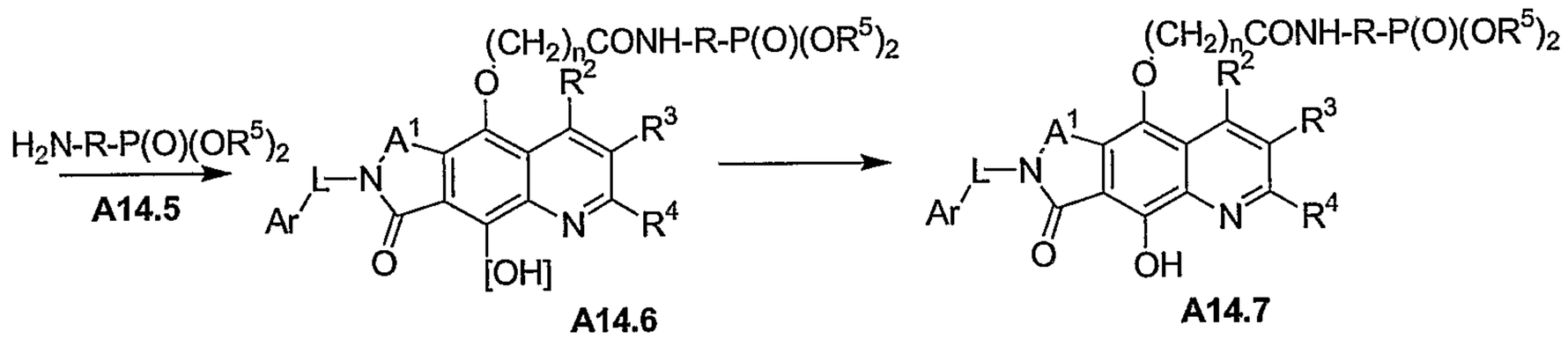


Scheme A14. Phosphonates Ibb.

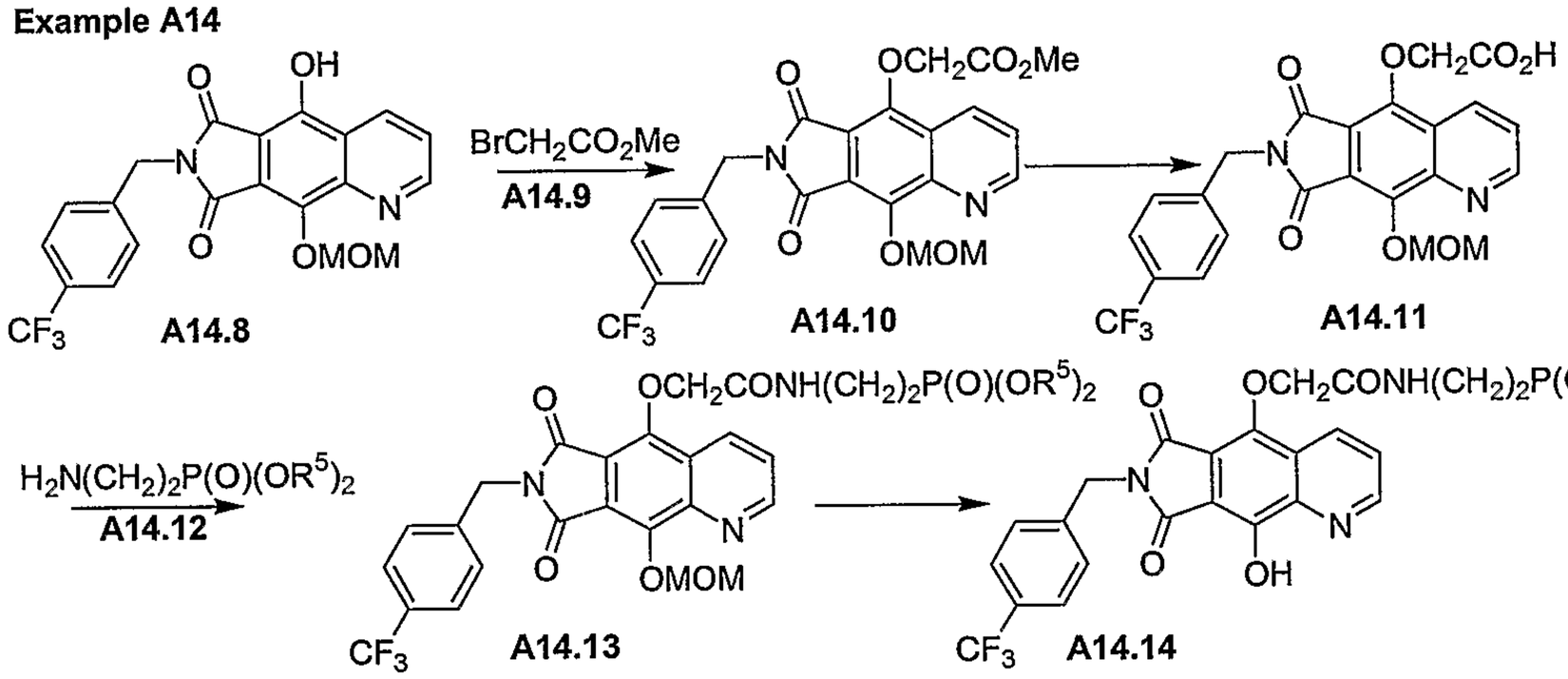
Method



A14.1 A14.3 A14.4

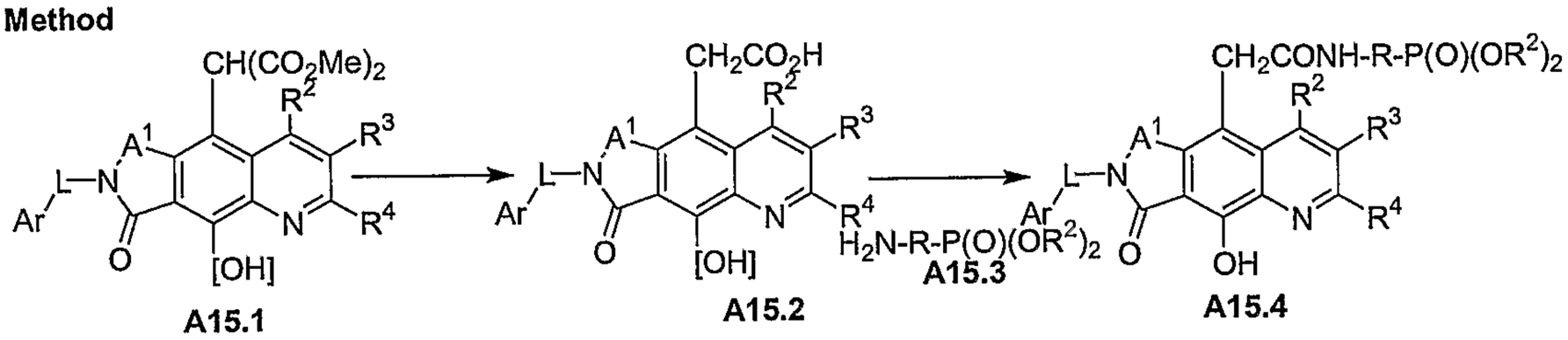


Example A14

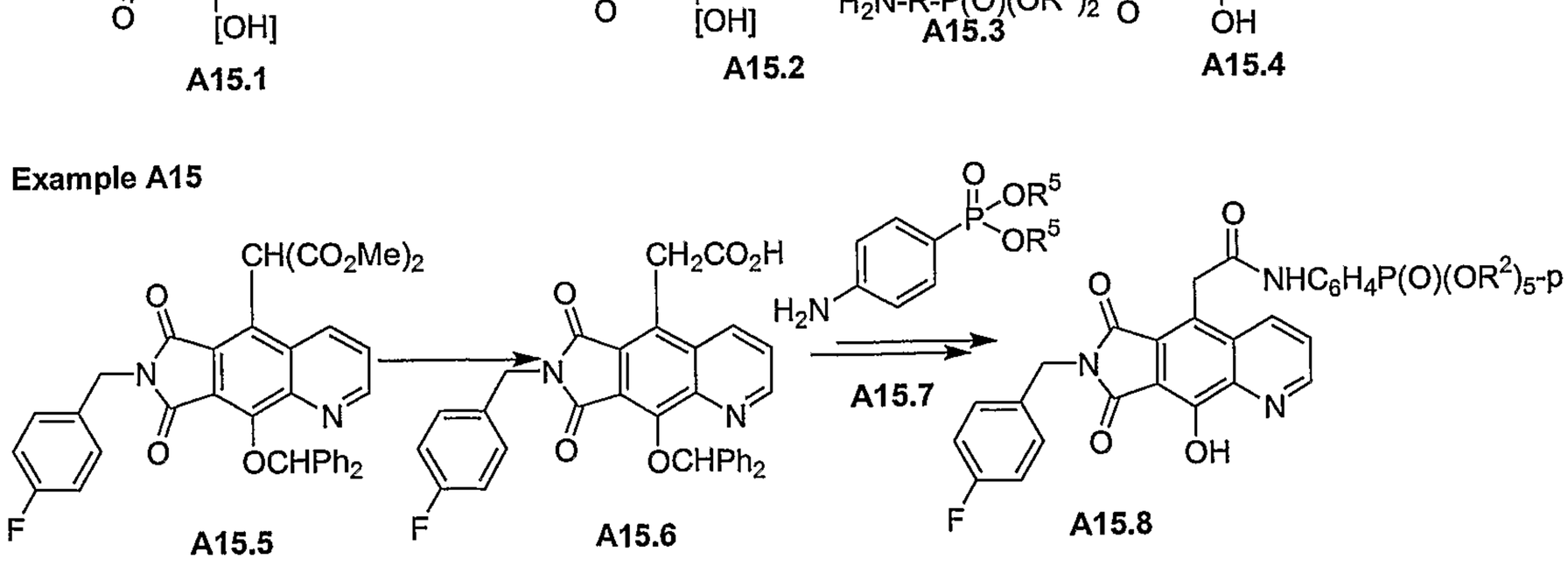


Scheme A15. Phosphonates Ibb.

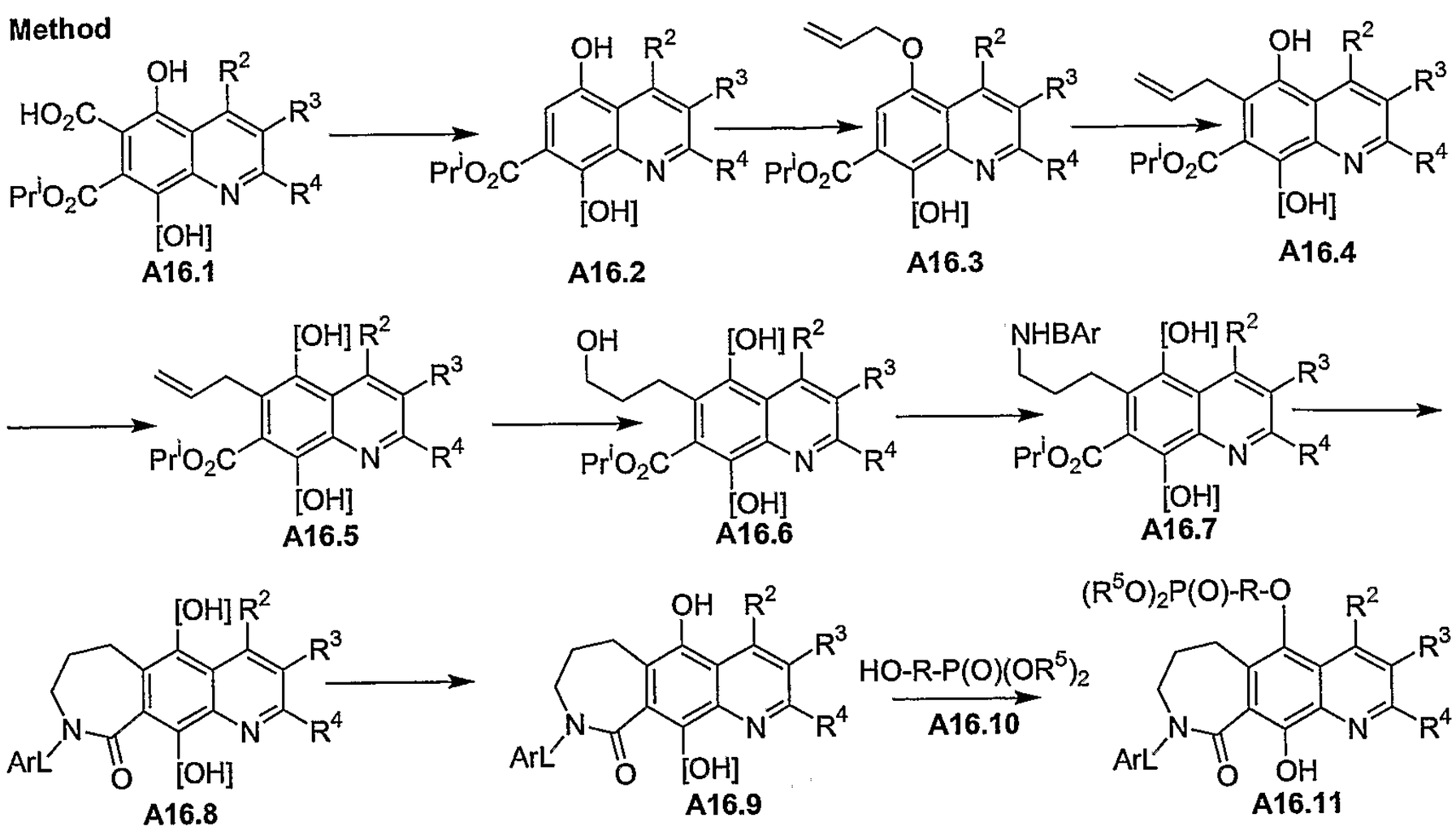
Method



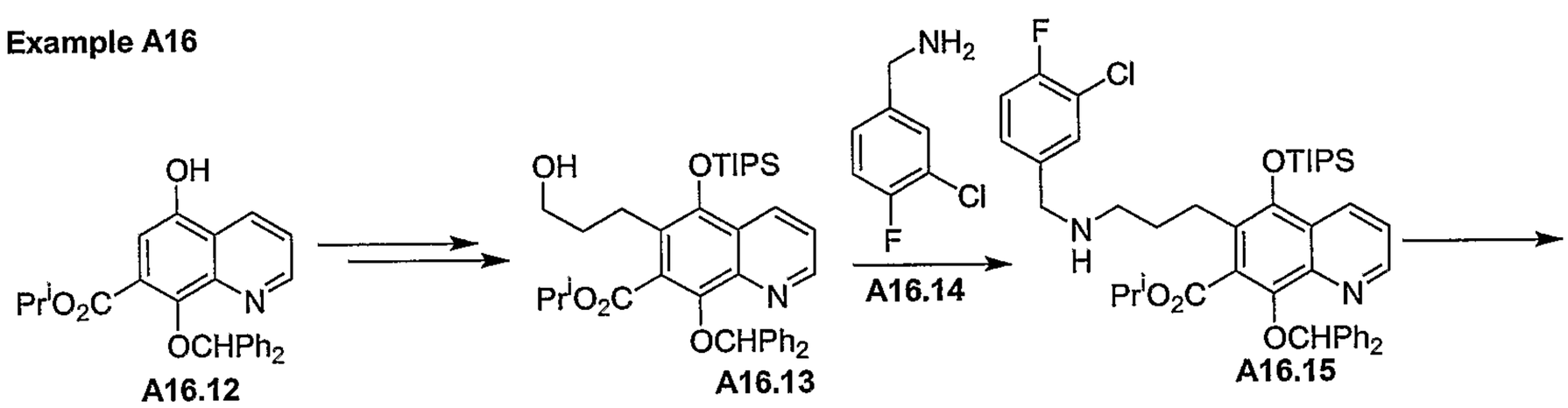
Example A15



Scheme A16. Phosphonates Ibb.



Example A16



Preparation of the intermediate phosphonate esters Icc.

Scheme **A17** illustrates methods for the preparation of phosphonate esters of structure **Icc** in which the phosphonate group is attached by means of a one-carbon link, or by saturated or unsaturated multicarbon chains optionally incorporating a heteroatom. In this procedure, a 4-methyl-substituted quinoline **A17.3** is prepared by means of a Doebner-von Miller condensation between an enone **A17.2** and a substituted aniline **A17.1**. The preparation of quinolines by means of the Doebner-von Miller reaction is described in Heterocyclic Chemistry, by T. L. Gilchrist, Longman,

1992, p. 158. The reaction is performed by heating equimolar amounts of the reactants in an inert solvent such as dimethylacetamide. The bromohydroxyquinoline **A17.3** is then transformed, by means of reaction sequence such as that illustrated in Scheme 8 into the protected tricyclic compound **A17.4**. Benzylic bromination of the latter compound, for example by reaction with N-bromosuccinimide or N-bromoacetamide in an inert solvent such as ethyl acetate at ca. 60°, then yields the bromomethyl derivative **A17.5**. This compound is then reacted in an Arbuzov reaction, as described above (Scheme **A11**), with a trialkyl phosphite to produce after deprotection the phosphonate ester **A17.8**.

Alternatively, the bromomethyl derivative **A17.5** is reacted, using the conditions described in Scheme **A12**, with a dialkyl hydroxy, mercapto or amino-substituted phosphonate **A17.6**, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety, to give after deprotection the ether, thioether or amino product **A17.7**.

Alternatively, the methyl-substituted tricyclic compound **A17.4** is condensed, under basic conditions, with a dialkyl formyl-substituted phosphonate **A17.9**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dioxan or dimethylformamide, in the presence of a strong base such as sodium hydride or lithium tetramethyl piperidide. The procedure affords after deprotection the unsaturated phenol **A17.10**. Reduction of the double bond, as described above (Scheme **A13**) then produces the saturated analog **A17.11**.

For example, benzoic acid 7-cyclopent-3-enylmethyl-4-methyl-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-9-yl ester **A17.12** is reacted with N-bromosuccinimide in refluxing ethyl acetate to afford benzoic acid 4-bromomethyl-7-cyclopent-3-enylmethyl-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-9-yl ester **A17.13**. This compound is heated to 120° with an excess of a trialkyl phosphite to give after deprotection the phenolic phosphonate ester **A17.14**.

As a further example, 4-bromomethyl-7-(4-fluoro-benzyl)-9-triisopropylsilanyloxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **A17.15**, prepared by bromination of the corresponding methyl compound is reacted with a dialkyl 2-mercaptoethyl phosphonate **A17.16** (Zh. Obschei. Khim., 1973, 43, 2793) and cesium

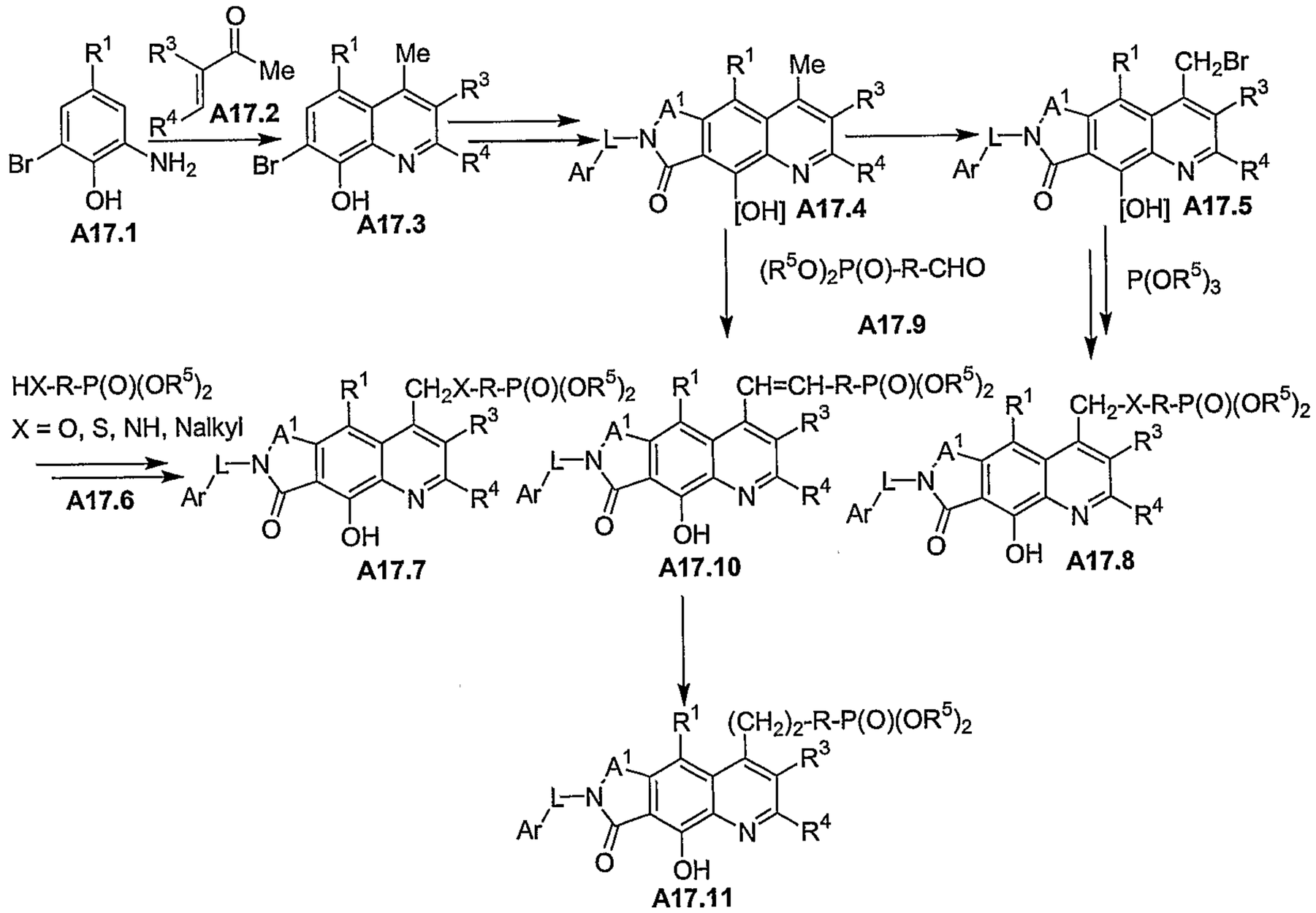
carbonate in acetonitrile, to give the thioether product **A17.17**. Deprotection yields the corresponding phenol **A17.18**.

As a further example, 7-(3-chloro-4-fluoro-benzyl)-9-methoxymethoxy-4-methyl-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **A17.19** is condensed in dioxan solution with a dialkyl formylmethyl phosphonate **A17.20** (Aurora) in the presence of lithium tetramethylpiperidide to form the unsaturated product **A17.21**. Deprotection then yields the phenol **A17.22**; reduction of the double bond then gives the saturated analog **A17.23**.

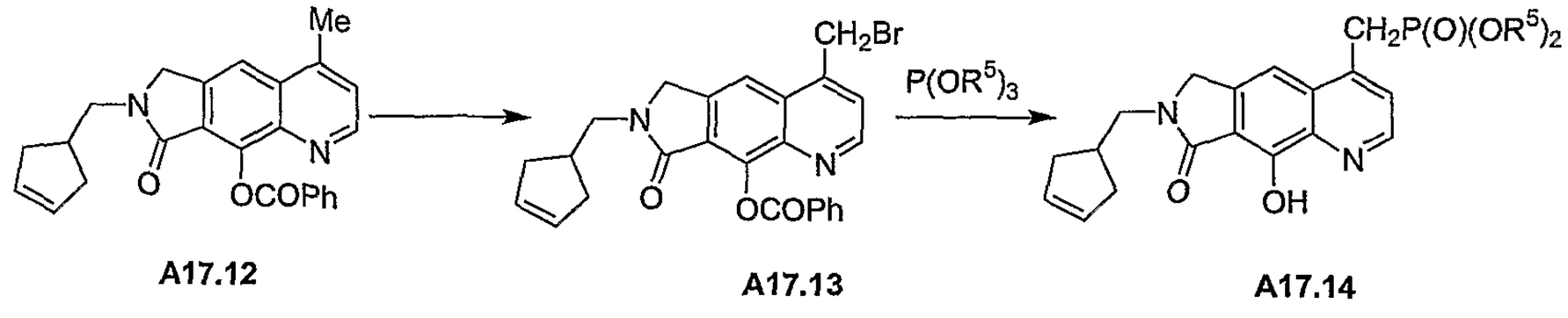
Using the above procedures, but employing, in place of the starting materials **A17.12**, **A17.15** and **A17.19**, different starting materials **A17.4** or **A17.5**, and/or different alcohols, thiols or amines **A17.6** or aldehydes **A17.9**, the corresponding products **A17.7**, **A17.8**, **A17.10** and **A17.11** are obtained.

Scheme A17. Phosphonates Icc.

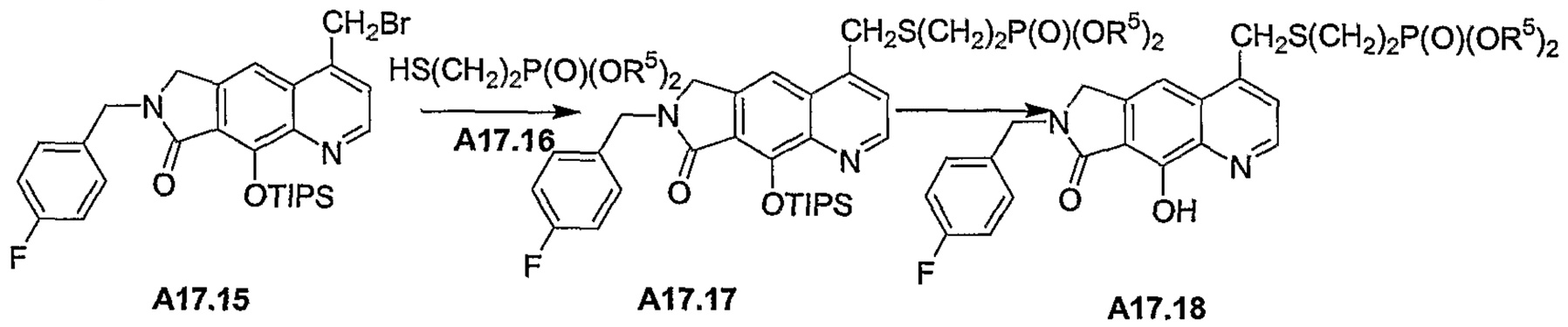
Method



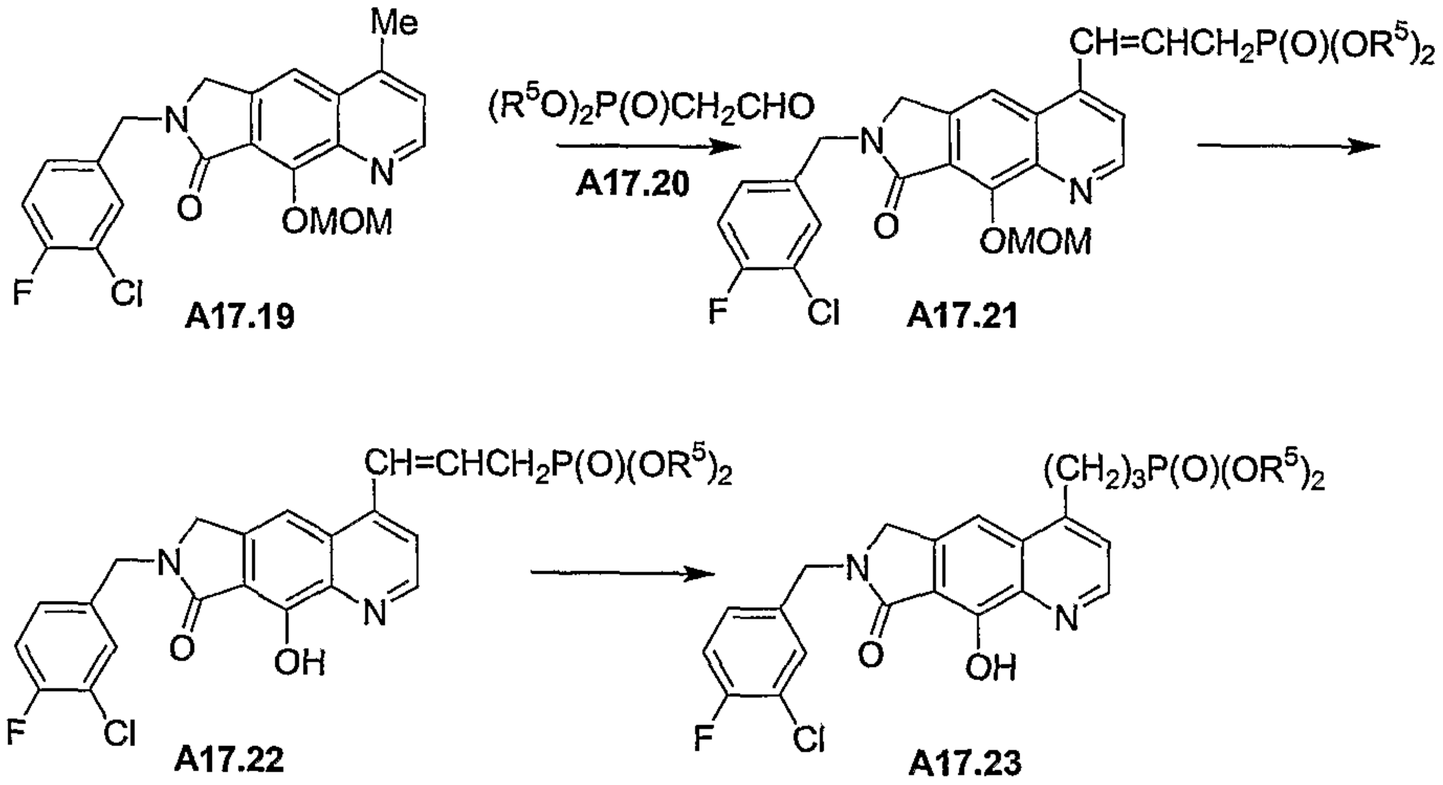
Example A17-1



Example A17-2



Example A17-3



Preparation of the intermediate phosphonate esters IIaa.

Schemes **A18** and **A19** illustrate the preparation of phosphonate esters of structure **IIaa**. Scheme **A18** depicts the preparation of phosphonate esters of structure **IIaa** in which the phosphonate group is attached by means of an alkoxy, alkylthio or alkylamino group. In this procedure, an alkoxyethene triester **A18.1** (JP 61289089) and a 3-aminopyridine **A18.2** are reacted together, as described in JP 61289089 and GB 1509695, to produce the pyridylamino triester **A18.3**. The reaction is performed using equimolar amounts of the reactants at a temperature of about 150°. The product is then cyclized to afford the 1,5-naphthyridine derivative **A18.4**. The reaction is performed in a high-boiling solvent such as diphenyl ether at a temperature of about 250°. The diester is then converted to the anhydride, and the latter compound is transformed by reaction with the amine $ArBNH_2$, and protection of the phenolic

hydroxyl group, into the cyclic imide **A18.5**. This material is then reduced, as described in Example 20, for example by the use of sodium borohydride, to afford the hydroxylactam **A18.6**. The latter compound is then reacted, in the presence of an acid catalyst, as described in Scheme **A4**, with a dialkyl hydroxy, mercapto or amino-substituted phosphonate **A18.7**, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety, to yield after deprotection of the phenolic hydroxy group, the ether, thioether or amino product **A18.8**.

For example, the triester **A18.1** is reacted with 3-aminopyridine **A18.9** to afford the pyridylamino triester **A18.10**. The product is heated in diphenyl ether at 250° to form the 1,5-naphthyridine **A18.11**. The latter compound is then transformed, as described above, into 7-(4-fluoro-benzyl)-6-hydroxy-9-triisopropylsilanyloxy-6,7-dihydro-pyrrolo[3,4-b][1,5]naphthyridin-8-one **A18.12**. The hydroxylactam is then reacted in dichloromethane solution with a dialkyl 4-hydroxybutyl phosphonate **A18.13** (J. Med. Chem., 1996, 39, 949) and trifluoroacetic acid, by a similar reaction as Example 23, to generate the phosphonate product **A18.14**.

Using the above procedures, but employing, in place of the pyridine **A18.9**, different pyridines **A18.2**, and/or different phosphonates **A18.7**, the corresponding products **A18.8** are obtained.

Scheme **A19** depicts the preparation of phosphonate esters of structure **IIaa** in which the phosphonate group is attached by means of variable carbon linkage, and the nucleus is a 1,3,5,9-tetraazaanthracene. In this procedure, the 1,5-naphthyridine **A18.4** is converted into the phenol-protected analog **A19.1**. The product is then subjected to a selective partial hydrolysis, for example by reaction with one molar equivalent of a base such as lithium hydroxide in an aqueous organic solvent mixture, to produce the carboxy ester **A19.2**. The product is then subjected to a Curtius rearrangement, as described in Scheme **A3**, to afford the amine **A19.3**. The product is then reductively aminated, as described in Scheme **A3**, by reaction with a dialkyl formyl-substituted phosphonate **A19.4**, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety, to give the amine **A19.5**. The ester group is then transformed, as described previously (Scheme **A3**), into the amide **A19.6**, by reaction with the amine $ArBNH_2$. The product is then cyclized to

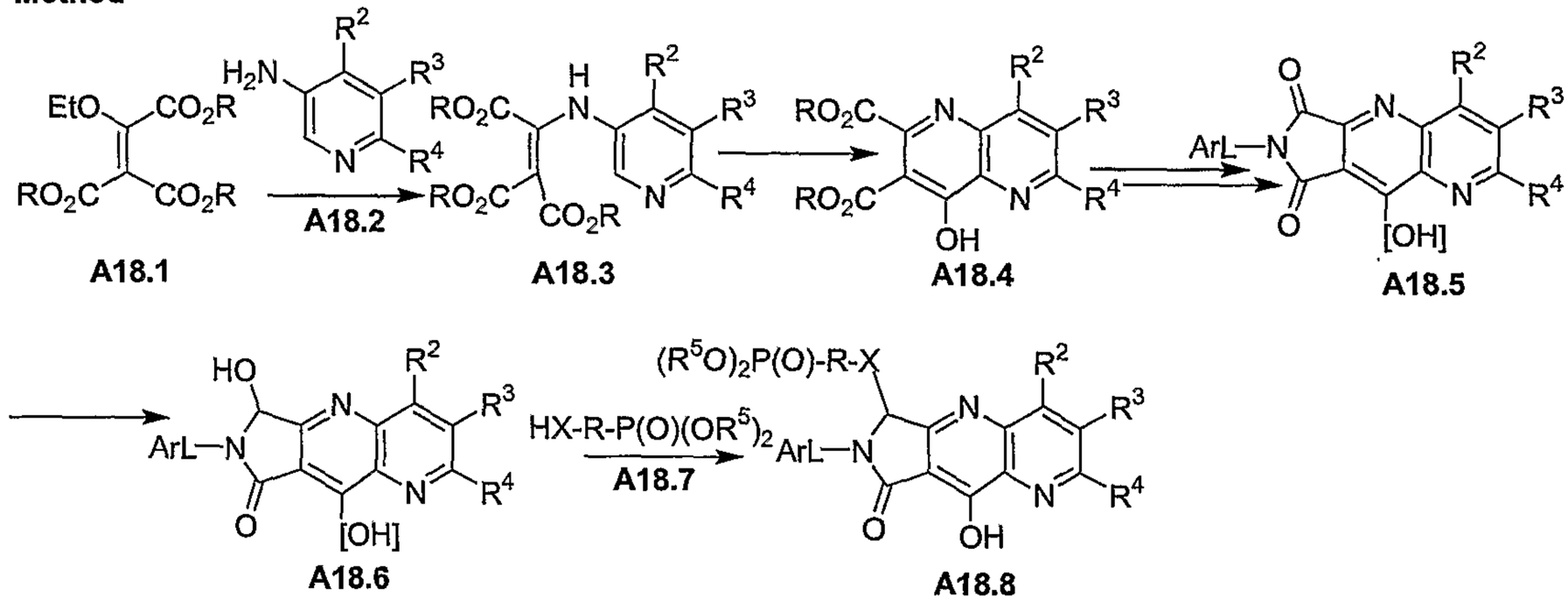
afford, after deprotection of the phenolic hydroxyl, the tricyclic product, **A19.7**, in which A is, for example, CO or CH_2, by reaction respectively with phosgene or an equivalent thereof, or with diiodomethane or a similar reagent.

For example, 2-amino-4-hydroxy-[1,5]naphthyridine-3-carboxylic acid methyl ester **A19.8**, prepared as described in Scheme **A18** by the reaction between 3-aminopyridine and 1,2,2-tris-(carbomethoxy)-1-ethoxyethene, is converted, as described above, into 2-amino-4-benzyloxy-[1,5]naphthyridine-3-carboxylic acid methyl ester **A19.9**. The amine is then reacted in isopropanol solution with a dialkyl 3-formylphenyl phosphonate **A19.10** (J. Med. Chem., 1984, 27, 654) and sodium triacetoxyborohydride, to yield the amine **A19.11**. The ester group of the latter compound is then transformed into the amide by reaction with 3,5-dichlorophenethylamine-trimethyl aluminum, as described previously, to afford the amide **A19.12**. The product is then reacted with triphosgene in pyridine solution at 80° to give the cyclized product **A19.13**. Deprotection then yields the phenol **A19.14**.

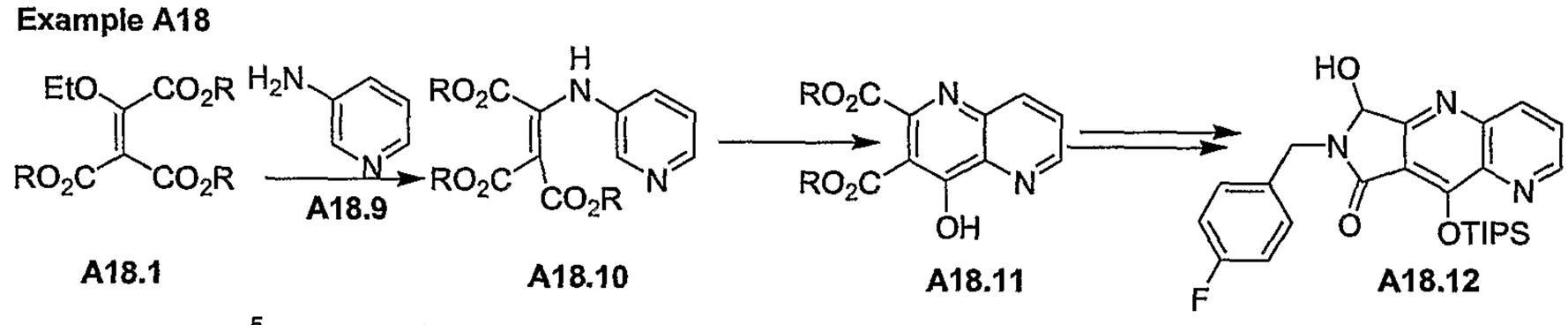
Using the above procedures, but employing, in place of the amine **A19.9**, different amines **A19.3**, and/or different formyl phosphonates **A19.4**, the corresponding products **A19.7** are obtained.

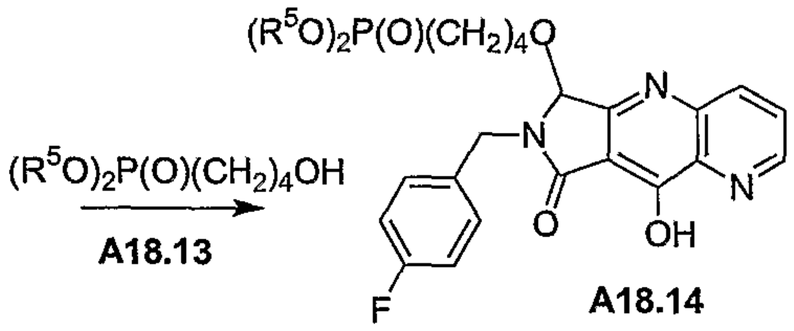
Scheme A18. Phosphonates IIaa.

Method

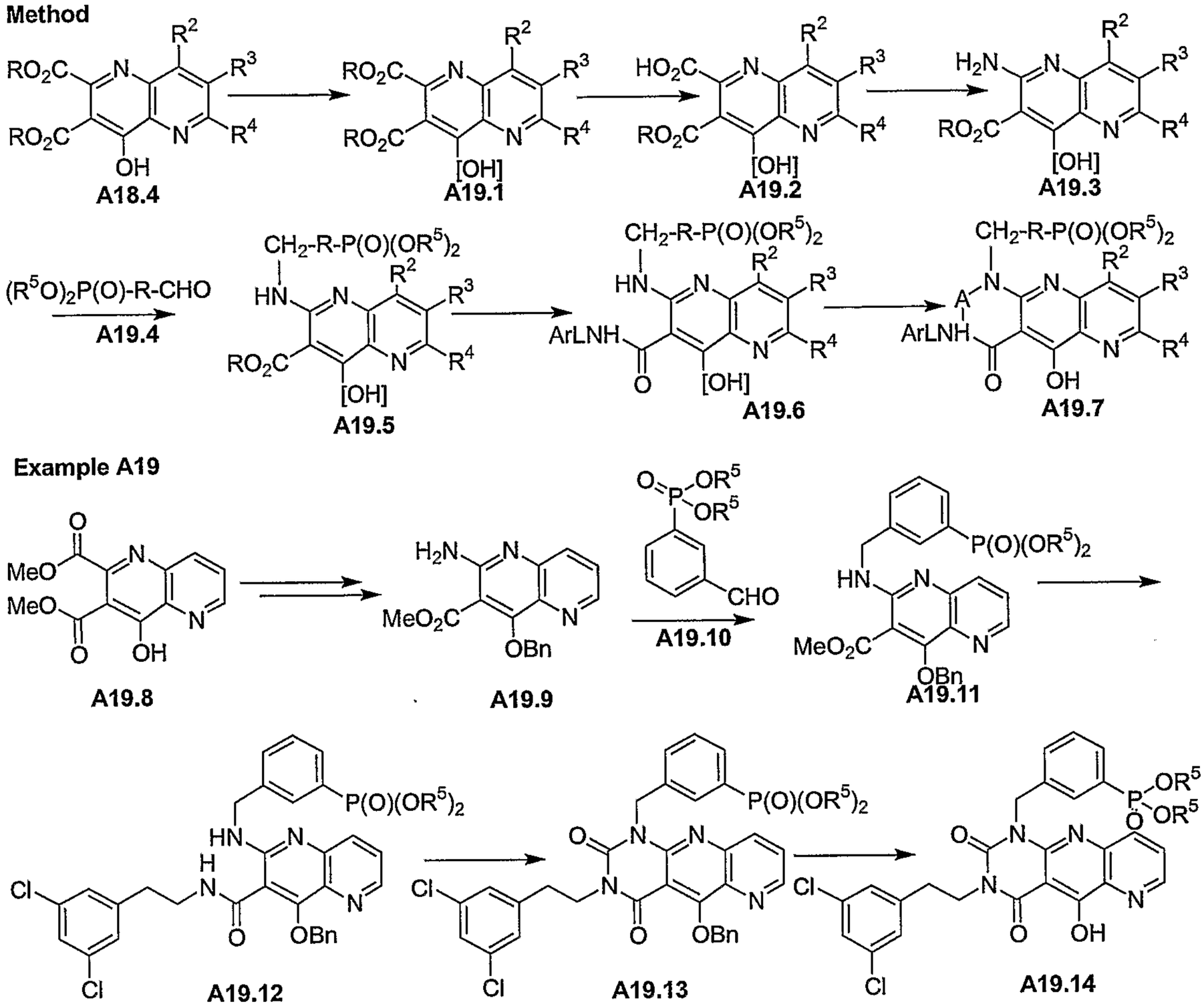


Example A18





Scheme A19. Phosphonates IIaa.



Preparation of the intermediate phosphonate esters IIcc.

Scheme **A20** illustrates the preparation of phosphonate esters of structure **IIcc**, in which the phosphonate group is attached by means of a one-carbon or multicarbon link, or by means of a heteroatom and a variable carbon linkage. In this procedure, the triester **A18.1** is reacted, as described in Scheme **A18**, with a 3-amino-4-methylpyridine **A20.1** to give the substituted pyridine product **A20.2**. The latter compound is then transformed, as described previously, into the methyl-substituted tricyclic compound **A20.3**. This compound is then subjected to benzylic bromination, for example by reaction with N-bromosuccinimide, to form the bromomethyl product **A20.4**. This compound is subjected to an Arbuzov reaction with a trialkyl phosphite, as described in Scheme **A11**, to afford after deprotection the phosphonate **A20.5**.

Alternatively, the bromomethyl compound **A20.4** is reacted with a dialkyl phosphonate **A20.6** in which X is O, S, NH or N-alkyl, and R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety, using the

procedures described in Scheme **A17**, to give, after deprotection of the phenolic hydroxyl, the ether, thioether or amine products **A20.7**.

Alternatively, the methyl compound **A20.3** is subjected, as described in Scheme **A17**, to a base-catalyzed condensation reaction with a dialkyl formyl-substituted phosphonate **A20.8**, in which R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety, to generate after deprotection of the phenolic hydroxyl, the unsaturated product **A20.9**. The double bond is then reduced, as described in Scheme **A17**, to afford the saturated analog **A20.10**.

For example, condensation between the triester **A18.1** and 3-amino-4-methylpyridine **A20.11** gives the pyridine product **A20.12**. The compound is then transformed, as described above, into 7-[1-(4-fluoro-phenyl)-1-methyl-ethyl]-4-methyl-9-triisopropylsilanyloxy-pyrrolo[3,4-b][1,5]naphthyridine-6,8-dione **A20.13**. The latter compound is then reacted with a dialkyl formylethyl phosphonate **A20.14** (Zh. Obschei. Khim., 1987, 57, 2793) and lithium tetramethylpiperidide in tetrahydrofuran to afford after deprotection the unsaturated product **A20.15**. The product is then reduced with diimide, as described above, (Scheme **A13**) to yield the saturated analog **A20.16**.

As a further example, 7-[1-(4-fluoro-phenyl)-cyclopropyl]-4-methyl-9-triisopropylsilanyloxy-pyrrolo[3,4-b][1,5]naphthyridine-6,8-dione **A20.17**, prepared according to the procedures described above, is reacted with N-bromosuccinimide in refluxing ethyl acetate to give 4-bromomethyl-7-[1-(4-fluoro-phenyl)-cyclopropyl]-9-triisopropylsilanyloxy-pyrrolo[3,4-b][1,5]naphthyridine-6,8-dione **A20.18**. The product is then heated at 120° with excess of a trialkyl phosphite to give after deprotection the phosphonate **A20.19**.

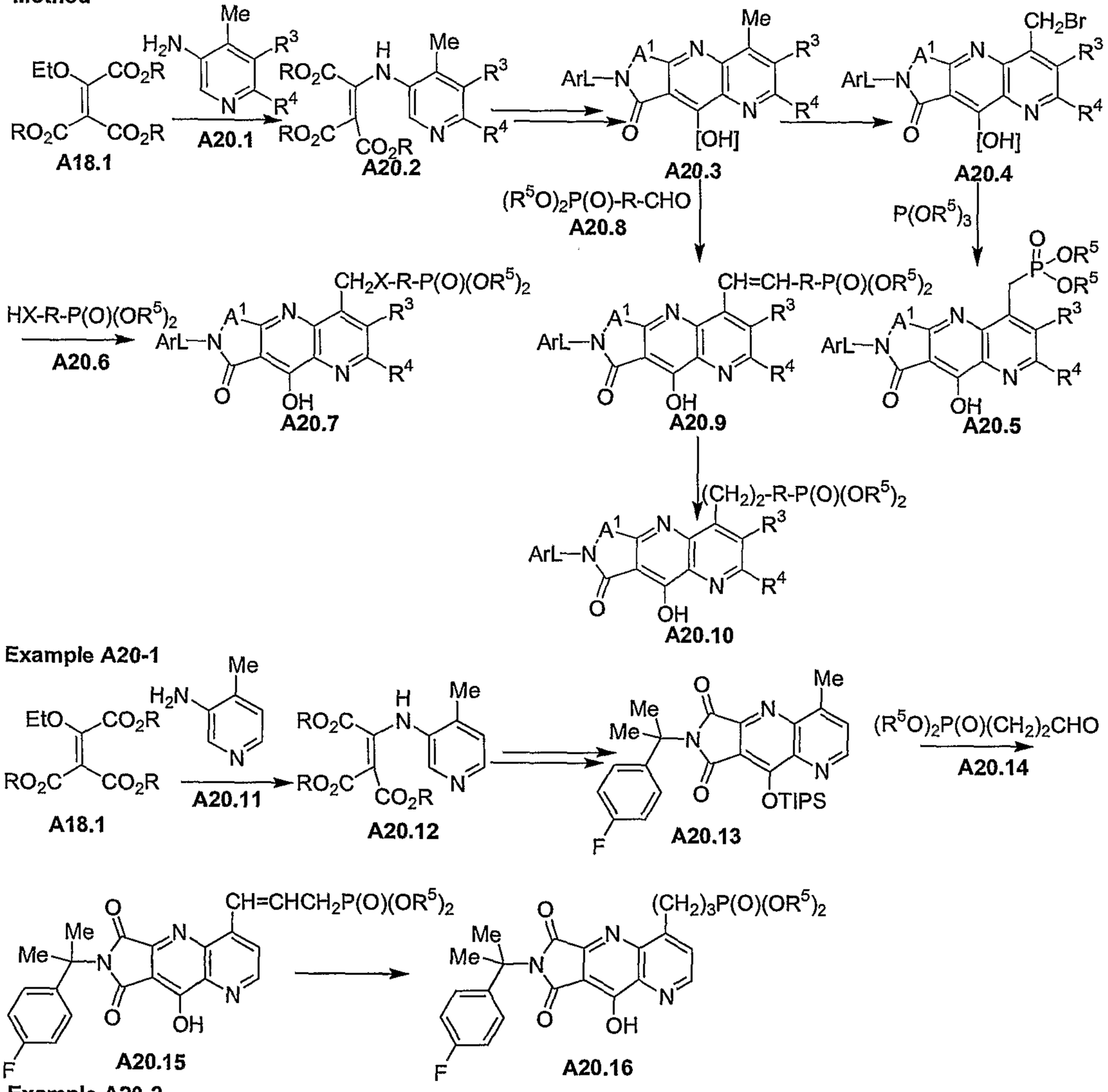
As a further example, 4-bromomethyl-7-(3-chloro-4-fluoro-benzyl)-9-triisopropylsilanyloxy-pyrrolo[3,4-b][1,5]naphthyridine-6,8-dione **A20.20**, prepared according to the procedures described above, is reacted in dimethylformamide solution with a dialkyl methylaminomethyl phosphonate **A20.21**(AsInEx) and potassium carbonate, to afford after deprotection the displacement product **A20.22**.

Using the above procedures, but employing, in place of the starting materials **A20.13**, **A20.17** and **A20.20**, different starting materials **A20.3** or **A20.4**, and/or

different alcohols, thiols or amines **A20.6** or aldehydes **A20.8**, the corresponding products **A20.5**, **A20.7**, **A20.9** and **A20.10** are obtained.

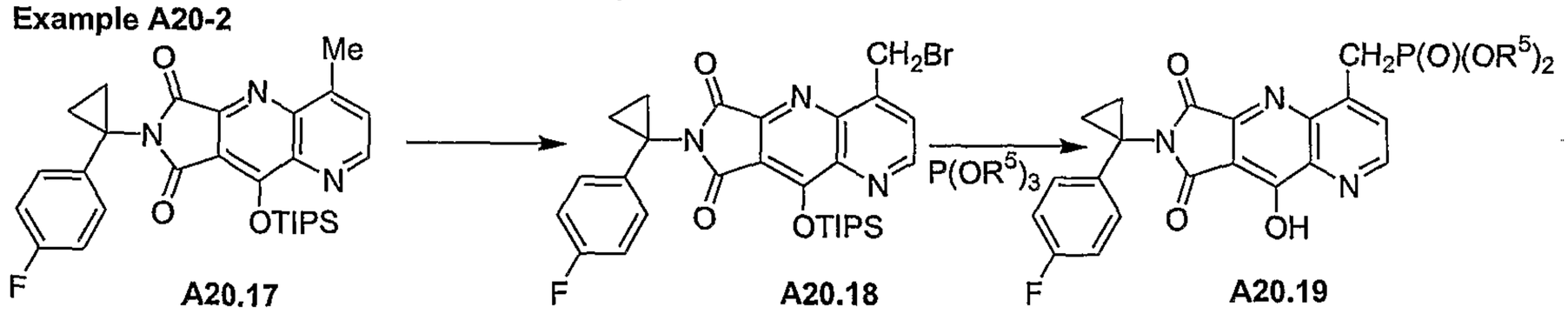
Scheme A20. Phosphonates IIcc.

Method

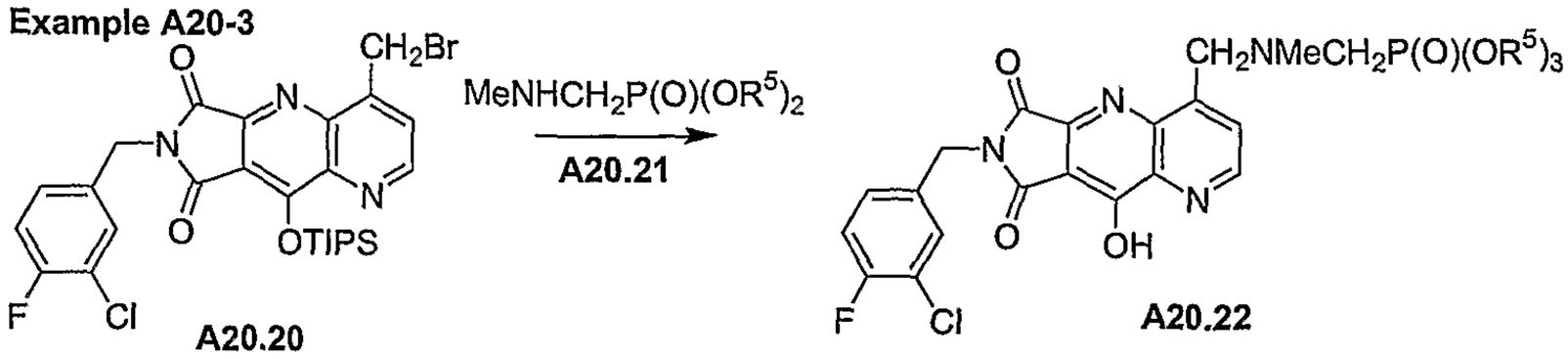


Example A20-1

Example A20-2



Example A20-3



Preparation of the intermediate phosphonate esters IIIaa.

Scheme **A21** illustrates methods for the preparation of phosphonates of structure **IIIaa** in which the phosphonate group is attached by means of a heteroatom and a variable carbon link. In this sequence, a carbomethoxymethyl derivative of the amine $ArBNH_2$, **A21.1** is coupled with the 1,6-naphthyridine carboxylic acid **A21.2**, prepared as described in WO 0230930, using the methods described previously, to prepare the amide **A21.3**. Bromination, for example using N-bromosuccinimide, yields the 5-bromo derivative **A21.4**. Protection of the phenolic hydroxyl group, followed by displacement of the bromine with a hydrazine or hydroxylamine nucleophile, as described for example in Example 69, affords the 5-imino derivative **A21.5** in which X is NH_2 or OH. Lactam formation, for example by the use of potassium tert. butoxide in refluxing xylene, or by the use of trimethylaluminum, then gives the tricyclic product **A21.6**, which upon protection of the X substituent gives the product **A21.7**. Reduction of this material, for example by treatment with sodium borohydride, for example as in Example 20, then gives the aminol **A21.8**. The latter compound is reacted with a dialkyl hydroxy, mercapto, or amino-substituted phosphonate **A21.9**, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety, in the presence of an acid such as trifluoroacetic acid, as described in Scheme **A4**, to yield the ether, thioether or amine product **A21.10**. Deprotection then gives the phenol **A21.11**.

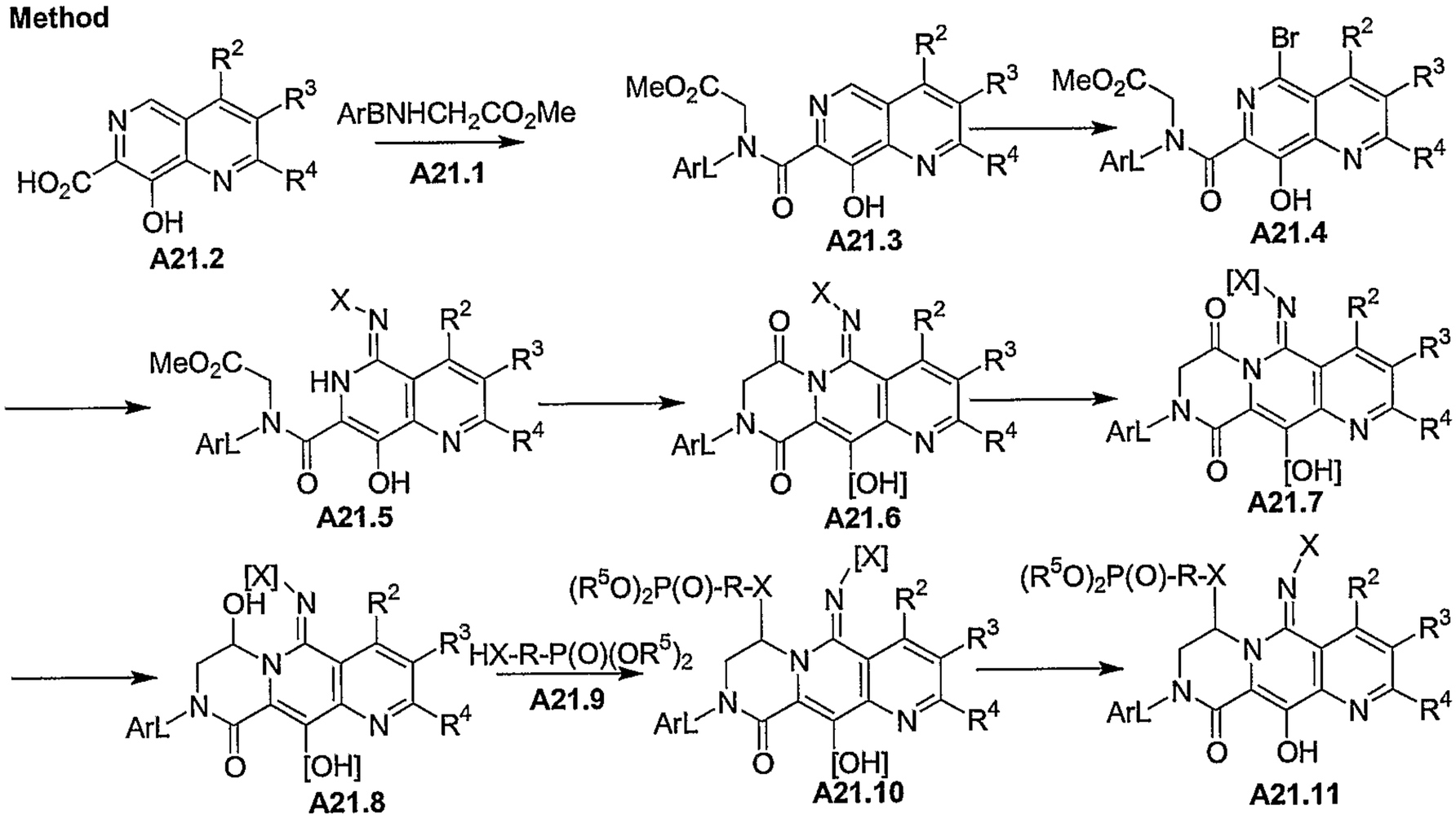
For example, (4-fluoro-benzylamino)-acetic acid methyl ester **A21.12** is coupled in tetrahydrofuran solution with one molar equivalent of 8-hydroxy-[1,6]naphthyridine-7-carboxylic acid **A21.13**, (WO 0230930) in the presence of diisopropyl carbodiimide, to form [(4-fluoro-benzyl)-(8-hydroxy-[1,6]naphthyridine-7-carbonyl)-amino]-acetic acid methyl ester **A21.14**. The latter compound is then transformed, by bromination, displacement and cyclization, as described above into the tricyclic product, 9-benzyloxy-7-(4-fluoro-benzyl)-10-hydrazono-6,7-dihydro-10H-1,7,10a-triaza-anthracene-5,8-dione **A21.15**. The hydrazono compound is then converted into the N, N-dibenzyl derivative **A21.16**. The conversion of amines into dibenzylamines, for example by treatment with benzyl bromide in a polar solvent such as acetonitrile or aqueous ethanol, in the presence of a base such as triethylamine or sodium carbonate, is described in Protective Groups in Organic Synthesis, by T.W.

Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 364. The tribenzylated compound is then reduced with a limited amount of sodium borohydride in isopropanol to afford the aminal **A21.17**. This compound is reacted with a dialkyl 2-mercaptoethyl phosphonate **A21.18** (Zh. Obschei. Khim., 1973, 43, 2364), and trifluoroacetic acid in dichloromethane, to give the thioether **A21.19**. Debenzylation, for example by the use of 5% palladium on carbon in the presence of ammonium formate, as described in Tet. Lett., 28, 515, 1987, then affords the hydrazono phenol **A21.20**.

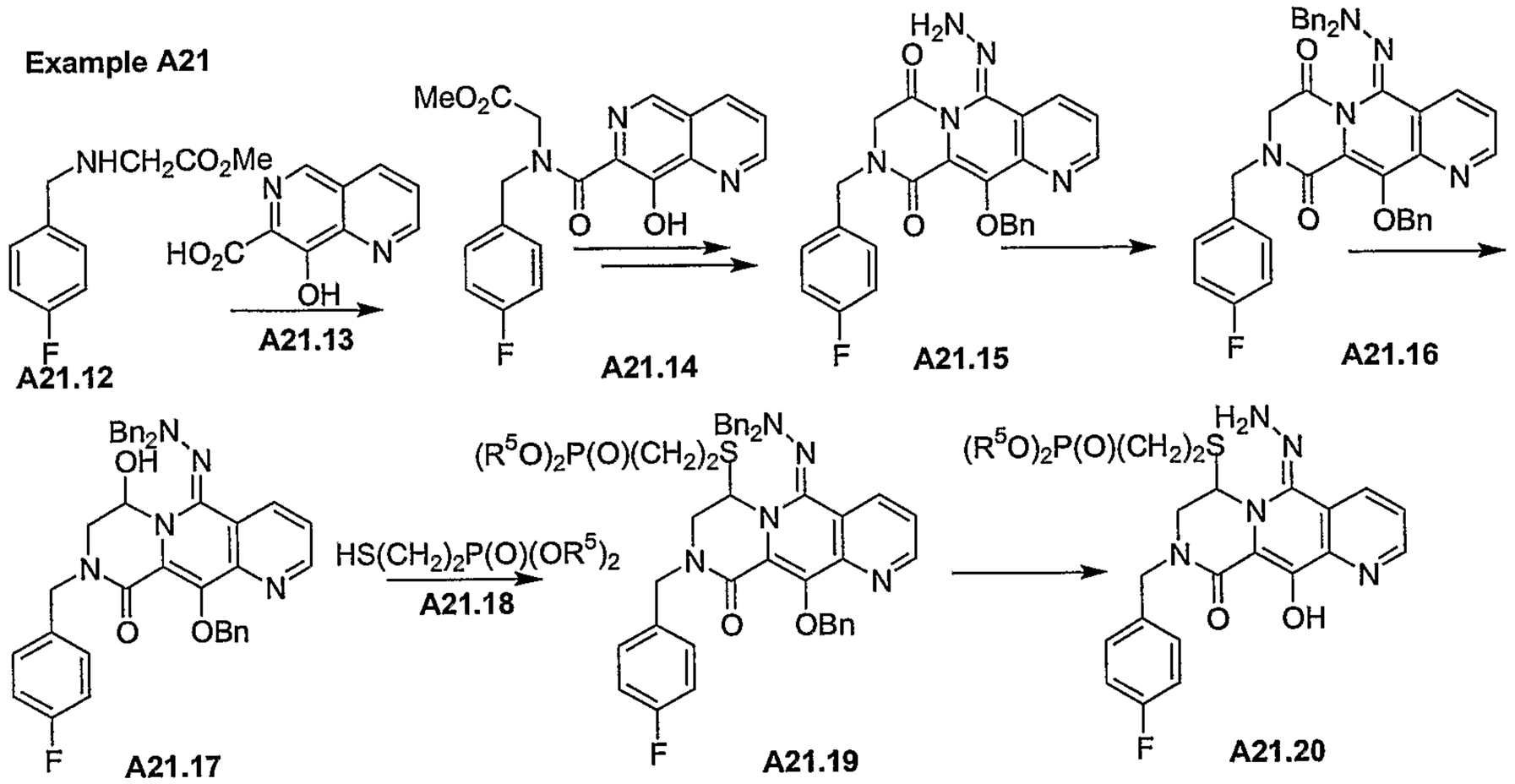
Using the above procedures, but employing, in place of the amide **A21.14**, different amides **A21.3**, and/or different phosphonates **A21.9**, the corresponding products **A21.11** are obtained.

Scheme A21. Phosphonates IIIaa.

Method



Example A21



Preparation of the intermediate phosphonate esters IIIbb.

Schemes **A22** - **A24** illustrate methods for the preparation of phosphonate esters of structure **IIIbb**.

Scheme **A22** illustrates methods for the preparation of phosphonates of structure **IIIbb** in which the phosphonate group is attached by means of a variable carbon linkage. In this sequence, the naphthyridine carboxylic acid **A21.2** is coupled, as described previously, with the amine derivative **A22.1**, following a procedure similar to Example 28, to form the amide **A22.2**. Bromination, as described above, yields the 5-bromo derivative **A22.3**, which upon protection of the phenolic hydroxyl yields the compound **A22.4**. Displacement of the bromine, by reaction with a dialkyl amino-substituted phosphonate **A22.5**, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety, affords the amine **A22.6**. The reaction is performed in a polar organic solvent such as dimethylformamide in the presence of a base such as potassium carbonate.

Deprotection of the alcoholic hydroxyl group affords the alcohol **A22.7**, which upon activation and cyclization, for example as described in Scheme 11 then gives the tricyclic product **A22.8**, which upon deprotection affords the phenol **A22.9**.

For example, acetic acid 5-bromo-7-[(4-fluoro-benzyl)-propyl-carbamoyl]-[1,6]naphthyridin-8-yl ester **A22.10**, is reacted with one molar equivalent of a dialkyl aminopropyl phosphonate **A22.11**, (Acros) to yield the amine **A22.12**. Deprotection and activation of the alcoholic hydroxyl group, for example by conversion to the

mesylate, followed by cyclization under basic conditions, and deprotection of the phenolic hydroxyl group, then affords the enol **A22.13**.

Using the above procedures, but employing, in place of the bromide **A22.10**, different bromides **A22.4**, and/or different aminophosphonates **A22.5**, the corresponding products **A22.9** are obtained.

Scheme **A23** illustrates methods for the preparation of phosphonates of structure **IIIbb** in which the phosphonate group is attached by means of a nitrogen and a variable carbon linkage. In this sequence, a tricyclic imine **A23.1** (Scheme 12) is reacted with a dialkyl bromoalkyl phosphonate **A23.2** to give the alkylated product **A23.3**. The reaction is performed in a polar organic solvent such as acetonitrile or dimethylsulfoxide, in the presence of a base such as diisopropylethylamine or 2,6-lutidine.

Alternatively, the imine **A23.1** is converted into a hydrazone **A23.5** by reaction with a dialkyl formyl-substituted phosphonate **A23.4** in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety. The hydrazone is prepared by the reaction of equimolar amounts of the reactants in a polar organic solvent such as ethanol, optionally in the presence of a catalytic amount of an acid such as acetic acid. Optionally, the hydrazone product **A23.5** is reduced, for example by treatment with sodium borohydride, to give the dihydro derivative **A23.6**.

For example, acetic acid 7-(4-fluoro-benzyl)-10-hydrazono-8-oxo-6,7,8,10-tetrahydro-5H-1,7,10a-triaza-anthracen-9-yl ester **A23.7** (Scheme 12) is reacted at 60° in dimethylformamide solution containing potassium carbonate with one molar equivalent of a dialkyl 2-bromoethyl phosphonate **A23.8** (Aldrich), to prepare the alkylated product which upon deprotection yields the enol **A23.9**.

As a further example, the hydrazone **A23.7** is reacted in ethanol solution at ambient temperature with one molar equivalent of a dialkyl 2-formylphenyl phosphonate **A23.10** (Epsilon) to give the hydrazone product **A23.11**. Reduction of the double bond, by treatment with sodium cyanoborohydride in isopropanol, followed by deprotection, affords the enol product **A23.12**.

Using the above procedures, but employing, in place of the hydrazone **A23.7**, different hydrazones **A23.1**, and/or different bromophosphonates **A23.2**, or formyl

phosphonates **A23.4** the corresponding products **A23.3**, **A23.5** and **A23.6** are obtained.

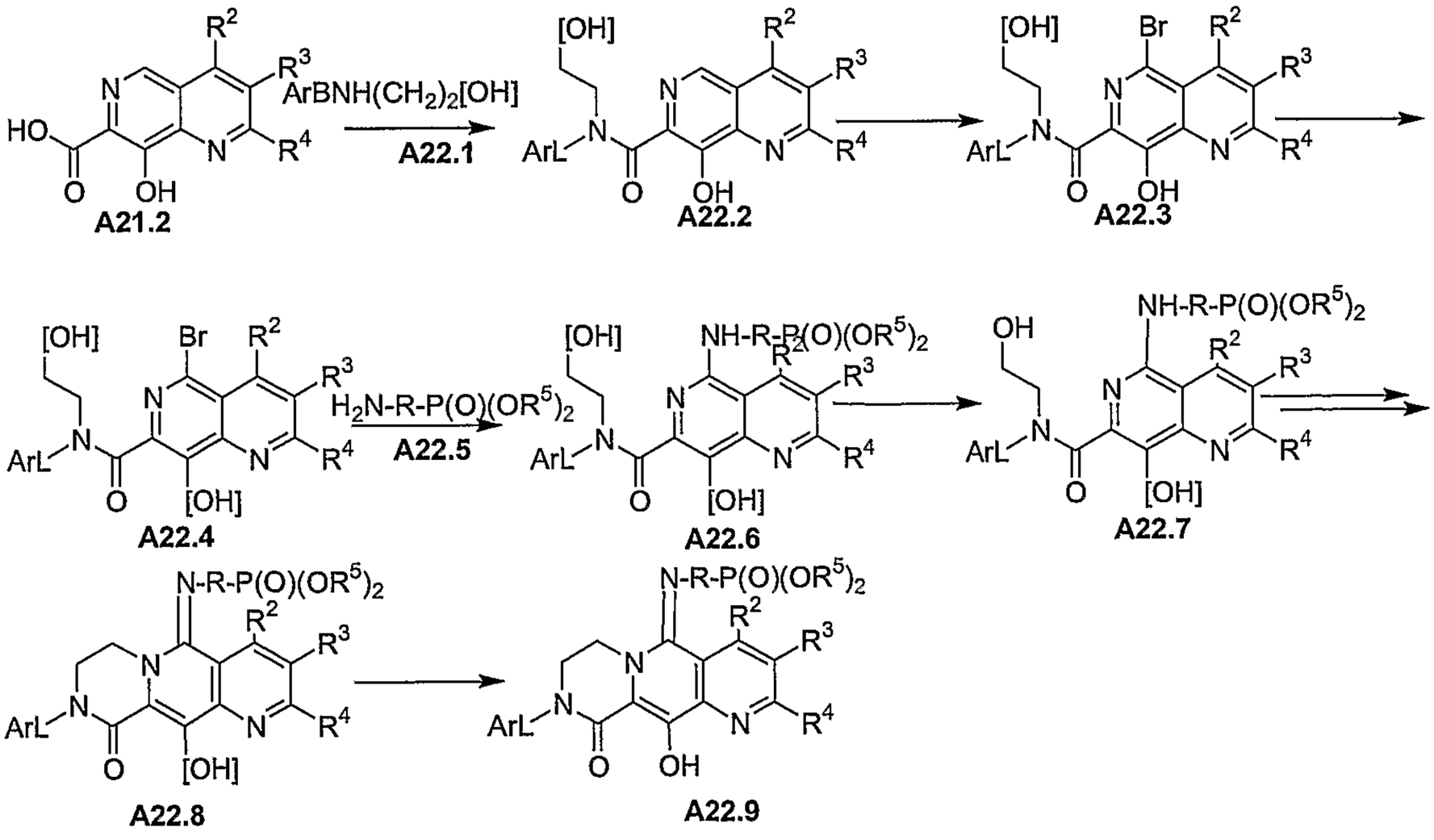
Scheme **A24** illustrates methods for the preparation of phosphonates of structure **IIIbb** in which the phosphonate group is attached by means of a hydroxyimino linkage. In this sequence, a tricyclic oxime **A24.1** (Scheme 14) is reacted with a dialkyl bromo-substituted phosphonate **A24.2** in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety. The reaction is performed in a polar organic solvent in the presence of a base such as sodium hydride or lithium hexamethyldisilazide. Deprotection then yields the enol **A24.4**.

For example, acetic acid 7-(4-fluoro-benzyl)-10-hydroxyimino-8-oxo-6,7,8,10-tetrahydro-5H-1,7,10a-triaza-anthracen-9-yl ester **A24.5** (Scheme 14) is reacted in dimethylformamide solution with one molar equivalent of sodium hydride, followed by the addition of one molar equivalent of a dialkyl 4-(bromomethyl)phenyl phosphonate **A24.6** (Tet., 1998, 54, 9341) to afford after deprotection the iminoether **A24.7**.

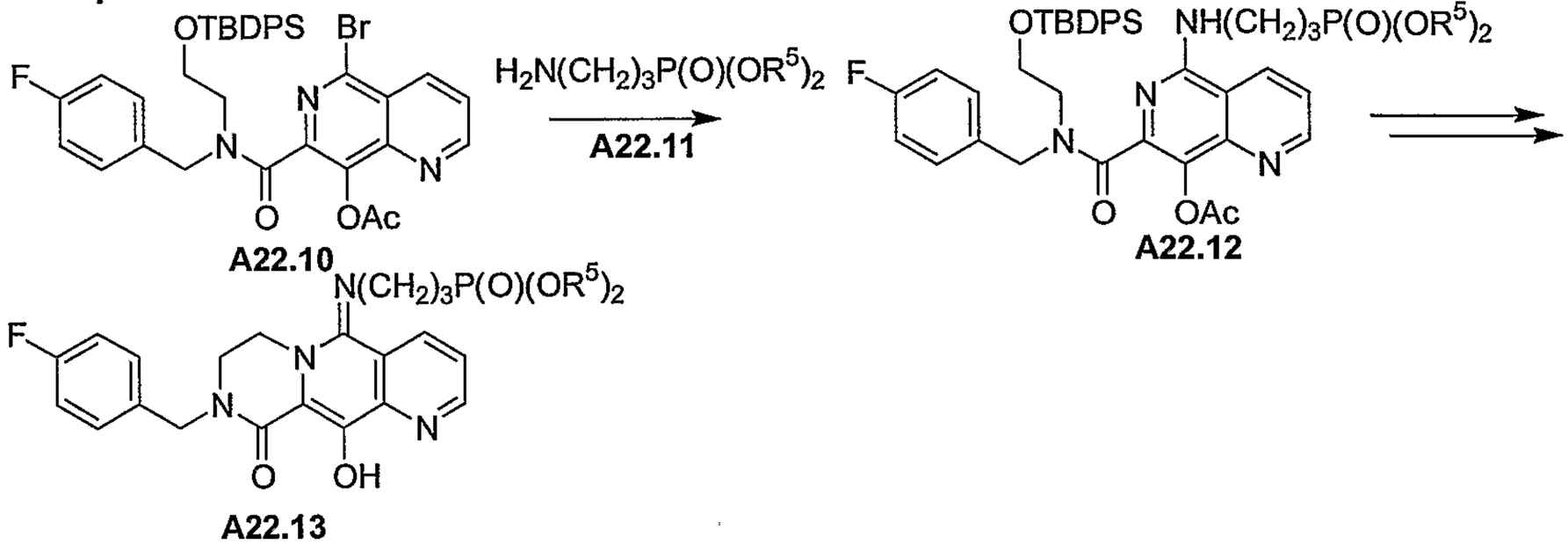
Using the above procedures, but employing, in place of the oxime **A24.5**, different oximes **A24.1**, and/or different phosphonates **A24.2**, the corresponding products **A24.4** are obtained.

Scheme A22. Phosphonates IIIbb.

Method

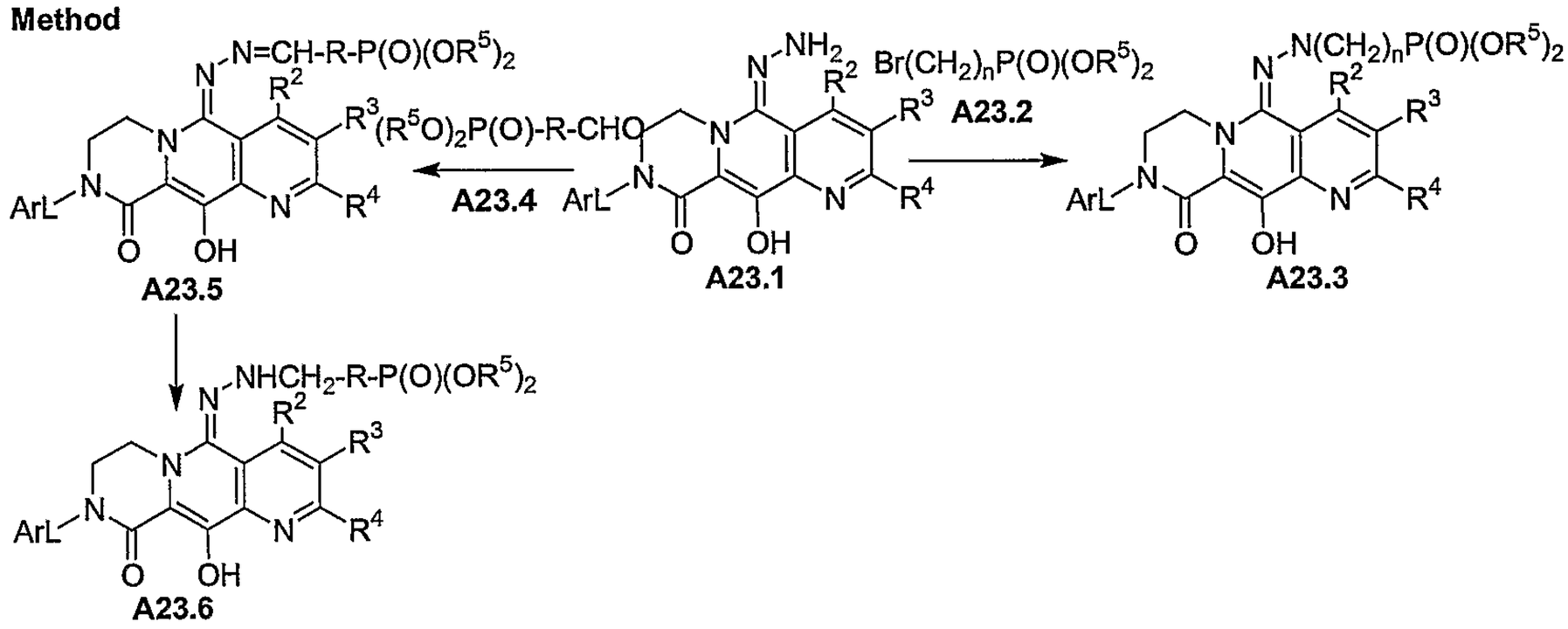


Example A22

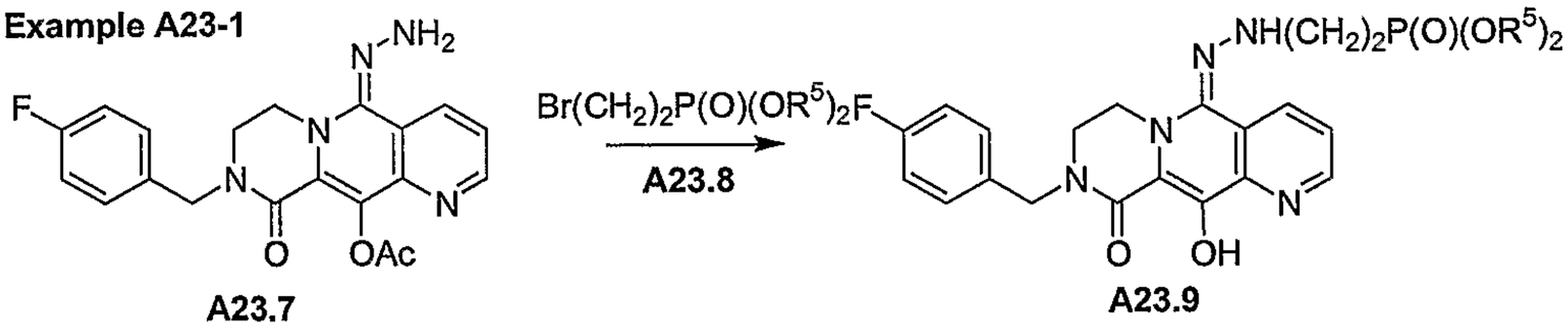


Scheme A23. Phosphonates IIIbb.

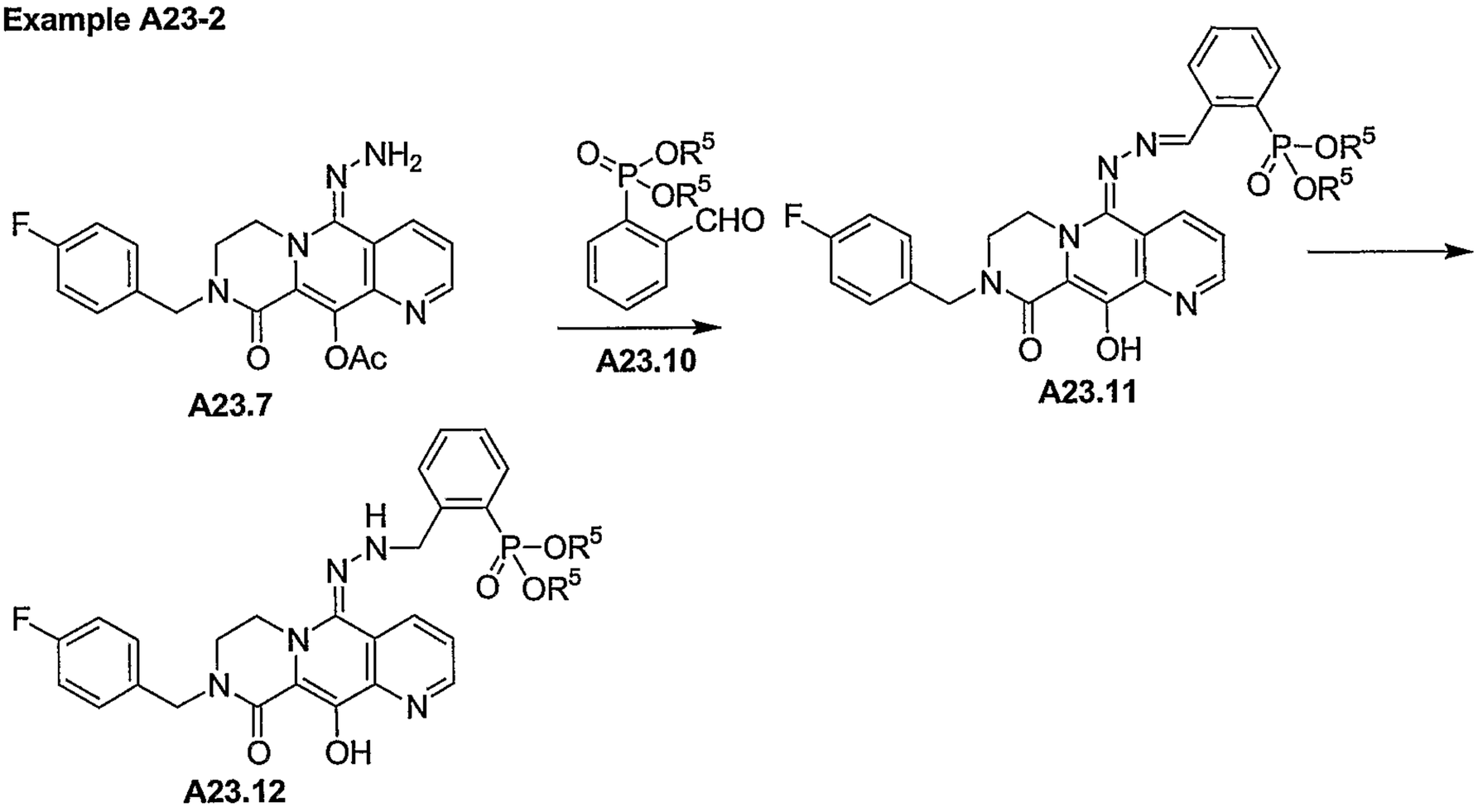
Method



Example A23-1

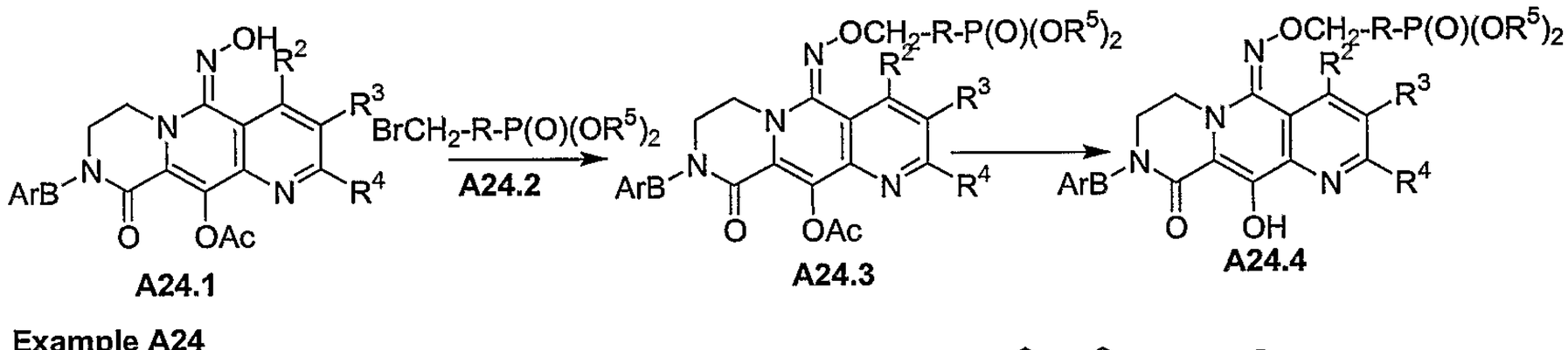


Example A23-2

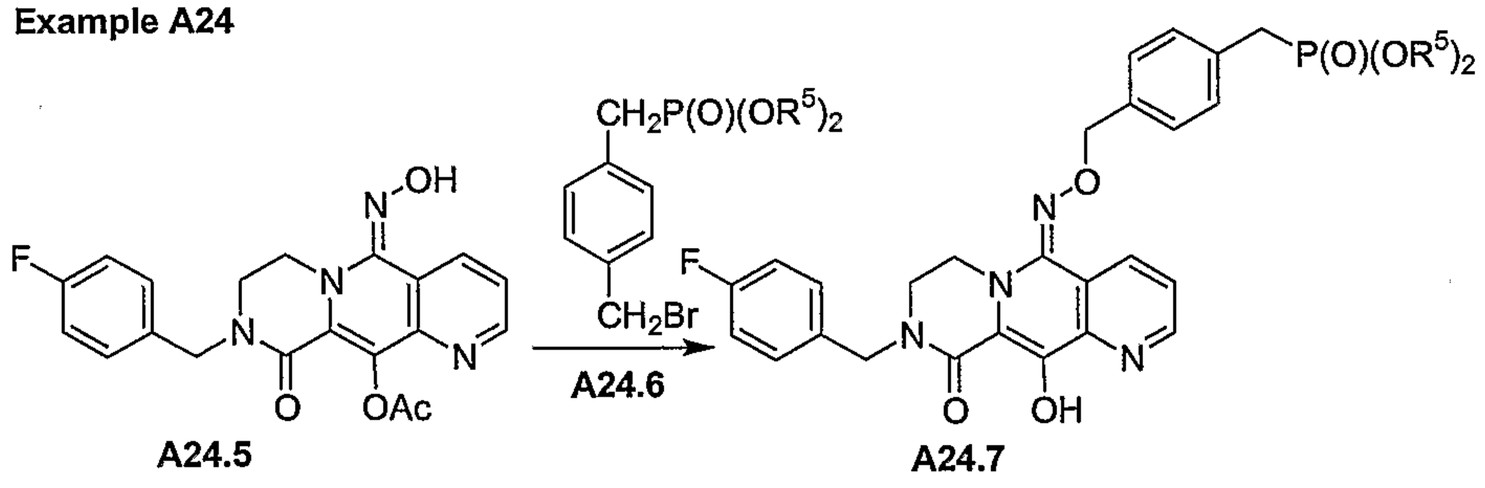


Scheme A24. Phosphonates IIIbb.

Method



Example A24



Preparation of the intermediate phosphonate esters IIIcc.

Scheme **A25** illustrates methods for the preparation of phosphonates of structure **IIIcc**. The conversion of pyridine-2,3-dicarboxylic anhydride (**A25.1**, R =H) into the naphthyridine **A25.2**, R=H, is described in WO 0255079. Using the same procedure, 4-methylpyridine-2,3-dicarboxylic anhydride **A25.1**, R = Me, (J. Org. Chem., 1961, 26, 808) is converted into the naphthyridine **A25.2**, R = Me. This compound is then transformed, as described in Scheme 12, into the imine **A25.3**. Protection of the hydroxyl and amino groups then furnishes the derivative **A25.4**. The product is then condensed under basic conditions, as described in Scheme **A20**, with a

dialkyl formyl-substituted phosphonate **A25.5**, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety. After deprotection, the product **A25.6** is optionally reduced, as described in Scheme **A20**, to give the saturated analog **A25.17**.

Alternatively, the methyl-substituted tricycle **A25.4** is brominated, for example by reaction with N-bromosuccinimide, to give the bromomethyl product **A25.7**. The compound is then subjected to a Arbuzov reaction with a trialkyl phosphite, to yield after deprotection the phosphonate **A25.8**.

Alternatively, the bromomethyl compound **A25.7** is reacted, as described previously (Scheme **A20**) with a dialkyl hydroxy, mercapto or amino-substituted phosphonate **A25.18**, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety, to give after deprotection the ether, thioether or amine product **A25.9**.

For example, acetic acid 7-[2-(4-fluoro-phenyl)-ethyl]-10-hydrazono-4-methyl-8-oxo-6,7,8,10-tetrahydro-5H-1,7,10a-triaza-anthracen-9-yl ester **A25.10**, prepared according to the procedures described above, is converted into the phthalimido derivative by reaction with one molar equivalent of phthalic anhydride, as described in J. Org. Chem., 43, 2320, 1978. The protected product is then reacted with N-bromosuccinimide in hexachloroethane to give the bromomethyl derivative **A25.12**. This compound is heated to 120° with an excess of a trialkyl phosphite to produce the phosphonate **A25.13**. Deprotection, for example by reaction with ethanolic hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the phosphonate **A25.14**.

As a further example, the phthalimido-protected methyl-substituted tricycle **A25.11** is reacted in dioxan solution with a dialkyl formylphosphonate **A25.12** (Tet., 1994, 50, 10277) and lithium tetramethyl piperidide, to yield, after removal of the protecting groups, the unsaturated phosphonate **A25.13**. Reduction of the double bond then gives the saturated analog **A25.14**.

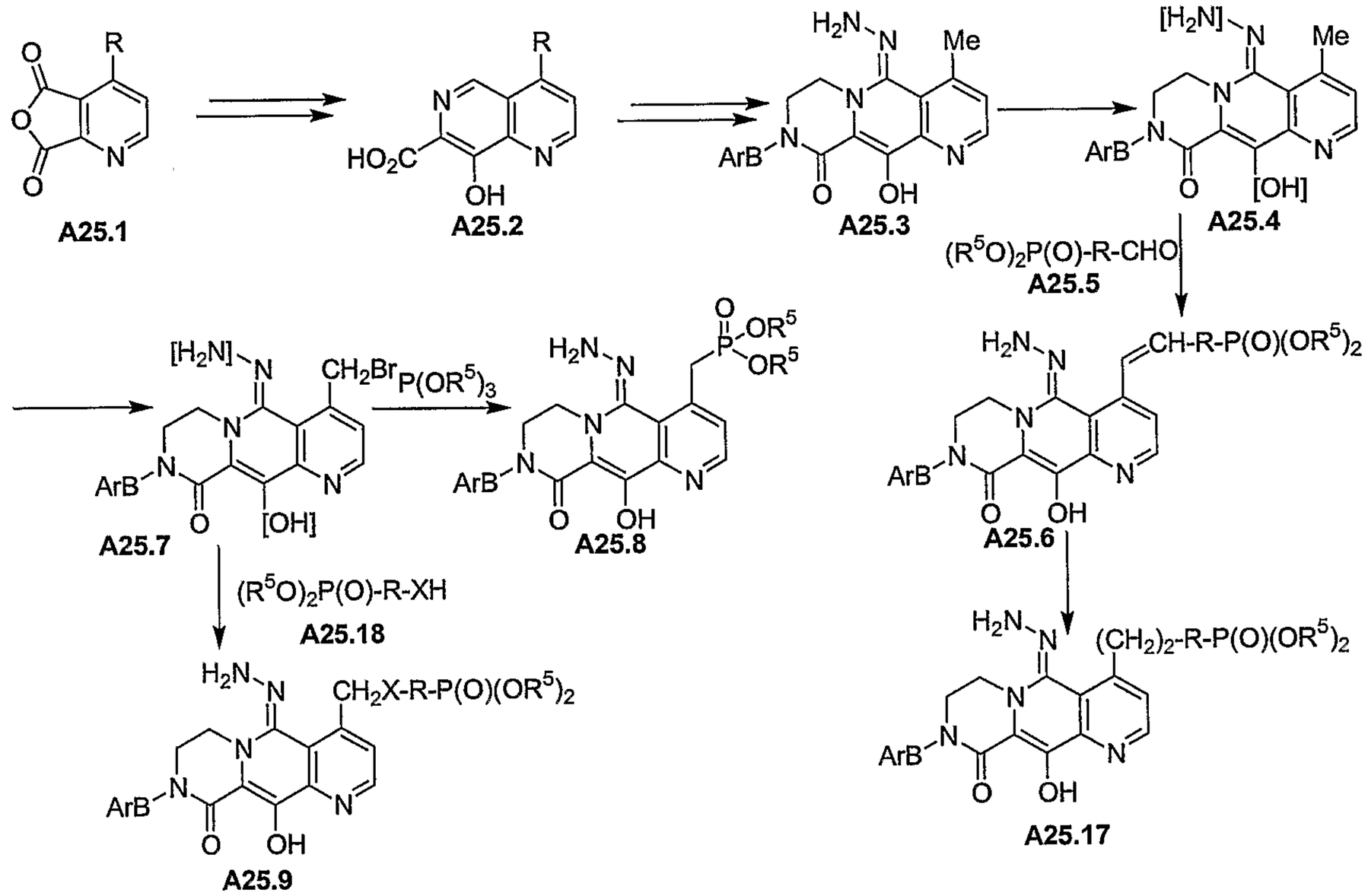
As a further example, the bromomethyl derivative **A25.12** is reacted in acetonitrile solution with one molar equivalent of a dialkyl 2-mercaptopropyl phosphonate **A25.15**(WO 007101) and diisopropylethylamine, to produce after deprotection the phosphonate **A25.16**.

Using the above procedures, but employing, in place of the starting materials **A25.10**, **A25.11** or **A25.12**, different starting materials **A25.4** and **A25.7**, and/or different aldehydes **A25.5** or alcohols, thiols or amines **A25.18**, the corresponding products **A25.6**, **A25.8**, **A25.9** and **A25.17** are obtained.

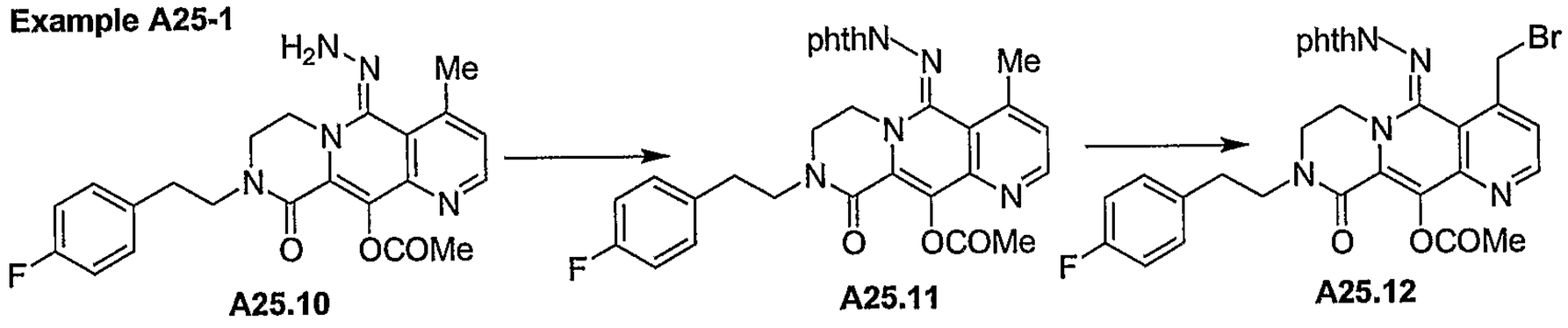
5

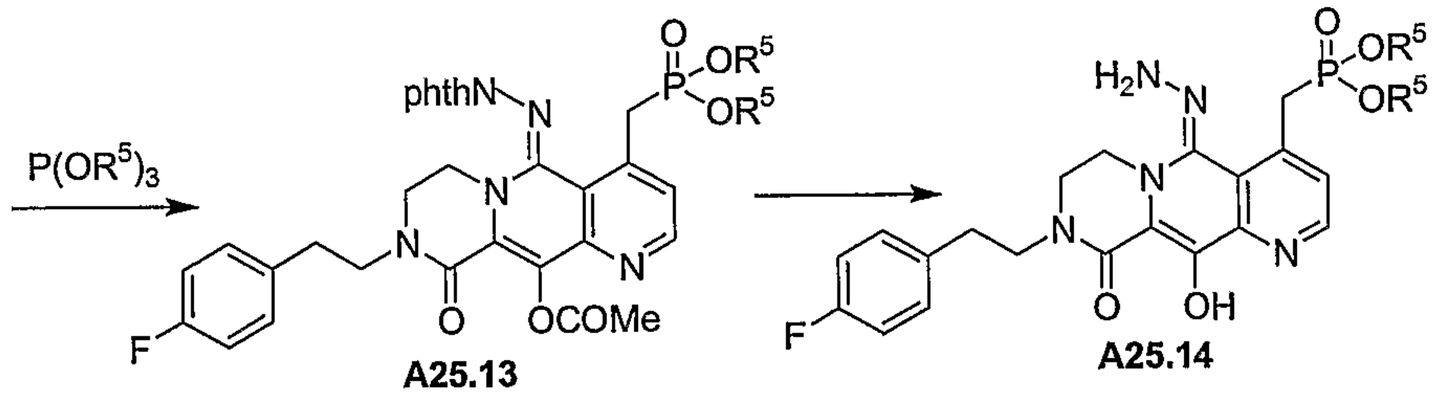
Scheme A25. Phosphonates IIIcc.

Method

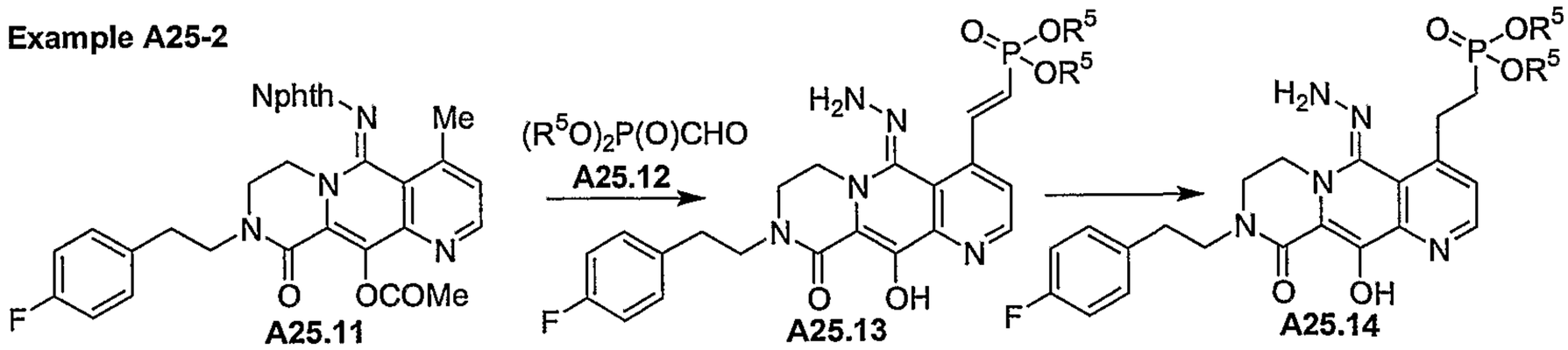


Example A25-1

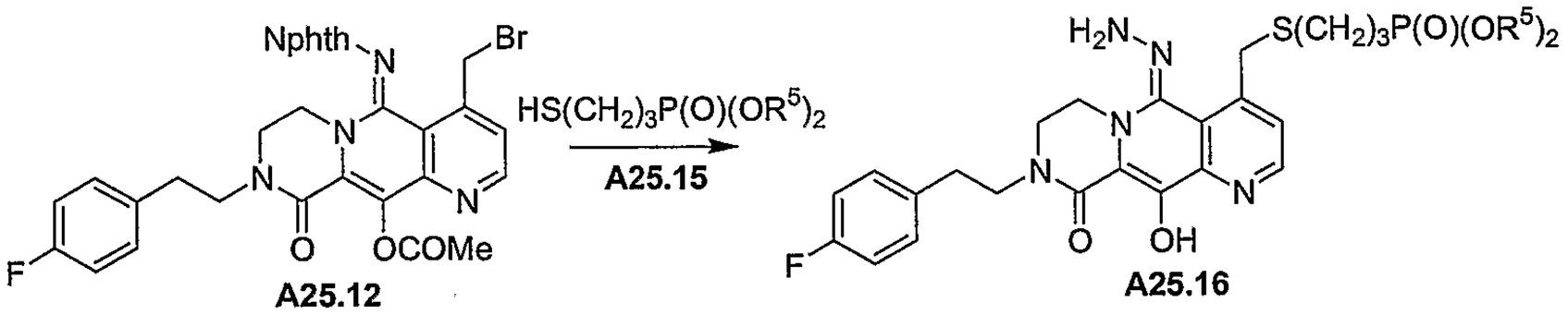




Example A25-2



Example A25-3



Preparation of the intermediate phosphonate esters IVaa.

Schemes **A29** and **A30** illustrates the preparation of phosphonate esters of structure **IVaa**.

Scheme **A29** illustrates the preparation of compounds in which phosphonate is attached by means of an ether, thioether of amine linkage. In this procedure, a substituted succinimide **A29.1** is condensed, as described in Scheme 1 and Example 2, with a heterocyclic diester **A29.2** to afford after protection the tricyclic product **A29.3**. Reduction with sodium borohydride then yields the aminal **A29.4**, which upon acid-catalyzed reaction with a dialkyl hydroxy, mercapto or amino-substituted phosphonate **A29.5**, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety, to give after deprotection the ether, thioether or amine products **A29.6**.

For example, 1-[2-(4-fluoro-phenyl)-cyclopropyl]-pyrrolidine-2,5-dione **A29.7**, prepared from 4-fluorophenylcyclopropylamine (J. Med. Chem., 1996, 39, 1485) and succinic anhydride, is reacted with 4,5-dicarbomethoxyisoxazole **A29.8** (Chem. Ber., 97, 1414, 1964) to afford after protection 6-[2-(4-fluoro-phenyl)-cyclopropyl]-4,8-bis-methoxymethoxy-oxazolo[4,5-f]isoindole-5,7-dione **A29.9**. Reduction with sodium borohydride then gives the aminal **A29.10**, which upon reaction with a dialkyl 3-mercaptopropyl phosphonate **A29.11** (WO 0077101) and trifluoroacetic acid in dichloromethane yields the phosphonate thioether **A29.12**.

Using the above procedures, but employing, in place of the starting materials **A29.7** and **A29.8**, different starting materials **A29.1** and **A29.2**, and/or different phosphonates **A29.5**, the corresponding products **A29.6** are obtained.

Preparation of the intermediate phosphonate esters IVaa.

Scheme **A30** illustrates the preparation of phosphonate esters of structure **IVaa** in which the phosphonate is attached by means of a variable carbon linkage. In this procedure, dimethyl succinate **A30.1** is condensed, under base catalysis, for example using the procedure described on Scheme 1 and Example 2 with a heterocyclic diester **A30.2**, to yield after protection of the phenolic hydroxyl groups, the diester **A30.3**. Partial basic hydrolysis, for example by reaction with one molar equivalent of lithium hydroxide in aqueous dimethoxyethane, then affords the monoacid **A30.4**. The carboxylic acid is homologated to produce the corresponding acetic acid **A30.5**. The transformation is effected by means of the Arndt Eistert reaction. In this procedure, which is described in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 641, and in Advanced Organic Chemistry, By J. Marsh, McGraw Hill, 1968, p. 809, the carboxylic acid is converted into the acid chloride, which is reacted with diazomethane to give the corresponding diazoketone. Silver-catalyzed Wolff rearrangement of the diazoketone in an alcoholic solvent then yields the acetic acid ester, which upon hydrolyis yields the acetic acid **A30.5**. This material is coupled with the amine **A30.6** to give the amide **A30.7**. Base-catalyzed thermal cyclization of the latter compound, for example by refluxing in xylene with sodium methoxide, then gives the cyclized product **A30.8**. The latter compound is then alkylated, as described above, (Scheme **A10**) with a dialkyl bromo-substituted phosphonate **A30.9**, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety, to afford after deprotection the phosphonate **A30.10**.

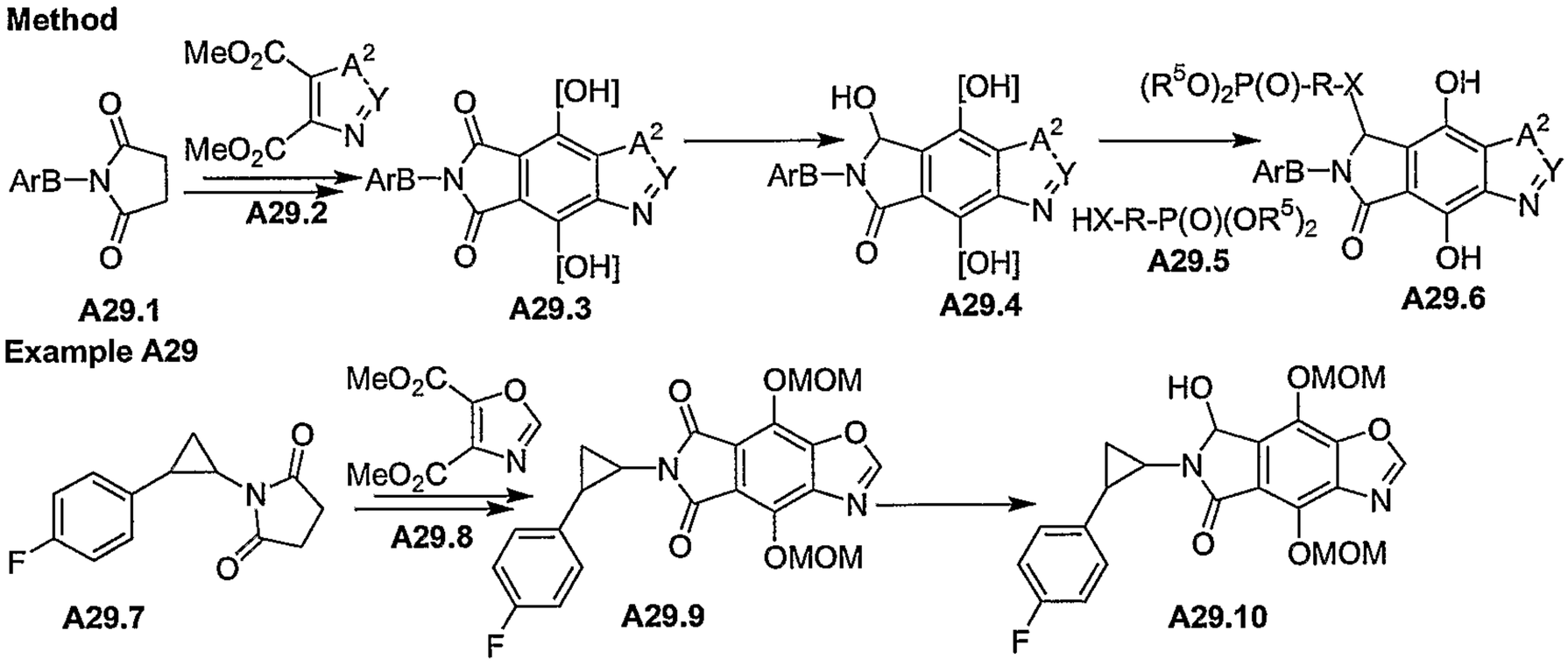
For example, condensation between dimethyl succinate and methyl 1-methylimidazole-4,5-dicarboxylate **A30.11** (Eqypt. J. Chem., 1985, 28, 139) yields, after protection of the phenolic hydroxyl groups, 4,7-bis-methoxymethoxy-1-methyl-1H-benzoimidazole-5,6-dicarboxylic acid dimethyl ester **A30.12**. Partial hydrolysis then gives the monocarboxylic acid **A30.13**, and this compound is subjected to Arndt

Eistert homologation to give the corresponding acetic acid **A30.14**. The carboxylic acid is coupled, in the presence of dicyclohexyl carbodiimide, with cyclohexylmethylamine **A30.15** to give the amide **A30.16**. Cyclization is effected as described above to prepare 6-cyclohexylmethyl-4,9-bis-methoxymethoxy-1-methyl-1,5,6,8-tetrahydro-1,3,6-triaza-cyclopenta[b]naphthalen-7-one **A30.17**. The product is then reacted in dioxan solution with a dialkyl bromoethyl phosphonate **A30.18** (Aldrich) and lithium hexamethyldisilazide, to give after deprotection the phosphonate **A30.19**.

Using the above procedures, but employing, in place of the starting materials **A30.1** and **A30.11**, different starting materials **A30.1** and **A30.2**, and/or different phosphonates **A30.9**, the corresponding products **A30.10** are obtained.

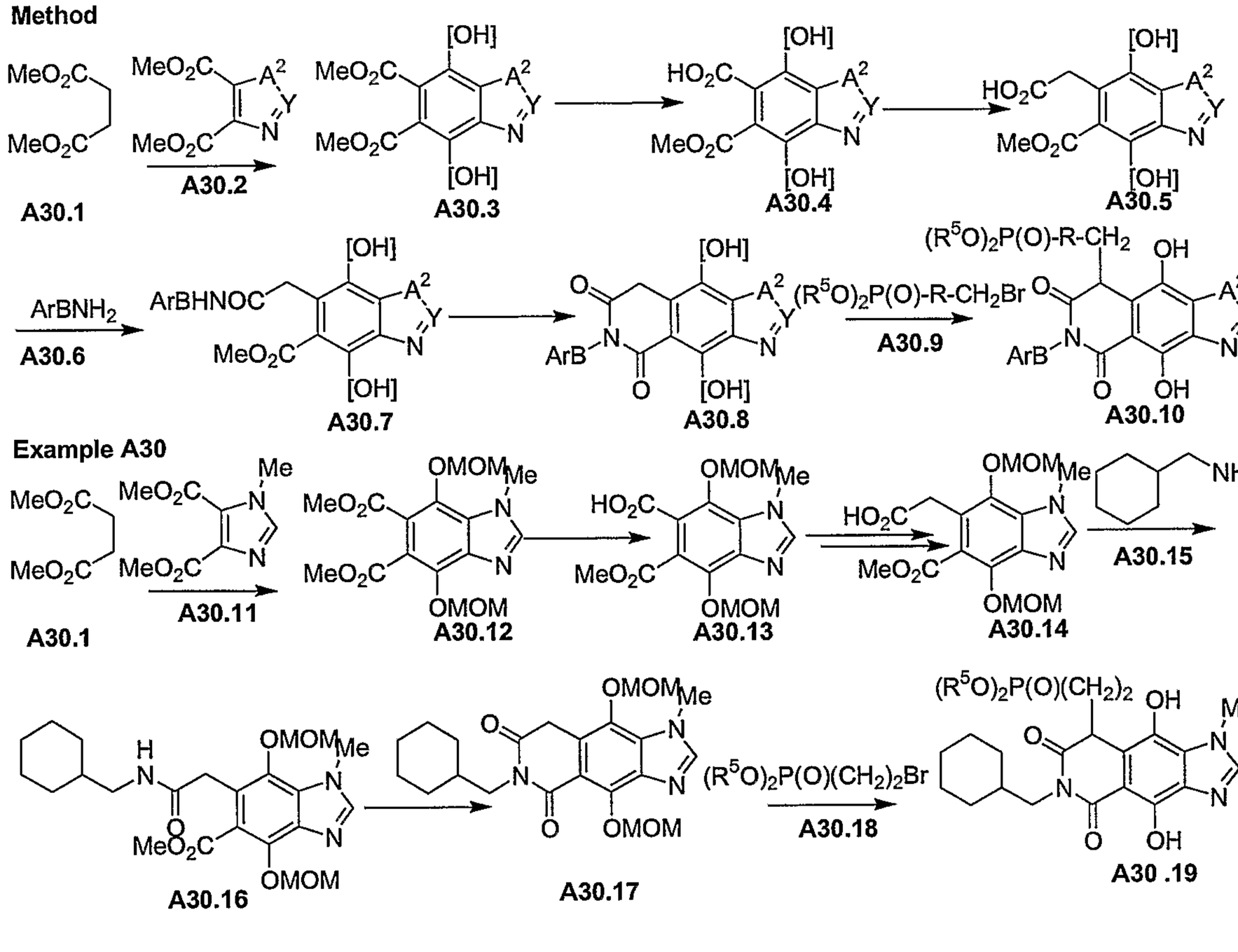
Scheme A29. Phosphonates IVaa.

Method



Scheme A30. Phosphonates IVaa.

Method



Example A30

Preparation of the intermediate phosphonate esters IVbb.

Schemes **A31** and **A32** illustrates the preparation of phosphonate esters of structure **IVbb**. Scheme **A31** illustrates the preparation of phosphonate esters in which the phosphonate is attached by means of a variable carbon linkage linkage. In this procedure, the doubly protected phenol **A29.3** is selectively deprotected to give the phenol **A31.1**. The product is converted into the triflate **A31.2** and this material is reacted with a dialkyl hydroxy, mercapto or amino-substituted phosphonate **A31.3**, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety, in the presence of a base, as described in Scheme **A8**, to afford the displacement product **A31.4**, which upon deprotection gives the phenol **A31.5**.

For example, 2-naphthylmethylsuccinimide **A31.6** is reacted with dimethyl pyrimidine 4,5-dicarboxylate **A31.7** (Chem. Ber., 1975, 108, 3877) to afford after differential protection, as describe in Scheme 1 and Example 2 and triflate formation, trifluoro-methanesulfonic acid 7-naphthalen-2-ylmethyl-6,8-dioxo-9-triisopropylsilanyloxy-7,8-dihydro-6H-pyrrolo[3,4-g]quinazolin-5-yl ester **A31.8**. The

compound is then reacted with a dialkyl 3-hydroxyphenyl phosphonate **A31.9** (Aurora) and triethylamine in dichloromethane to give the phosphonate **A31.10**.

Using the above procedures, but employing, in place of the starting materials **A31.6** and **A31.7**, different starting materials **A29.3** and/or different phosphonates **A31.3**, the corresponding products **A31.5** are obtained.

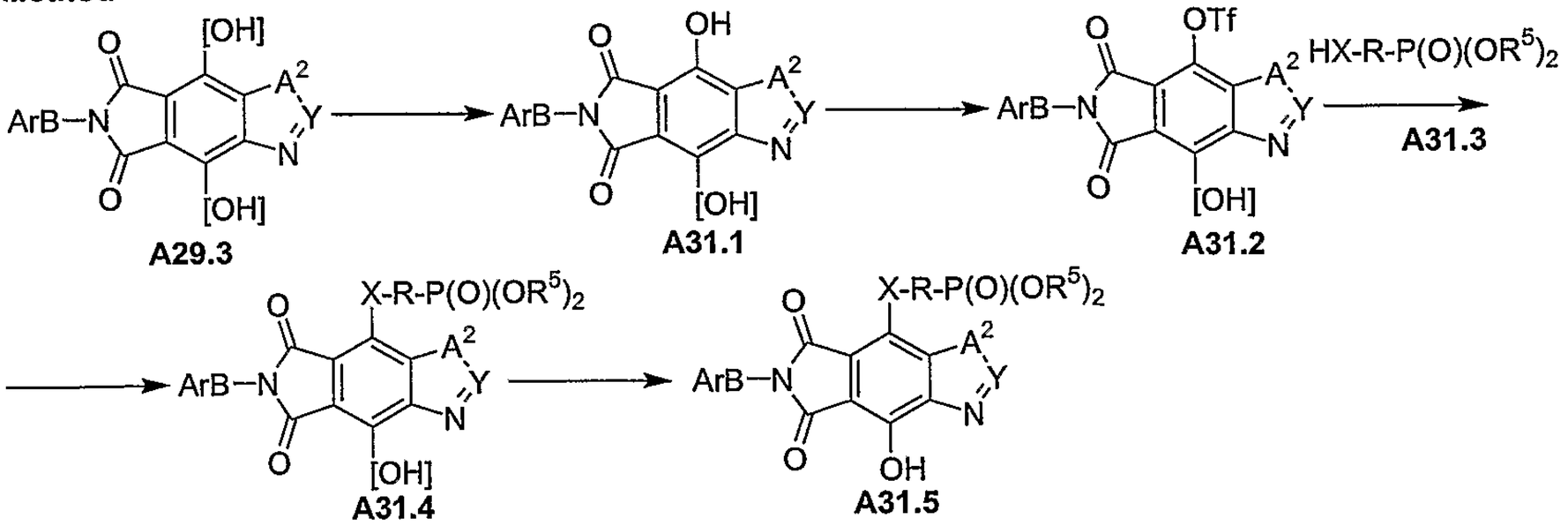
Scheme **A32** depicts the preparation of phosphonate esters of structure **Vbb** in which the phosphonate is attached by means of an ether linkage. In this procedure, dimethyl succinate **A32.1** is condensed under basic conditions, with a heterocyclic dicarboxylic ester **A32.2** to afford the bicyclic product **A32.3**. Hydrolysis of the ester groups, followed by anhydride formation and selective protection of the phenolic hydroxyl groups, then gives the product **A32.4**. The anhydride is then reacted, as described on (***06/03/0 page 31***), with the substituted hydrazine **A32.5**, to yield the tricyclic product **A32.6**. Selective deprotection then affords the phenol **A32.7**, and this compound is then reacted with a dialkyl hydroxy-substituted phosphonate **A32.8**, in which the group R is an acyclic or cyclic saturated or unsaturated alkylene, or aryl, aralkyl or heteroaryl moiety, under the conditions of the Mitsonobu reaction, as described in Scheme **A6**, to form after deprotection the phenol **A32.9**.

For example, condensation between dimethyl succinate and dimethyl 1,3,4-triazine-5,6-dicarboxylate **A32.10** (J. Org. Chem., 23, 1931, 1958) affords after selective silylation, following a procedure similar to Example 12, 6-(4-fluoro-benzyl)-9-hydroxy-10-triisopropylsilanyloxy-6,7-dihydro-1,2,4,6,7-pentaaza-anthracene-5,8-dione **A32.11**. The product is then reacted in tetrahydrofuran with a dialkyl hydroxyethyl phosphonate **A32.12**, (Epsilon) diethyl azodicarboxylate and triphenyl phosphine to yield after deprotection the phenolic phosphonate **A32.13**.

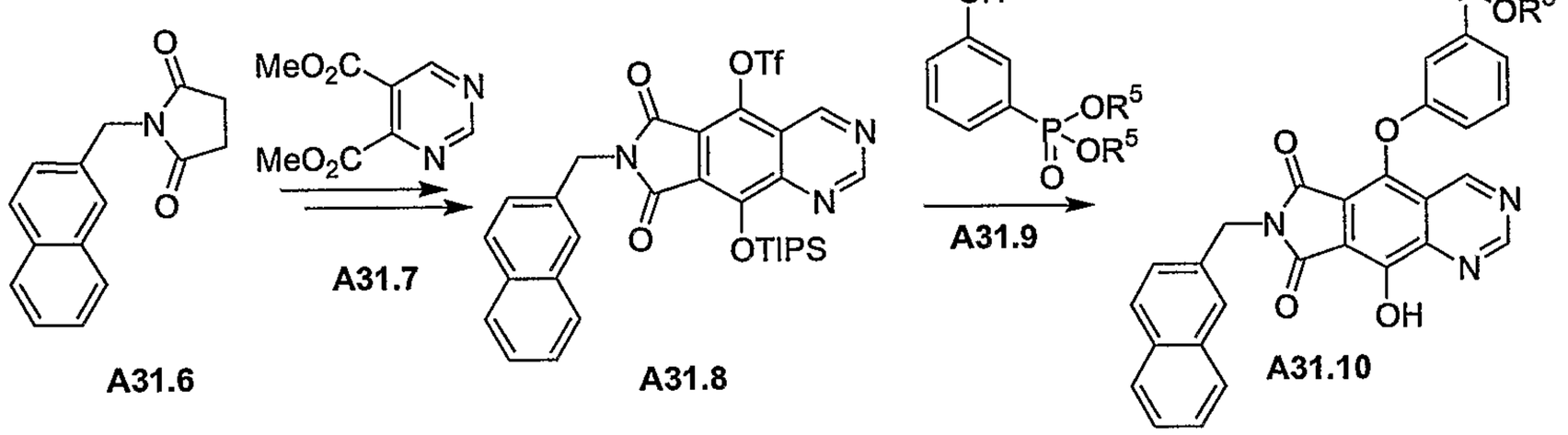
Using the above procedures, but employing, in place of the starting material **A32.10** different starting materials **A32.2** and/or different phosphonates **A32.8**, the corresponding products **A32.9** are obtained.

Scheme A31.Phosphonates IVbb.

Method

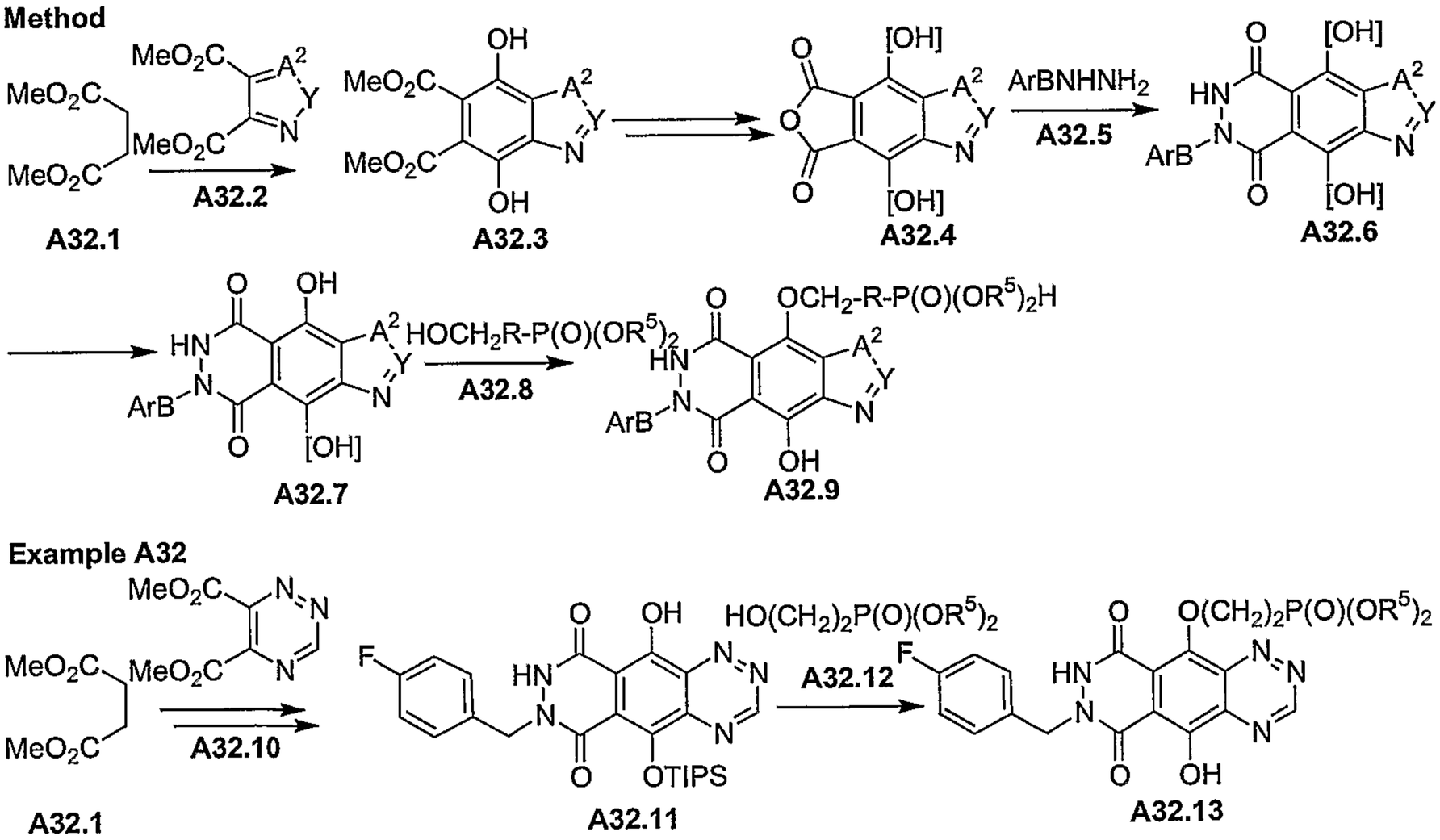


Example A31



Scheme A32. Phosphonates IVbb.

Method



Example A32

Preparation of the intermediate phosphonate esters IVcc.

Scheme **A33** illustrates the preparation of phosphonate esters of structure **IVcc** in which the phosphonate is attached by means of a carbon linkage. In this procedure, a substituted succinimide **A33.1** is reacted with a heterocyclic diester **A33.2** to afford

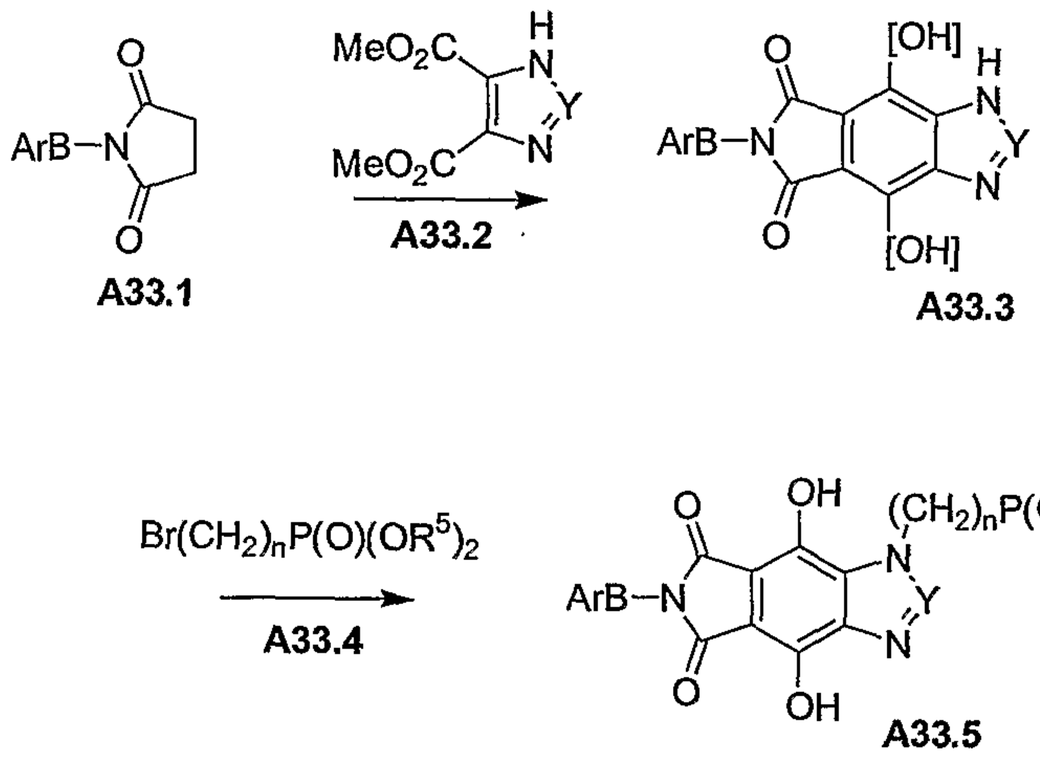
after protection the bicyclic product **A33.3**. The amino group of the product is then alkylated by reaction with a dialkyl bromo-substituted phosphonate **A33.4** to yield after deprotection the phenolic phosphonate **A33.5**.

For example, 1-(6-fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-pyrrolidine-2,5-dione **A33.6**, prepared by the reaction of 2-amino-7-fluoro-1,2,3,4-tetrahydronaphthalene (US 5538988) and succinic anhydride, is reacted with dimethyl 1,2,3-triazole-4,5-dicarboxylate **A33.7** (Interchim) to afford after silylation of the phenolic hydroxyl groups 6-(6-fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-4,8-bis-triisopropylsilanyloxy-1H-pyrrolo[3',4':4,5]benzo[1,2-d][1,2,3]triazole-5,7-dione **A33.8**. The product is then reacted, in dimethylformamide solution with one molar equivalent of sodium hydride and a dialkyl 4-bromobutyl phosphonate **A33.9** (Syn., 1994, 9, 909) to afford after deprotection the phosphonate **A33.10**.

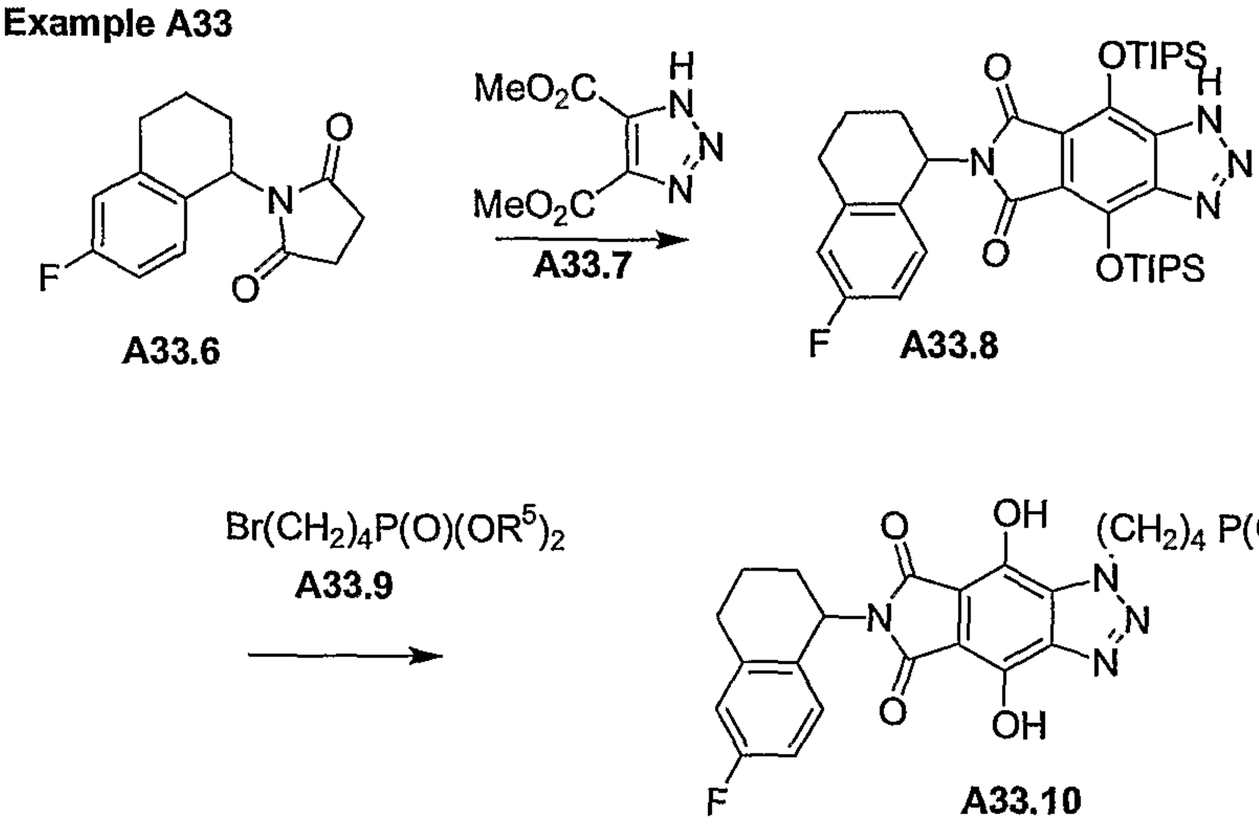
Using the above procedures, but employing, in place of the starting materials **A33.6** and **A33.7** different starting materials **A33.1** and **A33.2** and/or different phosphonates **A33.4**, the corresponding products **A33.5** are obtained.

Scheme A33. Phosphonates IVcc.

Method



Example A33



SYNTHESIS OF FORMULA II AZA-QUINOLINOL PHOSPHONATE COMPOUNDS

Aza-quinolinol compounds have been prepared, including naphthyridine compounds (US 2003/0119823 A1; WO 03/016315 A1; WO 03/016309 A1; WO 02/30930 A2; WO 02/055079 A2; WO 02/30931 A2; WO 02/30426 A1; WO 02/36734 A2). Quinoline derivatives have been reported (WO 03/031413 A1; US 2002/0103220 A1; US 2002/0055636 A1; US 6211376; US 6114349; US 6090821; US 5883255; US 5739148; US 5639881; US 3113135).

Preparation of the intermediate phosphonate esters 1-9.

The structures of the intermediate phosphonate esters **1-9** are shown in Chart **1**, in which the substituent R^1 is H, alkyl, alkenyl, aryl or aralkyl, and the substituents R^2, R^3, R^4, X and X^1 are as previously defined. Subsequent chemical modifications to the compounds **1 - 9** as described below, permit the synthesis of the final compounds of this invention.

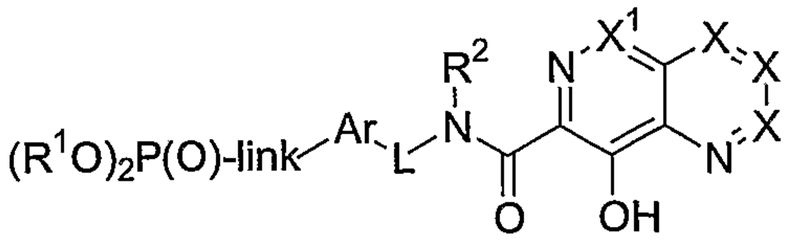
The intermediate compounds **1 - 9** incorporate a phosphonate group $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **2** and **3** illustrates examples of the linking groups present in the structures **1 - 9**.

Schemes **1 - 31** illustrate the syntheses of the intermediate phosphonate compounds of this invention, **1 - 9**, and of the intermediate compounds necessary for their synthesis.

The methods described for the introduction of phosphonate substituents are, with modifications made by one skilled in the art, transferable within the substrates **1 - 9**. For example, reaction sequences which produce the phosphonates **1** are, with appropriate modifications, applicable to the preparation of the phosphonates **2 - 9**. Methods described below for the attachment of phosphonate groups by means of reactive substituents such as OH, Br, NH_2, CH_3, CH_2Br, COOH, CHO etc are applicable to each of the scaffolds **1 - 9**.

Scheme **32** illustrates methods for the interconversion of phosphonate diesters, monoesters and acids, and Scheme **33** illustrates methods for the preparation of carbamates.

Chart 1. Structures of the naphthyridine phosphonates 1 - 9.



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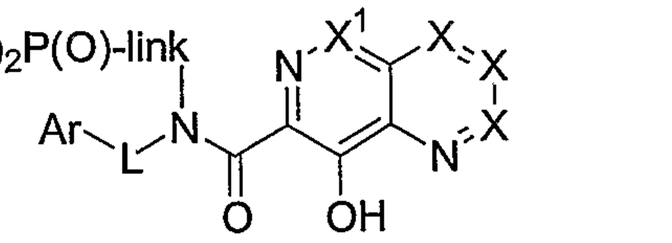

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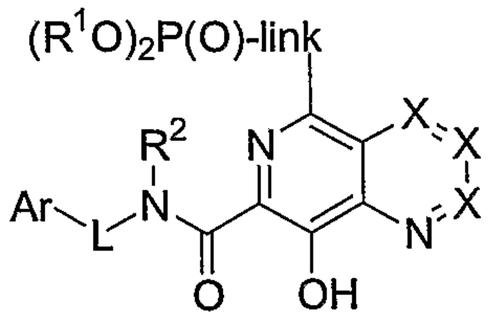

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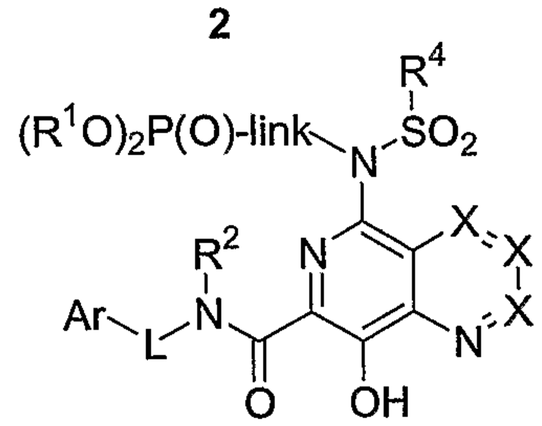

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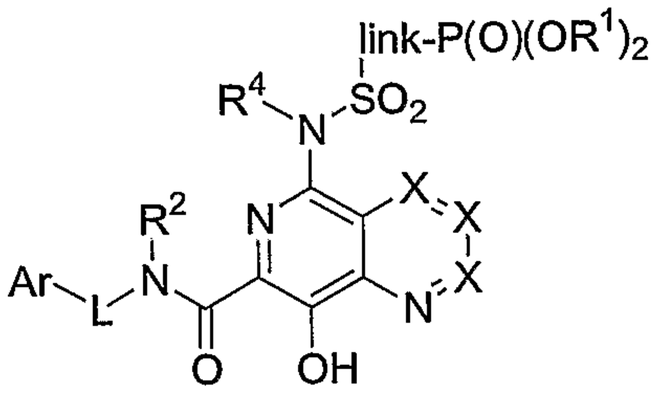

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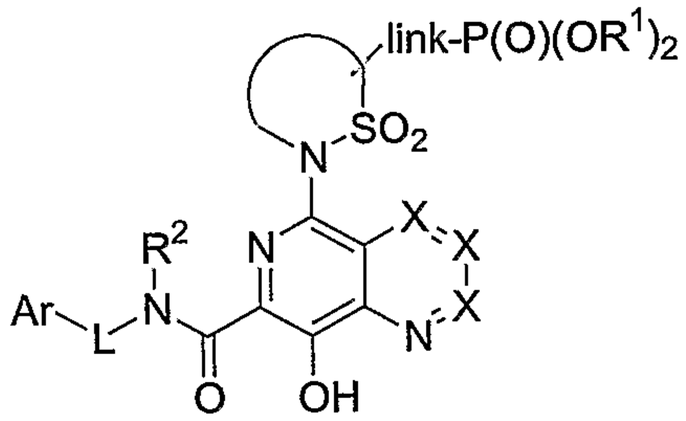

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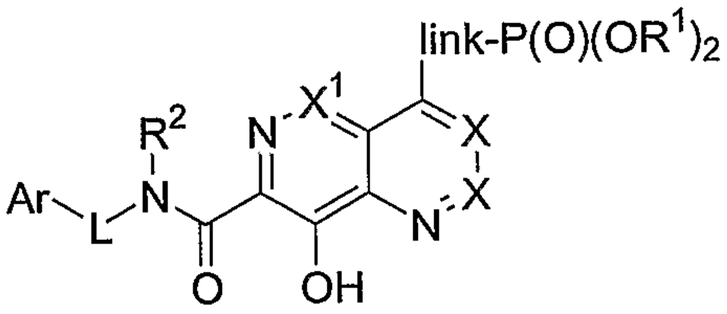

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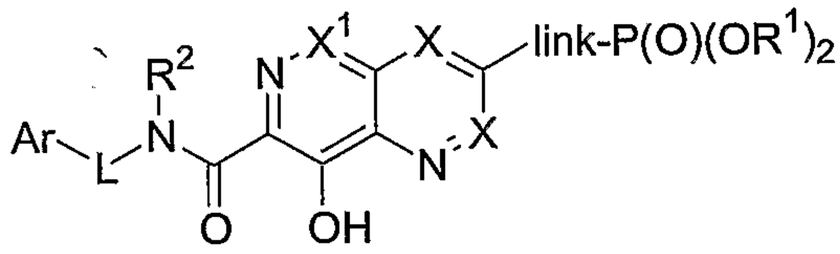

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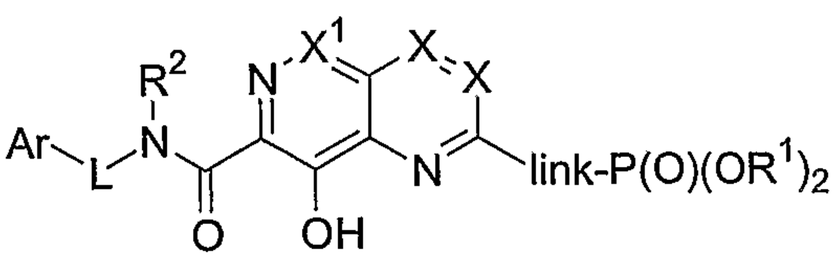


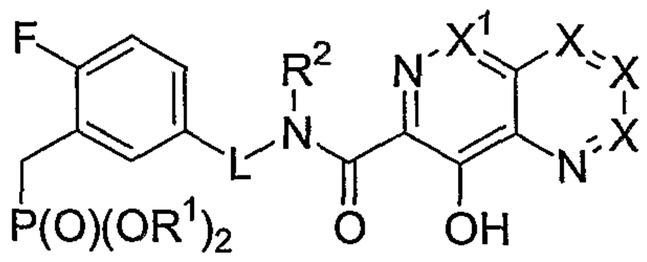
9

X = N or CR^3

X^1 = X or $CN(R^4)SO_2R_4$ or

Chart 2. Examples of phosphonate linkages

Phosphonate esters 1



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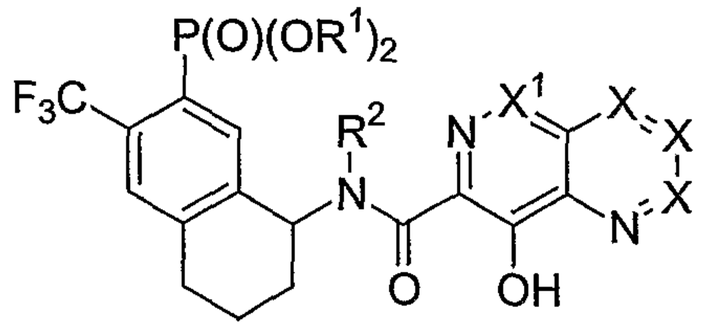

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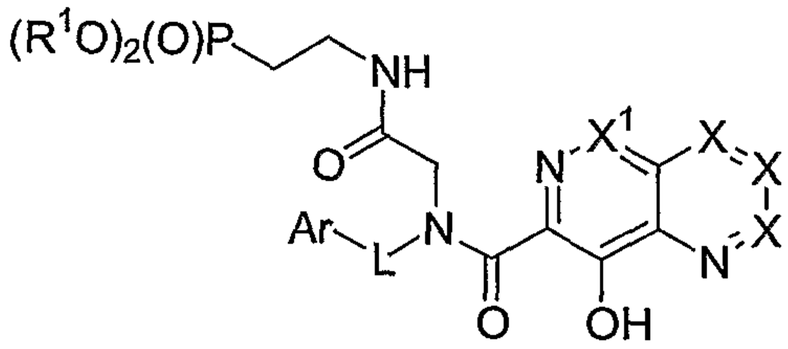
Phosphonate esters 2



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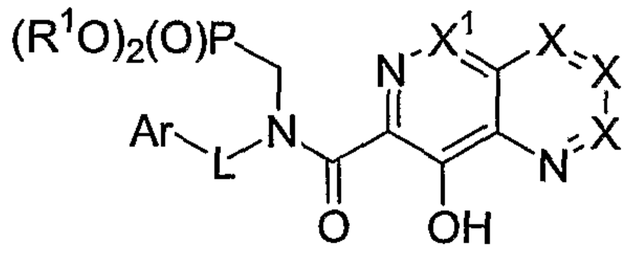

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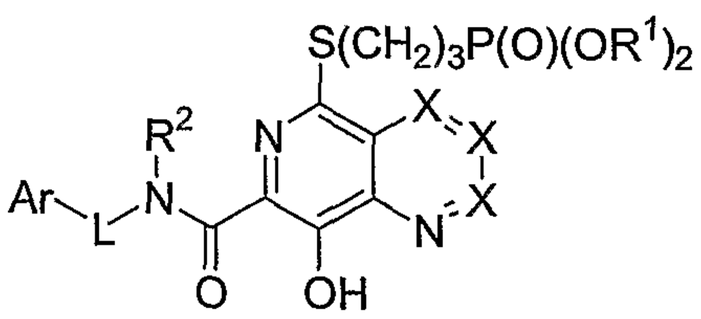
Phosphonate esters 3



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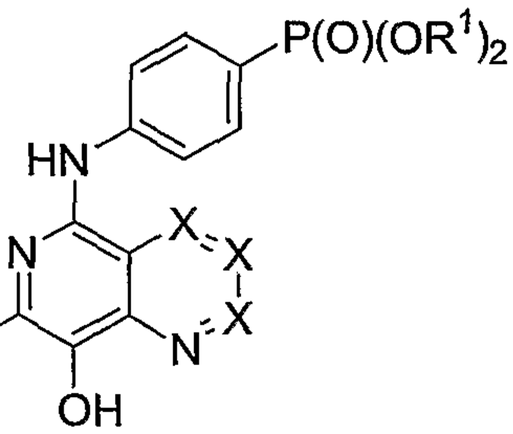

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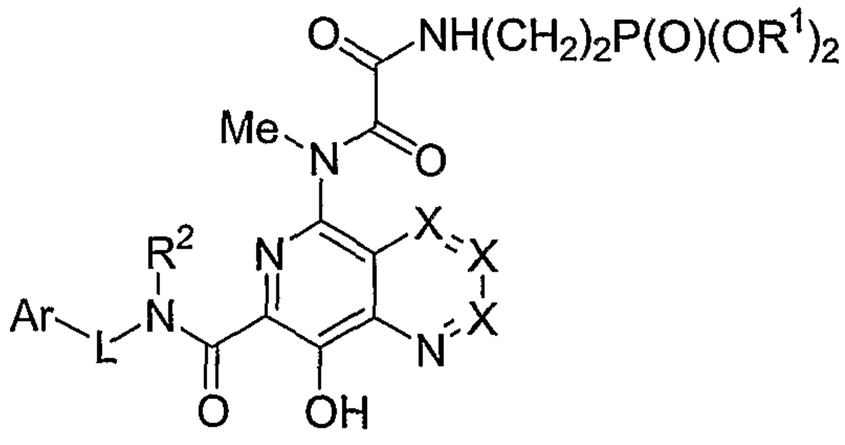

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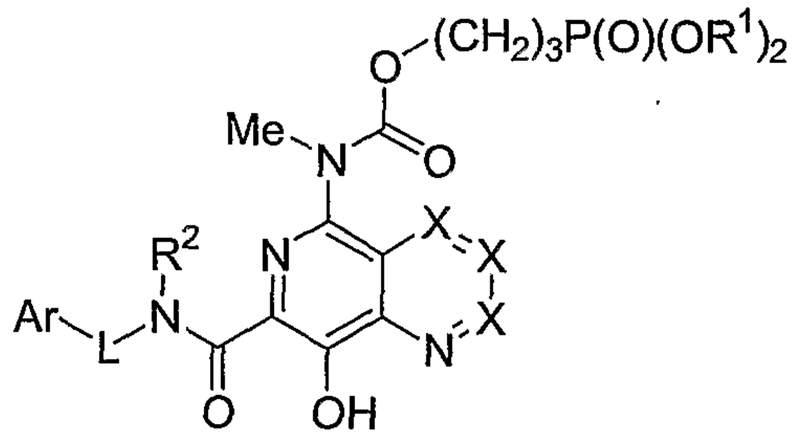

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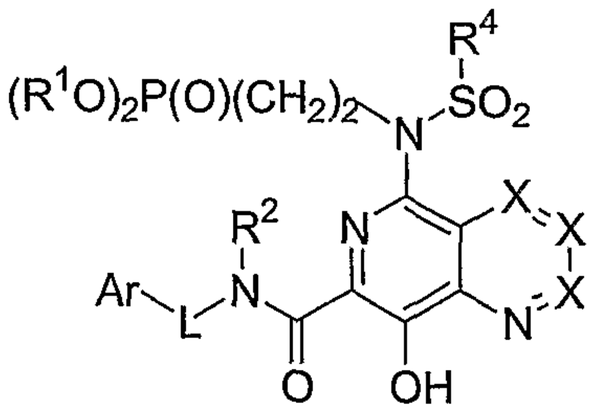
Phosphonate esters 4



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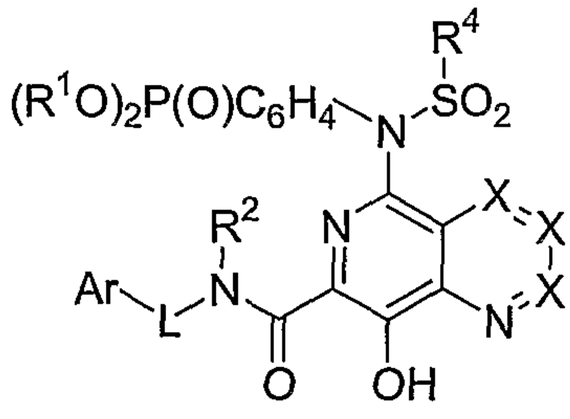

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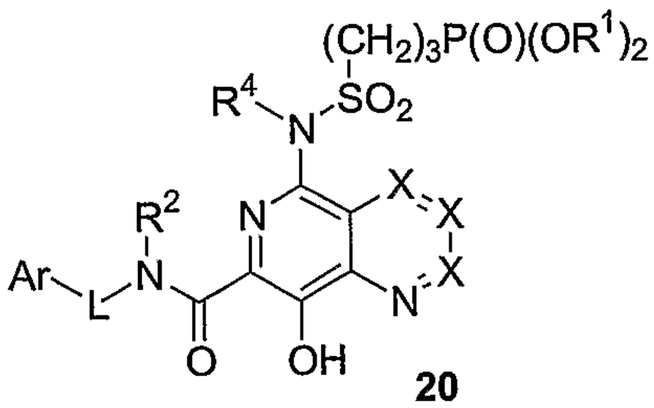
Chart 3. Examples of phosphonate linkages

Phosphonate esters 5



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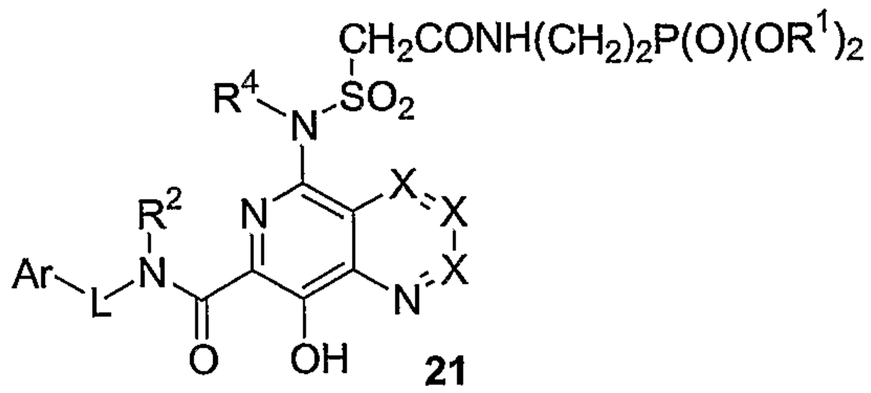

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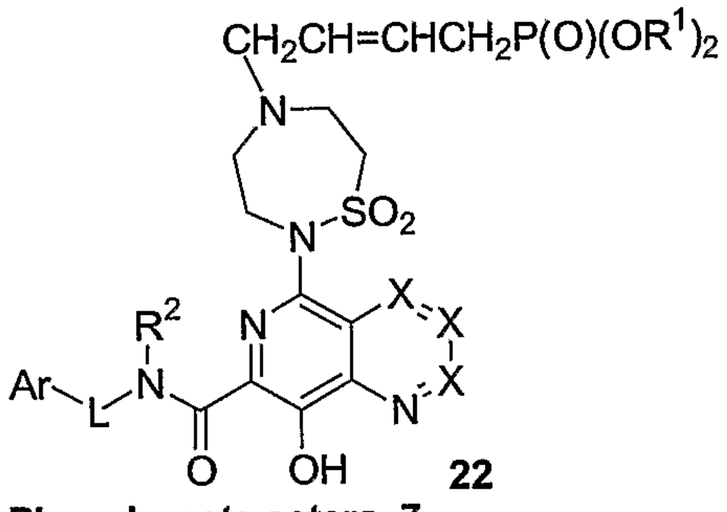
Phosphonate esters 6



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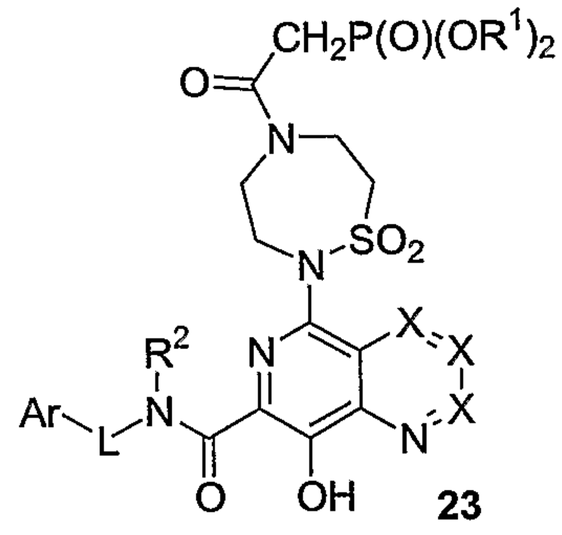

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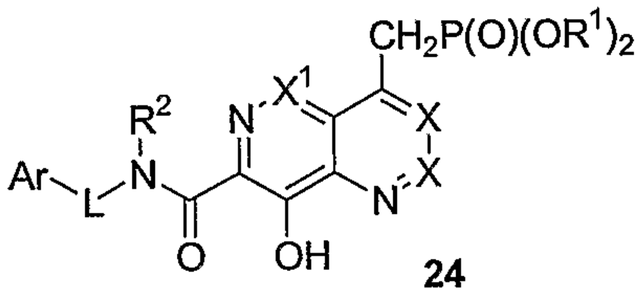
Phosphonate esters 7



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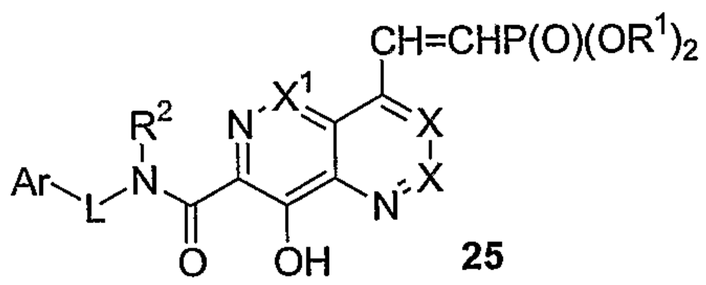

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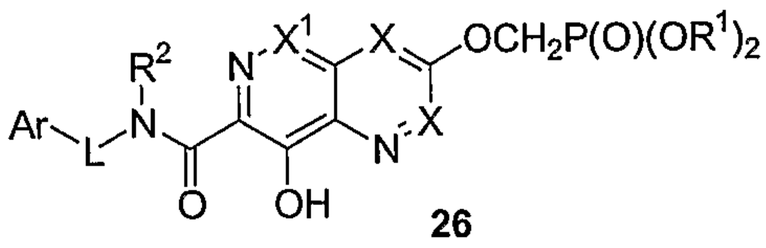
Phosphonate esters 8



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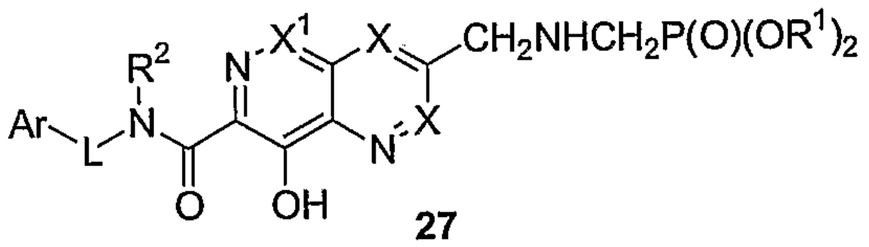

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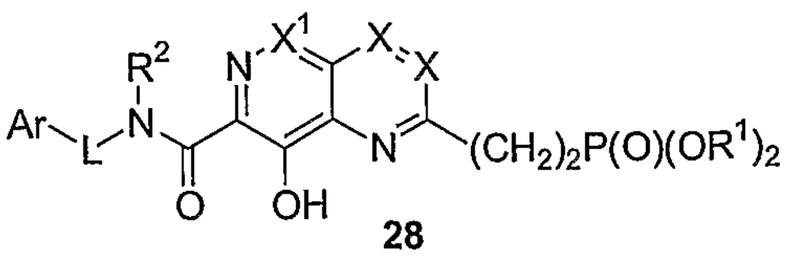
Phosphonate esters 9



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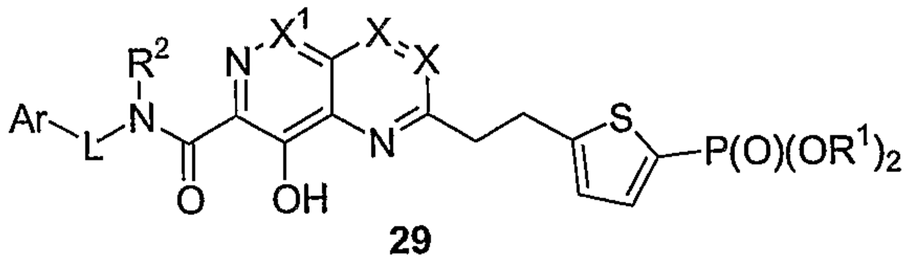

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Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the

sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH], etc.

Preparation of the intermediate bicyclic hydroxyesters and hydroxyacids.

Scheme **1** illustrates the preparation of bicyclic hydroxyesters **1.2** from the corresponding anhydrides **1.1**, in which at least one of the groups X is C-R^3. The conversion is effected by means of one or more of the methods described in WO 0230930 A2, Schemes 2, 3, 3A and 5. The resultant ester is then converted into the carboxylic acid **1.3**, for example by means of basic hydrolysis using sodium hydroxide, as described in WO 0230930 A2 Scheme 2.

As shown in Example **1**, furo[3,4-c]pyridazine-5,7-dione **1.4** (WO 994492) is converted, as described above, into 8-hydroxy-pyrido[4,3-c]pyridazine-7-carboxylic acid methyl ester **1.5**, and the ester is hydrolyzed with sodium hydroxide to give 8-hydroxy-pyrido[4,3-c]pyridazine-7-carboxylic acid **1.6**.

In a similar manner, as shown in Examples **2** and **3**, furo[3,4-b]pyrazine-5,7-dione **1.7** (Aldrich) and furo[3,4-e][1,2,4]triazine-5,7-dione **1.10** (J. Org. Chem., 1958, 23, 1931) are converted respectively into 8-hydroxy-pyrido[3,4-b]pyrazine-7-carboxylic acid methyl ester **1.8** and 8-hydroxy-pyrido[3,4-e][1,2,4]triazine-7-carboxylic acid methyl ester **1.11** and the corresponding carboxylic acids **1.9** and **1.12**.

As shown in Example **4**, 3-methyl-furo[3,4-b]pyridine-5,7-dione **1.13** is converted, as described above, 8-hydroxy-3-methyl-[1,6]naphthyridine-7-carboxylic acid methyl ester **1.14** and the corresponding carboxylic acid **1.15**.

Scheme **1A** illustrates the preparation of bicyclic hydroxyesters **1A.3** in which a substituent Nu is introduced at the 5-position. In this procedure, the bicyclic hydroxyester **1A.1**, prepared as described in Scheme **1**, is halogenated to give the 5-halo product **1A.2** in which Ha is Cl, Br or I. The halogenation reaction is performed, for example, as described in WO 0230930 A2, p. 159, by reaction of the phenolic

ester with N-bromosuccinimide in chloroform, to give the product **1A.2** in which Ha is Br. Alternatively, the hydroxyester **1A.1** is reacted with N-iodosuccinimide, as described in WO 0230930 A2 p. 166, to give the product **1A.2** in which Ha is iodo. The halogenated product is then reacted with a nucleophile Nu, to prepare the displacement product **1A.3**. Examples of nucleophiles include hydroxy, mercapto or amino compounds, or cyclic or acyclic sulfonamides. The displacement reaction is performed in a polar organic solvent such as pyridine, dimethylformamide, DMPU, dimethylsulfoxide and the like, for example as described in WO 0230930 A2, Examples 57-78. Optionally, the phenolic hydroxyl group is protected prior to the displacement reaction, and deprotected afterwards.

For example, 8-hydroxy-[1,6]naphthyridine-7-carboxylic acid methyl ester **1A.4** (WO 0230930 A2, p. 171) is reacted with one molar equivalent of N-bromosuccinimide in dichloromethane, to yield 5-bromo-8-hydroxy-[1,6]naphthyridine-7-carboxylic acid methyl ester, **1A.5**. The phenol is then reacted with p-toluenesulfonyl chloride and triethylamine in chloroform, for example as described in WO 02 30931 A2 p. 72, to give 5-bromo-8-(toluene-4-sulfonyloxy)-[1,6]naphthyridine-7-carboxylic acid methyl ester **1A.6**. The product is then reacted with [1,2]thiazinane 1,1-dioxide **1A.7** and cuprous oxide in pyridine at reflux, for example as described in WO 0230931 A2, p. 73, to produce 5-(1,1-dioxo-1,2]thiazinan-2-yl)-8-(toluene-4-sulfonyloxy)-[1,6]naphthyridine-7-carboxylic acid methyl ester **1A.8**. Deprotection, for example by reaction with methanolic sodium methoxide in dimethylformamide, as described in WO 0230931 A2 p. 74, then affords the phenol **1A.9**.

Using the above procedures, but employing different hydroxyesters **1A.1** in place of the hydroxyester **1A.4**, and/or different nucleophiles, the corresponding products **1A.3** are obtained.

Alternative methods for the preparation of the phosphonate ester amides 2.4.

As shown in Scheme **2**, the hydroxyester **2.1**, prepared as described above, is transformed, using the procedures described below, (Schemes **3 - 31**) into the phosphonate ester **2.2**. The ester, or the corresponding carboxylic acid, is then

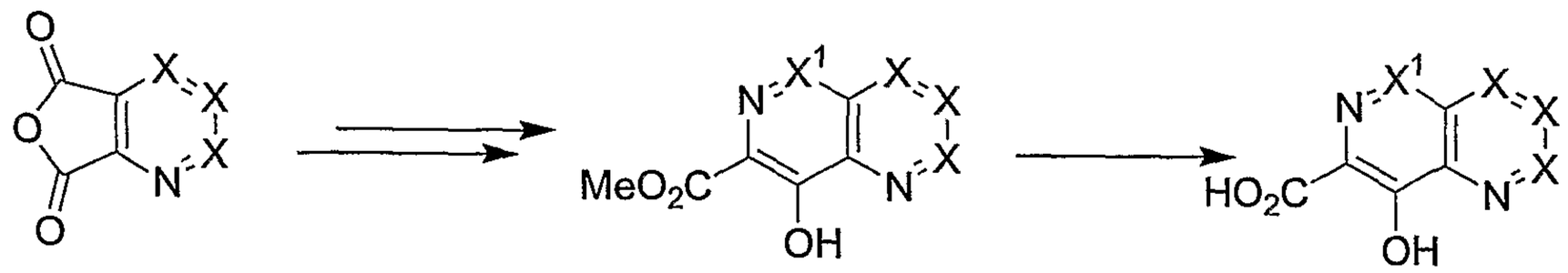
converted, using, for example, the procedures described in WO 0230930 A2, Schemes 1, 2, 3 and 5, into the phosphonate amide **2.4**.

Alternatively, the ester **2.1**, or the corresponding carboxylic acid, is transformed, as described above, into the amide **2.3**, and the latter compound is then converted, using the procedures described below, (Schemes **3 - 31**) into the phosphonate amide **2.4**.

The selection of a suitable stage in the synthetic sequence for the introduction of the phosphonate group is made by one skilled in the art, depending on the reactivities and stabilities of the substrates in a given reaction sequence.

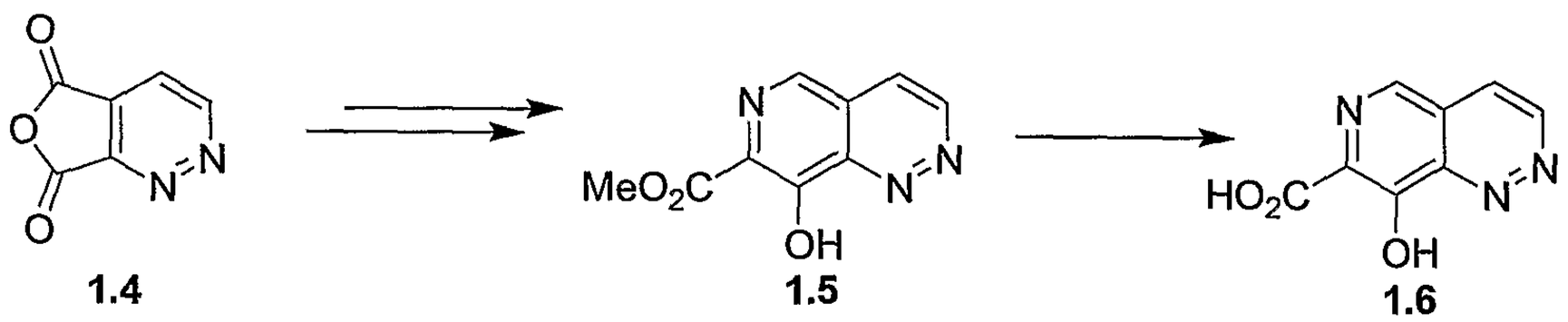
Scheme 1.

Method



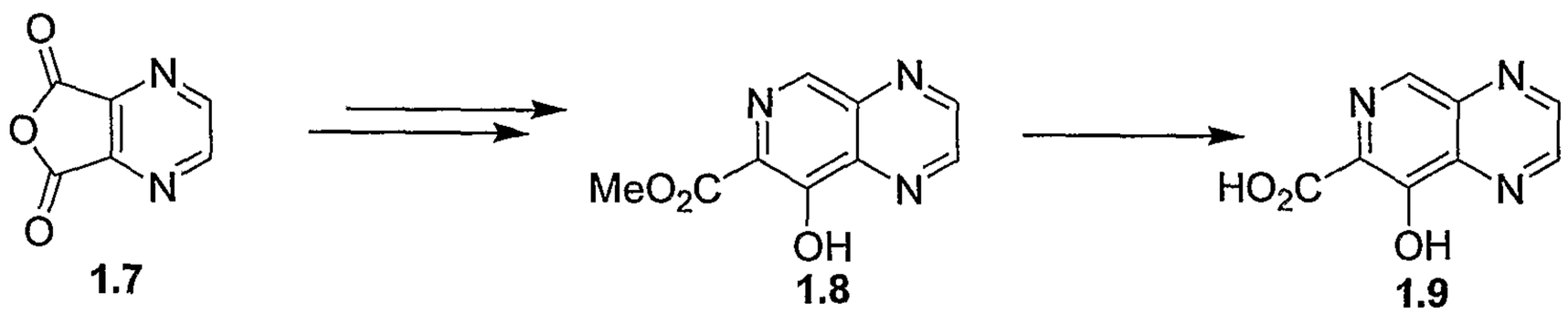
1.1 **1.2** **1.3**

Example 1



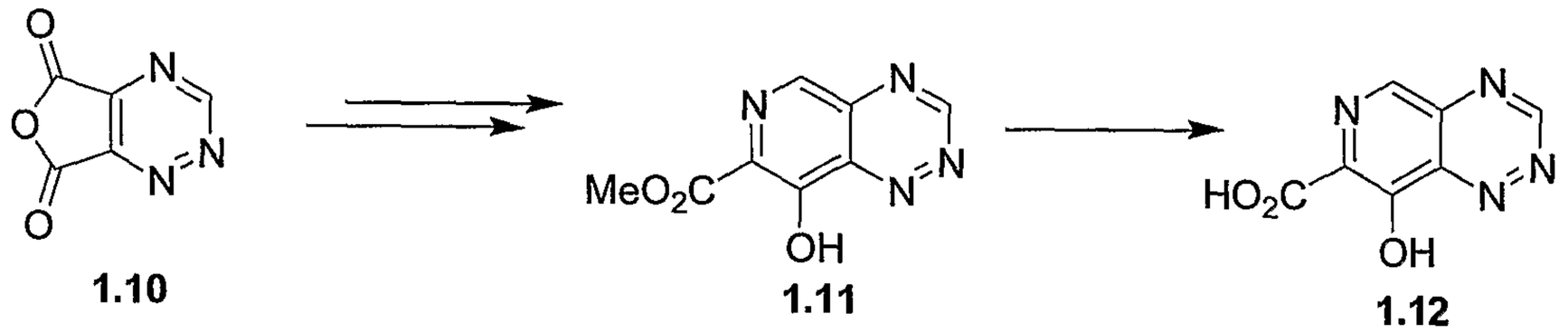
1.4 **1.5** **1.6**

Example 2



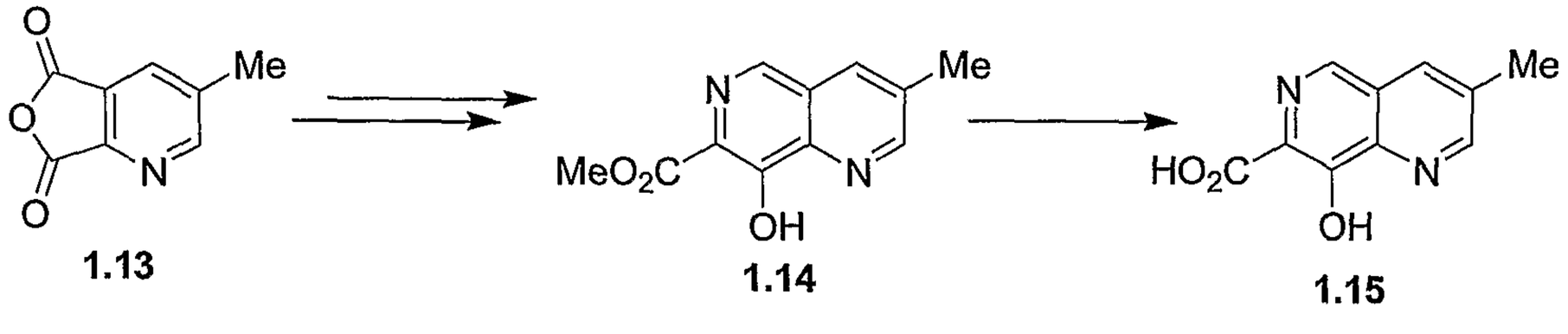
1.7 **1.8** **1.9**

Example 3



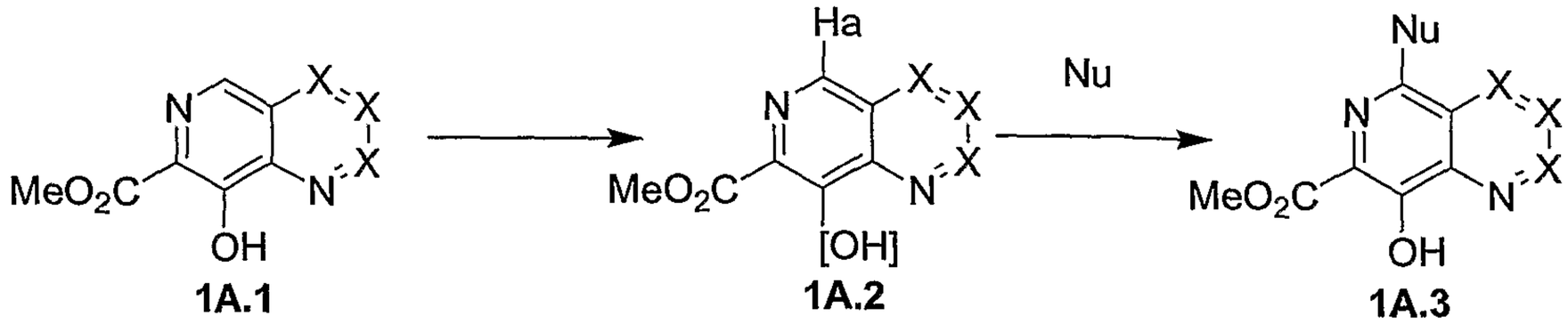
1.10 **1.11** **1.12**

Example 4

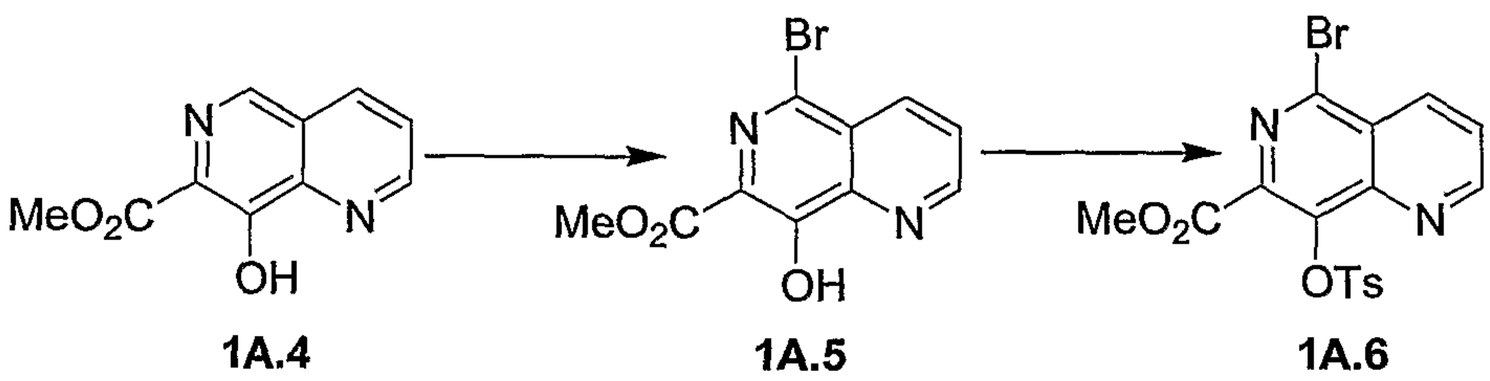


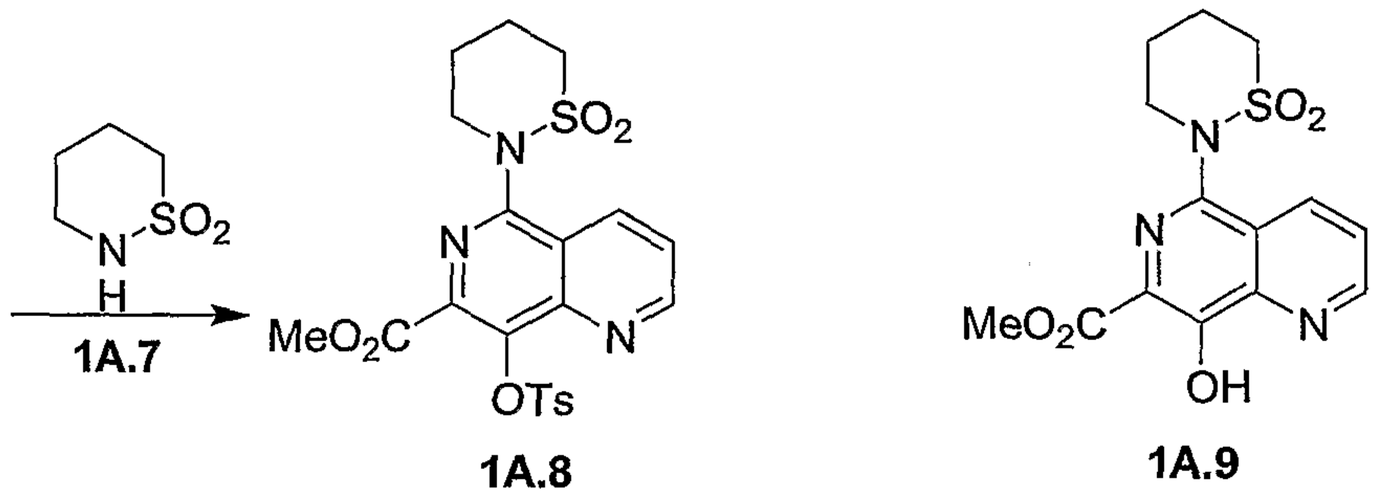
1.13 **1.14** **1.15**

Scheme 1A

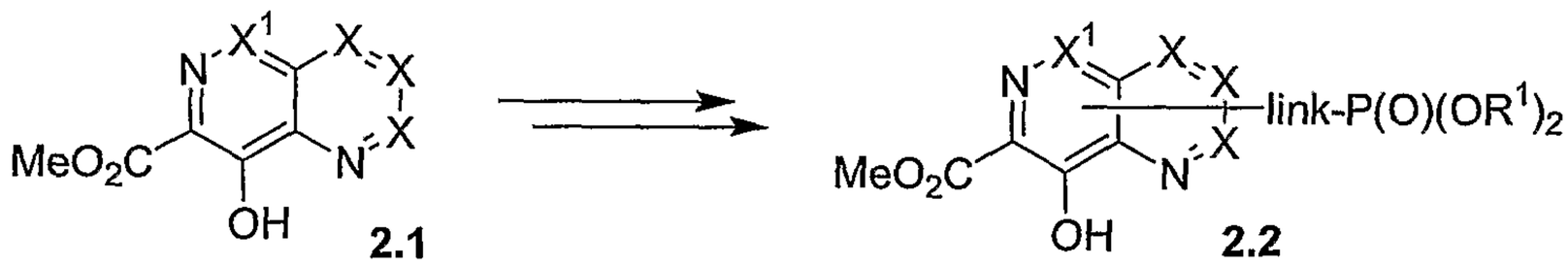


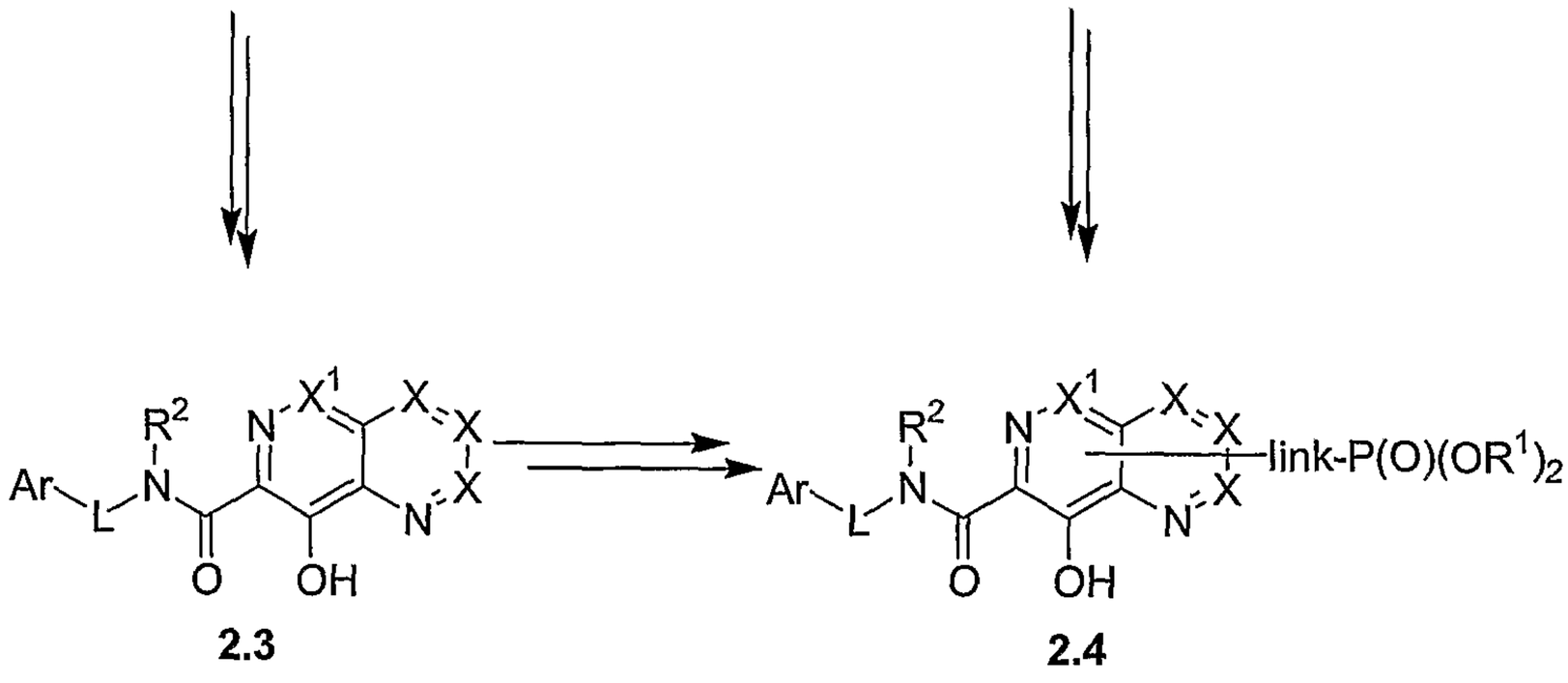
Example





Scheme 2.





Preparation of the intermediate phosphonate esters 1.

Schemes **3** - **7** illustrate methods for the preparation of the phosphonate esters **1**.

Scheme **3** depicts the preparation of phosphonate esters **1** in which the phosphonate group is directly attached to the group Ar. In this procedure, a bromo-substituted amine **3.1**, in which Ar is an aromatic or heteroaromatic group, is reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **3.2** to yield the aryl phosphonate **3.3**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. This reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a palladium (0) catalyst such as tetrakis(triphenylphosphine)palladium(0). Optionally, the amine group is protected prior to the coupling reaction, and deprotected afterwards. The amine is then reacted with the ester **3.4** to afford the amide **3.5**. The conversion of esters into amides is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 987. The reactants are combined in a solvent such as toluene or xylene, in the presence of a base such as sodium methoxide under azeotropic conditions, or of a dialkyl aluminum or trialkyl tin derivative of the amine. The use of trimethylaluminum in the conversion of esters to amides is described in J. Med. Chem. Chim. Ther., 34, 1999, 1995, and Syn. Comm., 25, 1401, 1995. The reaction is conducted in an inert solvent such as dichloromethane or toluene. The conversion of bicyclic esters such as **3.4**, or the corresponding carboxylic acids, into amides is described in WO 0230930 A2, Schemes 1, 2, 3 and 6. Optionally, the phenolic hydroxyl group of the bicyclic ester **3.4** is protected, for example as a p-toluenesulfonyl derivative, as described in WO 0230930 A2, Example 1, prior to reaction with the amine component **3.3**.

For example, 3-bromo-4-fluorobenzylamine **3.6** (Lancaster) is reacted in toluene solution at ca. 100°, with one molar equivalent of a dialkyl phosphite **3.7**, triethylamine and 3 mol % of tetrakis(triphenylphosphine)palladium(0), to give the phosphonate product **3.8**. The latter compound is then reacted, in toluene solution at reflux temperature with 5-(1,1-dioxo[1,2]thiazinan-2-yl)-8-hydroxy-

[1,6]naphthyridine-7-carboxylic acid methyl ester **3.9**, prepared by the methods described in WO 0230930 A2, and Schemes **1**, **1A** and **2**, to yield the amide **3.10**.

Using the above procedures, but employing, in place of the amine **3.6**, different amines **3.1**, and/or different bicyclic esters **3.4**, the corresponding amides **3.5** are obtained.

Scheme **4** depicts the preparation of phosphonate esters **1** in which the phosphonate group is attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromo-substituted amine **4.1**, in which Ar is an aryl or heteroaryl group, is subjected to a Heck coupling reaction, in the presence of a palladium catalyst, with a dialkyl alkenyl phosphonate **4.2**, in which R^5 is a direct bond, an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, to give the amine **4.3**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the amine substituent is protected prior to the coupling reaction, and deprotected afterwards. The phosphonate amine **4.3** is then coupled, as described above, with the ester **4.4**, or the corresponding carboxylic acid, to produce the amide **4.5**. Optionally, the double bond is reduced to give the saturated analog **4.6**. The reduction of olefinic bonds is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

For example, 3-bromo-4-methoxybenzylamine **4.7** (Lancaster) is reacted in dioxan solution with one molar equivalent of a dialkyl vinyl phosphonate **4.8** (Aldrich) and potassium carbonate, to yield the olefinic phosphonate **4.9**. The product is then reacted, as described above, with 5-(1,1-dioxo-isothiazolidin-2-yl)-8-hydroxy-

[1,6]naphthyridine-7-carboxylic acid methyl ester **4.10**, prepared as described in Scheme **1A**, and by methods described in WO 0230930 A2, to give the amide **4.11**. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product **4.12**.

Using the above procedures, but employing, in place of the amine **4.7**, different amines **4.1**, and/or different phosphonates **4.2**, and/or different bicyclic esters **4.4**, the corresponding amides **4.5** and **4.6** are obtained.

Scheme **5** depicts the preparation of phosphonate esters **1** in which the phosphonate group is attached by means of an amide linkage. In this procedure, the amine group of a carboxy-substituted amine **5.1** is protected to afford the derivative **5.2**. The protection of amino groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 309ff. Amino groups are protected, for example by alkylation, such as by mono or dibenzylation, or by acylation. The conversion of amines into mono or dibenzylamines, for example by treatment with benzyl bromide in a polar solvent such as acetonitrile or aqueous ethanol, in the presence of a base such as triethylamine or sodium carbonate, is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 364. The N-protected carboxylic acid **5.2** is then coupled with an amino-substituted dialkyl phosphonate **5.3**, in which the group R^5 is as defined in Scheme **4**, to yield the amide **5.4**. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid is first converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and

then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

The amino-protecting group is then removed from the product **5.4** to give the free amine **5.5**. Deprotection of amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 309ff. The amine is then coupled with the carboxylic acid **5.6**, as described above, to produce the amide **5.7**.

For example, 4-carboxycyclohexylmethylamine **5.8** (Aldrich) is converted into the phthalimido derivative **5.9**. The conversion of amines into phthalimido derivatives is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 358. The conversion is effected by reaction of the amine with an equimolar amount of 2-carbomethoxybenzoyl chloride, N-carboethoxyphthalimide, or preferably, phthalic anhydride. The reaction is performed in an inert solvent such as toluene, dichloromethane or acetonitrile, to prepare the phthalimido derivative **5.9**. This material is then reacted with one molar equivalent of a dialkyl aminoethyl phosphonate **5.10**, (J. Org. Chem., 2000, 65, 676) and dicyclohexylcarbodiimide in dimethylformamide, to give the amide **5.11**. The phthalimido protecting group is then removed, for example by reaction with ethanolic hydrazine at ambient temperature, as described in J. Org. Chem., 43, 2320, 1978, to afford the amine **5.12**. This compound is coupled in dimethylformamide solution with 5-(methanesulfonyl-methyl-amino)-8-hydroxy-[1,6]naphthyridine-7-carboxylic acid **5.13**, prepared as described in Scheme **1A** and WO 0230930 A2 Example 154, and 1-ethyl-3-(dimethylaminopropyl)carbodiimide, to afford the amide **5.14**.

Using the above procedures, but employing, in place of the amine **5.8**, different amines **5.1**, and/or different phosphonates **5.3**, and/or different carboxylic acids **5.6**, the corresponding products **5.7** are obtained.

Scheme **6** depicts the preparation of phosphonates **1** in which the phosphonate is attached by means of an ether linkage. In this procedure, the amino group of a hydroxy-substituted amine **6.1** is protected, as described above, to give the derivative **6.2**. The alcohol is then reacted, with base catalysis, with a dialkyl bromomethyl phosphonate **6.3**, in which the group R^5 is as defined in Scheme **4**. The reaction is conducted in a polar aprotic solvent such as tetrahydrofuran, dimethylformamide or dimethylsulfoxide, in the presence of a base such as potassium carbonate, for cases in which Ar is an aromatic group, or a strong base such as sodium hydride, for cases in which Ar is an aliphatic group. The amino group of the resulting ether **6.4** is then deprotected, as previously described, to give the amine **6.5**. The amine is then reacted with the ester **6.6**, as described in Scheme **3**, to give the amide **6.7**.

For example, N-methyl 3-hydroxyphenethylamine **6.8** is reacted with one molar equivalent of acetyl chloride in dichloromethane containing pyridine, to give the N-acetyl product **6.9**. The product is then reacted at ca. 60° in dimethylformamide solution with one molar equivalent of a dialkyl 3-bromopropenyl phosphonate **6.10** (Aurora) and cesium carbonate, to produce the ether **6.11**. The N-acetyl group is then removed, for example by treatment with hog kidney acylase, as described in Tet., 44, 5375, 1988, to give the amine **6.12**. The product is then reacted in toluene solution at reflux, as described above, with 5-(1,1-dioxo-[1,2]thiazepan-2-yl)-8-hydroxy-[1,6]naphthyridine-7-carboxylic acid methyl ester **6.13**, prepared as described in Scheme **1A** and in WO 0230931 Example 6, to yield the amide **6.14**.

Using the above procedures, but employing, in place of the amine **6.8**, different amines **6.1**, and/or different phosphonates **6.3**, and/or different bicyclic esters **6.6**, the corresponding products **6.7** are obtained.

Scheme **7** depicts the preparation of phosphonates **1** in which the phosphonate is attached by means of an ether or thioether linkage. In this procedure, a N-protected hydroxyamine **6.2**, in which Ar is an aromatic moiety, is subjected to a Mitsunobu reaction with a hydroxy or mercapto-substituted dialkyl phosphonate **7.1**, in which R^5 is as defined in Scheme **4**, to prepare the ether or thioether product **7.2**. The preparation of aromatic ethers and thioethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and

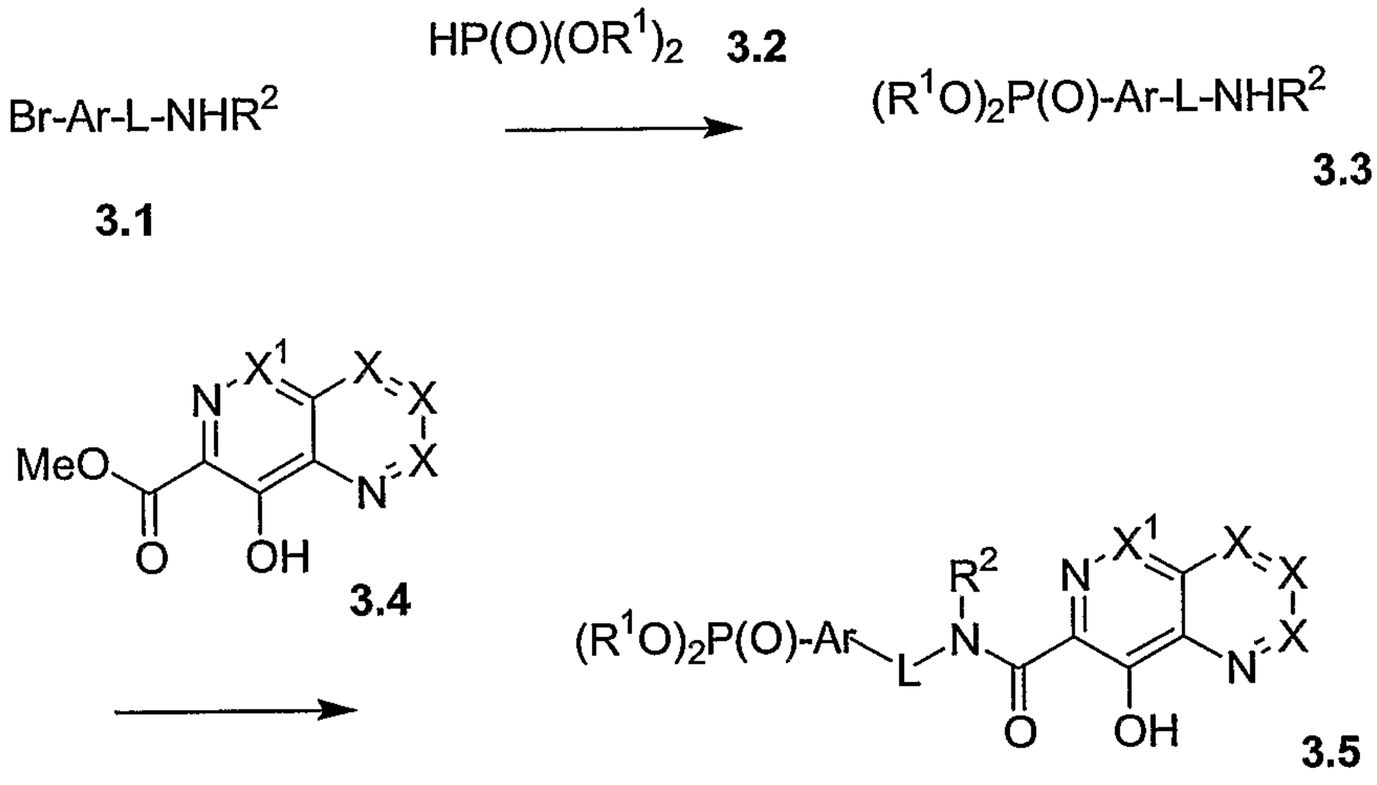
R. J. Sundberg, Plenum, 2001, p. 153-4 and in Org. React., 1992, 42, 335. The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran or dioxan, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The N-protecting group is then removed and the resultant amine is converted, as described in Scheme **6**, into the amide **7.3**.

For example, N-acetyl 3,5-dichloro-4-hydroxybenzylamine **7.4** is reacted tetrahydrofuran solution with one molar equivalent of a dialkyl mercaptoethyl phosphonate **7.5**, (Zh. Obschei. Khim., 1973, 43, 2364) diethyl azodicarboxylate and tri-o-tolylphosphine, to afford the thioether product **7.6**. The N-acetyl group is removed, as described in Scheme **6**, and the amine **7.7** is then reacted with 5-(1,1-dioxo-[1,2,5]thiadiazepan-2-yl)-8-hydroxy-[1,6]naphthyridine-7-carboxylic acid methyl ester **7.8**, (see, for example, WO 0230931 Example 3) to afford the amide **7.9**.

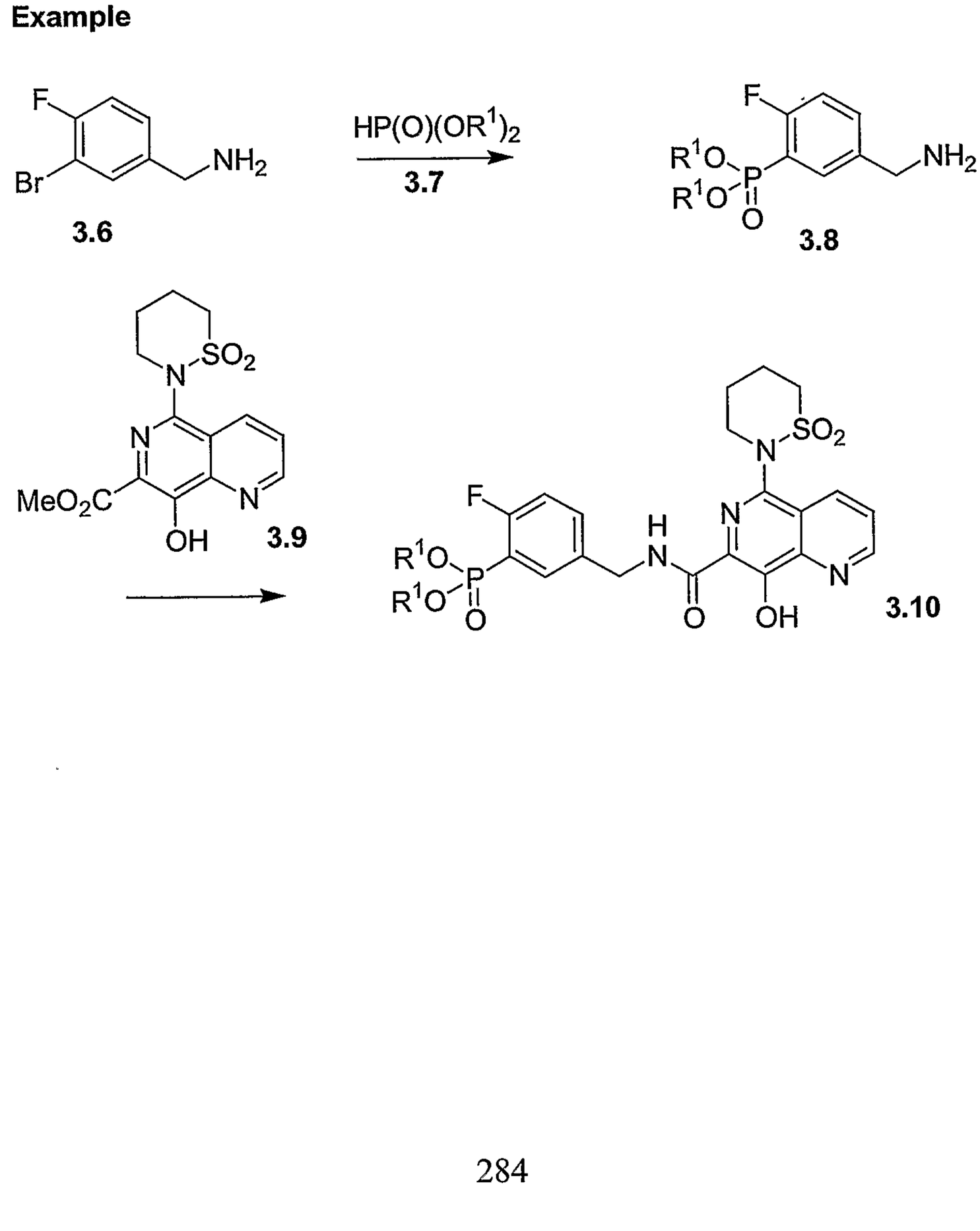
Using the above procedures, but employing, in place of the amine **7.4**, different amines **6.2**, and/or different phosphonates **7.2**, the corresponding products **7.3** are obtained.

Scheme 3. Phosphonates 1.

Method

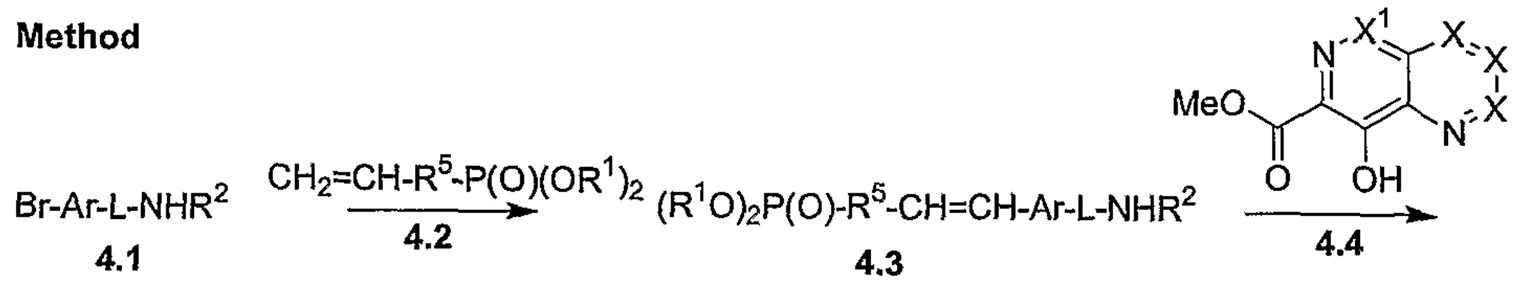


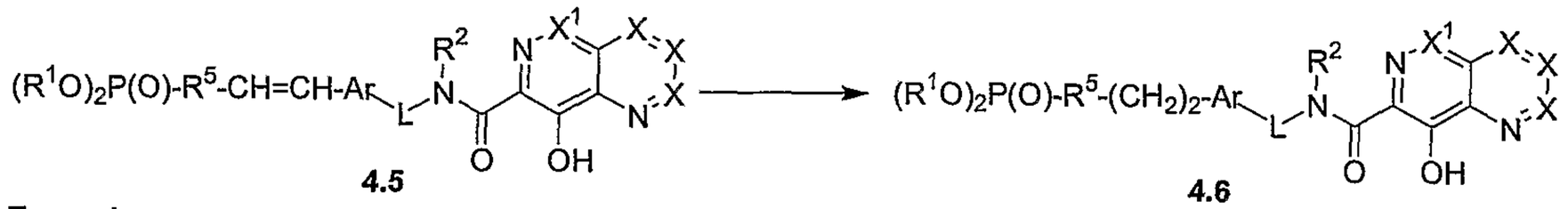
Example



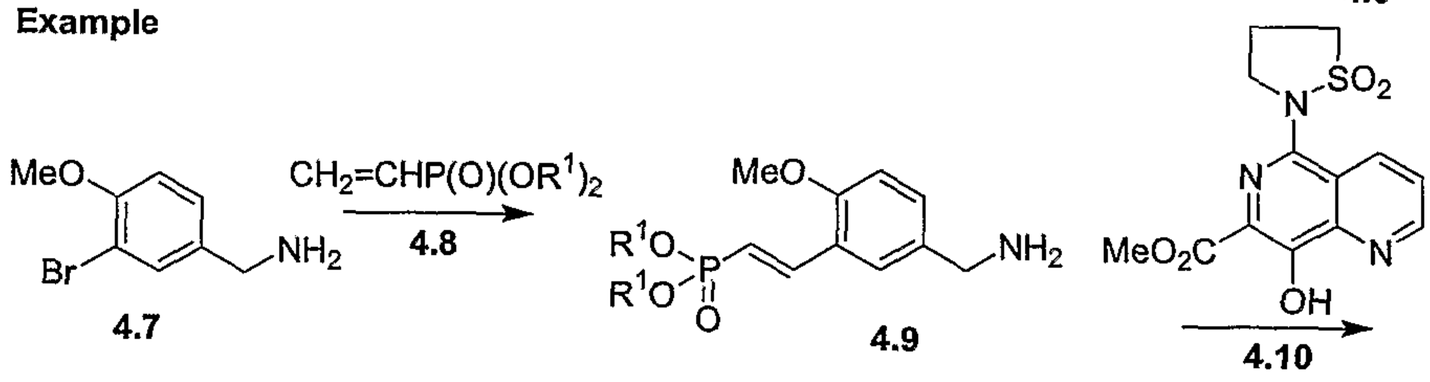
Scheme 4. Phosphonates 1.

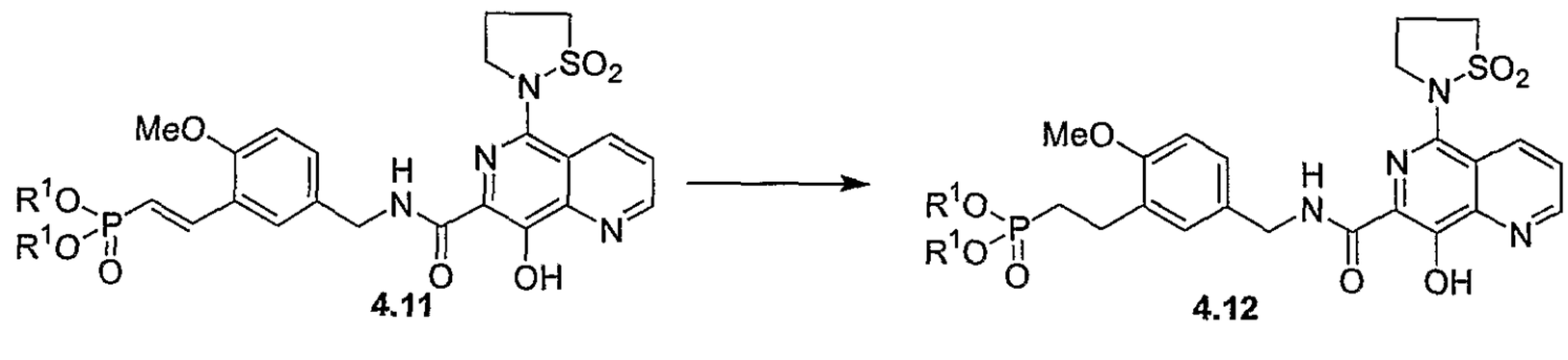
Method





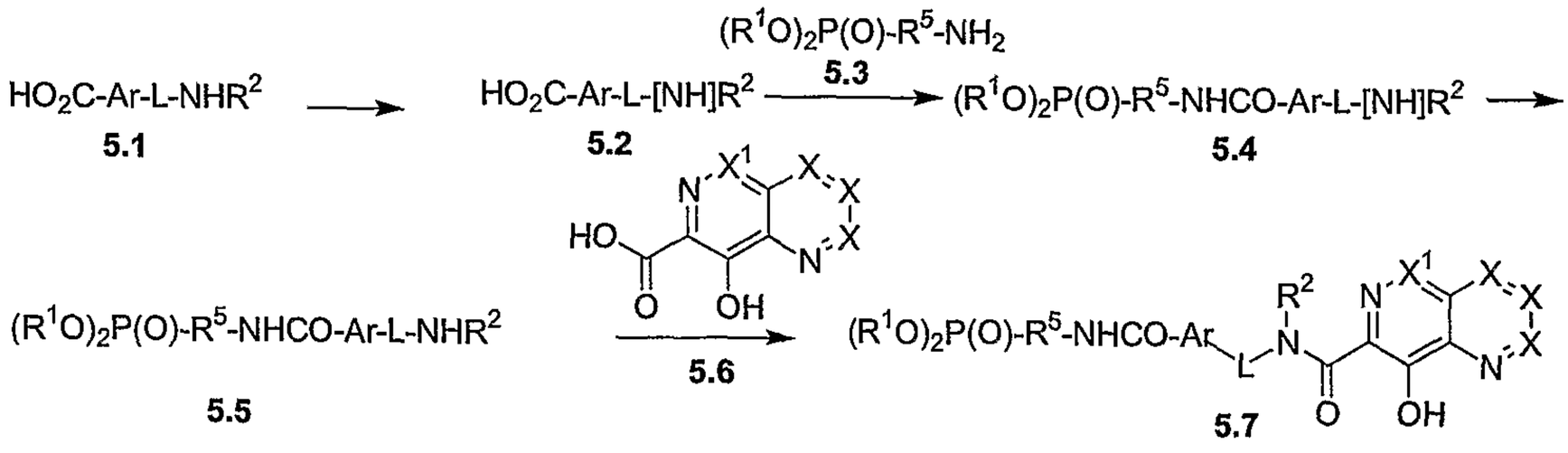
Example



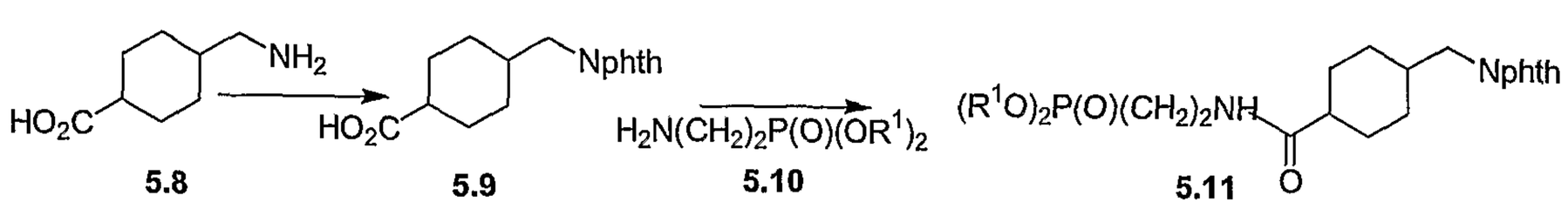


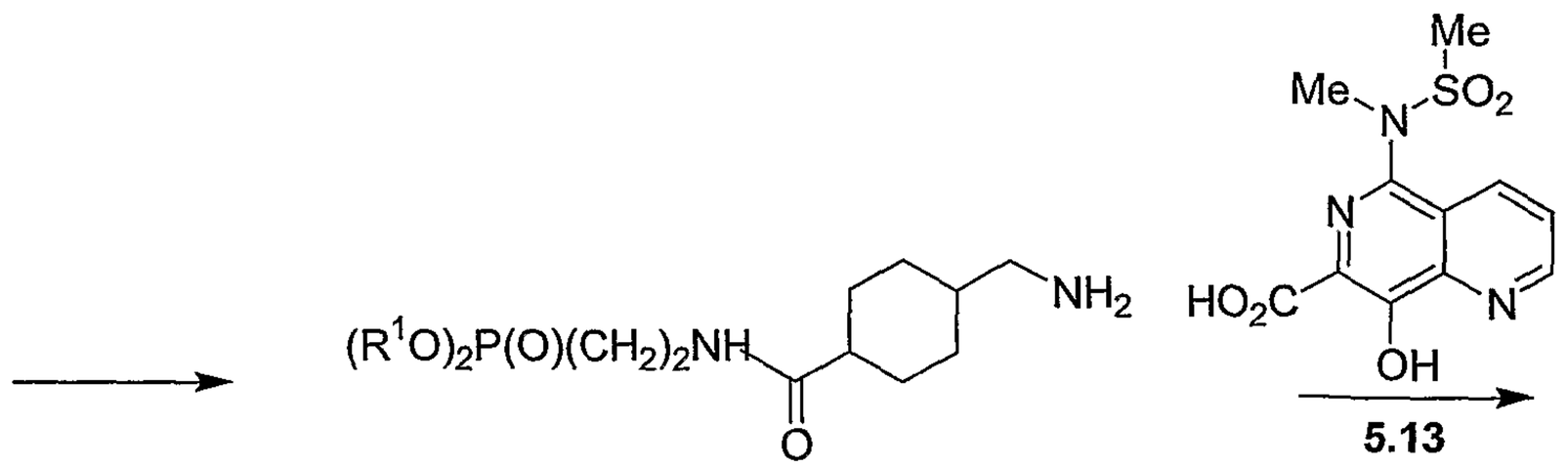
Scheme 5. Phosphonates 1.

Method



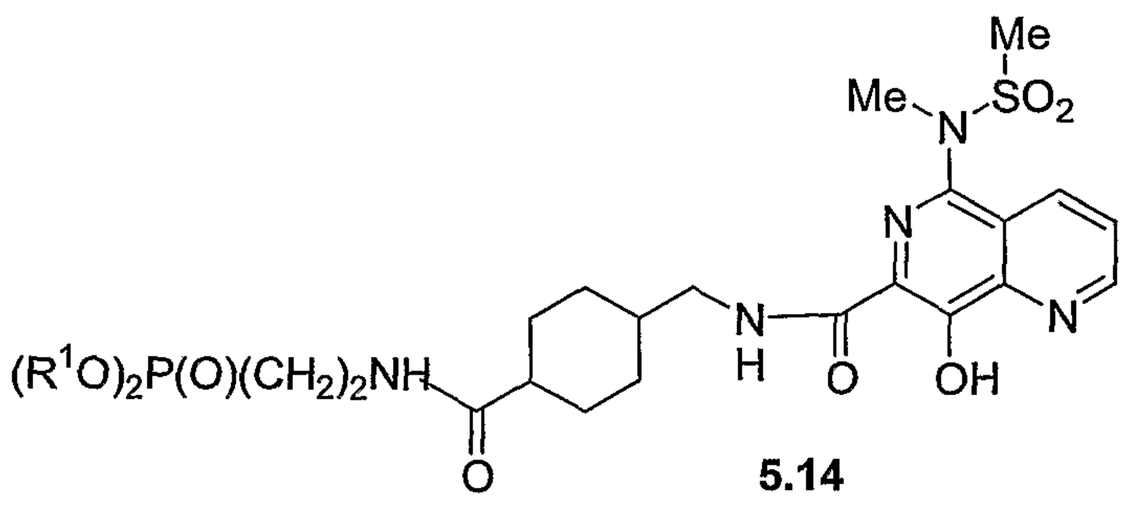
Example





5.13

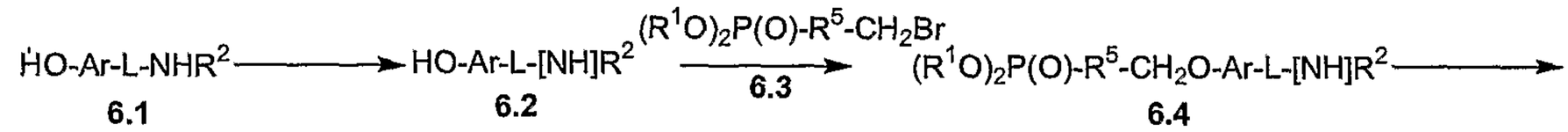
5.12

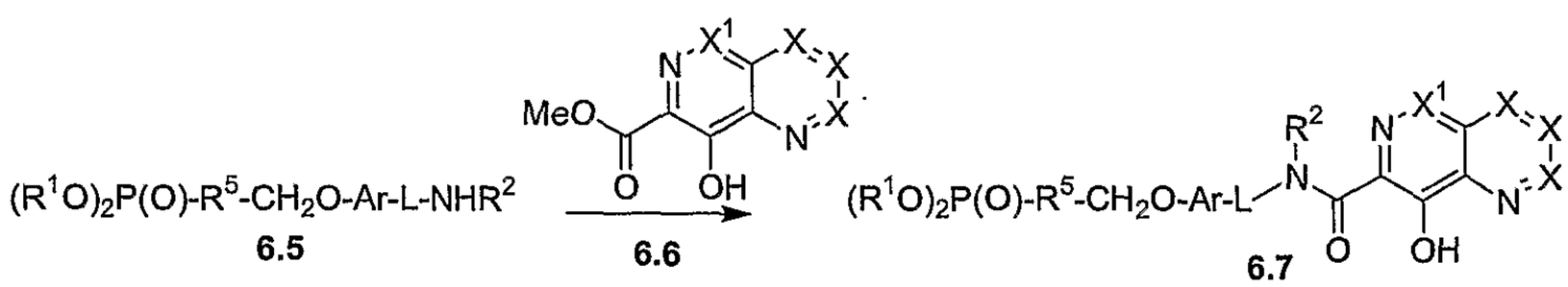


5.14

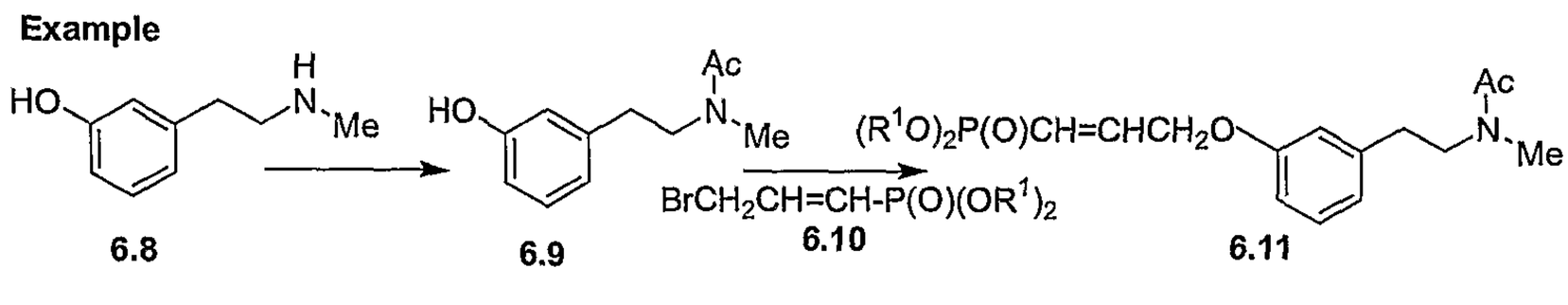
Scheme 6. Phosphonates 1.

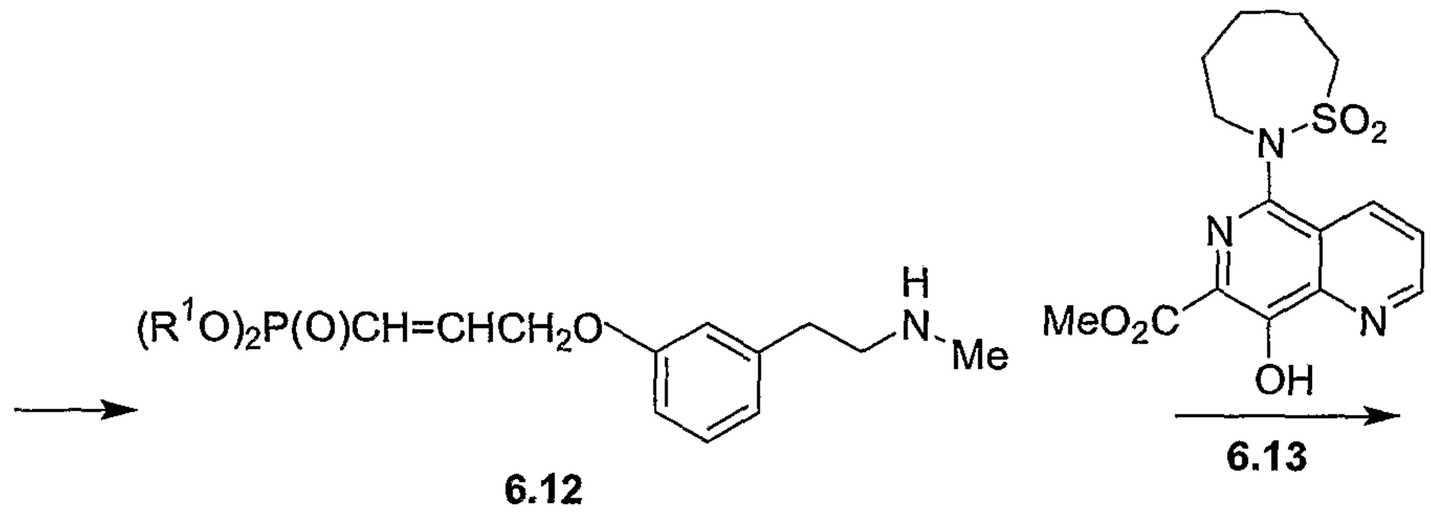
Method



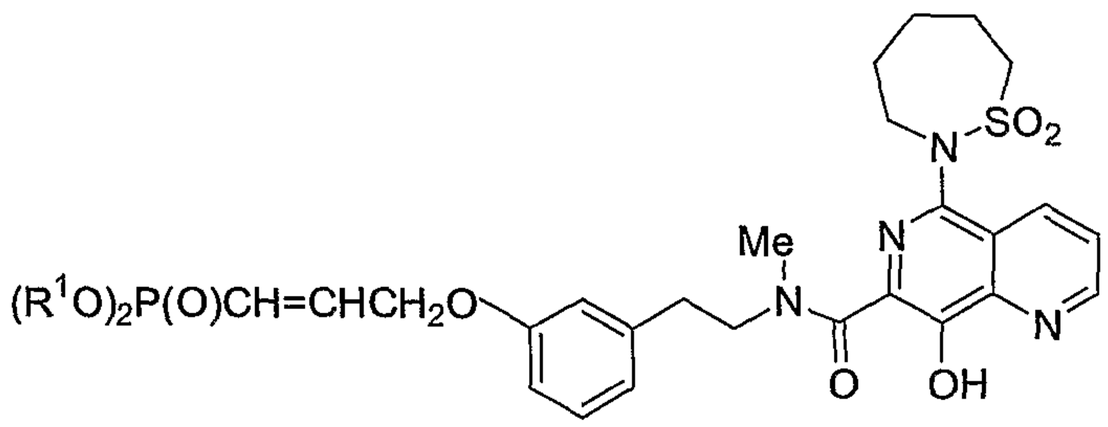


Example





6.12



6.14

Preparation of the intermediate phosphonate esters 2.

Schemes **8 - 10** illustrate methods for the preparation of the phosphonate esters **2**.

Scheme **8** depicts the preparation of phosphonates **2** in which the phosphonate is attached by means of an alkylene chain incorporating an amide linkage. In this procedure, an amine **8.1** is reacted with a bromoalkyl ester **8.2**, in which R^5 is as defined in Scheme **4**, to yield the alkylated amine **8.3**. The preparation of substituted amines by the reaction of amines with alkyl halides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 397. Equimolar amounts of the reactants are combined in a polar solvent such as an alkanol or dimethylformamide and the like, in the presence of a base such as cesium carbonate, diazabicyclononene or dimethylaminopyridine, to yield the substituted amine. The ester group is then hydrolyzed to give the carboxylic acid **8.4**, and this compound is then coupled, as described in Scheme **5**, with a dialkyl aminoalkyl phosphonate **8.5**, to produce the aminoamide **8.6**. Optionally, the amino group of the amine **8.4** is protected prior to the coupling reaction, and deprotected afterwards. The product is then reacted with the bicyclic hydroxyester **8.7** to afford the amide **8.8**.

For example, 4-trifluoromethylbenzylamine **8.9** is reacted in dimethylformamide with one molar equivalent of methyl bromoacetate **8.10** and

potassium carbonate to give the ester **8.11**. Hydrolysis, employing one molar equivalent of lithium hydroxide in aqueous dimethoxyethane, affords the carboxylic acid **8.12**, and this compound is coupled in tetrahydrofuran solution with a dialkyl aminomethyl phosphonate **8.13** (Aurora), in the presence of dicyclohexylcarbodiimide, to give the aminoamide **8.14**. The product is then reacted with 5-(1,1-dioxo-isothiazolidin-2-yl)-8-hydroxy-[1,6]naphthyridine-7-carboxylic acid methyl ester **8.15**, prepared by the methods described above, to yield the amide **8.16**.

Using the above procedures, but employing, in place of the amine **8.9**, different amines **8.1**, and/or different bromoesters **8.2**, and/or different phosphonates **8.5**, and/or different hydroxyesters **8.7**, the corresponding products **8.8** are obtained.

Scheme **9** depicts the preparation of phosphonates **2** in which the phosphonate is attached by means of a variable carbon chain. In this procedure, a primary amine **9.1** is subjected to a reductive amination reaction with a dialkyl formyl-substituted phosphonate **9.2**, in which R^5 is as defined in Scheme **4**, to afford the alkylated amine **9.3**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in a polar solvent in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The product **9.3** is then reacted, as described previously, with the bicyclic ester **9.4** to give the amide **9.5**.

For example, 3,4-dichlorobenzylamine is reacted in methanol solution with one molar equivalent of a dialkyl 3-formylphenyl phosphonate **9.7**, (Epsilon) and sodium cyanoborohydride, to yield the alkylated product **9.8**. This compound is then reacted with 5-(methanesulfonyl-methyl-amino)-8-hydroxy-[1,6]naphthyridine-7-carboxylic acid methyl ester **9.9**, prepared using the methods described above, from the corresponding bromo compound and N-methyl methanesulfonamide, to give the amide **9.10**.

Using the above procedures, but employing, in place of the amine **9.6**, different amines **9.1**, and/or different phosphonates **9.2**, and/or different bicyclic esters **9.4**, the corresponding products **9.5** are obtained.

Scheme **10** depicts an alternative method for the preparation of phosphonates **2** in which the phosphonate is attached by means of a variable carbon chain. In this procedure, the phenolic group of a bicyclic amide **10.1**, prepared as described above, and in WO 02 30930 A2, is protected to give the product **10.2**. The protection of phenolic hydroxyl groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 10ff. For example, hydroxyl substituents are protected as trialkylsilyloxy ethers. Trialkylsilyl groups are introduced by the reaction of the phenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, phenolic hydroxyl groups are protected as benzyl or substituted benzyl ethers, or as acetal ethers such as methoxymethyl or tetrahydropyranyl. The O-protected amide **10.2** is then reacted with the phosphonate-substituted trifluoromethanesulfonate **10.3**, in which R^5 is as defined in Scheme **4**, to produce the alkylated amide **10.4**. The alkylation reaction is conducted between equimolar amounts of the reactants in an aprotic organic solvent such as dimethylformamide or dioxan, in the presence of a strong base such as lithium hexamethyl disilylazide or sodium hydride, at from ambient temperature to about 90°. The hydroxyl group is then deprotected to give the phenol **10.5**. Deprotection of phenolic hydroxyl groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 10ff. For example, silyl protecting groups are removed by reaction with tetrabutylammonium fluoride, benzyl groups are removed by catalytic hydrogenation and acetal ethers are removed by treatment with acids.

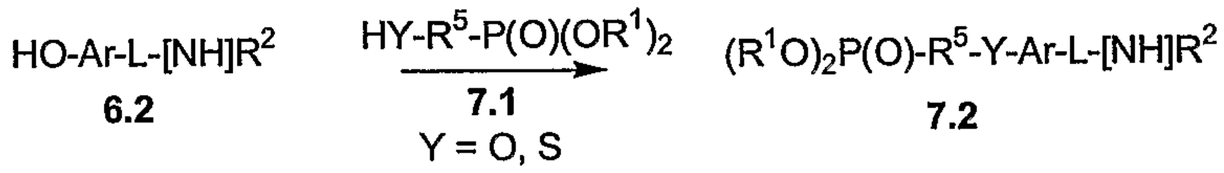
For example, furo[3,4-b]pyrazine-5,7-dione **10.6**, (J. Org. Chem., 1964, 29, 2128) is converted, as described above,(Schemes **1**, **1A** and **2**) and in WO 0230930 A2, into 5-(1,1-dioxo-1,2]thiazinan-2-yl)-8-hydroxy-pyrido[3,4-b]pyrazine-7-carboxylic acid (naphthalen-2-ylmethyl)-amide **10.7**. The product is then reacted with one molar equivalent of tert-butyl chlorodimethylsilane and imidazole in dichloromethane, to give the silyl ether **10.8**. This compound is then reacted at

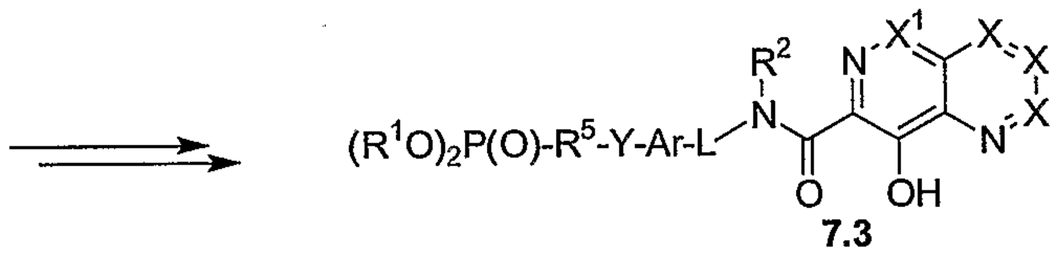
ambient temperature in dioxan solution with one molar equivalent of sodium hydride, followed by the addition of a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **10.9** (Tet. Lett., 1986, 27, 1477), to afford the alkylated product **10.10**. Deprotection, by reaction with tetrabutylammonium fluoride in tetrahydrofuran, then yields the product **10.11**.

Using the above procedures, but employing, in place of the amide **10.7**, different amides **10.1**, and/or different phosphonates **10.3**, the corresponding products **10.5** are obtained.

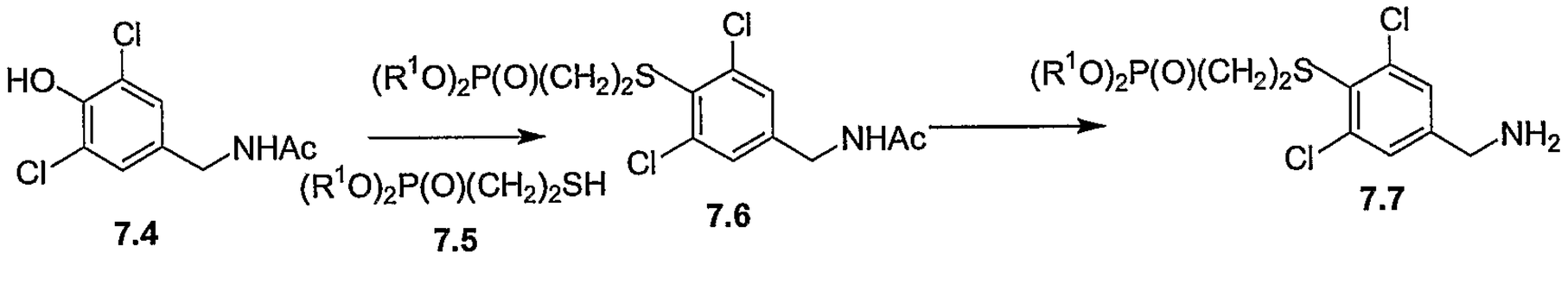
Scheme 7. Phosphonates 1.

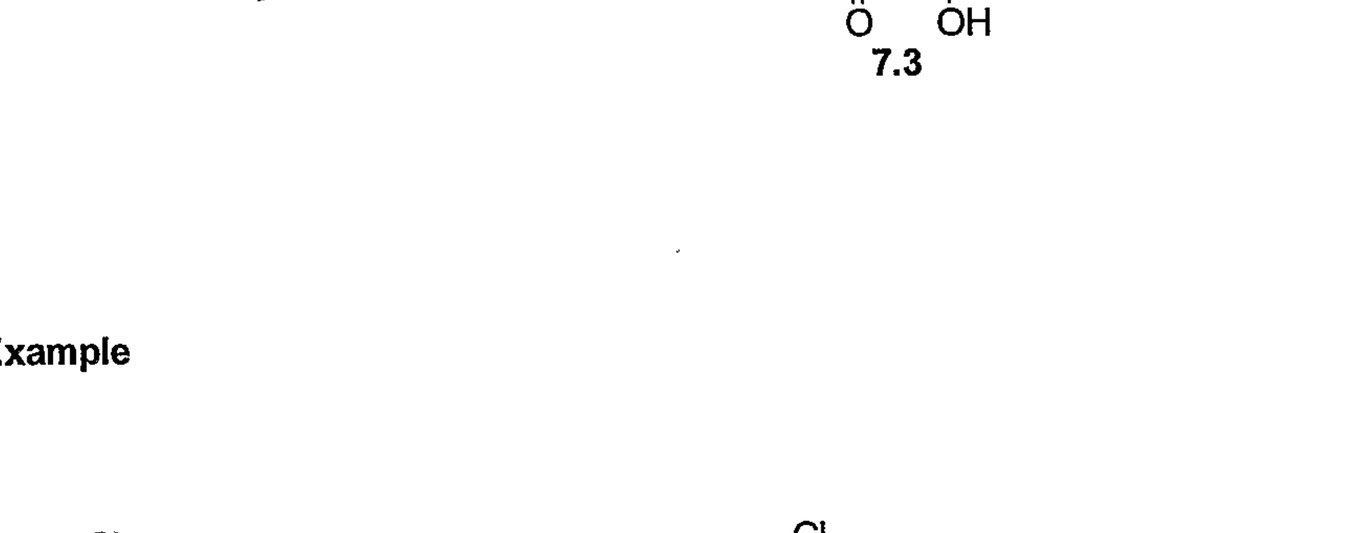
Method





Example

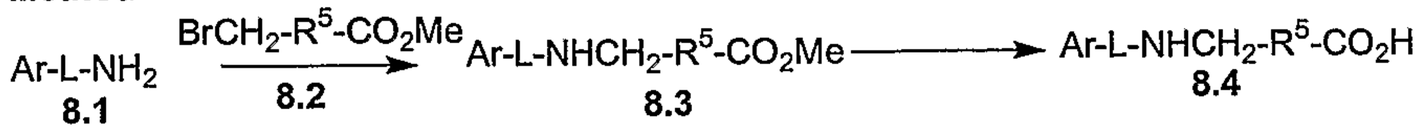


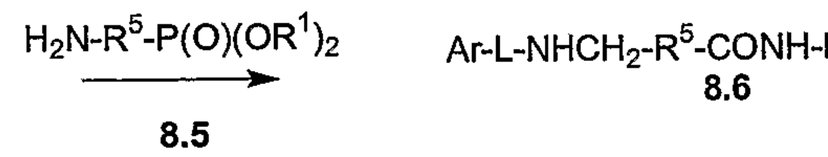


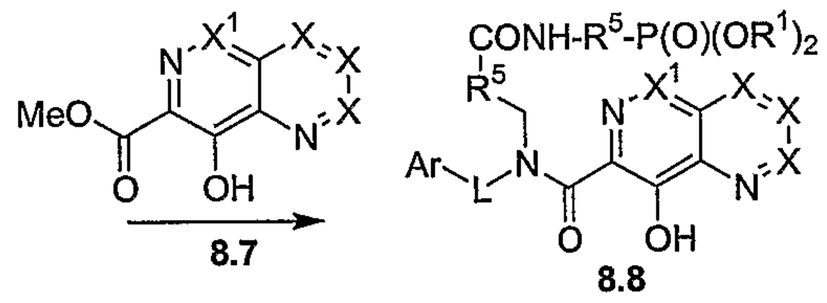
10

Scheme 8. Phosphonates 2.

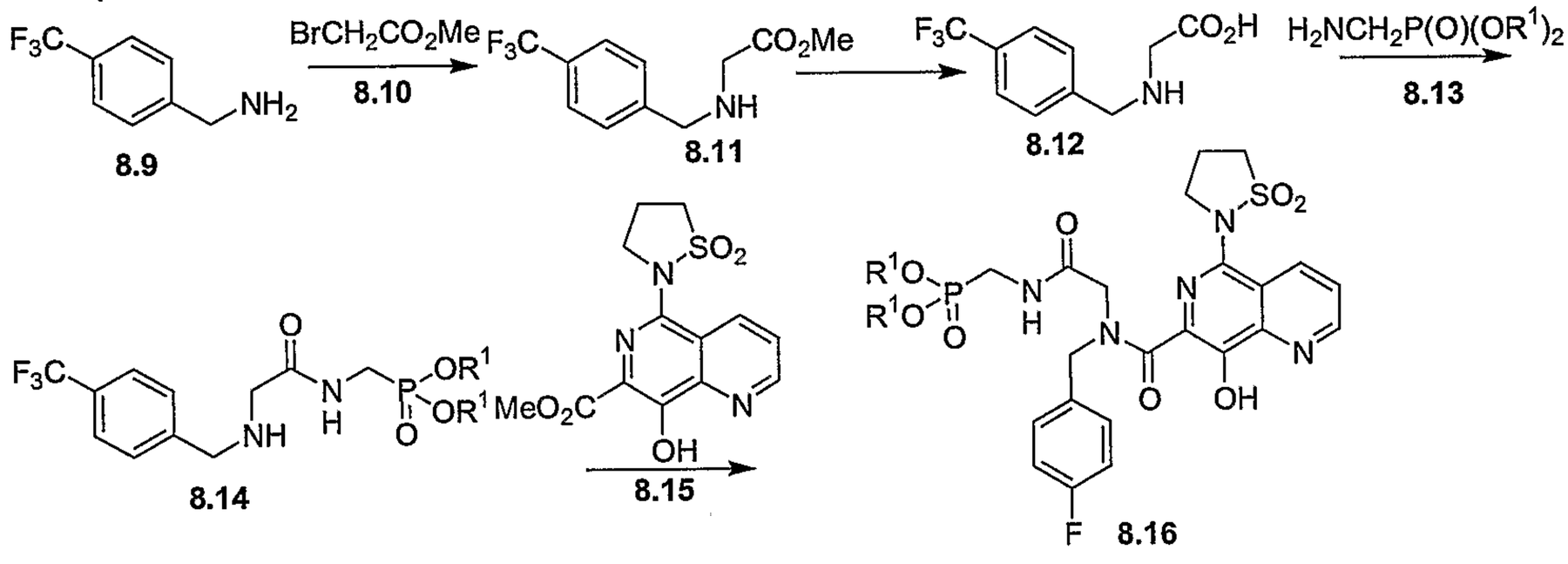
Method



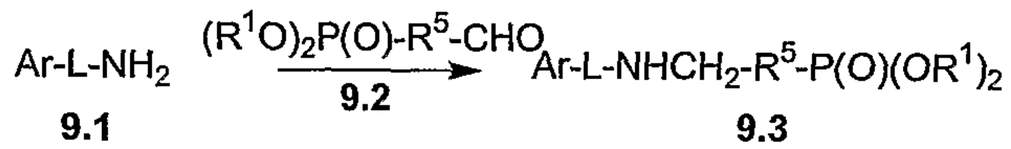




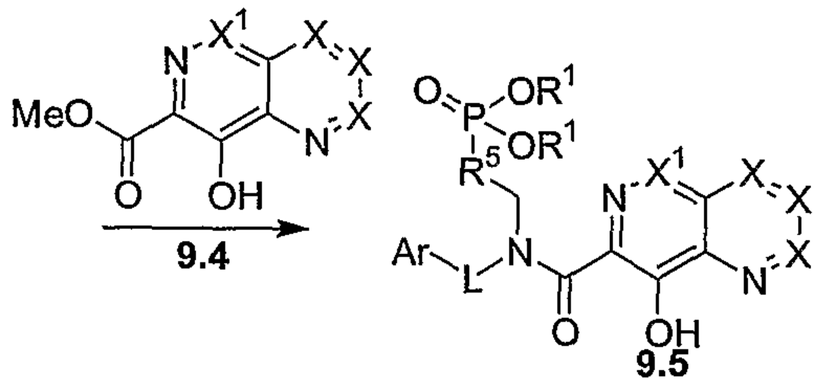
Example



Scheme 9. Phosphonates 2.
Method

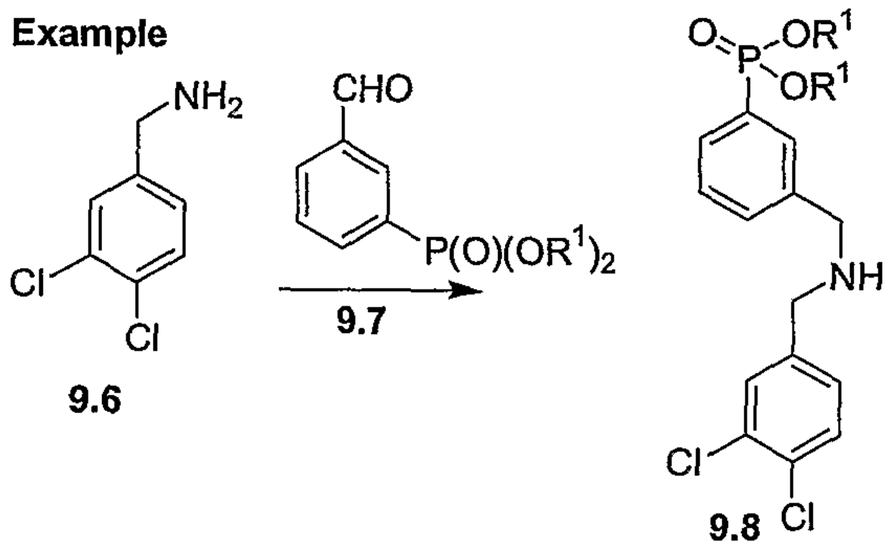


9.1 **9.3**

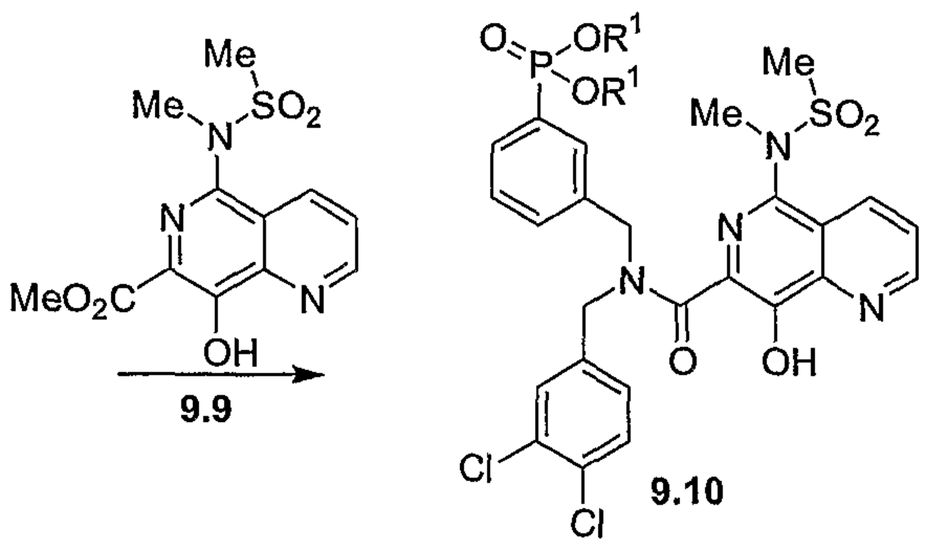


9.5

Example



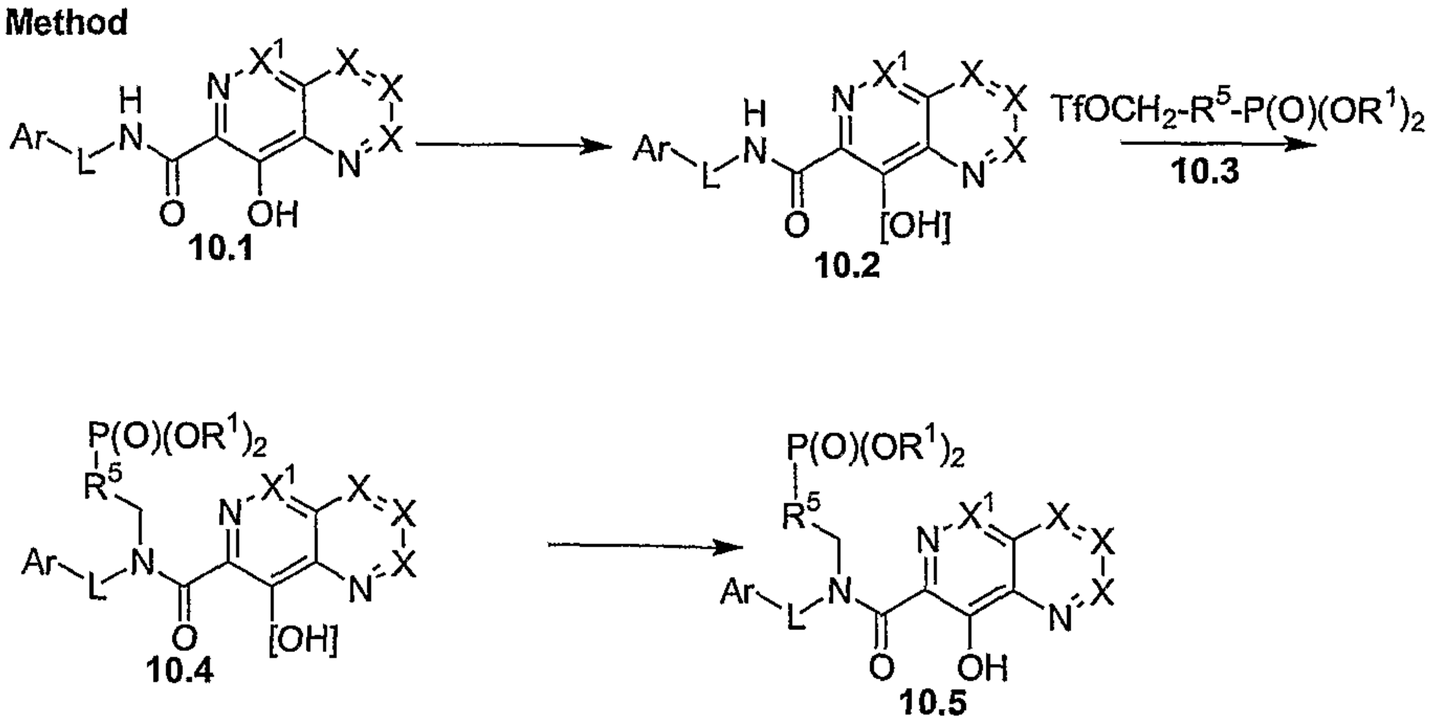
9.6 **9.8**



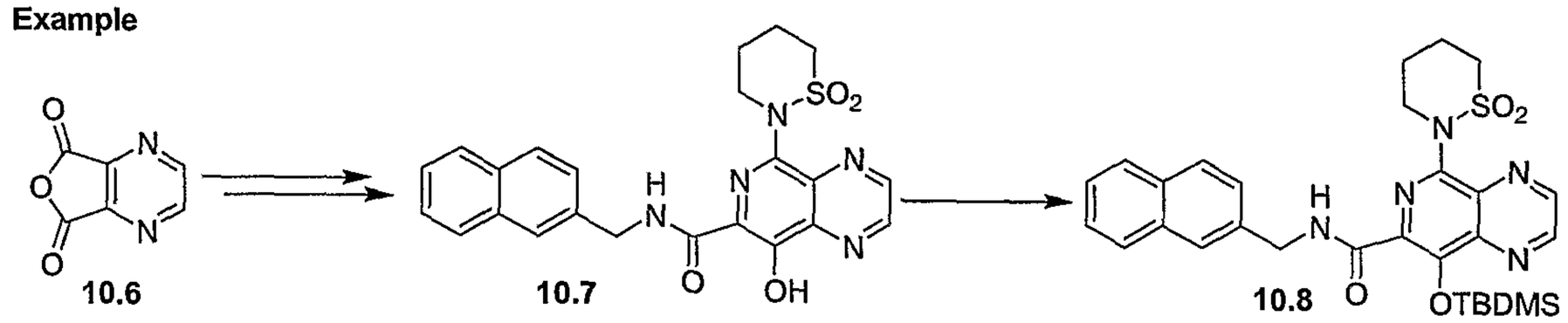
9.10

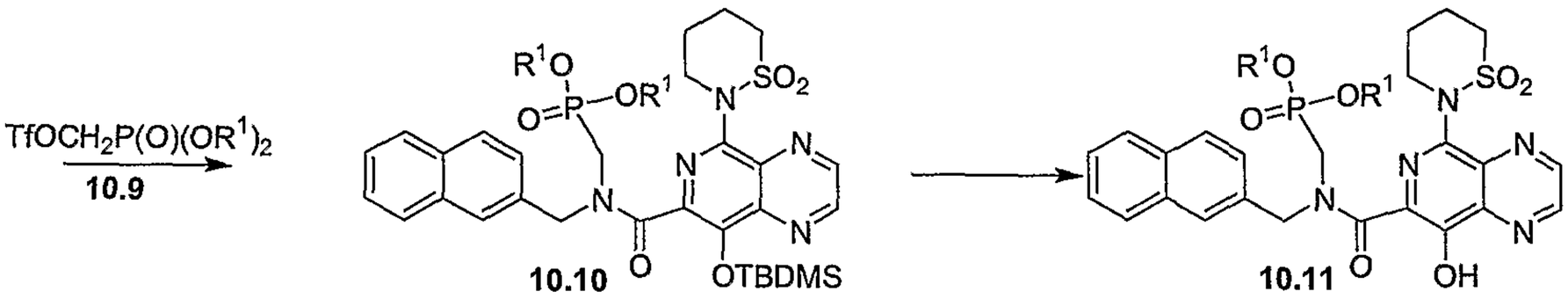
Scheme 10. Phosphonates 2.

Method



Example





Preparation of the intermediate phosphonate esters 3.

Schemes **11** - **15** illustrate methods for the preparation of the phosphonate esters **3**.

Scheme **11** depicts the preparation of phosphonates **3** in which the phosphonate is attached by means of a heteroatom O, S or N, and a variable carbon chain. In this procedure, a bicyclic amide **11.1**, prepared as previously described, is reacted in an aprotic solvent such as dichloromethane, hexachloroethane or ethyl acetate with a free radical brominating agent such as N-bromosuccinimide or N-bromoacetamide, to yield the 5-bromo product **11.2**. This compound is then reacted with a dialkyl hydroxy, mercapto or amino-substituted phosphonate **11.3**, in which R^5 is as defined as in Scheme **4**, to give the ether, thioether or amine product **11.4**. The displacement reaction is conducted in a polar aprotic organic solvent such as dimethylformamide or DMPU, at from 100° to about 150°, in the presence of a base

such as triethylamine or cesium carbonate, for example as described in WO 0230930 A2, Examples 57-69.

As shown in Example **1**, furo[3,4-d]pyrimidine-5,7-dione **11.5** (J. Het. Chem., 1993, 30, 1597) is converted, as described above, into 8-hydroxy-pyrido[4,3-d]pyrimidine-7-carboxylic acid cyclohexylmethyl-amide **11.6**. The product is reacted with one molar equivalent of N-bromosuccinimide in dichloromethane to yield the 5-bromo product **11.7**. This material is then reacted with a dialkyl mercaptoethyl phosphonate **11.8** (Zh. Obschei. Khim., 1973, 43, 2364) and triethylamine at ca 100° in a pressure vessel, to produce the thioether **11.9**.

As shown in Example **2**, the anhydride **11.10** is converted, as described previously, into 8-hydroxy-[1,6]naphthyridine-7-carboxylic acid 3,5-dichloro-benzylamide **11.11**. Bromination with N-bromosuccinimide in ethyl acetate at reflux temperature then yields the bromo compound **11.12** which is reacted with a dialkyl 3-aminophenyl phosphonate **11.13** (J. Med. Chem., 1984, 27, 654) in dimethylformamide at ca. 130°, using the procedure described in WO 0230930 A2 Example 63, to give the phosphonate **11.14**. The product is then reacted with N, N-dimethyloxamide **11.15**, (Japanese Patent 540467 18) and dicyclohexylcarbodiimide in dimethylformamide, to yield the amide product **11.16**.

Using the above procedures, but employing, in place of the amides **11.6** or **11.11**, different amides **11.1**, and/or different phosphonates **11.3**, the corresponding products **11.4** are obtained.

Scheme **12** depicts the preparation of phosphonates **3** in which the phosphonate is attached by means of a carbamate linkage. In this procedure, a protected bromophenol **12.1** is reacted, as described in Scheme **11**, with an amine **12.2** to give the displacement product **12.3**. This compound is then reacted with phosgene, triphosgene, carbonyl diimidazole or a functional equivalent thereof, and a dialkyl hydroxyalkyl phosphonate **12.4**, in which R^5 is as defined in Scheme **4**, to yield, after deprotection of the phenol, the carbamate **12.5**. Various methods for the preparation of carbamates are described in Scheme **33**.

For example, the hydroxyester **12.6** is converted, as described previously, into the amide **12.7**. This material is then reacted, in dimethylformamide solution at 100°, with ethylamine and cesium carbonate in dimethylformamide, to afford 8-(tert-butyl-

dimethyl-silanyloxy)-5-ethylamino-[1,6]naphthyridine-7-carboxylic acid [2-(4-fluoro-phenyl)-cyclopropyl]-amide **12.9**. The amine is treated with equimolar amounts of a dialkyl hydroxypropyl phosphonate **12.10** (Zh. Obschei. Khim., 1974, 44, 1834) and carbonyldiimidazole in dichloromethane, to prepare, after desilylation, the carbamate **12.11**.

Using the above procedures, but employing, in place of the amide **12.7**, different amides **12.3**, and/or different phosphonates **12.4**, the corresponding products **12.5** are obtained.

Scheme **13** depicts the preparation of phosphonates **3** in which the phosphonate is attached by means of an arylvinyl or arylethyl linkage. In this procedure, a bromophenol **13.1** is protected to give the product **13.2**. This compound is then coupled with tributylvinyltin to yield the 5-vinyl product **13.3**. The coupling reaction is effected in dimethylformamide solution at ca. 80° in the presence of a palladium(0) catalyst, such as tris(dibenzylideneacetone)palladium(0), a triarylphosphine such as tri(2-furyl)phosphine and copper(I) iodide, for example as described in WO 0230930A2, Example 176. The vinyl-substituted product is subjected to a palladium-catalyzed Heck coupling reaction, as described in Scheme **4**, with a dibromoaromatic or heteroaromatic compound **13.4**, to give the bromoaryl product **13.5**. The latter compound is then coupled, as described in Scheme **3**, with a dialkyl phosphite **13.6**, in the presence of a palladium catalyst, to give the aryl phosphonate **13.7**. Deprotection then affords the phenol **13.8**. Optionally, the double bond is reduced, for example as described in Scheme **4**, to give the saturated analog **13.9**.

For example, furo[3,4-c]pyridazine-5,7-dione **13.10**, (WO9944992) is converted, using the methods described above, into the silyl-protected bromophenol **13.11**. The product is coupled, as described above, with tri(n-butyl)vinyltin to produce the 5-vinyl compound **13.12**. This material is then coupled, in dimethylformamide solution at 80° with one molar equivalent of 2,5-dibromothiophene, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to afford 5-[2-(5-bromo-thiophen-2-yl)-vinyl]-8-(tert-butyl-dimethyl-silanyloxy)-pyrido[4,3-c]pyridazine-7-carboxylic acid 3,5-dichloro-benzylamide **13.14**. The product is coupled, in the presence of a palladium(0) catalyst and triethylamine, with a dialkyl phosphite **13.15**,

to afford the phosphonate **13.16**. Deprotection, for example by reaction with tetrabutylammonium fluoride in tetrahydrofuran, then yields the phenol **13.17**, and hydrogenation of the latter compound in methanol, using 5% palladium on carbon as catalyst, produces the saturated analog **13.18**.

Using the above procedures, but employing, in place of the amide **13.11**, different amides **13.1**, and/or different dibromides **13.4**, the corresponding products **13.8** and **13.9** are obtained.

Scheme **14** depicts the preparation of phosphonates **3** in which the phosphonate is attached by means of an acetylenic bond. In this procedure, a phenol **14.1** is reacted, as described in WO 0230930 A2 p. 166 and Example 112, with N-iodosuccinimide in dichloromethane-dimethylformamide, to give the 5-iodo product; protection of the phenolic hydroxyl group then affords the compound **14.2**. This material is coupled, as described in WO 0230930 A2 Example 79, in dimethylformamide solution, in the presence of dichlorobis(triphenylphosphine) palladium (II), copper iodide and triethylamine, with a dialkyl ethynyl phosphonate **14.3**, in which R^5 is as defined in Scheme **4**, to give, after deprotection of the phenol, the acetylenic phosphonate **14.4**.

For example, furo[3,4-e][1,2,4]triazine-5,7-dione **14.5**, (J. Org. Chem., 1958, 23, 1931) is converted, as described previously, into the hydroxyester **14.6**. This material is then converted into 5-iodo-8-(tert-butyl-dimethyl-silanyloxy)-pyrido[3,4-e][1,2,4]triazine-7-carboxylic acid (cyclopent-3-enylmethyl)-amide **14.7**, as described above. The product is coupled, as described above, with a dialkyl propynyl phosphonate **14.8**, (Syn., 1999, 2027) to yield, after deprotection, the acetylenic phosphonate **14.9**.

Using the above procedures, but employing, in place of the iodoamide **14.7**, different iodoamides **14.2**, and/or different acetylenic phosphonates **14.3**, the corresponding products **14.4** are obtained.

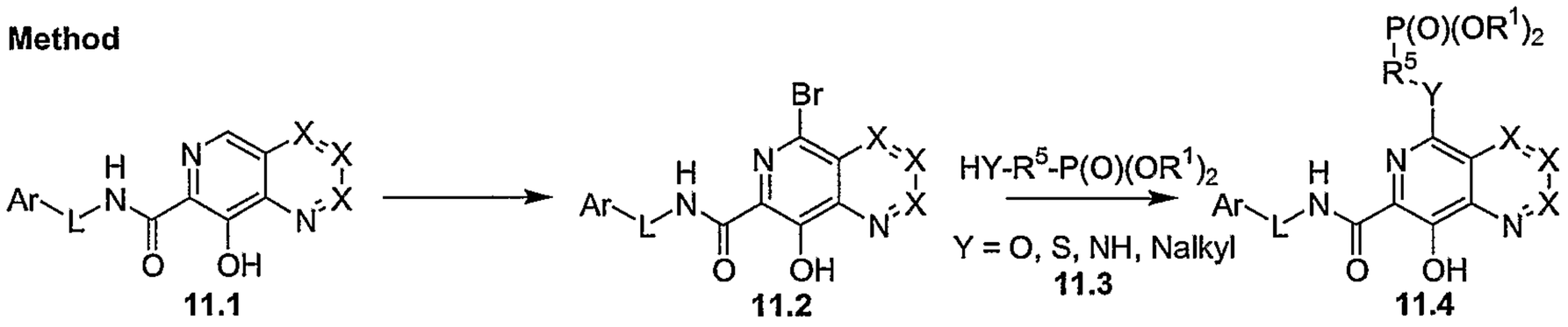
Scheme **15** depicts the preparation of phosphonates **3** in which the phosphonate is directly attached to the bicyclic nucleus. In this procedure, a protected bicyclic bromophenol **15.1** is coupled, in the presence of a palladium catalyst, as described in Scheme **3**, with a dialkyl phosphite **15.2**, to give after deprotection the aryl phosphonate **15.3**.

For example, 3-methyl-furo[3,4-b]pyridine-5,7-dione **15.4**, (German Patent DE 3707530) is converted, using the procedures described above, into 5-bromo-8-(tert-butyl-dimethyl-silanyloxy)-3-methyl-[1,6]naphthyridine-7-carboxylic acid [1-(3-chloro-4-fluoro-phenyl)-1-methyl-ethyl]-amide **15.5**. The product is then coupled, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, as described in Scheme **3**, with a dialkyl phosphite **15.6**, to afford, after desilylation of the phenol, the arylphosphonate **15.7**.

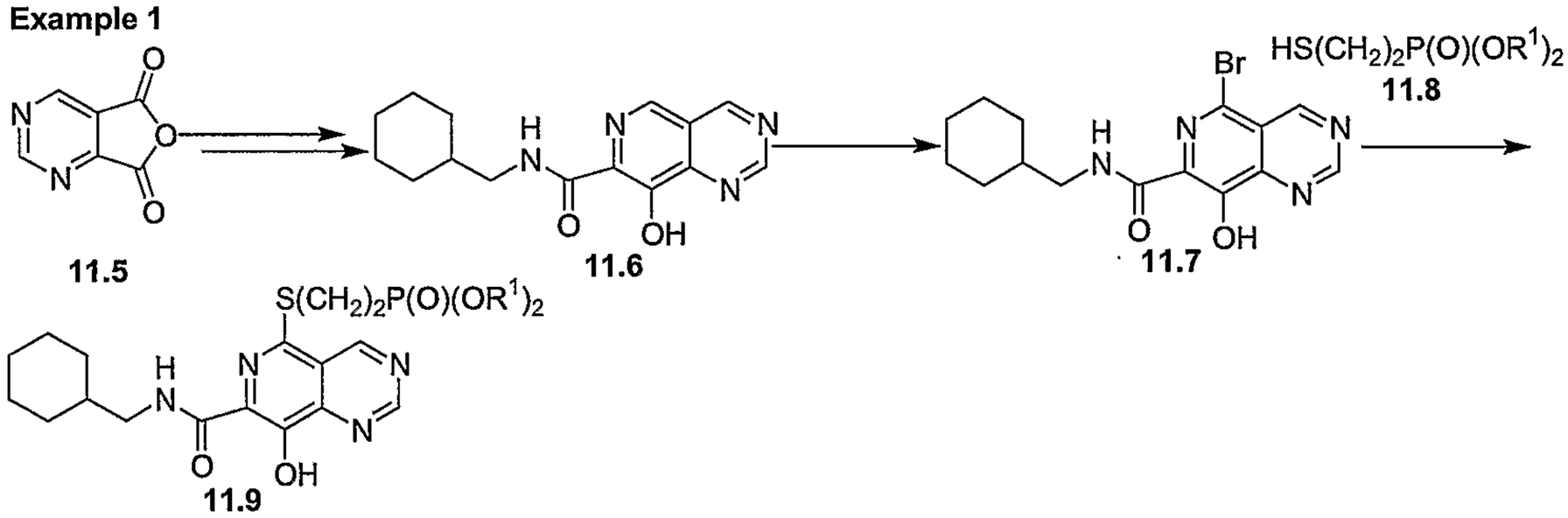
Using the above procedures, but employing, in place of the bromoamide **15.5**, different bromoamides **15.1**, the corresponding products **15.3** are obtained.

Scheme 11. Phosphonates 3.

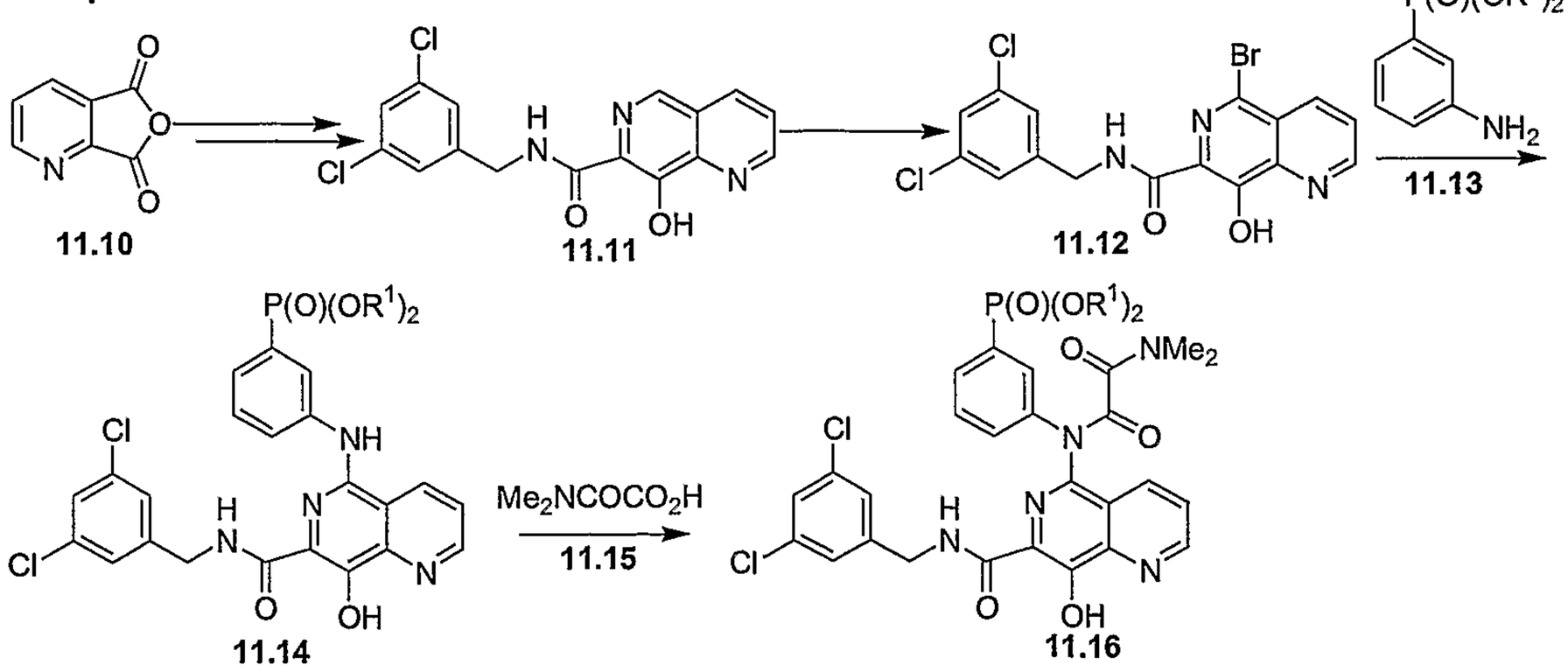
Method



Example 1

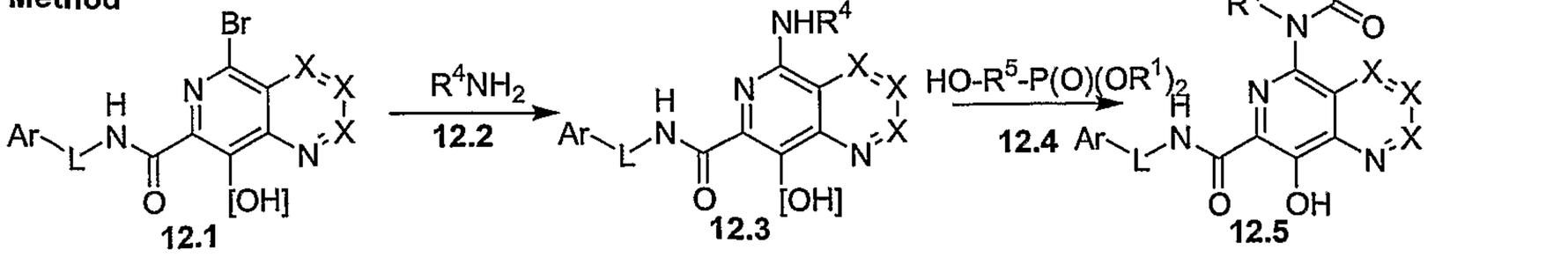


Example 2

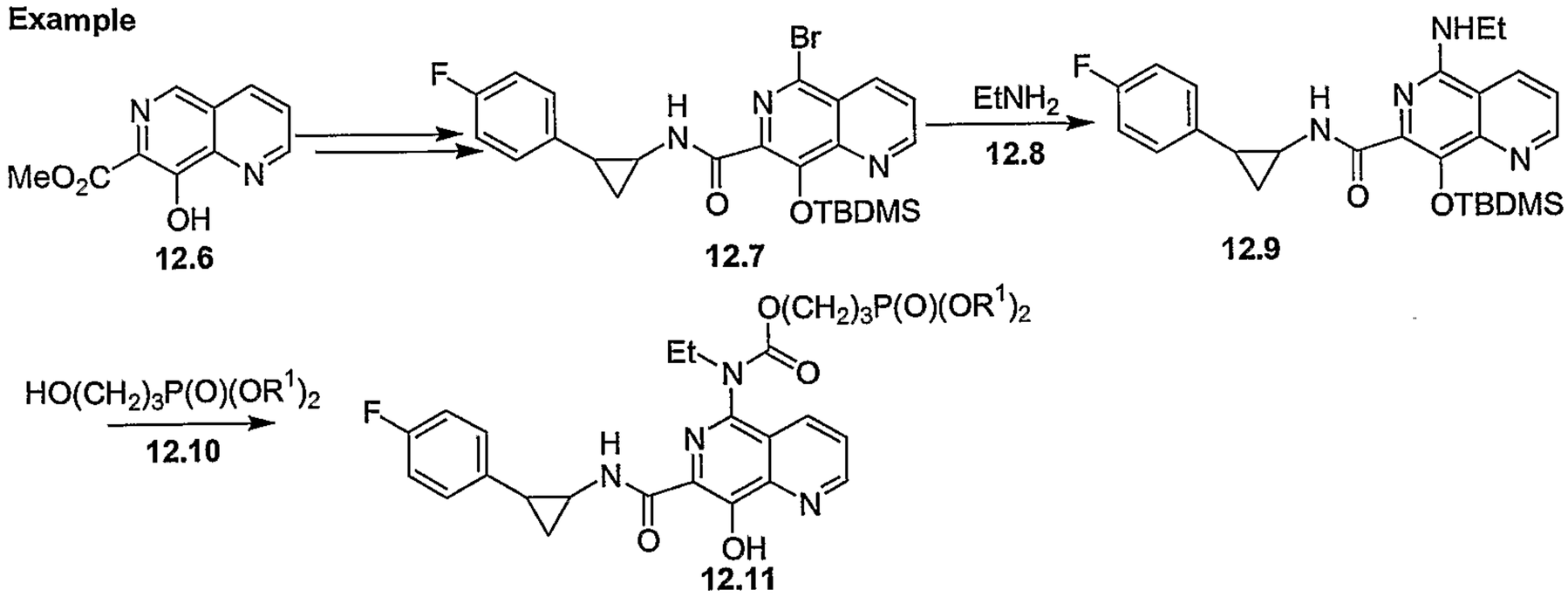


Scheme 12. Phosphonates 3.

Method

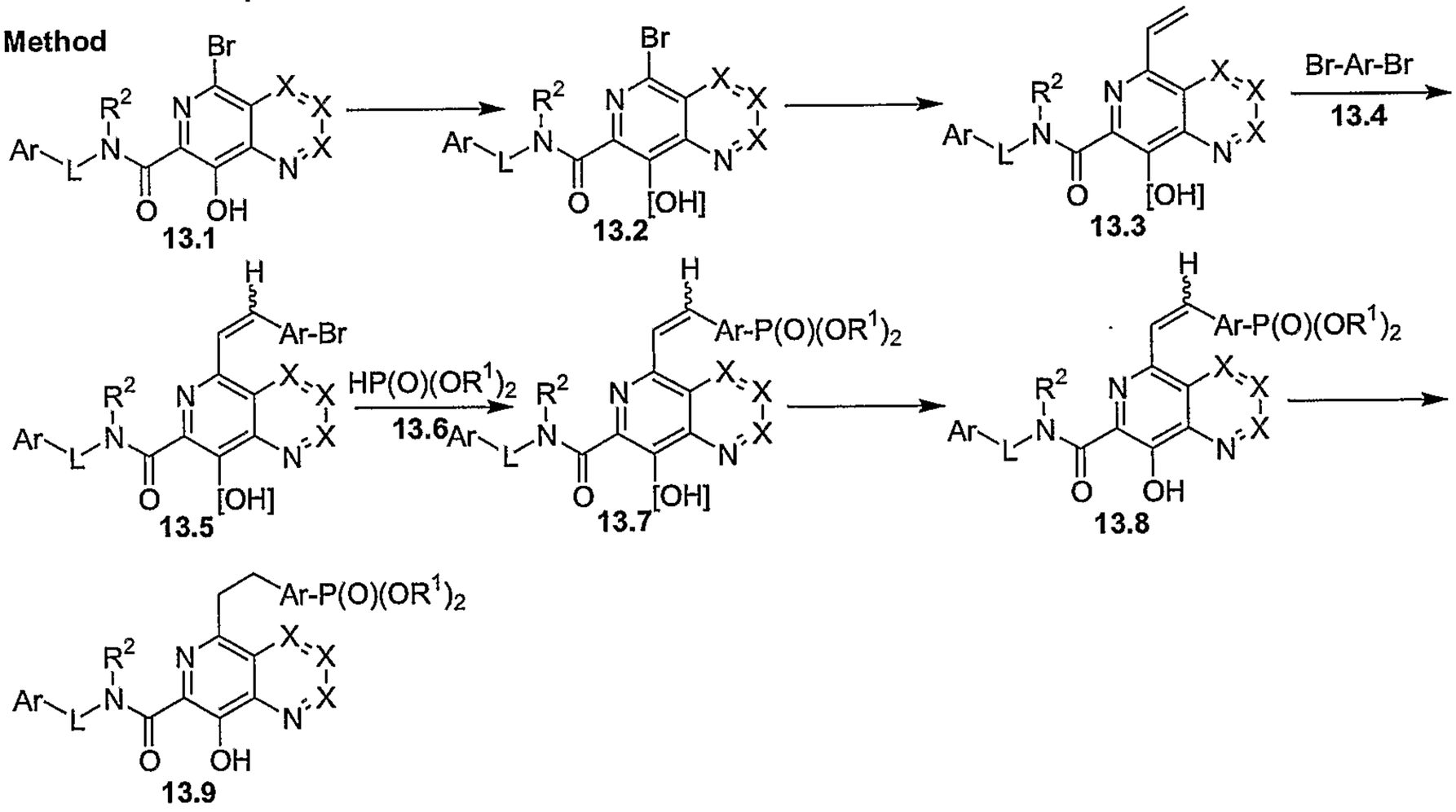


Example



Scheme 13. Phosphonates 3.

Method



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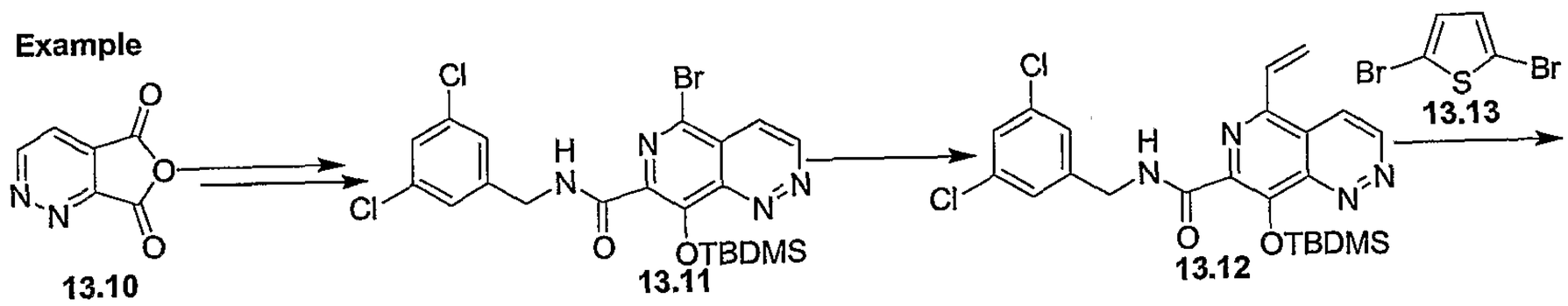
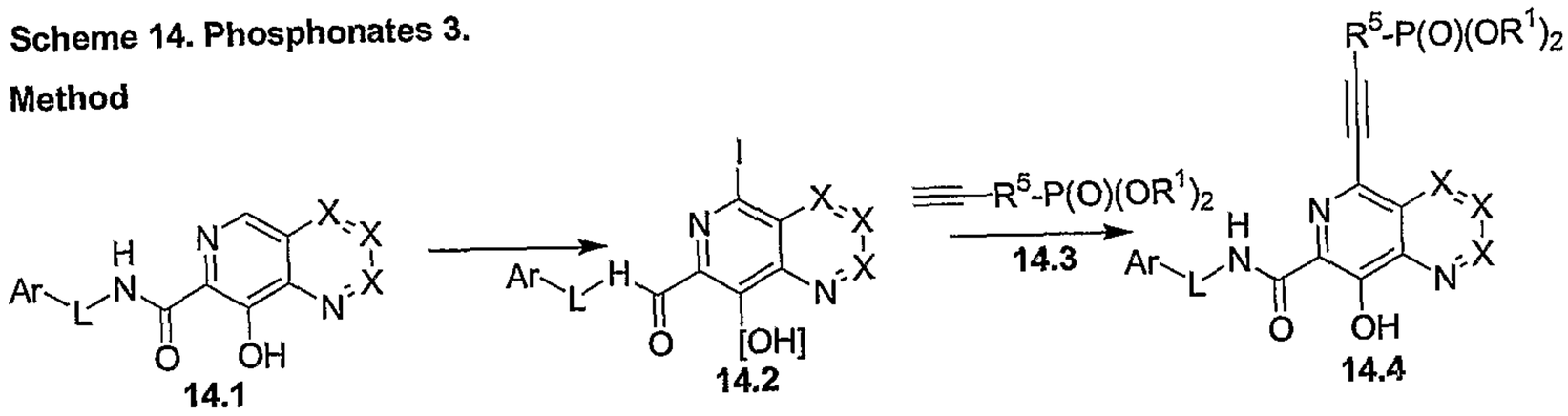
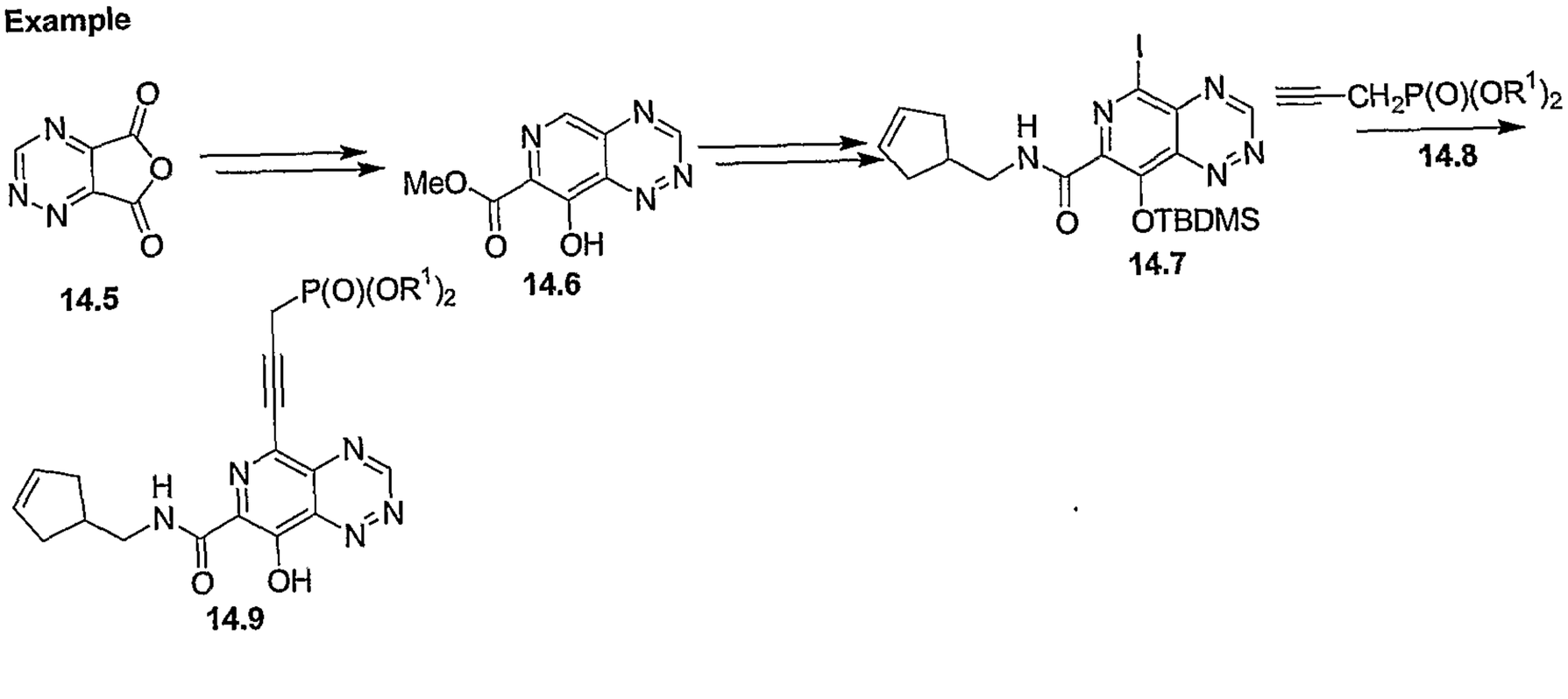


Scheme 14. Phosphonates 3.

Method

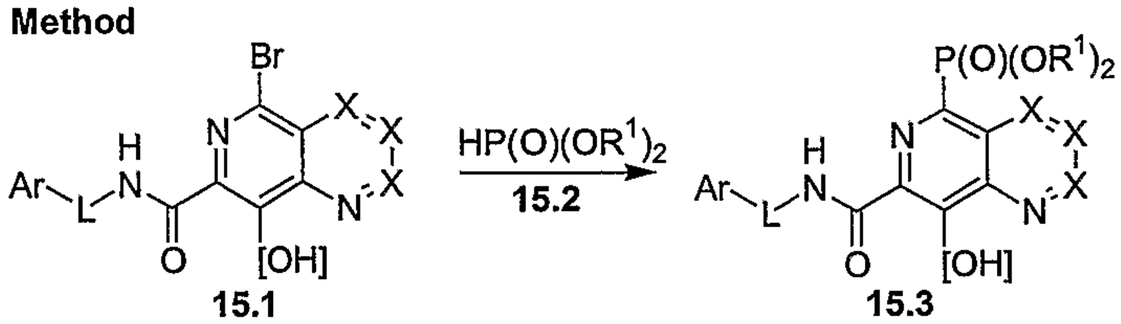


Example



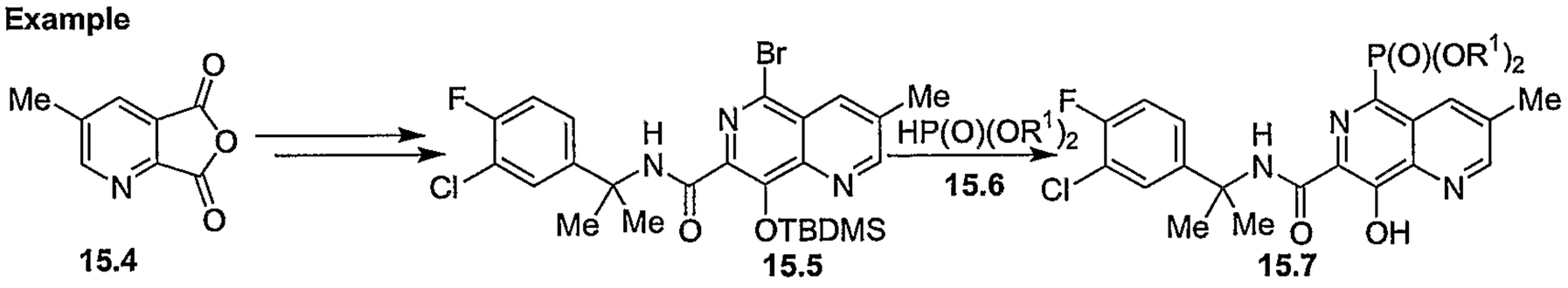
Scheme 15. Phosphonates 3.

Method



15.1 **15.3**

Example



15.4 **15.5** **15.7**

Preparation of the intermediate phosphonate esters 4.

Schemes **16 - 18** illustrate methods for the preparation of the phosphonate esters **4**.

Scheme **16** depicts the preparation of phosphonate esters **4** in which the phosphonate group is attached by means of a variable carbon chain. In this procedure, the phosphonate **16.1**, in which the phenolic hydroxyl group is protected, prepared as described in Scheme **11**, is reacted with the sulfonyl chloride **16.2** or the sulfonic acid **16.3** to afford after deprotection the sulfonamide **16.4**. The reaction between an amine and a sulfonyl chloride, to produce the sulfonamide, is conducted at ambient temperature in an inert solvent such as dichloromethane, in the presence of a tertiary base such as triethylamine. The reaction between a sulfonic acid and an amine to afford a sulfonamide is conducted in a polar solvent such as dimethylformamide, in the presence of a carbodiimide such as dicyclohexyl carbodiimide, for example as described in Syn., 1976, 339.

For example, the protected amine phosphonate **16.5**, prepared by the methods described above, is reacted in dichloromethane solution with one molar equivalent of ethyl sulfonyl chloride **16.6** and triethylamine, to produce, after desilylation, the sulfonamide **16.7**.

Using the above procedures, but employing, in place of the amine phosphonate **16.5**, different phosphonates **16.1**, and/or different sulfonyl chlorides **16.2** or sulfonic acids **16.3**, the corresponding products **16.4** are obtained.

Scheme **17** depicts an alternative method for the preparation of phosphonate esters **4** in which the phosphonate group is attached by means of a variable carbon

chain. In this procedure, a dialkyl amino-substituted phosphonate **17.1**, in which the group R^5 is as defined in Scheme **4**, is reacted with a sulfonyl chloride **17.2** or sulfonic acid **17.3**, as described in Scheme **16**, to yield the sulfonamide **17.4**. The product is then reacted with a bromoamide **17.5**, to prepare the displacement product **17.6**. The displacement reaction is performed in a basic solvent such as pyridine or quinoline, at from about 80° to reflux temperature, optionally in the presence of a promoter such as copper oxide, as described in WO 0230930 A2 Example 154.

For example, a dialkyl 4-aminophenyl phosphonate **17.7** (Epsilon) is reacted in dichloromethane solution with one molar equivalent of methanesulfonyl chloride **17.8** and triethylamine, to give the sulfonamide **17.9**. The product is then reacted in pyridine solution at reflux temperature with 5-bromo-8-hydroxy-pyrido[3,4-b]pyrazine-7-carboxylic acid 4-fluoro-benzylamide **17.10**, prepared by the methods described above, and copper oxide, to yield the sulfonamide **17.11**.

Using the above procedures, but employing, in place of the amine phosphonate **17.7**, different phosphonates **17.1**, and/or different sulfonyl chlorides **17.2** or sulfonic acids **17.3**, the corresponding products **17.6** are obtained.

Scheme **18** depicts an alternative method for the preparation of phosphonate esters **4** in which the phosphonate group is attached by means of a variable carbon chain. In this procedure, a phenol-protected 5-bromo substituted amide **18.1** is reacted, as described in Scheme **17**, with a sulfonamide **18.2**, to give the displacement product **18.3**. The product is then reacted with a dialkyl bromoalkyl phosphonate **18.4** to afford, after deprotection of the phenol, the alkylated compound **18.5**. The alkylation reaction is performed in a polar aprotic solvent such as dimethylformamide or DMPU, at from ambient temperature to about 100°, in the presence of a base such as sodium hydride or lithium hexamethyl disilylazide.

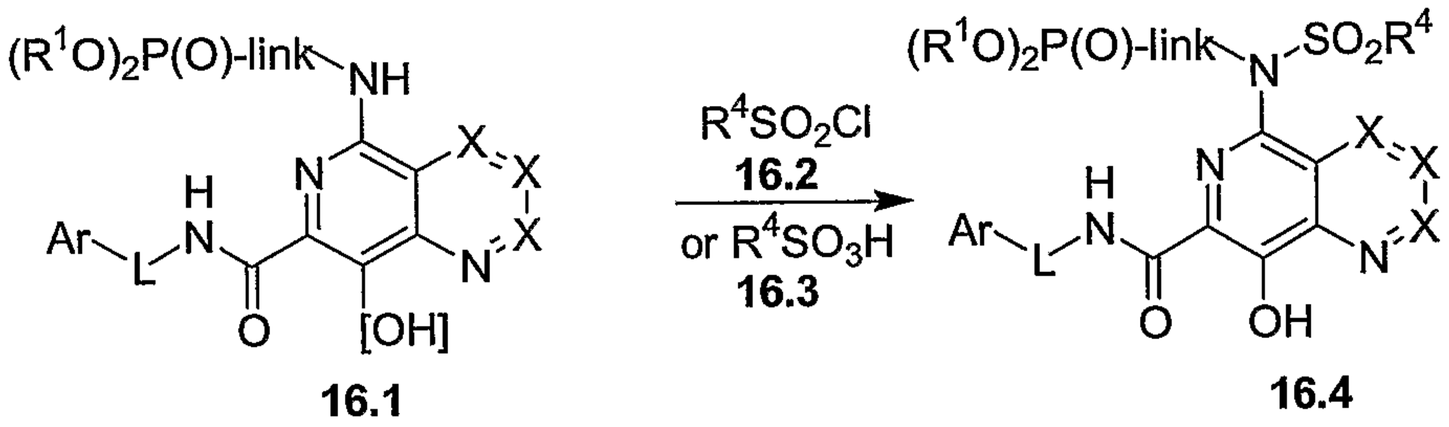
For example, benzoic acid 5-bromo-7-[1-(3-methoxy-phenyl)-1-methyl-ethylcarbamoyl]-[1,6]naphthyridin-8-yl ester **18.6**, prepared by the methods described above, is reacted in pyridine solution at reflux temperature with one molar equivalent of propanesulfonamide **18.7** and copper oxide, to afford the sulfonamide **18.8**. The product is then reacted in dimethylformamide solution with one molar equivalent of a dialkyl bromoethyl phosphonate **18.9** (Aldrich) and lithium hexamethyl disilylazide, to give after debenzoylation, the sulfonamide phosphonate **18.10**. The benzoyl

protecting group is removed, for example, by reaction with 1% methanolic sodium hydroxide at ambient temperature, as described in Tet., 26, 803, 1970.

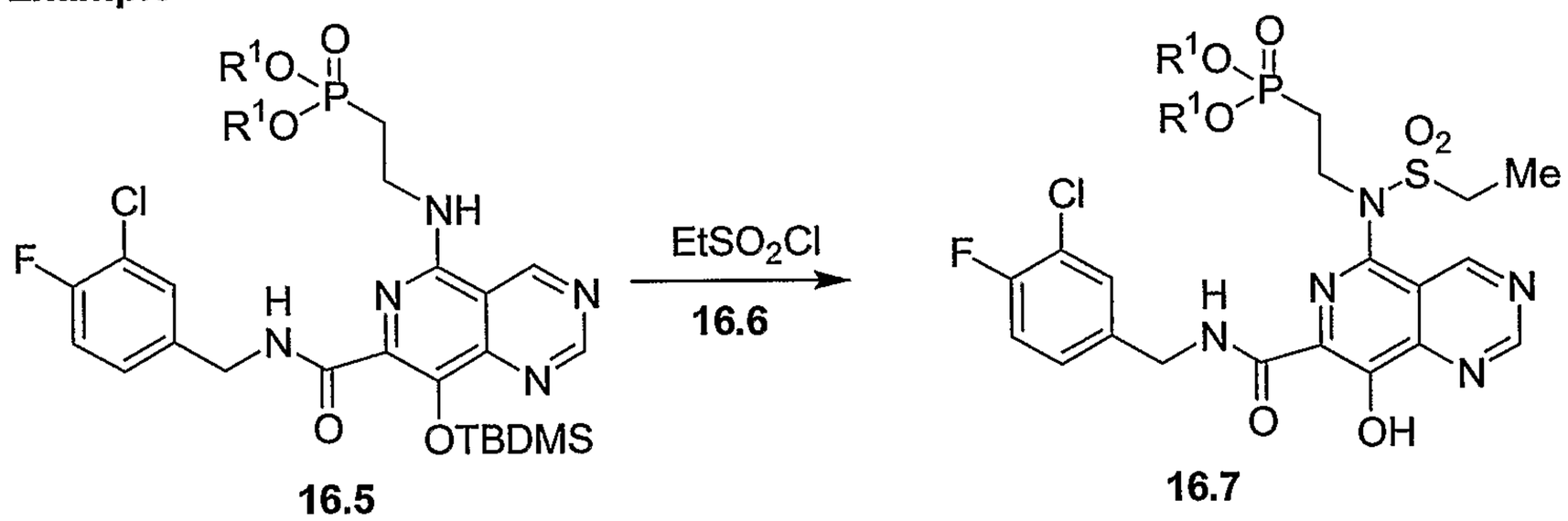
Using the above procedures, but employing, in place of the bromo compound **18.6**, different bromo compounds **18.1**, and/or different sulfonamides **18.2**, and/or different phosphonates **18.4**, the corresponding products **18.5** are obtained.

Scheme 16. Phosphonates 4.

Method

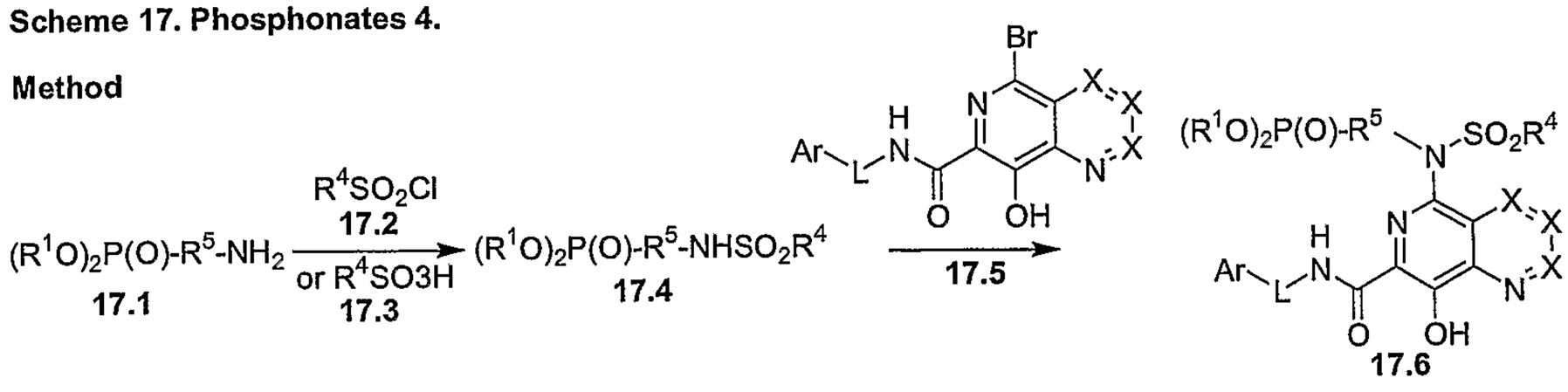


Example

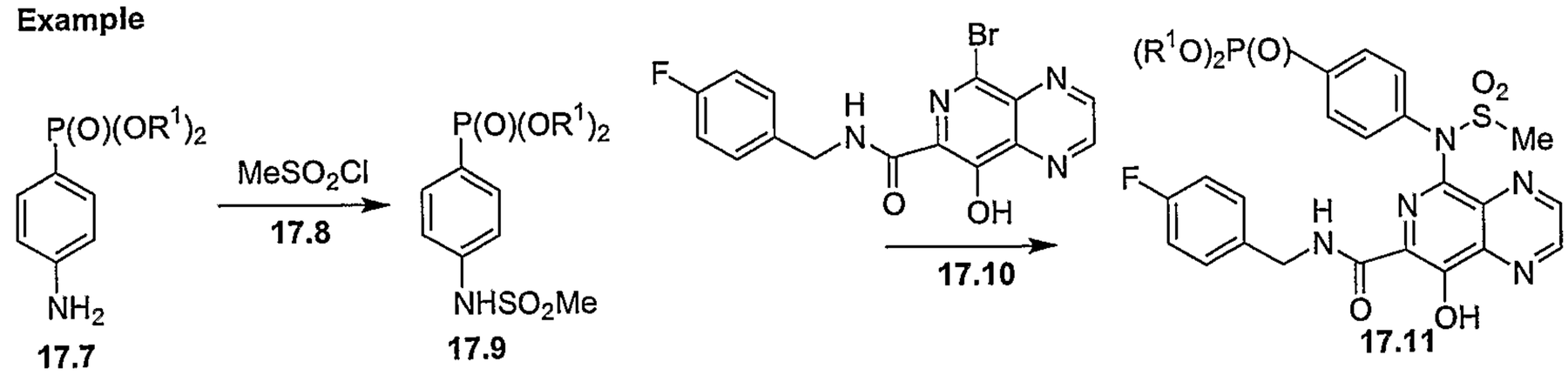


Scheme 17. Phosphonates 4.

Method

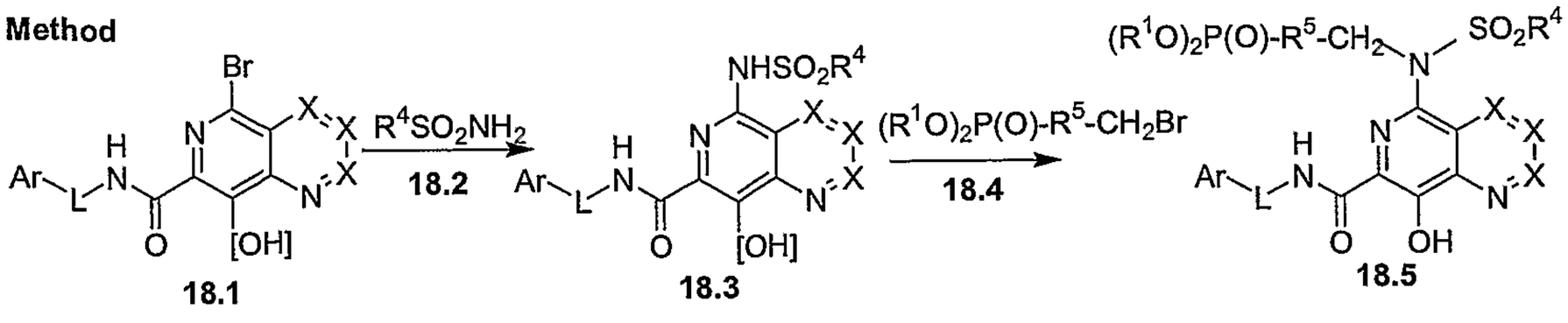


Example

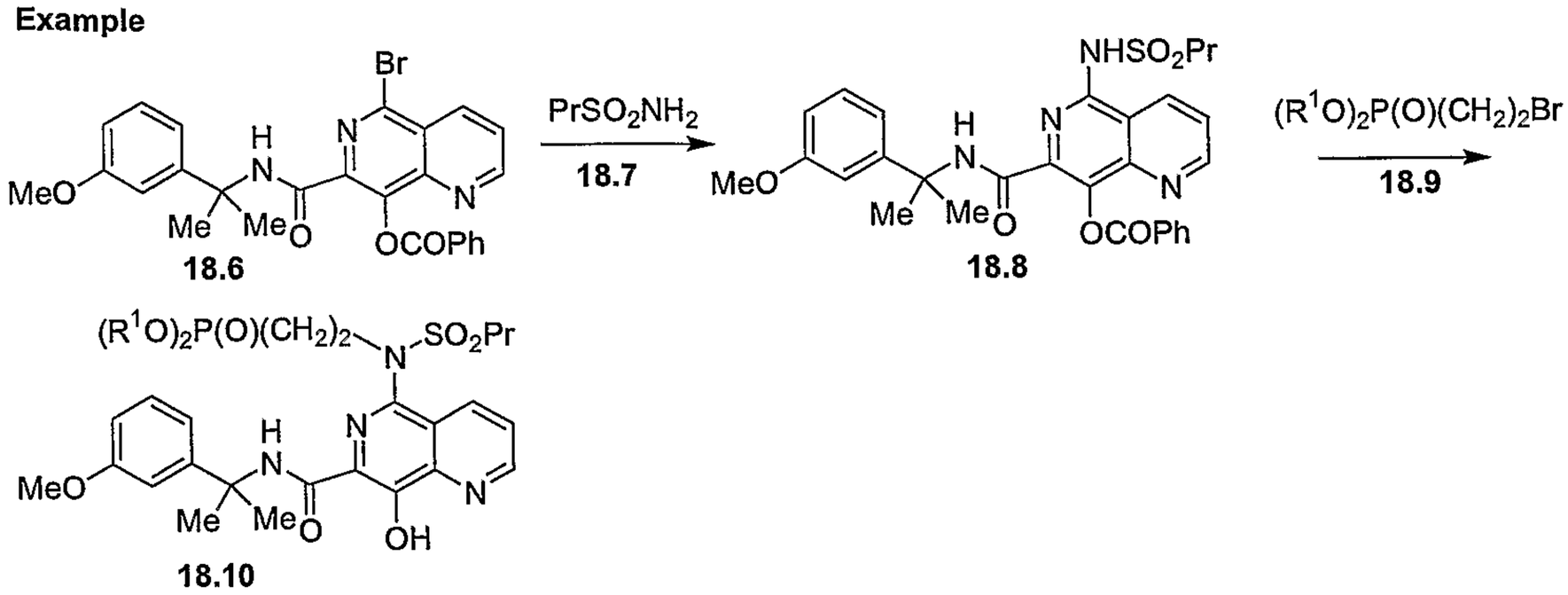


Scheme 18. Phosphonates 4.

Method



Example



Preparation of the intermediate phosphonate esters 5.

Schemes **19** - **21** illustrate methods for the preparation of the phosphonate esters **5**.

Scheme **19** illustrates the preparation of phosphonates **5** in which the phosphonate group is attached by means of a variable carbon chain. In this procedure, a bromo-substituted sulfonic acid **19.1** is subjected to an Arbuzov reaction with a trialkyl phosphite **19.2** to give the phosphonate **19.3**. The Arbuzov reaction is performed by heating the bromo compound with an excess of the trialkyl phosphite at from 100° to 150°, as described in Handb. Organophosphorus Chem., 1992, 115-72. The resulting phosphonate is then reacted with an amine **19.4**, either directly, in the presence of a carbodiimide, or by initial conversion to the sulfonyl chloride, as described in Scheme **16**, to afford, after deprotection of the phenolic hydroxyl group, the sulfonamide **19.5**.

For example, 3-bromopropanesulfonic acid **19.6** (Sigma) is heated at 130° with a trialkyl phosphite **19.7** to give the phosphonate **19.8**. The product is then reacted in DMPU solution with 8-(tert-butyl-dimethyl-silanyloxy)-5-ethylamino-[1,6]naphthyridine-7-carboxylic acid 4-fluoro-benzylamide **19.9**, prepared by the methods described above, in the presence of dicyclohexylcarbodiimide, to give, after

desilylation, by reaction with tetrabutylammonium fluoride in tetrahydrofuran, the sulfonamide **19.10**.

Using the above procedures, but employing, in place of the bromo sulfonic acid **19.6**, different bromosulfonic acids **19.1**, and/or different amines **19.4**, the corresponding products **19.5** are obtained.

Scheme **20** illustrates the preparation of phosphonates **5** in which the phosphonate group is attached by means of a saturated or unsaturated carbon chain and an aromatic or heteroaromatic group. In this procedure, a vinyl-substituted sulfonic acid **20.1** is coupled, in a palladium-catalyzed Heck reaction, as described in Scheme **4**, with a dibromoaromatic or heteroaromatic compound **20.2**, to yield the sulfonic acid **20.3**. The product is then coupled, in the presence of a palladium catalyst, as described in Scheme **3**, with a dialkyl phosphite $HP(O)(OR^1)_2$, to give the phosphonate **20.4**. The latter compound is then reacted, as described above, with an amine **20.5**, either directly, in the presence of a carbodiimide, or by initial conversion to the sulfonyl chloride, as described in Scheme **16**, to afford, after deprotection of the phenolic hydroxyl group, the sulfonamide **20.6**. Optionally, the double bond is reduced, either catalytically or chemically, as described in Scheme **4**, to afford the saturated analog **20.7**.

For example, vinylsulfonic acid **20.8** (Sigma) is coupled, in dioxan solution, in the presence of tetrakis(triphenylphosphine)palladium (0) and potassium carbonate, with 2,5-dibromothiophene **20.9**, to form the coupled product **20.10**. The product is then reacted in toluene solution at 100° with a dialkyl phosphite **20.11**, triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium (0), to produce the phosphonate **20.12**. This material is then reacted, in dimethylformamide solution at ambient temperature, as described above, with 8-(tert-butyl-dimethyl-silanyloxy)-5-cyclopropylamino-pyrido[4,3-d]pyrimidine-7-carboxylic acid 4-fluoro-benzylamide **20.13**, prepared by the methods described above, in the presence of dicyclohexylcarbodiimide, to give, after desilylation, using tetrabutylammonium fluoride, the sulfonamide **20.14**. Hydrogenation of the double bond, for example using 5% palladium on carbon as catalyst, then yields the saturated analog **20.15**.

Using the above procedures, but employing, in place of the sulfonic acid **20.8**, different sulfonic acids **20.1**, and/or different dibromoaromatic compounds **20.2**, and/or different amines **20.5**, the corresponding products **20.6** and **20.7** are obtained.

Scheme **21** illustrates the preparation of phosphonates **5** in which the phosphonate group is attached by means of a variable carbon chain. In this procedure, an aliphatic bromo-substituted sulfonic acid **21.1** is subjected to an Arbuzov reaction with a trialkyl phosphite, as described in Scheme **19**, to give the phosphonate **21.2**. Alternatively, an aryl bromosulfonic acid **21.1** is coupled, as described in Scheme **3**, with a dialkyl phosphite, to give the phosphonate **21.2**. The product is then reacted with an amine **21.3** to afford the sulfonamide **21.4**. The latter compound is then reacted, as described in Scheme **17**, with a bromoamide **21.5**, to give the displacement product **21.6**.

For example, 4-bromobenzenesulfonic acid **21.7** is reacted, as described in Scheme **20**, with a dialkyl phosphite to form the phosphonate **21.8**. The product is then reacted with phosphoryl chloride to afford the corresponding sulfonyl chloride, and the latter compound is reacted, in dichloromethane solution, in the presence of triethylamine, with 2-methoxyethylamine **21.9**, to yield the sulfonamide **21.10**. This material is then reacted, in pyridine solution at reflux temperature, with 5-bromo-8-hydroxy-[1,6]naphthyridine-7-carboxylic acid 4-fluoro-benzylamide **21.11**, prepared by the methods described above, and copper oxide, to give the sulfonamide **21.12**.

Using the above procedures, but employing, in place of the sulfonic acid **21.7**, different sulfonic acids **21.1**, and/or different amines **21.3**, and/or different bromo compounds **21.5**, the corresponding products **21.6** are obtained.

Preparation of the intermediate phosphonate esters 6.

Schemes **22 - 24** illustrate methods for the preparation of the phosphonate esters **6**.

Scheme **22** depicts the preparation of phosphonates **6** in which the phosphonate group is attached by means of an amide linkage and a variable carbon chain. In this procedure, a cyclic sulfonamide **22.1**, incorporating a secondary amine, is coupled, as described in Scheme **5**, with a dialkyl carboxy-substituted phosphonate **22.2** to produce the amide **22.3**. The product is then reacted with a bromoamide **22.4** to afford the displacement product **22.5**.

Alternatively, the cyclic sulfonamide **22.1** is protected to give the analog **22.6**. Sulfonamides are protected, for example, by conversion into the N-acyloxymethyl derivatives, such as the pivalyloxymethyl derivative or the benzoyloxymethyl derivative, by reaction with the corresponding acyloxymethyl chloride in the presence of dimethylaminopyridine, as described in Bioorg. Med. Chem. Lett., 1995, 5, 937, or by conversion into the carbamate derivative, for example the tert. butyl carbamate, by reaction with an alkyl, aryl or aralkyl chloroformate, in the presence of a base such as triethylamine, as described in Tet. Lett., 1994, 35, 379. The protected sulfonamide is reacted with a dialkyl bromoalkyl phosphonate **22.7** to form the alkylated product **22.8**. The alkylation reaction is effected as described in Scheme **8**. The product is then deprotected to yield the sulfonamide **22.9**. Deprotection of pivalyloxymethyl amides is effected by treatment with trifluoroacetic acid; deprotection of benzyloxymethyl amides is effected by catalytic hydrogenation, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 398. Sulfonamide carbamates, for example the tert. butyl carbamate, are deprotected by treatment with trifluoroacetic acid. The sulfonamide **22.9** is then reacted with the bromoamide **22.10** to give the displacement product **22.11**.

For example, [1,2,5]thiadiazepane 1,1-dioxide **22.11A** (WO 0230930 A2 p. 321) is reacted in dioxan solution with equimolar amounts of a dialkyl 3-carboxypropyl phosphonate **23.12**, (Epsilon) and dicyclohexyl carbodiimide, to produce the amide **22.13**. This material is reacted in pyridine solution at reflux temperature with 5-bromo-8-hydroxy-[1,6]naphthyridine-7-carboxylic acid 4-fluoro-benzylamide **22.14**, prepared by the methods described above, and copper oxide, to afford the displacement product **22.15**.

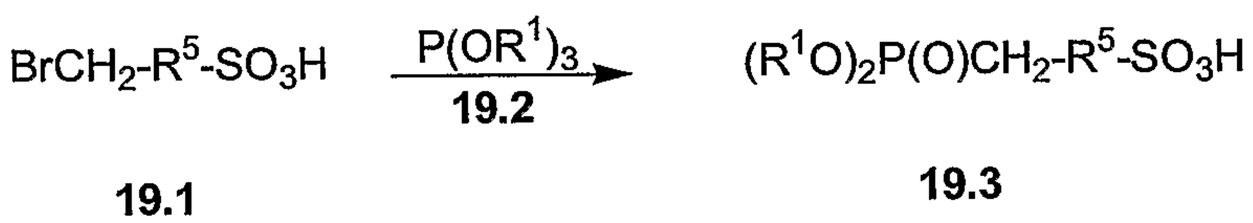
As a further example, the sulfonamide **22.11A** is reacted in dichloromethane with one molar equivalent of t-Boc anhydride, triethylamine and dimethylaminopyridine, to give 1,1-dioxo-[1,2,5]thiadiazepane-2-carboxylic acid tert-butyl ester **22.16**. The product is then reacted at ambient temperature in dimethylformamide solution with a dialkyl 4-bromomethyl benzyl phosphonate **22.17**, (Tet., 1998, 54, 9341) and potassium carbonate, to yield the alkylation product **22.18**. The BOC group is removed by treatment with trifluoroacetic acid to give the sulfonamide **22.19**, and this material is reacted, as described above, with 5-bromo-8-

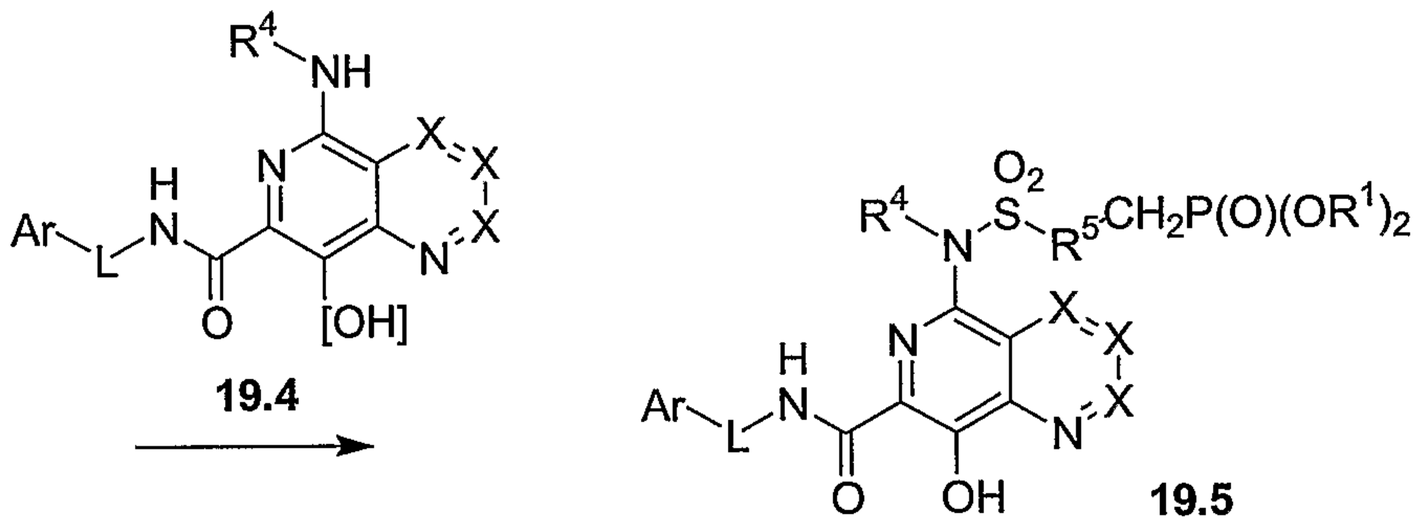
hydroxy-[1,6]naphthyridine-7-carboxylic acid 3-fluoro-benzylamide **22.20**, prepared by the methods described above, to afford the displacement product **22.21**.

Using the above procedures, but employing, in place of the sulfonamide **22.11A**, different sulfonamides **22.1**, and/or different carboxylic acids **22.2** or alkyl bromides **22.7**, and/or different bromides **22.4**, the corresponding products **22.5** and **22.11** are obtained.

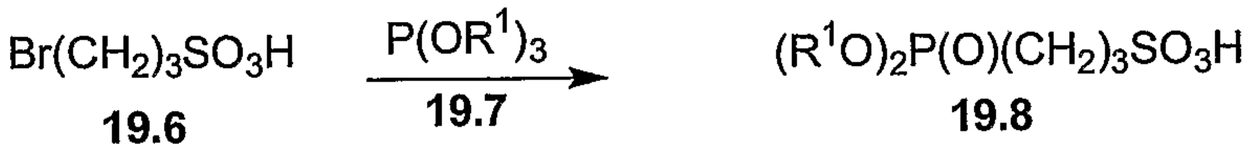
Scheme 19. Phosphonates 5.

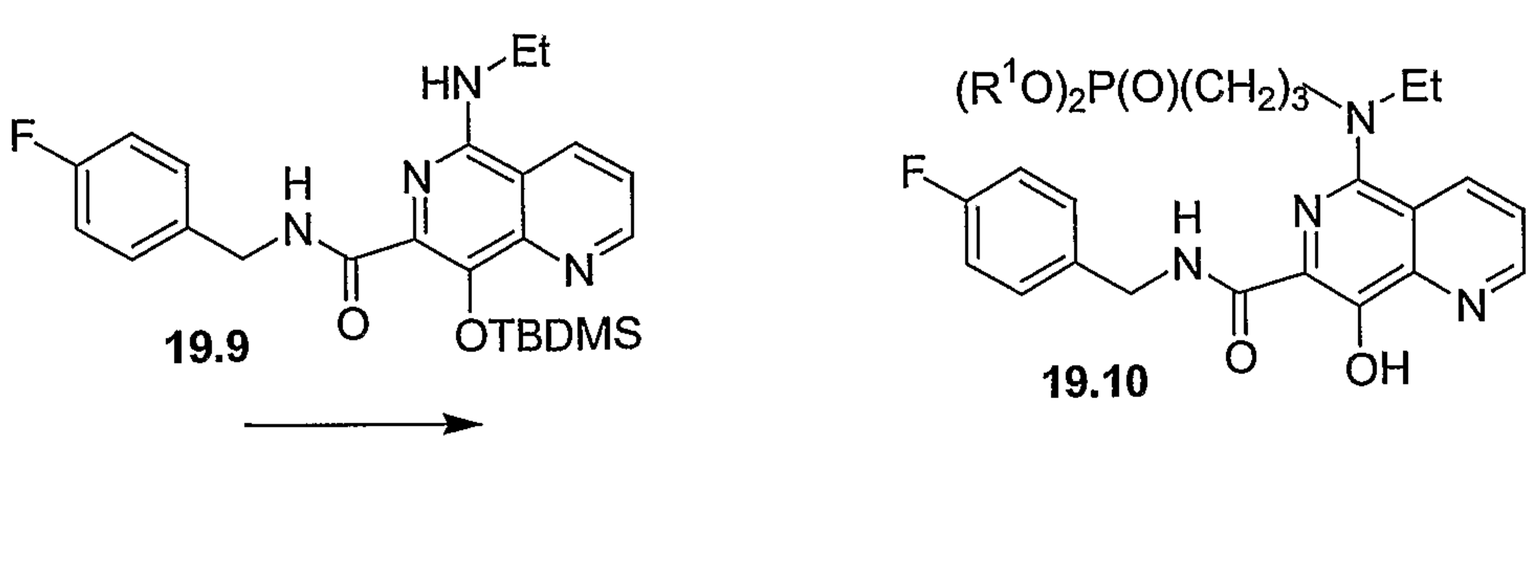
Method





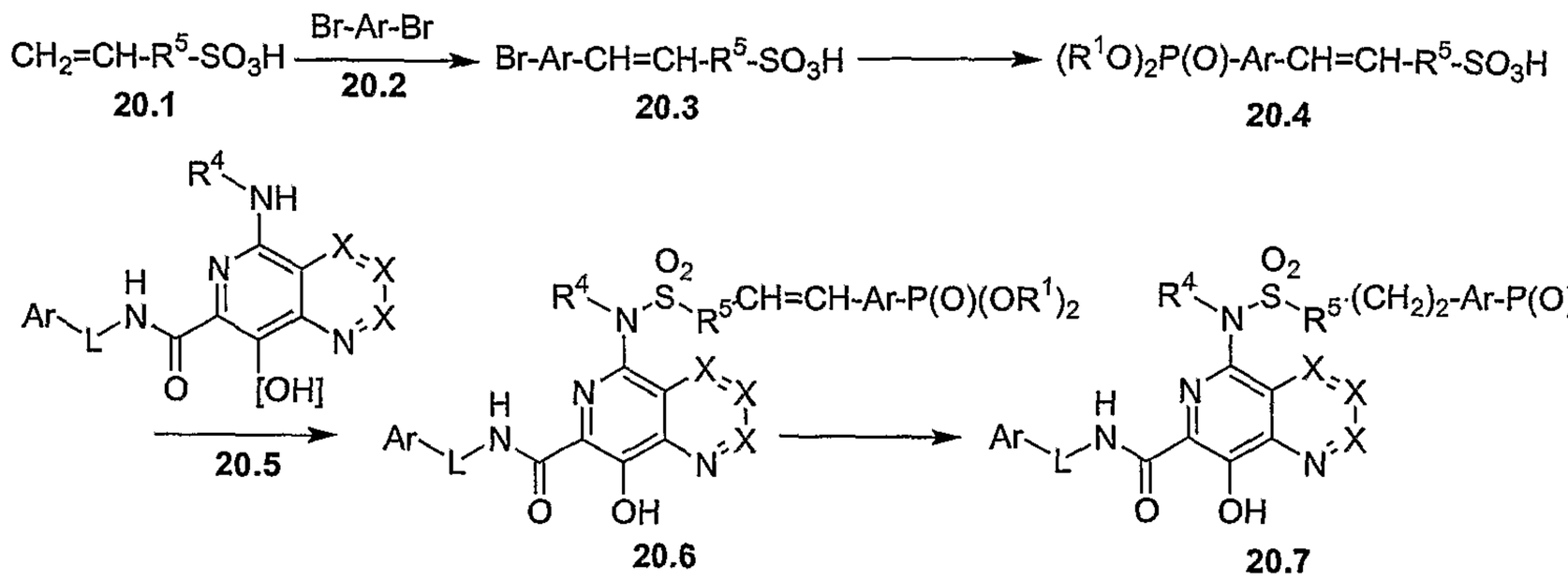
Example





Scheme 20. Phosphonates 5.

Method



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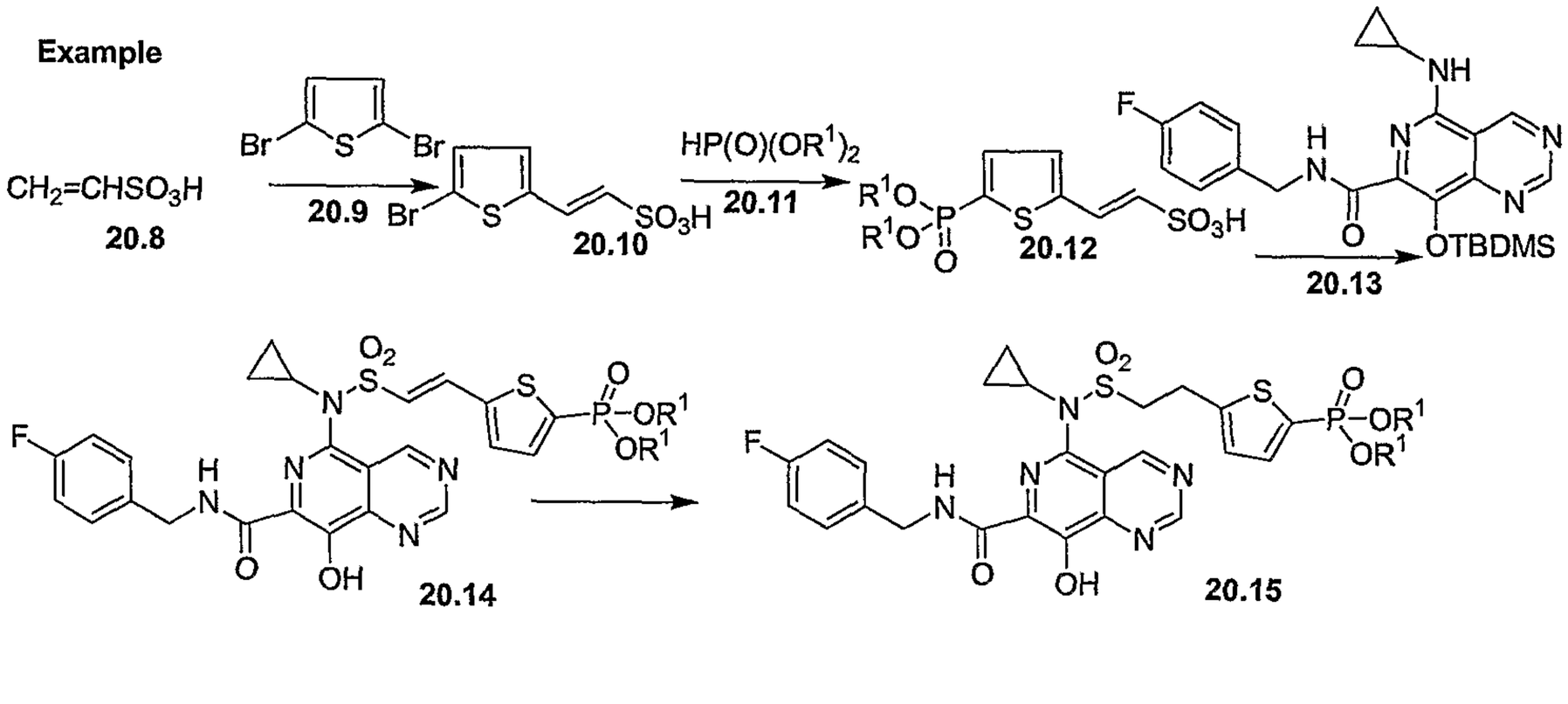
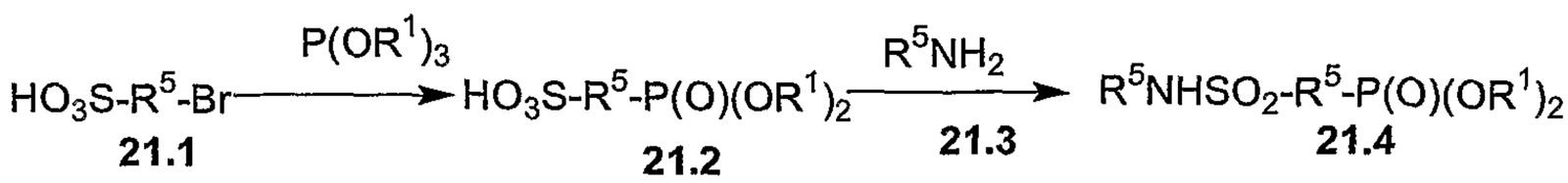
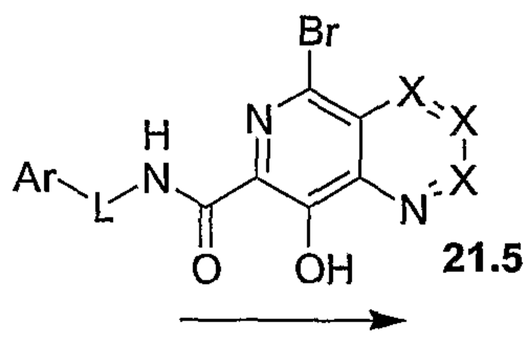
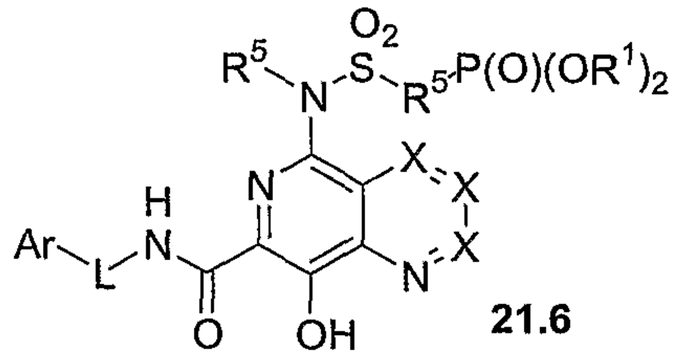


Scheme 21. Phosphonates 5.

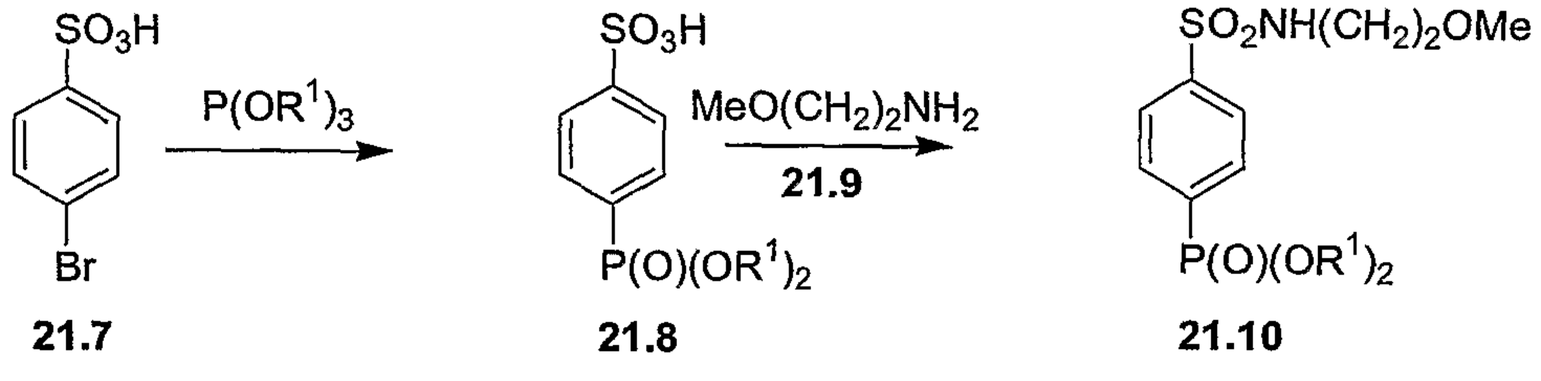
Method

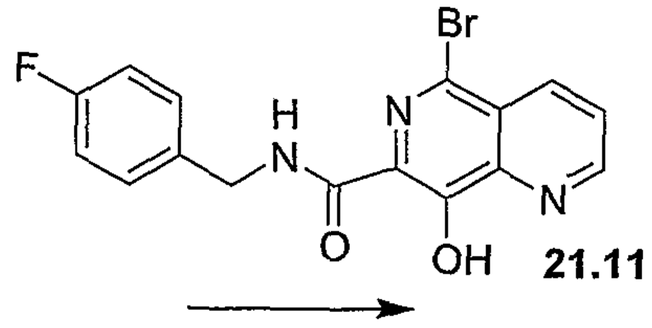


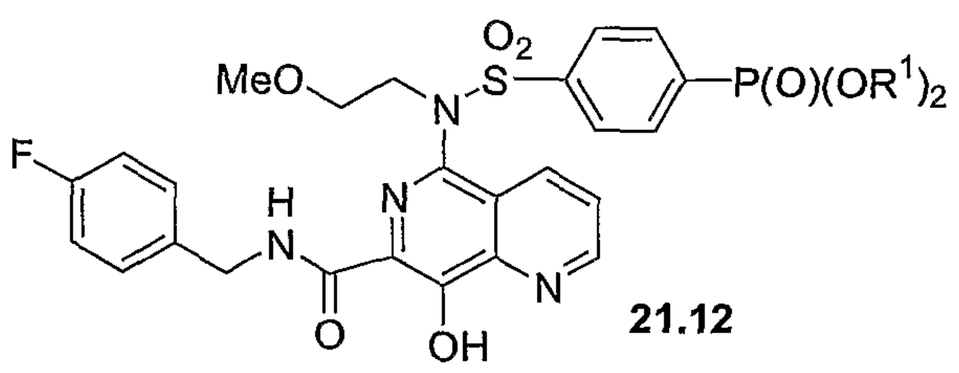




Example

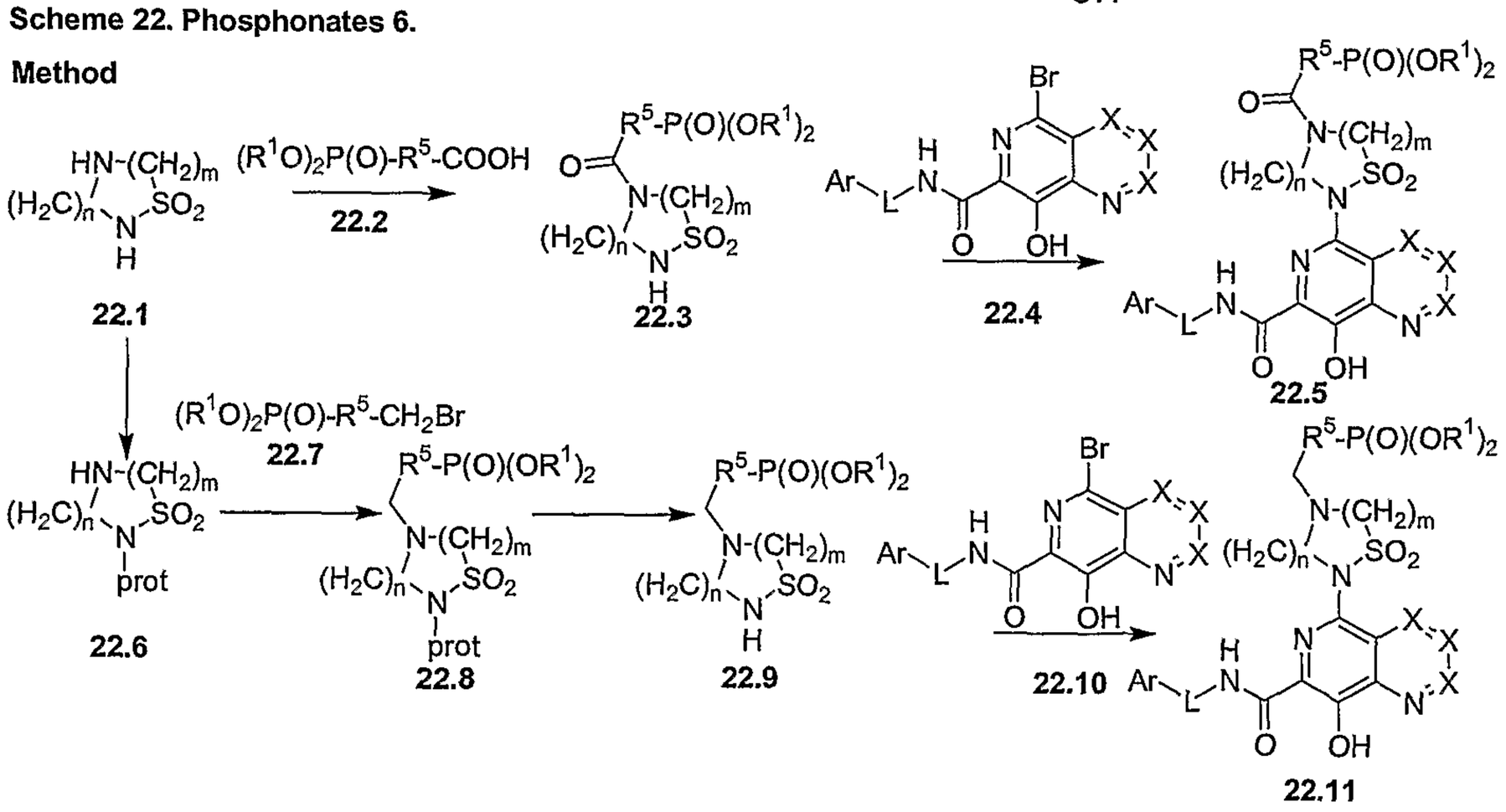






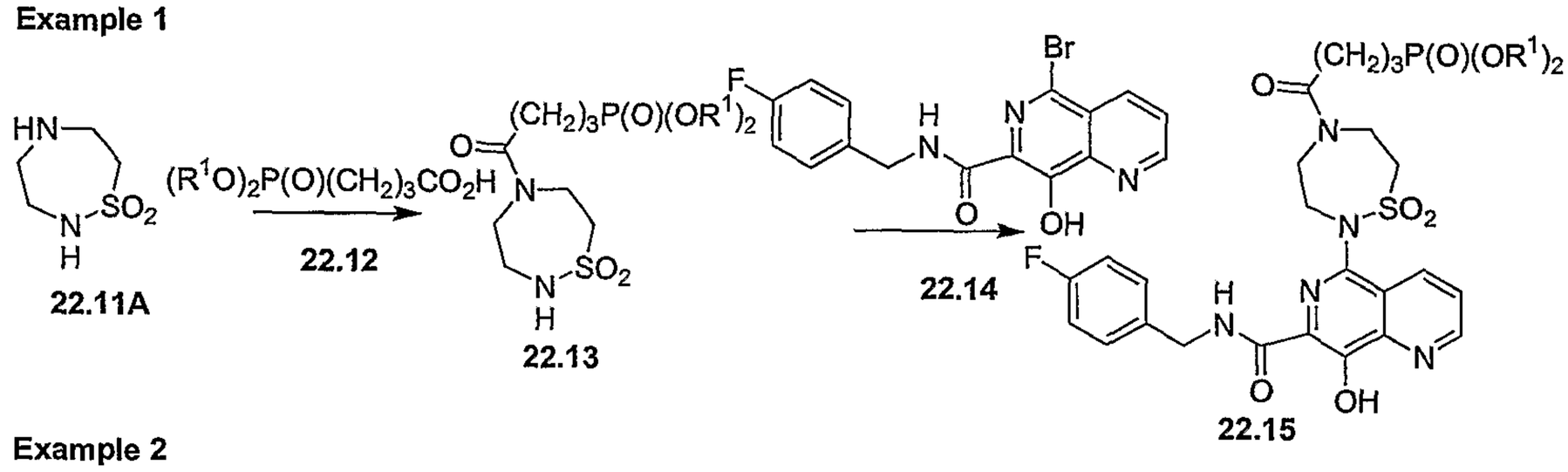
Scheme 22. Phosphonates 6.

Method

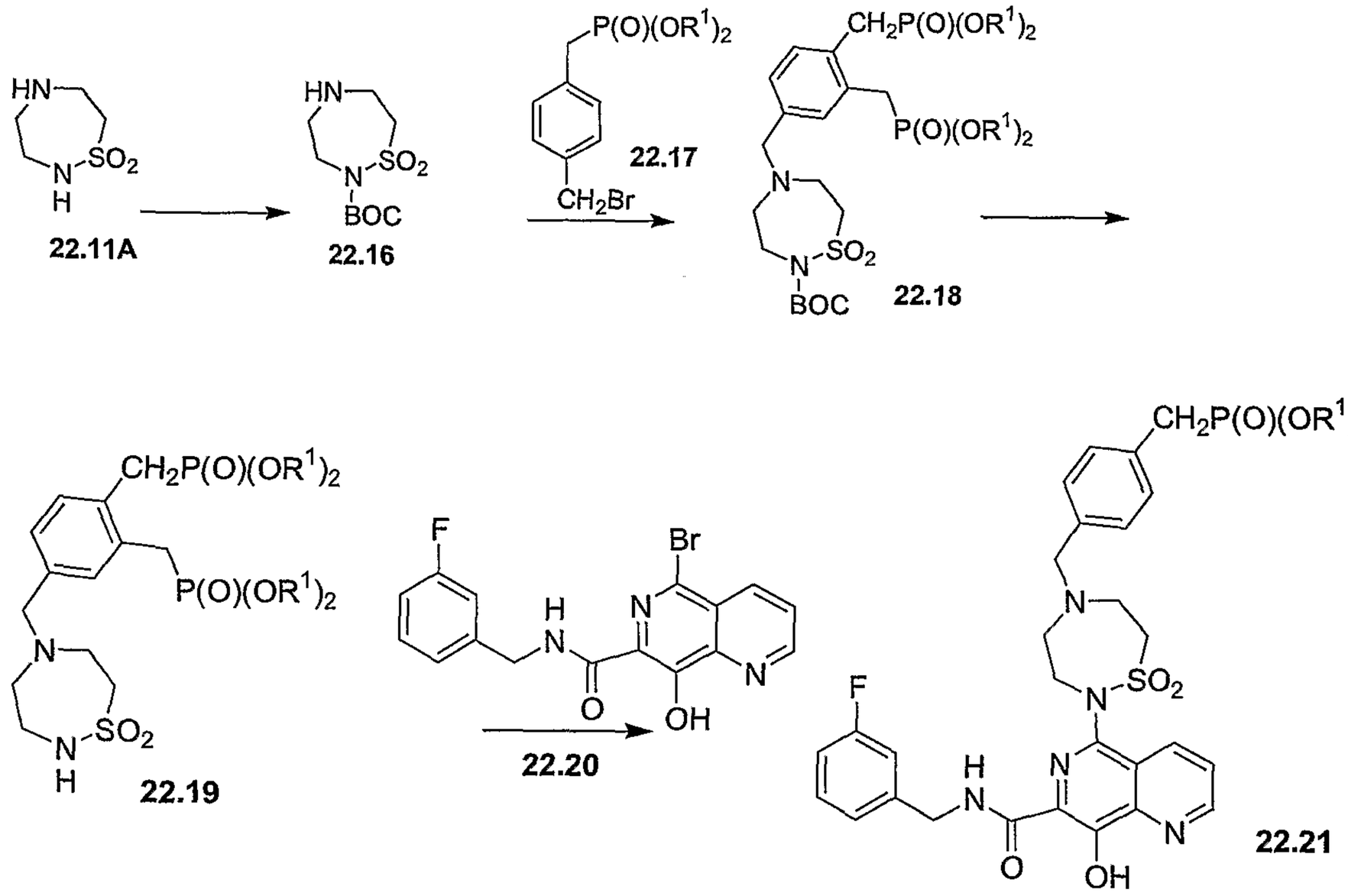


Scheme 22. Phosphonates 5.

Example 1



Example 2



Scheme **23** depicts the preparation of phosphonates **6** in which the phosphonate group is attached by means of an aryl or heteroaryl group. In this procedure, a bromoaryl-substituted cyclic sulfonamide, prepared as described in J. Org. Chem., 1991, 56, 3549, from the corresponding bromoaryl or bromoheteroaryl acetic acid and a vinyl sulfonic ester, is coupled, as described in Scheme **3**, with a dialkyl phosphite to afford the phosphonate **23.2**. The product is then reacted, as described above, with a bromoamide **23.3** to yield the displacement product **23.4**.

For example, 4-(4-bromo-phenyl)-[1,2]thiazinane 1,1-dioxide **23.5** (J. Org. Chem., 1991, 56, 3549) is reacted in dimethylformamide solution with a dialkyl phosphite **23.6** and tetrakis(triphenylphosphine)palladium(0), to give the phosphonate **23.7**. The product is then reacted with 5-bromo-8-hydroxy-[1,6]naphthyridine-7-

carboxylic acid (5-fluoro-indan-1-yl)-amide **23.8**, prepared by the methods described above, to give the phosphonate **23.9**.

Using the above procedures, but employing, in place of the sulfonamide **23.5**, different sulfonamides **23.1**, and/or different bromo compounds **23.3**, the corresponding products **23.4** are obtained.

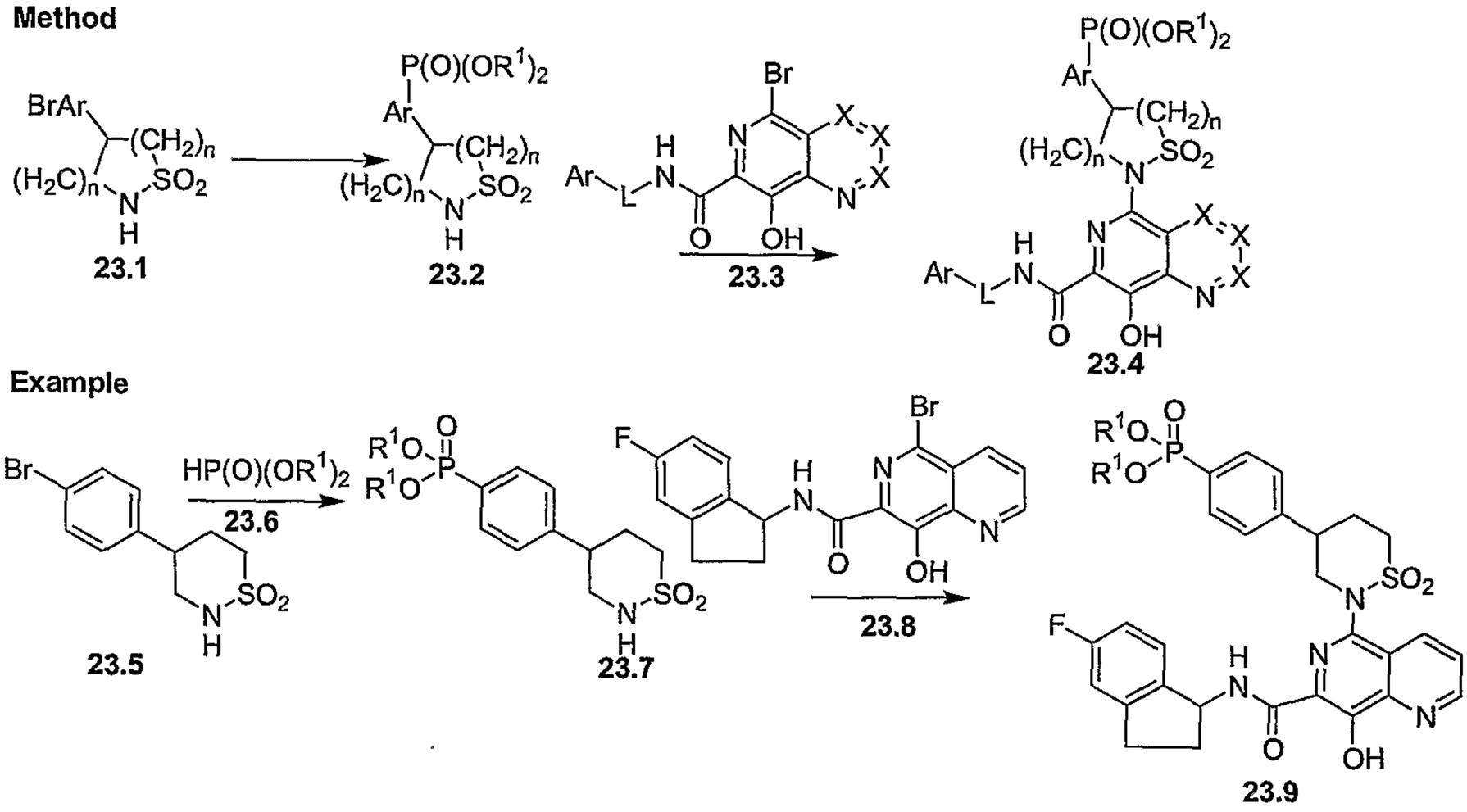
Scheme **24** depicts the preparation of phosphonates **6** in which the phosphonate group is attached by means of an amide linkage. In this procedure, a carboxy-substituted cyclic sulfonamide **24.1** is coupled with an amino-substituted dialkyl phosphonate **24.2**, as described in Scheme **5**, to give the amide **24.3**. The product is then reacted with the bromoamide **24.4** to afford the displacement product **24.5**.

For example, 1,1-dioxo-[1,2]thiazinane-3-carboxylic acid **24.6** (Izvest. Akad. Nauk. SSSR Ser. Khim., 1964, 9, 1615) is reacted in dimethylformamide solution with equimolar amounts of an amino-substituted butyl phosphonate **24.7** (Acros) and dicyclohexylcarbodiimide, to afford the amide **24.8**. The latter compound is then condensed with 5-bromo-8-hydroxy-[1,6]naphthyridine-7-carboxylic acid [1-(3-chloro-4-fluoro-phenyl)-ethyl]-amide **24.9**, prepared by the methods described above, to give the product **24.10**.

Using the above procedures, but employing, in place of the sulfonamide **24.6**, different sulfonamides **24.1**, and/or different bromo compounds **24.4**, the corresponding products **24.5** are obtained.

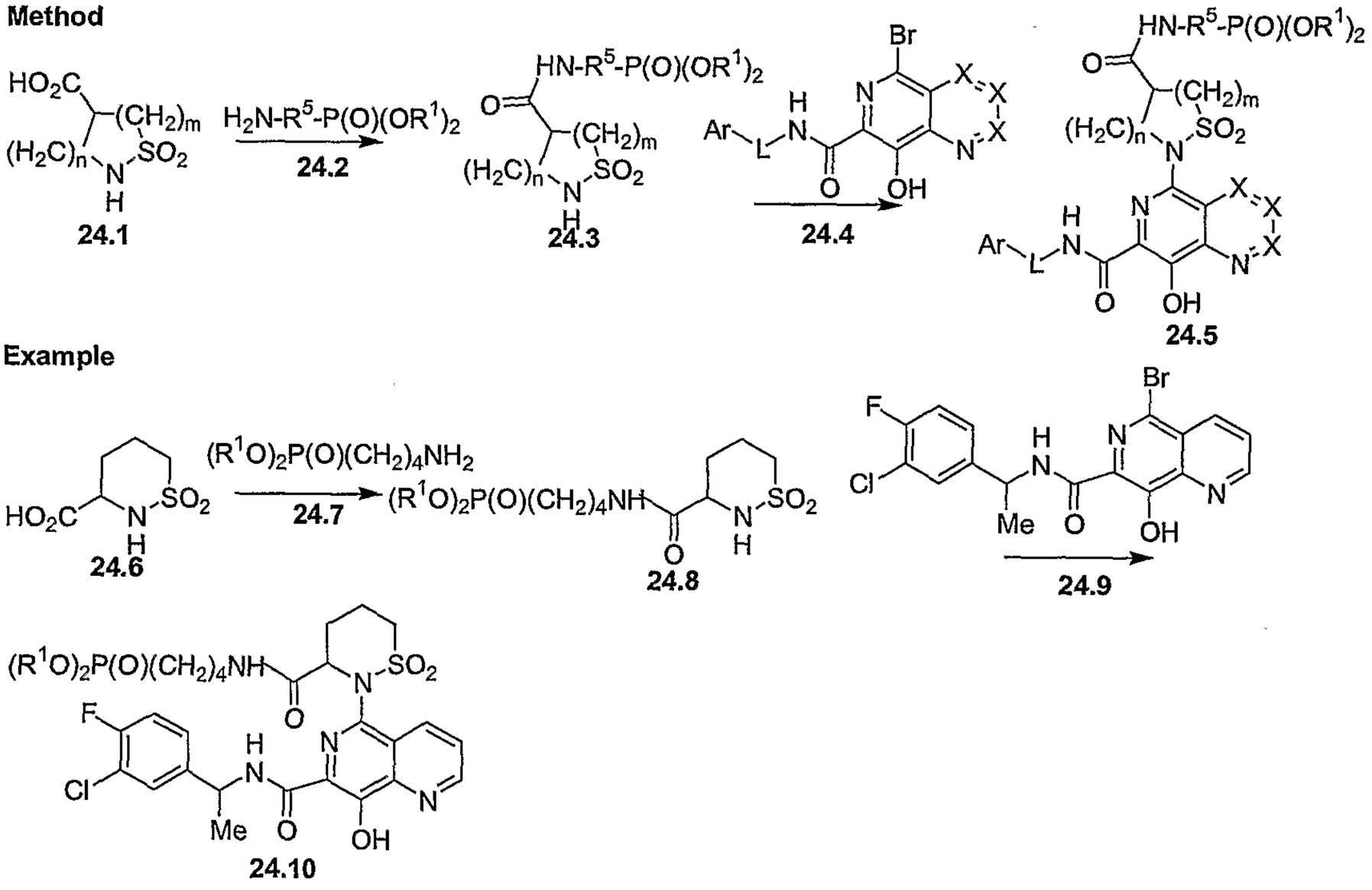
Scheme 23. Phosphonates 6.

Method



Scheme 24. Phosphonates 6.

Method



Preparation of the intermediate phosphonate esters 7.

Schemes **25** - **27** illustrate methods for the preparation of the phosphonate esters **7**.

Scheme **25** illustrates the preparation of phosphonate esters **7** in which the phosphonate is attached by means of a carbon link or a variable carbon chain

incorporating a heteroatom. In this procedure, a methyl-substituted cyclic anhydride **25.1** is converted, as described in Schemes **1** and **2**, into the bicyclic amide **25.2**, in which the phenolic hydroxyl group is protected. The compound is reacted with a free radical brominating agent such as N-bromosuccinimide to prepare the bromomethyl derivative **25.3**. The benzylic bromination reaction is performed at reflux temperature in an inert organic solvent such as hexachloroethane or ethyl acetate, optionally in the presence of an initiator such as dibenzoyl peroxide. The bromomethyl compound **25.3** is then reacted with a trialkyl phosphite in an Arbuzov reaction, as described in Scheme **19**, to give, after deprotection of the phenolic hydroxyl group, the phosphonate **25.4**.

Alternatively, the benzylic bromide **25.3** is reacted with a dialkyl hydroxy, mercapto or amino-substituted phosphonate **25.5**, to afford, after deprotection of the phenolic hydroxyl group, the displacement product **25.6**. The displacement reaction is effected at from ambient temperature to about 100°, in a polar organic solvent such as dimethylformamide or DMPU, in the presence of a suitable base such as sodium hydride or lithium hexamethyldisilazide, for instances in which Y is O, or cesium carbonate or triethylamine for instances in which Y is S or N.

For example, 4-methyl-furo[3,4-b]pyridine-5,7-dione **25.7**, (J. Org. Chem., 1961, 26, 808) is converted, using the methods described above, into 5-(1,1-dioxo-isothiazolidin-2-yl)-4-methyl-8-triisopropylsilanyloxy-[1,6]naphthyridine-7-carboxylic acid 4-fluoro-benzylamide **25.8**. The compound is then reacted with one molar equivalent of N-bromosuccinimide in ethyl acetate at reflux, to afford the bromomethyl analog **25.9**. This product is reacted with a dialkyl hydroxyethyl phosphonate **25.11** (Epsilon) and sodium hydride in dimethylformamide at 80°, to yield, after desilylation, the phosphonate **25.12**. Alternatively, the bromomethyl compound **25.9** is reacted at 120° with a trialkyl phosphite, to obtain, after desilylation, the phosphonate **25.10**.

Using the above procedures, but employing, in place of the anhydride **25.7**, different anhydrides **25.1**, and/or different phosphonates **25.5**, the corresponding products **25.4** and **25.6** are obtained.

Scheme **26** illustrates the preparation of phosphonate esters **7** in which the phosphonate is attached by means of an aminomethyl linkage. In this procedure, a

bromomethyl-substituted bicyclic amide **25.3**, prepared as described in Scheme **25**, is oxidized to the corresponding aldehyde **26.1**. The oxidation of halomethyl compounds to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 599ff. The transformation is effected by treatment with dimethylsulfoxide and base, optionally in the presence of a silver salt, or by reaction with trimethylamine N-oxide or hexamethylene tetramine. The aldehyde **26.1** is then reacted with a dialkyl amino-substituted phosphonate **26.2** in a reductive amination reaction, as described in Scheme **9**, to yield, after deprotection of the phenolic hydroxyl group, the aminomethyl product **26.3**.

For example, 4-bromomethyl-5-(methanesulfonyl-methyl-amino)-8-triisopropylsilanyloxy-[1,6]naphthyridine-7-carboxylic acid 3,5-dichloro-benzylamide **26.4**, prepared from the anhydride **25.7**, using the methods described in Scheme **25**, is reacted with dimethylsulfoxide and 2,4,6-collidine at 90°, as described in J. Org. Chem., 51, 1264, 1986, to afford the aldehyde **26.5**. The product is then reacted with one molar equivalent of a dialkyl aminoethyl phosphonate **26.6** (Epsilon) and sodium triacetoxyborohydride to produce, after desilylation, the phosphonate **26.7**.

Using the above procedures, but employing, in place of the bromomethyl compound **26.4**, different bromomethyl compounds **25.3**, and/or different phosphonates **26.2**, the corresponding products **26.3** are obtained.

Scheme **27** illustrates the preparation of phosphonate esters **7** in which the phosphonate is attached by means of an amide linkage. In this procedure, an aldehyde **26.1** (Scheme **26**) is oxidized to the corresponding carboxylic acid **27.1**. The conversion of aldehydes to the corresponding carboxylic acids is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 838. The reaction is effected by the use of various oxidizing agents such as, for example, potassium permanganate, ruthenium tetroxide, silver oxide or sodium chlorite. The resultant carboxylic acid **27.1** is then coupled, as described in Scheme **5**, with a dialkyl amino-substituted phosphonate **27.2**, to yield, after deprotection of the phenolic hydroxyl group, the amide **27.3**.

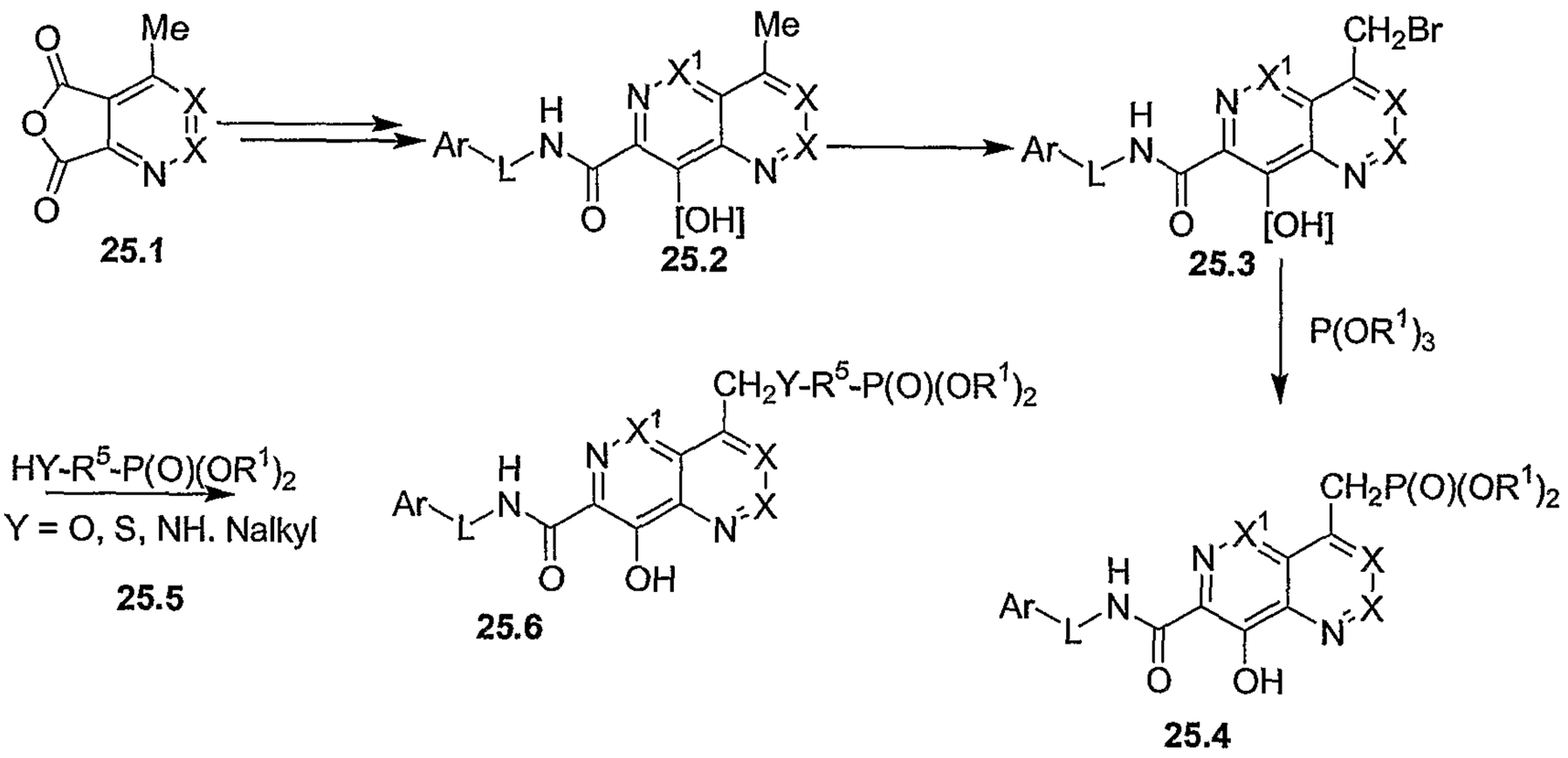
For example, the anhydride **27.4** is converted, as described above, and in Schemes **25** and **26**, into N-[7-(2-cyclohex-3-enyl-ethylcarbamoyl)-4-formyl-8-triisopropylsilanyloxy-[1,6]naphthyridin-5-yl]-N,N',N'-trimethyl-oxalamide **27.5**. The

aldehyde is then reacted with silver oxide in aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 4, 919, 1963, to afford the carboxylic acid **27.6**. The latter compound is then reacted in dioxan solution at ambient temperature with equimolar amounts of a dialkyl aminomethyl phosphonate **27.7** (Interchim) and dicyclohexylcarbodiimide, to give, after desilylation, the amide phosphonate **27.8**.

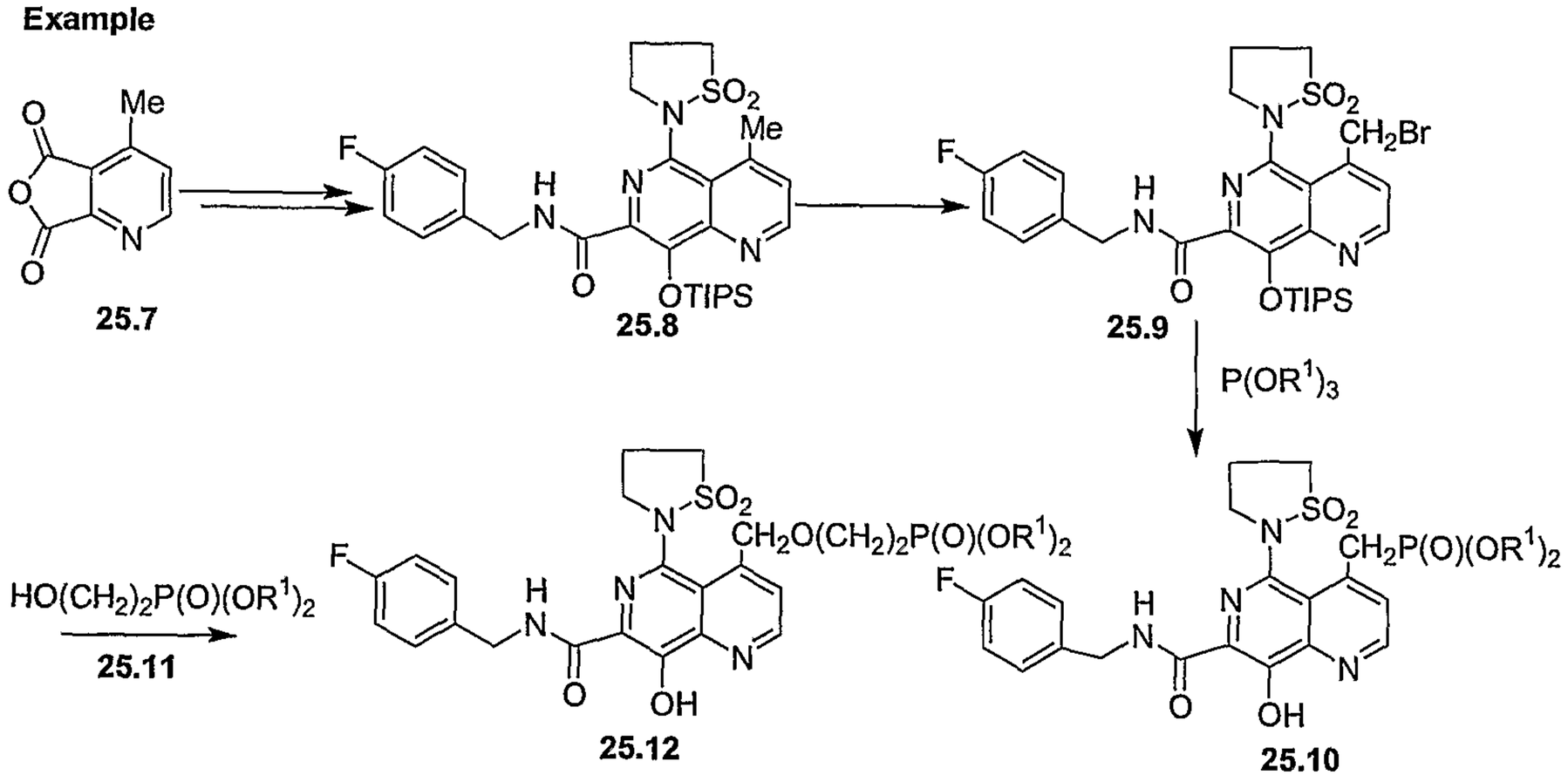
Using the above procedures, but employing, in place of the aldehyde **27.5**, different aldehydes **26.1**, and/or different phosphonates **27.2**, the corresponding products **27.3** are obtained.

Scheme 25. Phosphonates 7.

Method

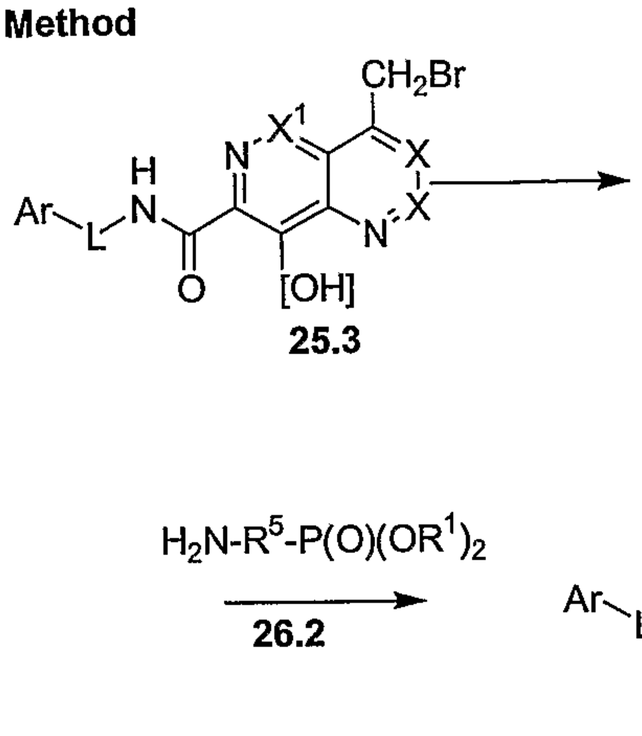


Example

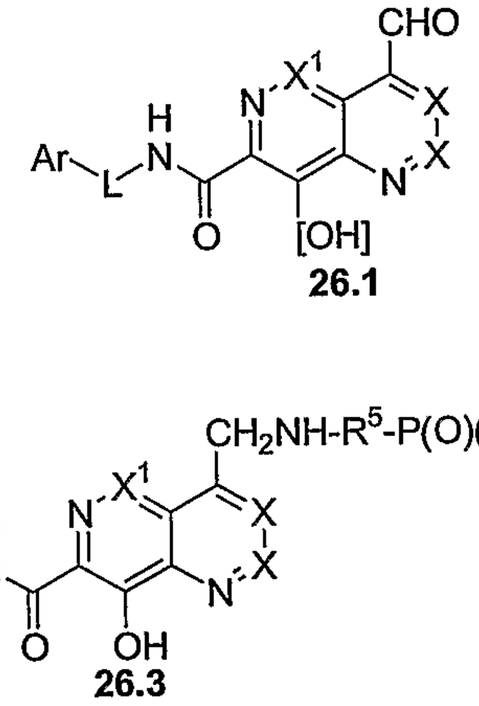


Scheme 26. Phosphonates 7.

Method



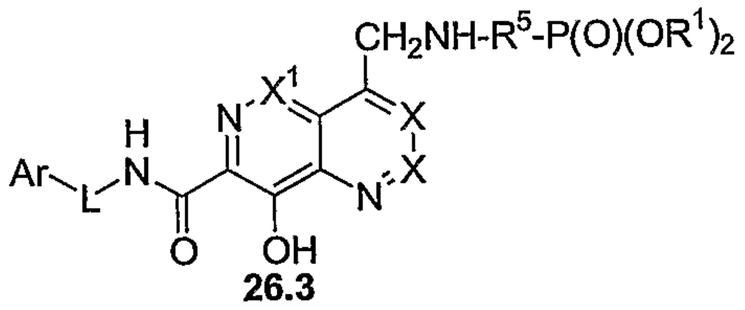
25.3



26.1

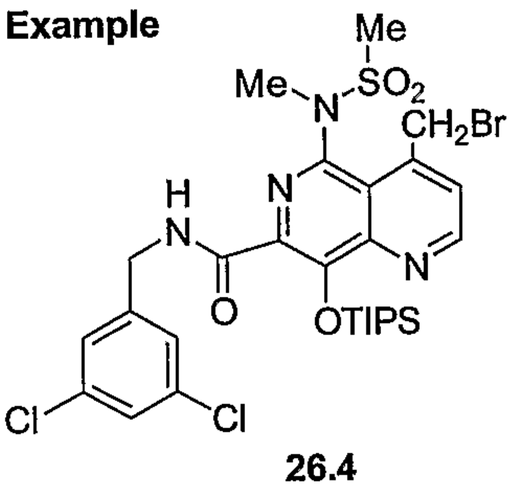
$H_2N\text{-}R^5\text{-}P(O)(OR^1)_2$

26.2

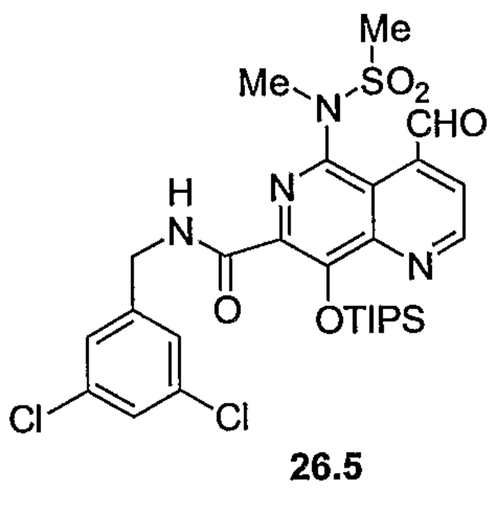


26.3

Example



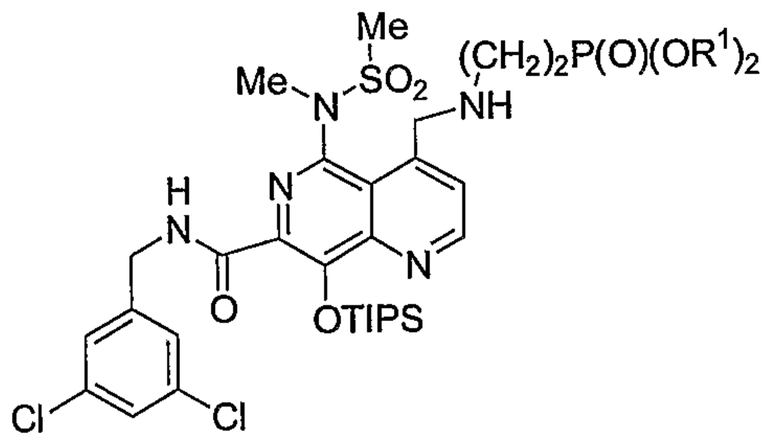
26.4



26.5

$H_2N(CH_2)_2P(O)(OR^1)_2$

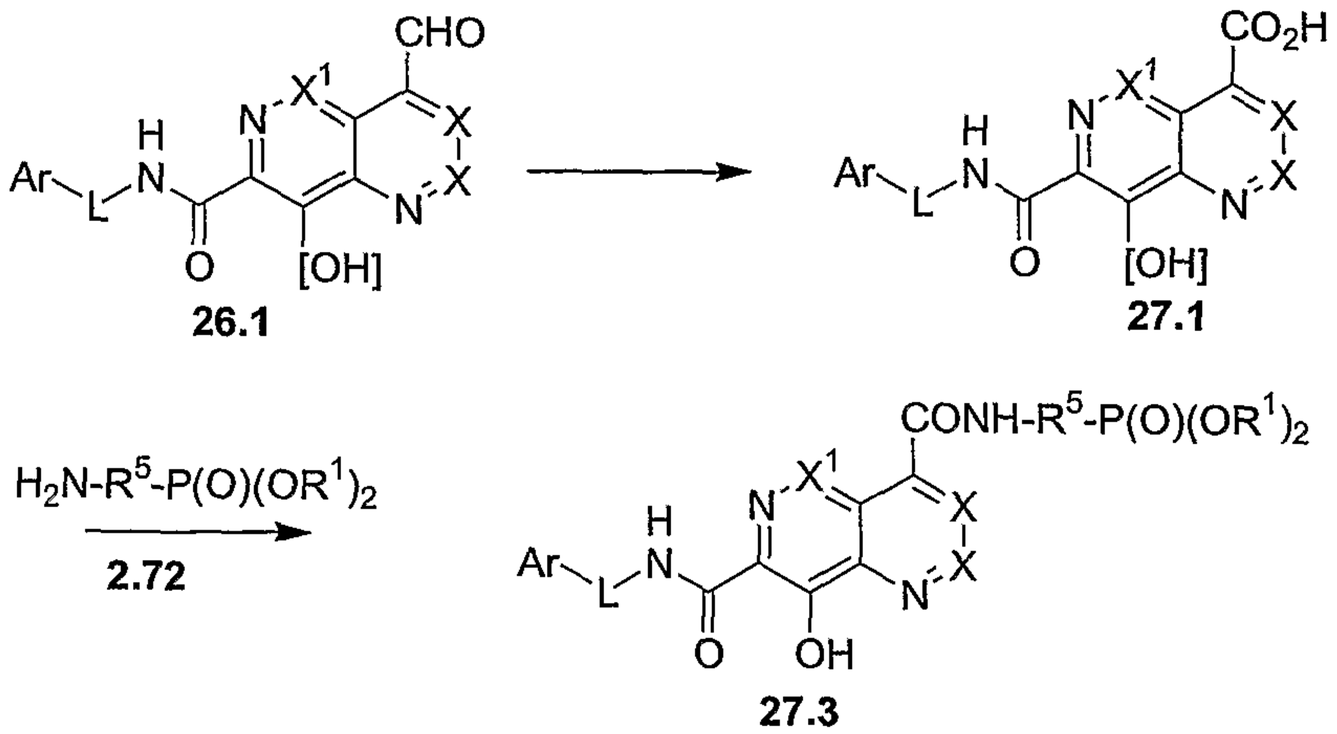
26.6



26.7

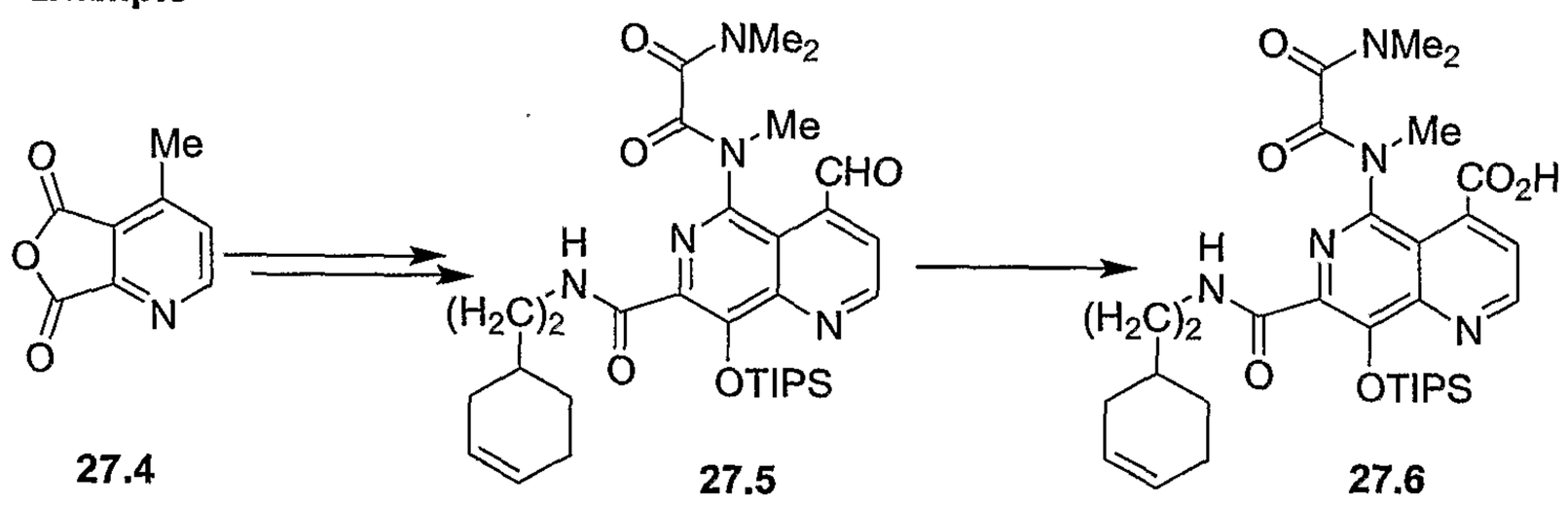
Scheme 27. Phosphonates 7.

Method



26.1 **27.1** **27.3**

Example



27.4 **27.5** **27.6** **27.8**

Preparation of the intermediate phosphonate esters 8.

Schemes **28** and **29** illustrate methods for the preparation of the phosphonate esters **8**.

Scheme **28** illustrates the preparation of phosphonate esters **8** in which the phosphonate is attached by means of a heteroatom O or S and a variable carbon link. In this procedure, the hydroxyl group of a hydroxy-substituted cyclic anhydride **28.1** is protected to afford the compound **28.2**. The product is then converted, as described in Scheme **1**, into the bicyclic ester **28.3**, in which the phenol protecting groups are

different. The original phenolic hydroxyl group is then deprotected to yield the phenol **28.4**, and the product is subjected to a Mitsunobu reaction, as described in Scheme **7**, with a dialkyl hydroxy or mercapto-substituted phosphonate **28.8**, to produce the ether or thioether phosphonate **28.9**. This material is then reacted, as described in Scheme **3**, with the amine $ArLNR^2H$, to give after deprotection of the phenolic hydroxyl group, the amide **28.10**.

Alternatively, the phenol **28.4** is reacted with a dialkyl bromoalkyl-substituted phosphonate **28.5**, as described in Scheme **6**, to yield the ether **28.6**. The latter compound is then transformed, as described above, into the amide **28.7**.

For example, 3-hydroxy-furo[3,4-b]pyridine-5,7-dione **28.11** (German Patent 4343923) is reacted in tetrahydrofuran solution at 50° with 4-methoxybenzyl bromide and potassium carbonate, to give the 4-methoxybenzyl ether **28.12**. The product is then converted, as described above, into the silyl-protected bicyclic ester **28.13**. The 4-methoxybenzyl ether is then removed by reaction with dichlorodicyanobenzoquinone in dichloromethane at ambient temperature, as described in Tet. Lett., 27, 3651, 1986, to give the phenol **28.14**. The product is then reacted in tetrahydrofuran solution with a dialkyl bromomethyl phosphonate **29.15** (Lancaster) and potassium carbonate, to produce the phosphonate **28.16**; the product is then converted, by desilylation, amide formation, bromination, reaction with methylamine and carbamate formation, using the procedures described above, into the hydroxyamide **28.17**.

Alternatively, the phenol **28.14** is reacted in tetrahydrofuran solution with one molar equivalent of a dialkyl 2-mercaptoethyl phosphonate **28.18** (Zh. Obschei. Khim., 1973, 43, 2364), diethylazodicarboxylate and triphenylphosphine, to prepare the thioether phosphonate **28.19**. The product is then converted, as described above, into the amide **28.20**.

Using the above procedures, but employing, in place of the anhydride **28.11**, different anhydrides **28.1**, and/or different phosphonates **28.5** or **28.8**, the corresponding products **28.7** and **28.10** are obtained.

Scheme **29** illustrates the preparation of phosphonate esters **8** in which the phosphonate is attached either directly, or by means of a saturated or unsaturated carbon chain. In this procedure, a bromo-substituted anhydride **29.1** is converted, as

described above, into the phenol-protected amide **29.2**. The product is then subjected to a Heck coupling reaction, in the presence of a palladium (0) catalyst, as described in Scheme **4**, with a dialkyl alkenyl phosphonate **29.3**, to afford, after deprotection of the phenol, the phosphonate **29.4**. Optionally, the olefinic bond is reduced, as described in Scheme **4**, to yield the saturated analog **29.5**.

Alternatively, the bromo-substituted amide **29.2** is coupled, as described in Scheme **3**, with a dialkyl phosphite, in the presence of a palladium (0) catalyst, to generate, after deprotection of the phenolic hydroxyl group, the amide phosphonate **29.6**.

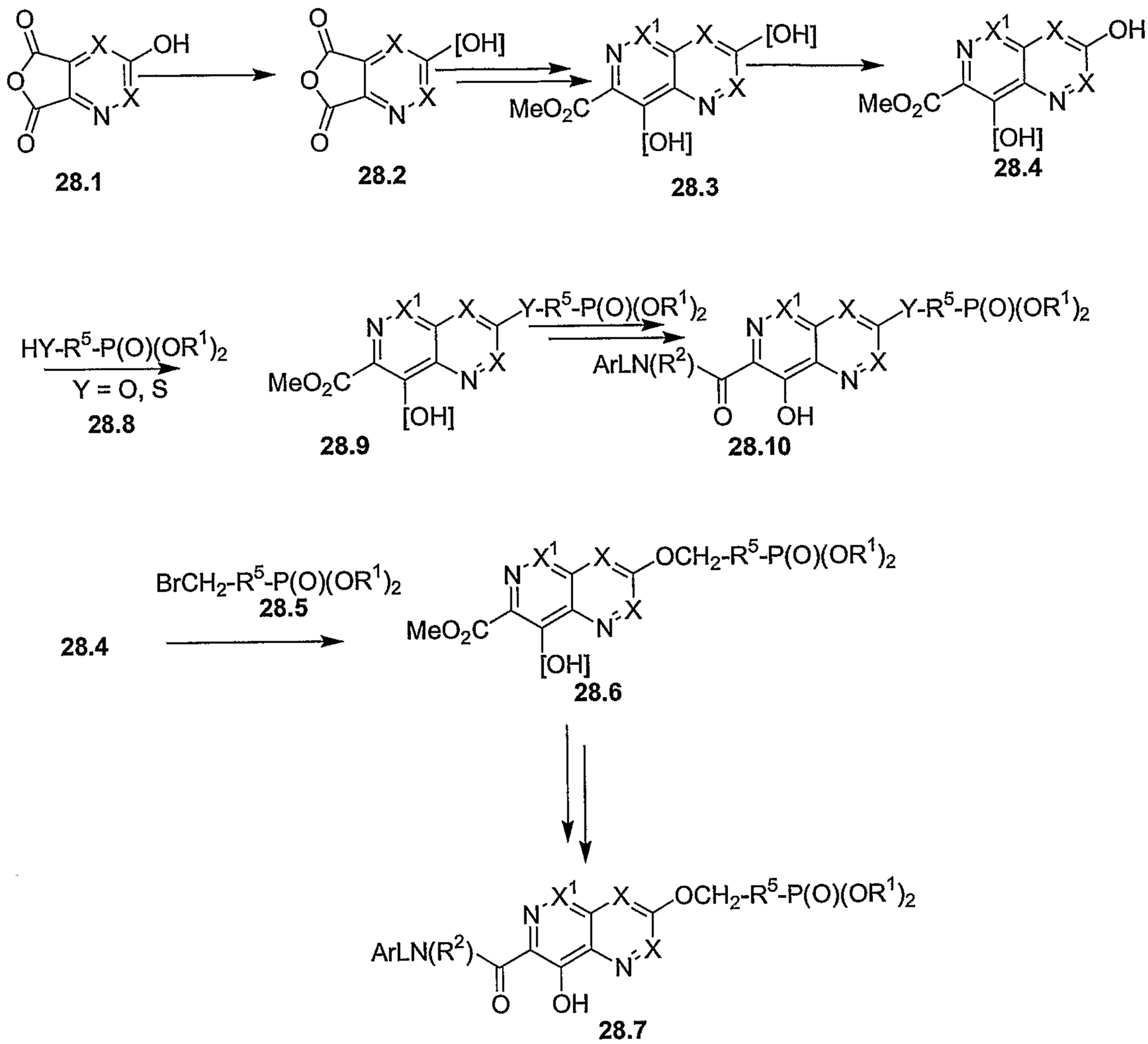
For example, 3-bromo-furo[3,4-b]pyridine-5,7-dione **29.7**, (Bioconjugate Chem., 2003, 14, 629) is converted, using the methods described above, into 3-bromo-5-(1,1-dioxo-[1,2]thiazinan-2-yl)-8-triisopropylsilanyloxy-[1,6]naphthyridine-7-carboxylic acid 4-trifluoromethyl-benzylamide **29.8**. This compound is then reacted, in dimethylformamide solution at 80°, with one molar equivalent of a dialkyl vinyl phosphonate **29.9**, (Aldrich), triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) to yield, after desilylation, the unsaturated phosphonate **29.10**. The product is then reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product **29.11**.

Alternatively, the bromo compound **29.8** is reacted in toluene solution at ca. 100°, with one molar equivalent of a dialkyl phosphite **29.2**, triethylamine and 3 mol % tetrakis(triphenylphosphine)palladium(0), to give, after desilylation, the phosphonate product **29.12**.

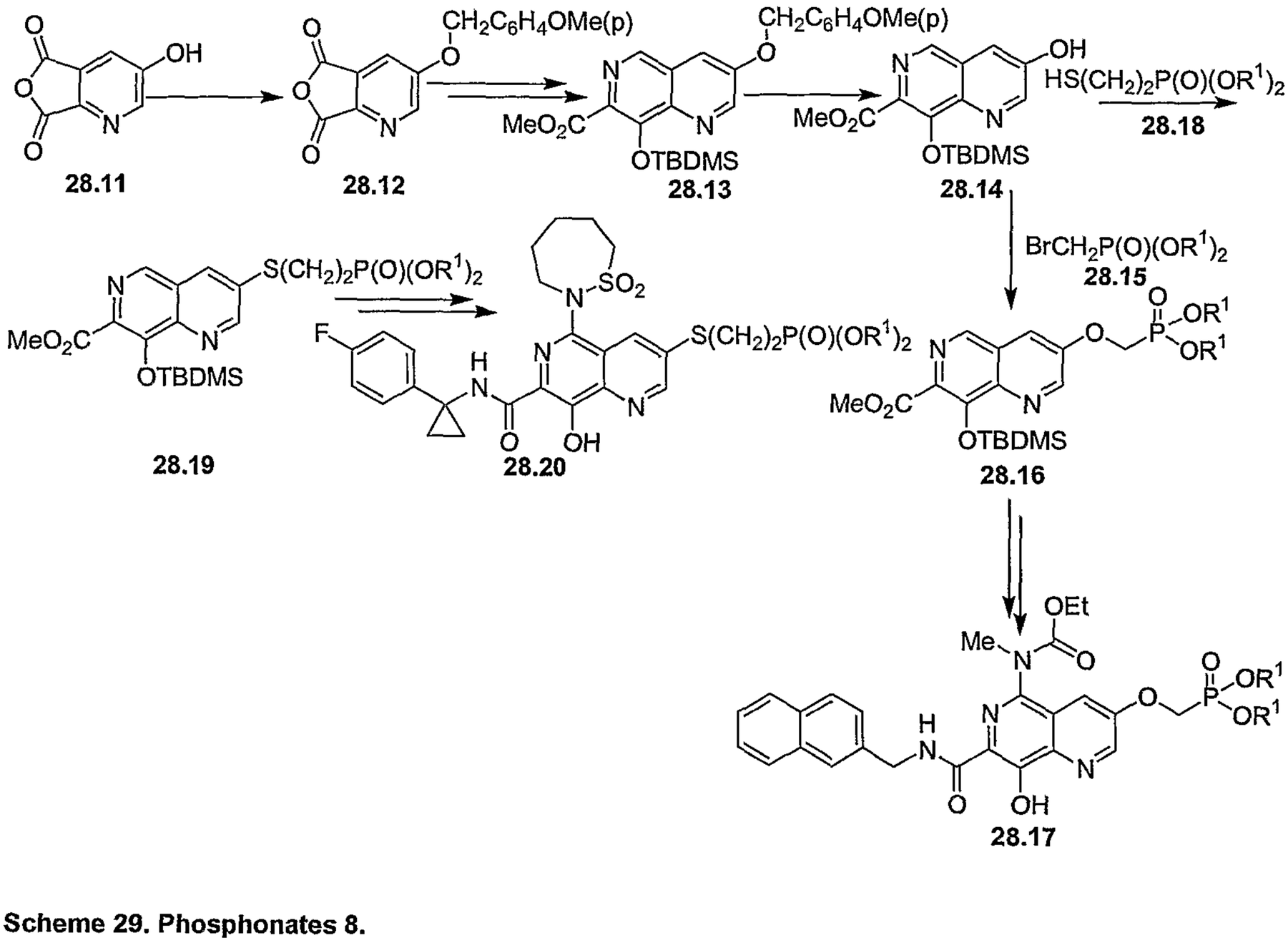
Using the above procedures, but employing, in place of the anhydride **29.7**, different anhydrides **29.1**, and/or different phosphonates **29.3**, the corresponding products **29.4**, **29.5** and **29.6** are obtained.

Scheme 28. Phosphonates 8.

Method

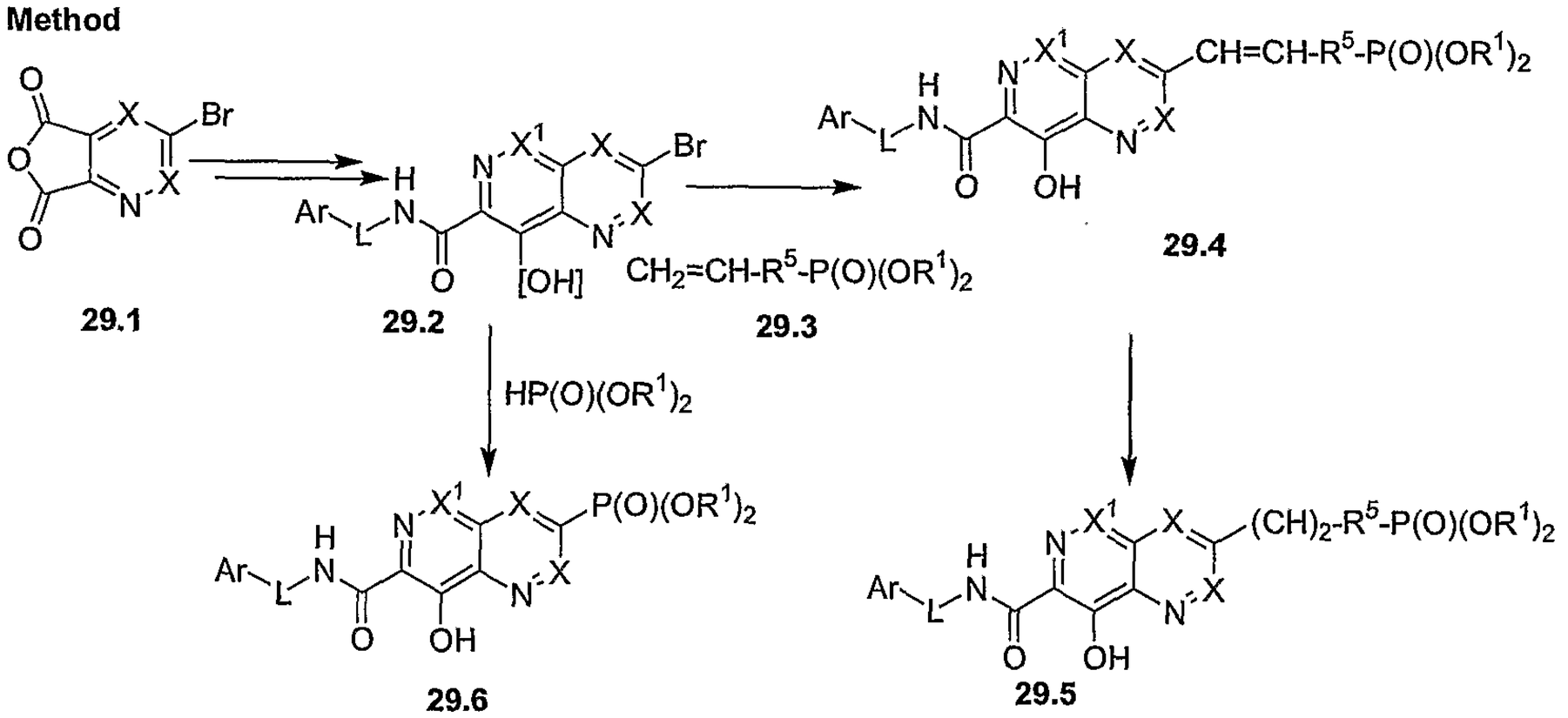


Example

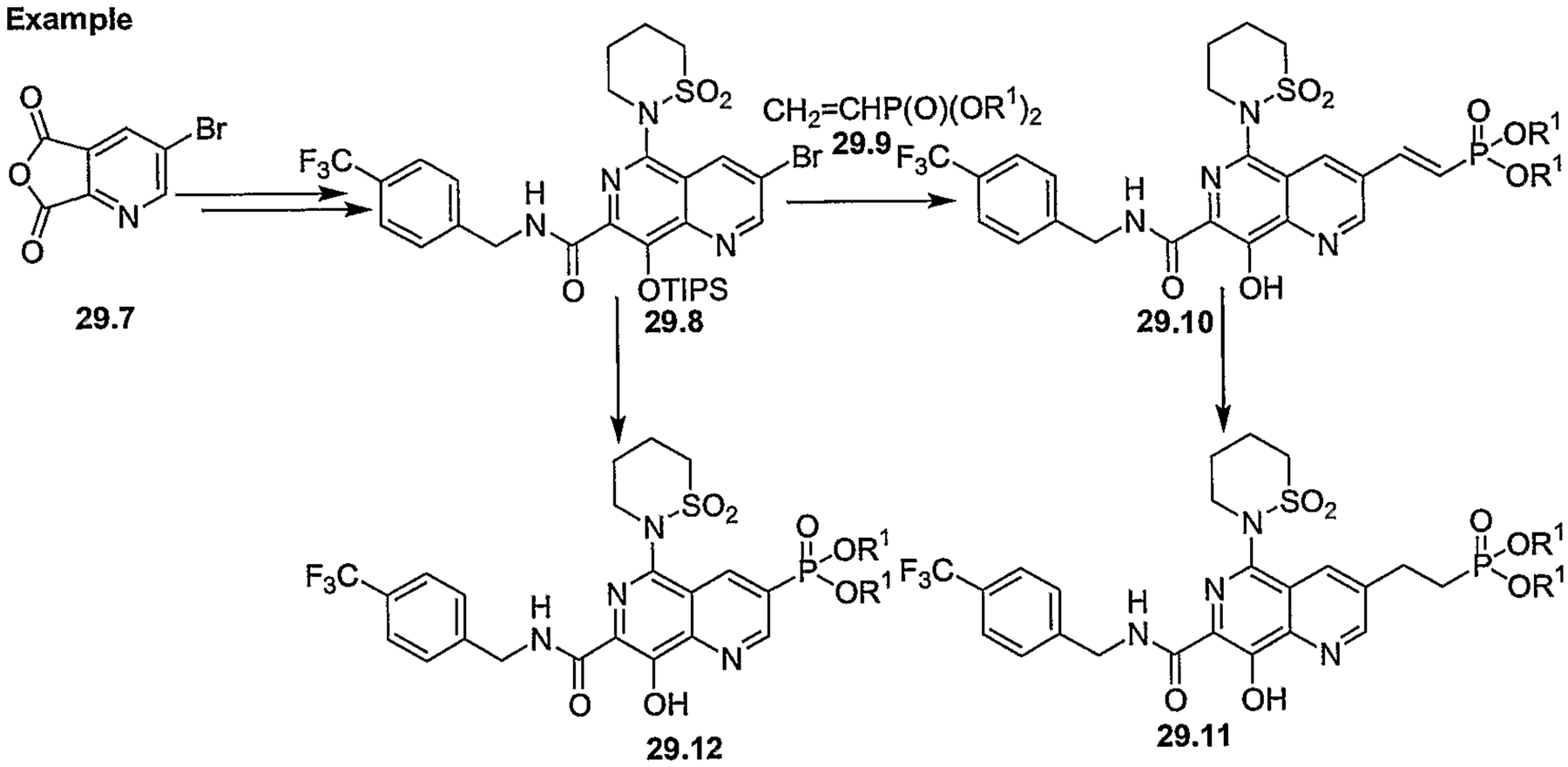


Scheme 29. Phosphonates 8.

Method



Example



Preparation of the intermediate phosphonate esters 9.

Schemes **30** and **31** illustrate methods for the preparation of the phosphonate esters **9**.

Scheme **30** illustrates the preparation of phosphonate esters **9** in which the phosphonate is attached by means of a saturated or unsaturated carbon link. In this procedure, a methyl-substituted bicyclic anhydride **30.1** is converted, using the methods described above, into the amide **30.2**. The product is then condensed, under basic conditions, with a dialkyl formyl-substituted phosphonate **30.3**, to afford the unsaturated phosphonate **30.4**. The reaction is conducted at from ambient temperature to about 100°, in a polar aprotic solvent such as dimethylformamide or dioxan, in the presence of a base such as sodium hydride, potassium tert. butoxide or lithium hexamethyldisilazide. Optionally, the product **30.4** is reduced, as described in Scheme **4**, to afford the saturated analog **30.5**.

For example, 2-methyl-furo[3,4-b]pyrazine-5,7-dione **30.6** (Nippon Noyaku Gakk., 1989, 14, 75) is converted, using the methods described above, into 5-(ethanesulfonyl-methyl-amino)-2-methyl-8-triisopropylsilanyloxy-pyrido[3,4-b]pyrazine-7-carboxylic acid (3,5-dichloro-benzyl)-ethyl-amide **30.7**. The product is then reacted, in dimethylformamide solution at 60°, with one molar equivalent of a dialkyl formylmethyl phosphonate **30.8** (Aurora) and sodium hydride, to give, after desilylation, the unsaturated phosphonate **30.9**. The product is then reacted with

diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product **30.10**.

Using the above procedures, but employing, in place of the anhydride **30.6**, different anhydrides **30.1**, and/or different phosphonates **30.3**, the corresponding products **30.4**, and **30.5** are obtained.

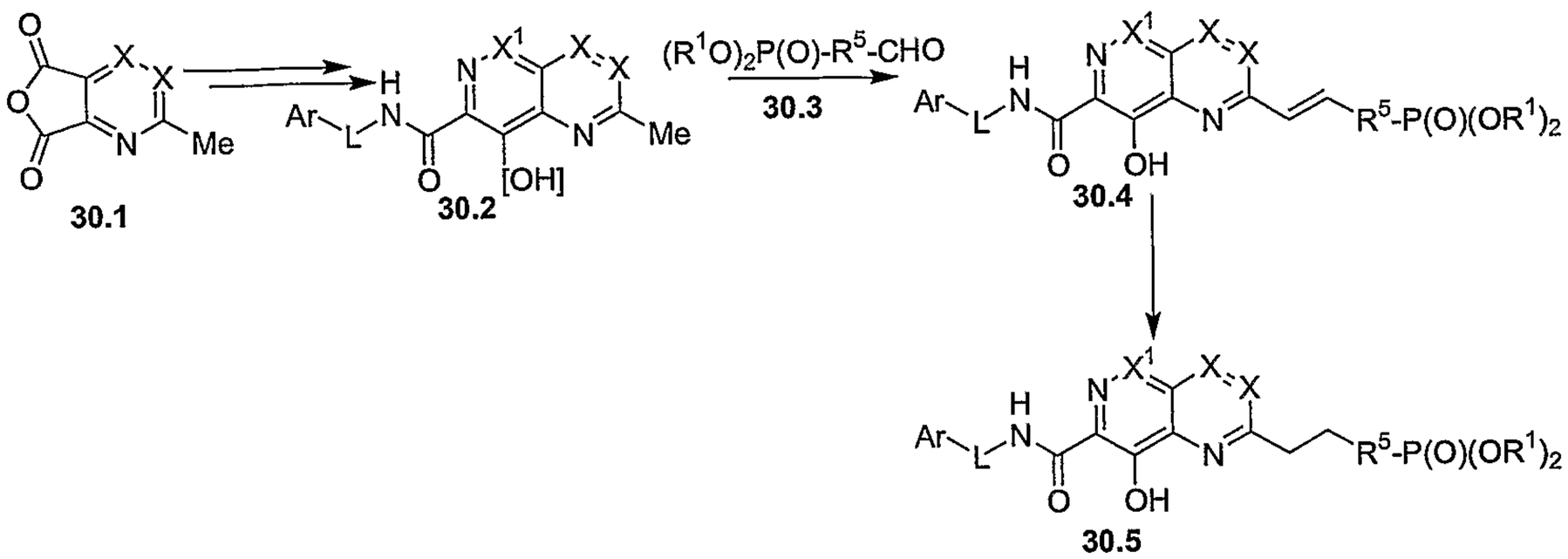
Scheme **31** illustrates the preparation of phosphonate esters **9** in which the phosphonate is attached by means of an oxime linkage. In this procedure, a methyl-substituted bicyclic anhydride **31.1** is converted, using the methods described above, into the methyl-substituted amide **31.2**. Benzylic bromination, as described in Scheme **25**, then gives the bromomethyl analog **31.3**, and oxidation, as described in Scheme **26** affords the corresponding aldehyde. The aldehyde is then converted, by reaction with hydroxylamine, into the oxime **31.5**. The latter compound is then reacted, in a polar solvent such as tetrahydrofuran or dimethylformamide, in the presence of a base such as sodium hydroxide or potassium carbonate, with a dialkyl bromomethyl-substituted phosphonate **31.6**, to prepare, after deprotection of the phenolic hydroxyl group, the oxime derivative **31.7**.

For example,, 2-methyl-furo[3,4-b]pyrazine-5,7-dione **30.6** (Nippon Noyaku Gakk., 1989, 14, 75) is converted, using the methods described above, into 5-(ethenesulfonyl-methyl-amino)-2-formyl-8-triisopropylsilanyloxy-pyrido[3,4-b]pyrazine-7-carboxylic acid 4-fluoro-benzylamide **31.9**. The aldehyde is then reacted in tetrahydrofuran solution with three molar equivalents of hydroxylamine hydrochloride and sodium acetate, to produce the oxime **31.10**. The latter compound is then reacted in dioxan solution at ambient temperature, with one molar equivalent of a dialkyl bromopropyl phosphonate **31.11** (Synthelec) and potassium carbonate, to yield, after desilylation of the phenolic hydroxyl group, the oxime ether **31.12**.

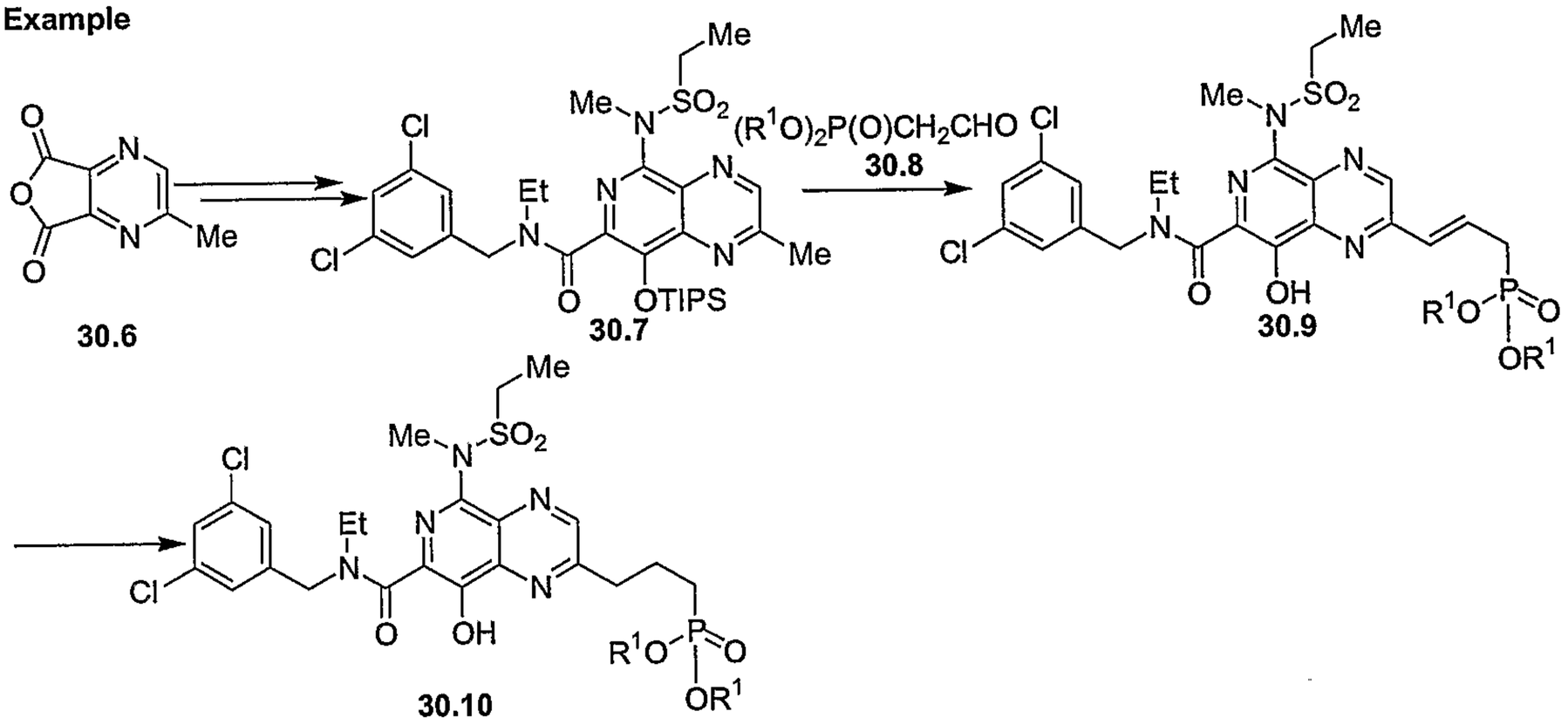
Using the above procedures, but employing, in place of the anhydride **31.8**, different anhydrides **31.1**, and/or different phosphonates **31.6**, the corresponding products **31.7** are obtained.

Scheme 30. Phosphonates 9.

Method

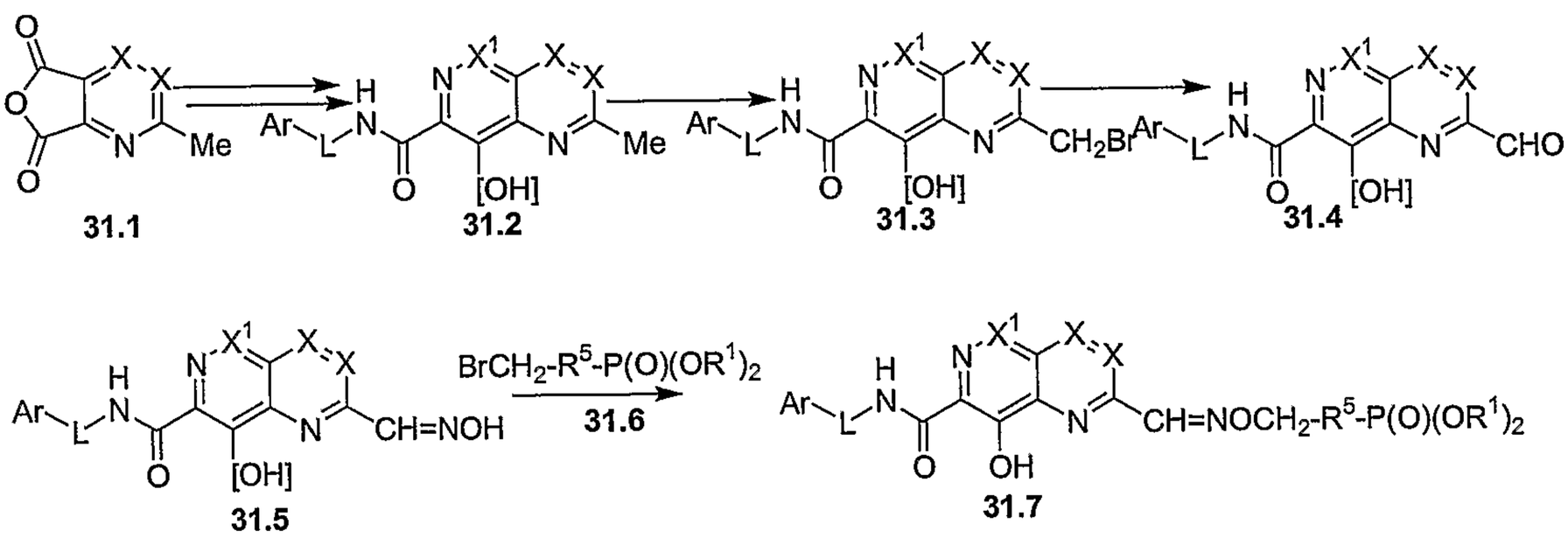


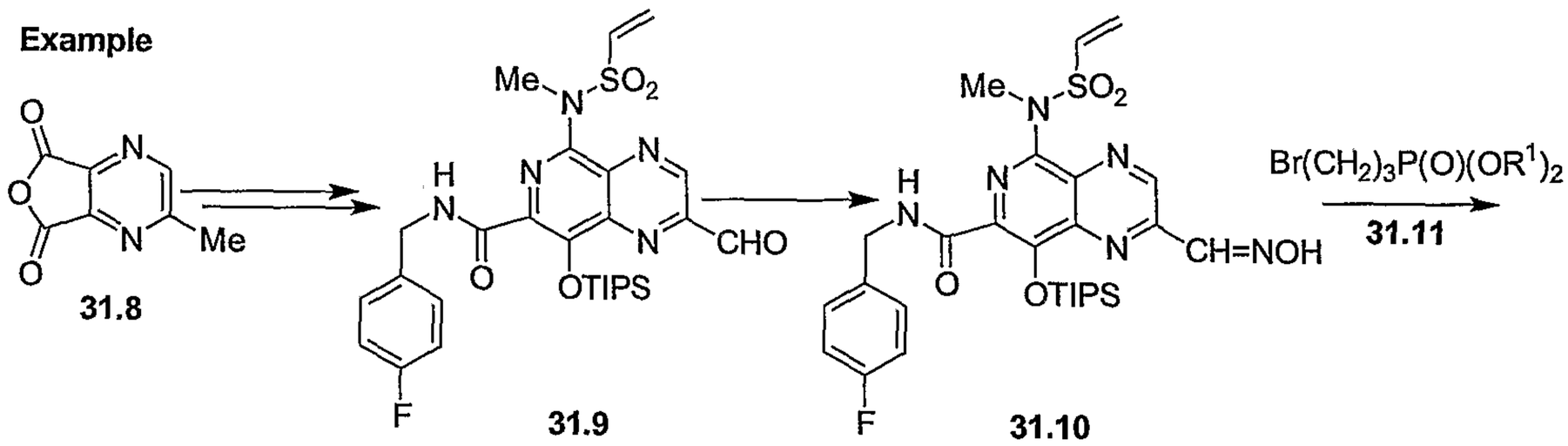
Example

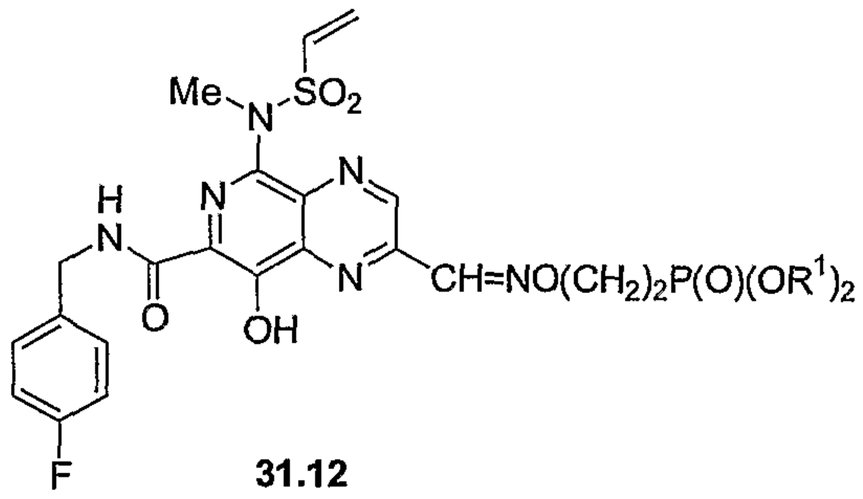


Scheme 31. Phosphonates 9.

Method







SYNTHESIS OF FORMULA IV PYRIMIDINE AND V PYRIMIDINONE PHOSPHONATE COMPOUNDS

Dihydroxypyrimidine carboxamide (WO 03/035076A1) and N-substituted hydroxypyrimidinone carboxamide (WO 03/035077A1) compounds have been disclosed.

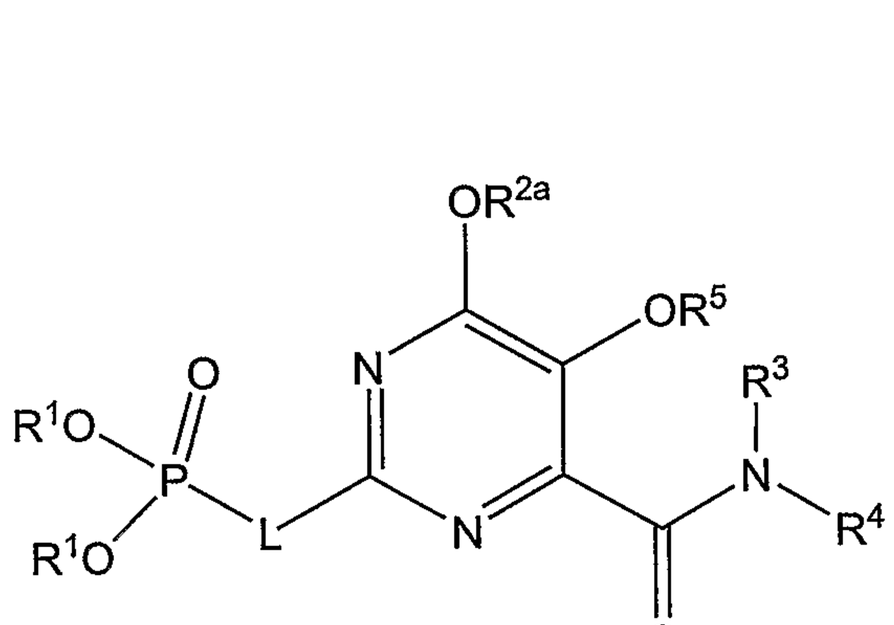
Preparation of Formula IVa-d and Formula Va-d phosphonate esters.

Structures of exemplary pyrimidine Formula IV phosphonate esters **IVa-d** are shown in Chart **1**. Structures of exemplary pyrimidine Formula II phosphonate esters **Va-d** are shown in Chart **2**. Ring substituents R^1, R^{2a}, R^{2b}, R^3, R^4, and R^5 are as previously defined. Phosphonate ester substituent R^x is as previously defined. Compounds of Formula **IVa-d** and Formula **Va-d** may each be an active pharmaceutical ingredient, or an intermediate for preparing other compounds of the invention by subsequent chemical modifications.

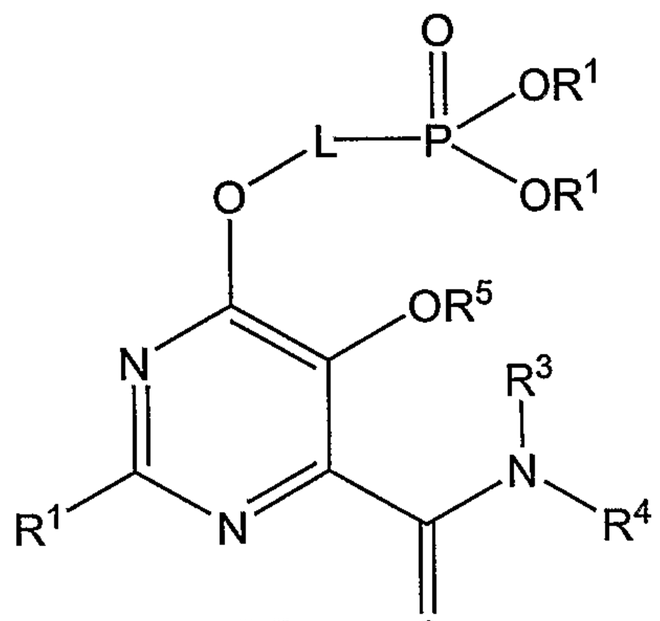
Compounds of Formula **IVa-d** and Formula **Va-d** incorporate a phosphonate group $(R^1O)_2P(O)$ connected to the pyrimidine and pyrimidinone scaffold, respectively, by means of a divalent and variable linking group, designated as "L" in the attached structures. Charts **3** and **4** illustrates examples of the phosphonate linking groups $(L\text{-}A^3)$ present in the structures **IVa-d** and **Va-d**.

The methods described for the introduction of phosphonate substituents are, with modifications made by one skilled in the art, transferable within the phosphonate esters **IVa-d** and **Va-d**. For example, reaction sequences which produce the phosphonates **IVa** are, with appropriate modifications, applicable to the preparation of the phosphonates **IVb-d** and **Va-d**. Methods described below for the attachment of phosphonate groups by means of reactive substituents such as OH, Br, NH_2, CH_3, CH_2Br, COOH, CHO etc are applicable to each of the scaffolds **IVa-d** and **Va-d**.

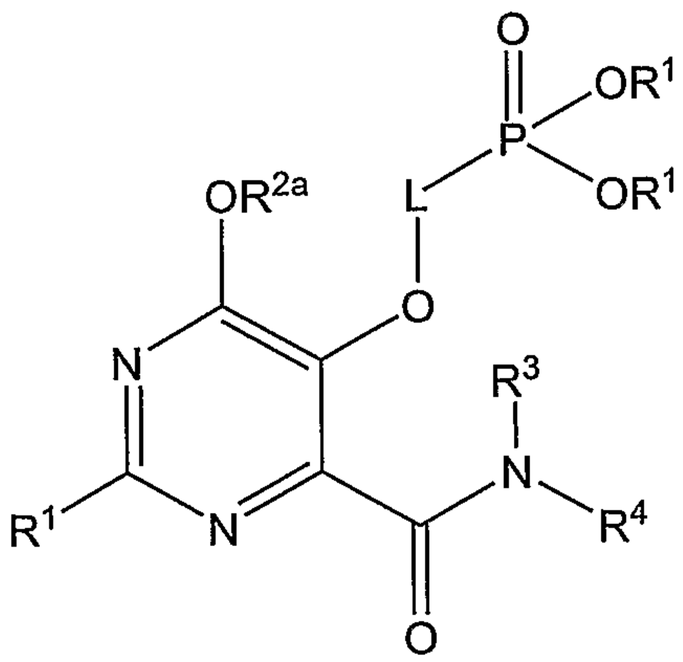
Chart 1. Structures of the pyrimidine phosphonates IVa-d



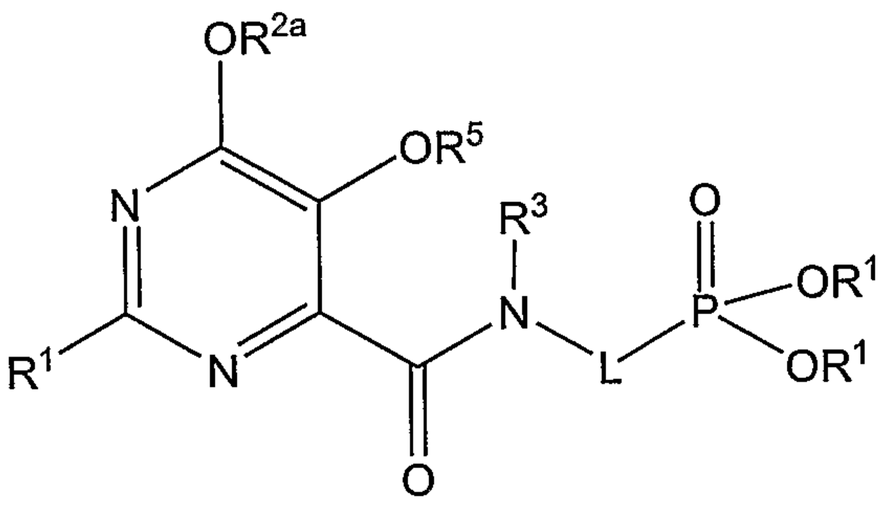
IVa



IVb

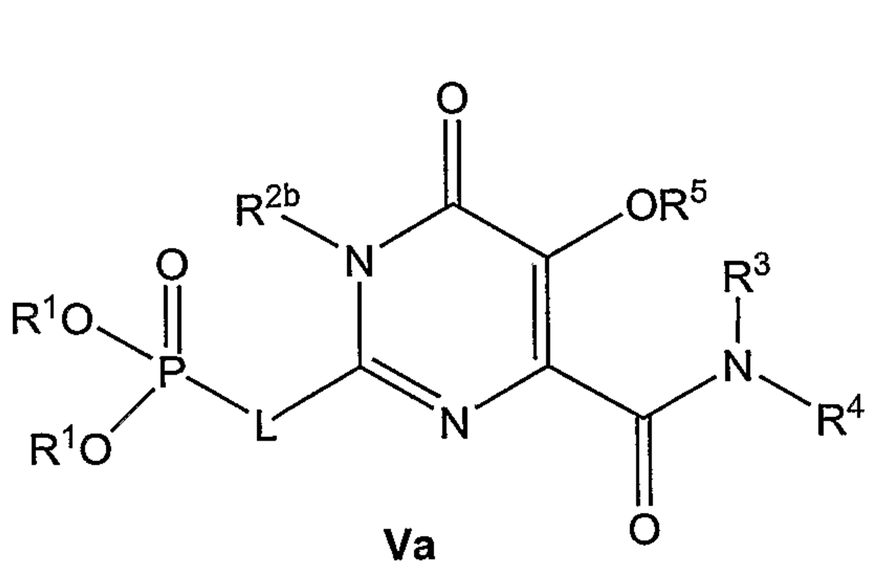


IVc

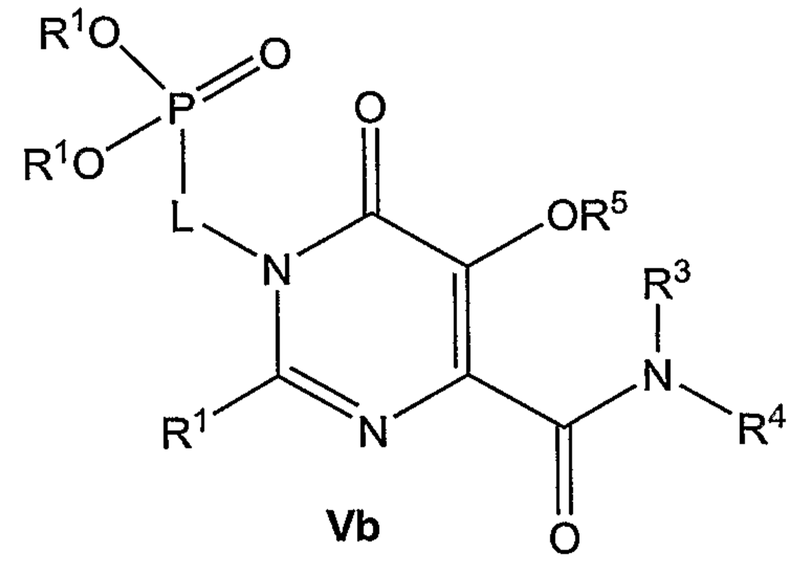


IVd

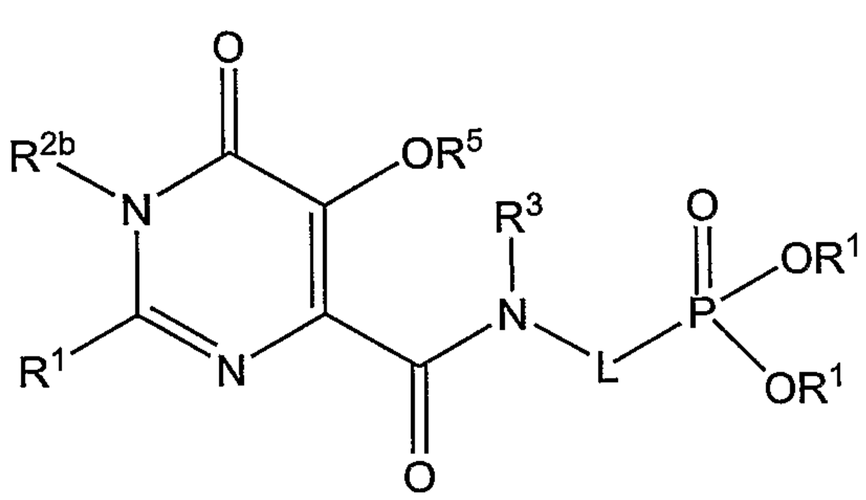
Chart 2. Structures of pyrimidinone phosphonates Va-d



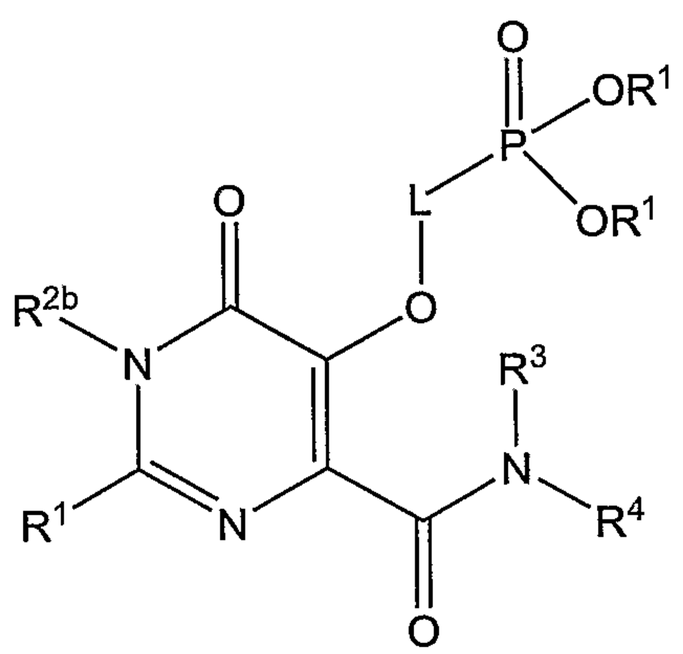
Va



Vb



Vc



Vd

Chart 3. Examples of phosphonate linkages L-A^3

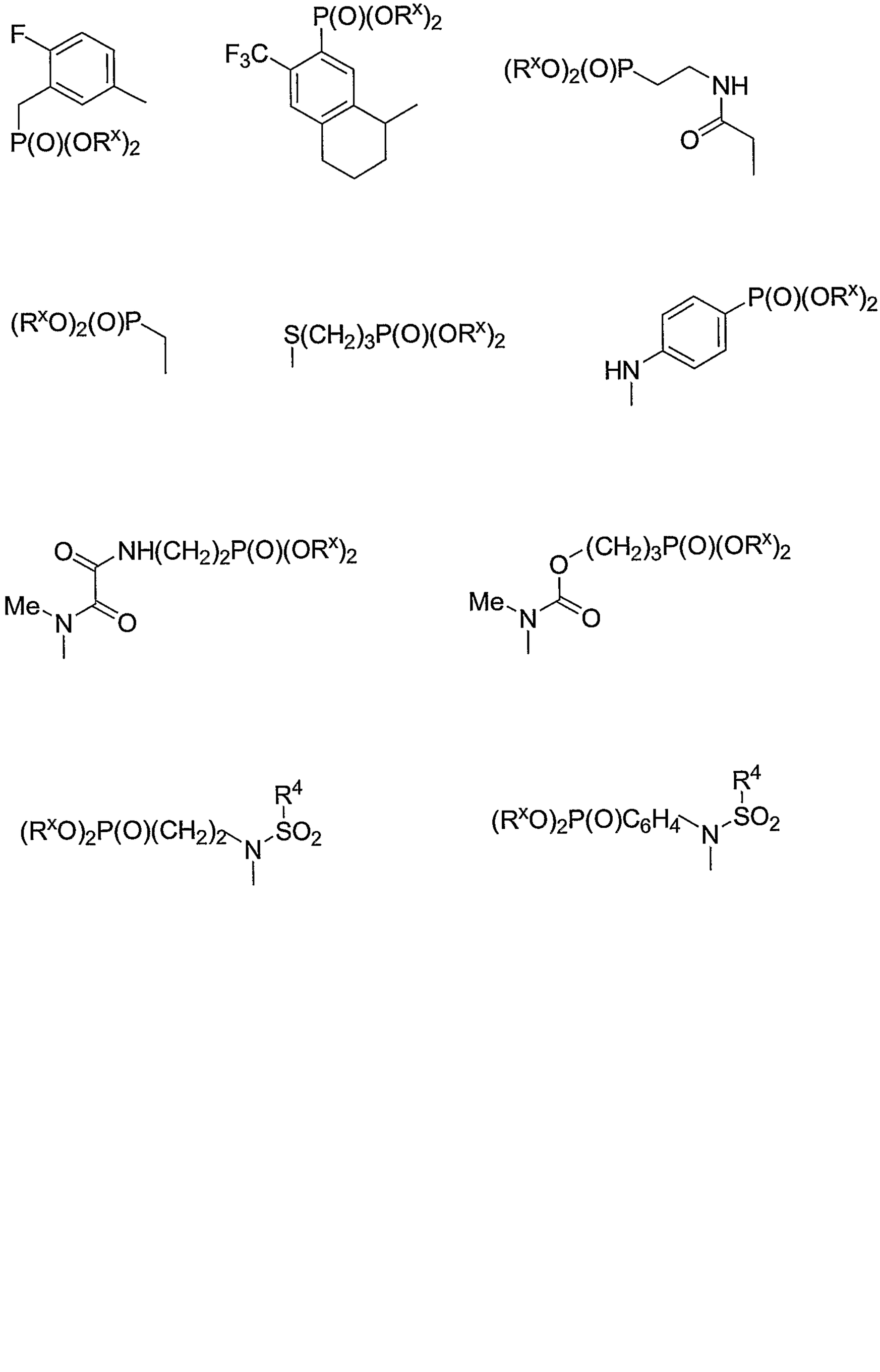
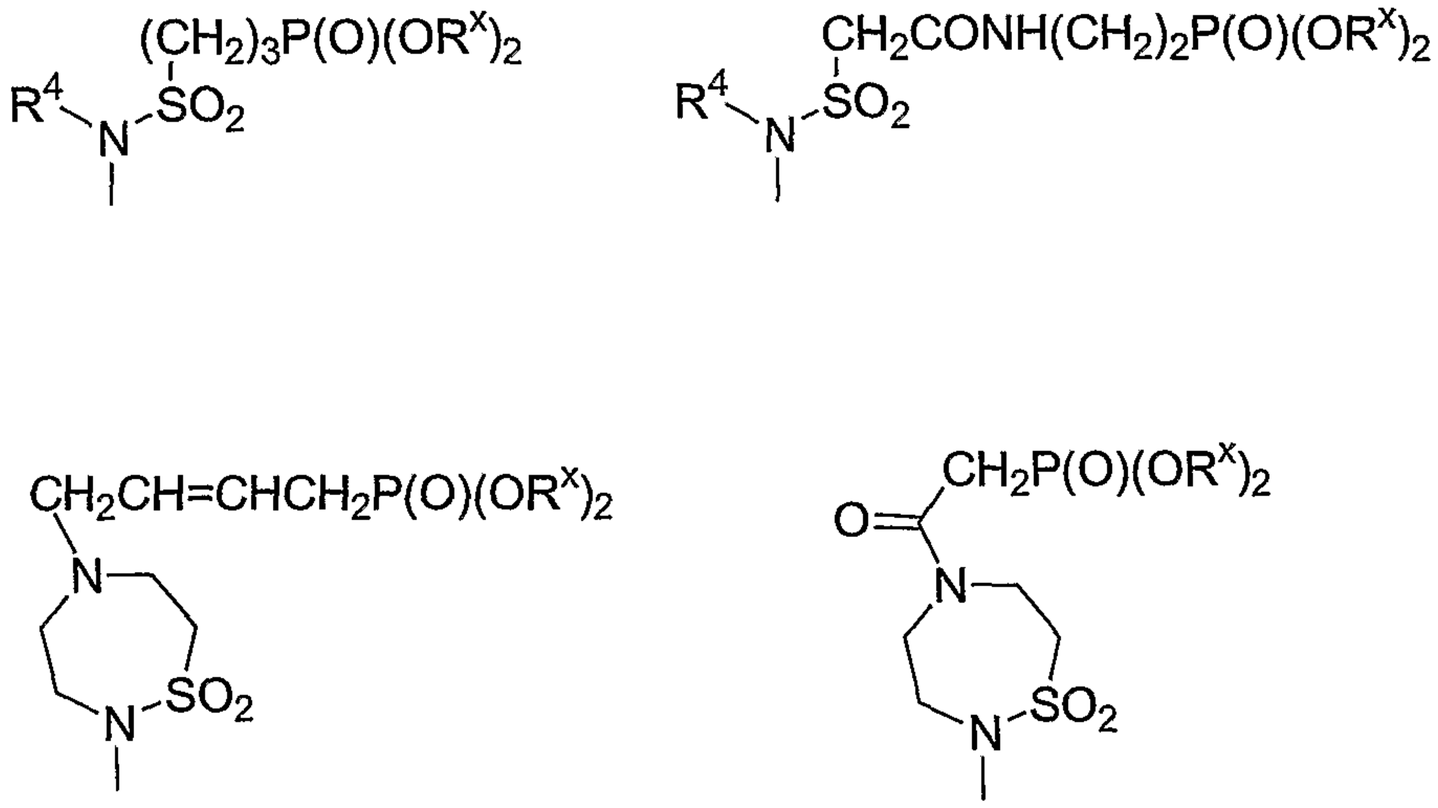


Chart 4. Examples of phosphonate linkages L-A^3



Schemes 1-31 illustrate the syntheses of the phosphonate compounds of this invention, Formulas I and II, and of the intermediate compounds necessary for their synthesis.

Scheme 32 illustrates methods for the interconversion of phosphonate diesters, monoesters and acids, and Scheme 33 illustrates methods for the preparation of carbamates. Schemes 34-37 illustrate the conversion of phosphonate esters and phosphonic acids into carboalkoxy-substituted phosphonbisamidates, phosphonamidates, phosphonate monoesters, phosphonate diesters. Scheme 38 illustrates further synthesis of gem-dialkyl amino phosphonate reagents for preparation of Formulas I and II compounds.

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH], [NH] etc. Protecting groups are also exemplified as "PG". The selection of a suitable stage in the synthetic sequence for the introduction of the phosphonate group is made by one skilled in the art, depending on the reactivity and stability of the substrates in a given reaction sequence.

Protection of phosphonate esters

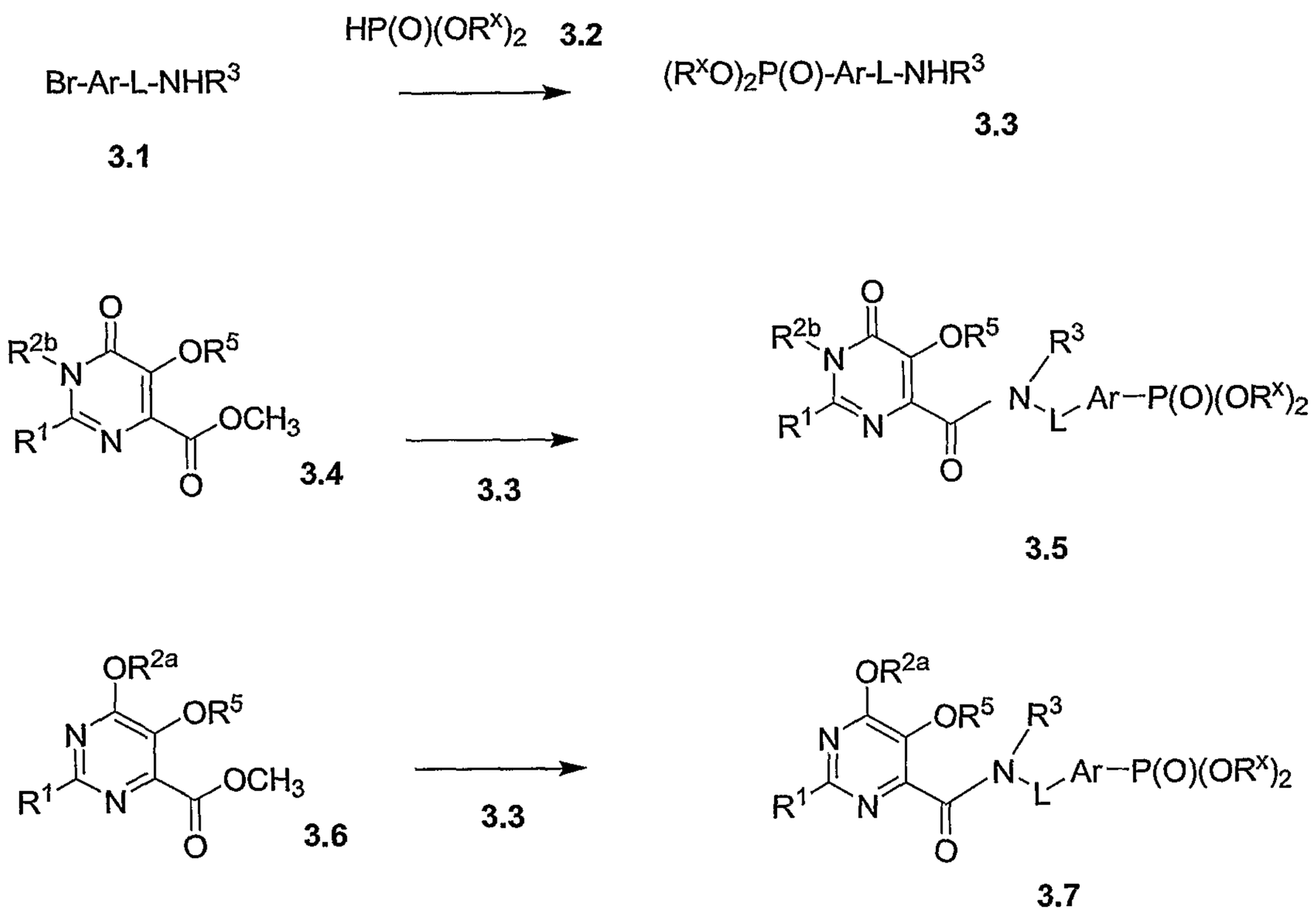
Scheme **3a** depicts the preparation of phosphonate esters **IVd** and **Vd** in which the phosphonate group is directly attached to the group Ar. In this procedure, a bromo-substituted amine **3.1**, in which Ar is an aromatic or heteroaromatic group, is reacted, in the presence of a palladium catalyst, with a dialkyl phosphite **3.2** to yield the aryl phosphonate **3.3**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, 35, 1371, 1992. This reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a palladium (0) catalyst such as tetrakis(triphenylphosphine)palladium(0). Optionally, the amine group is protected prior to the coupling reaction, and deprotected afterwards.

Amine reagent **3.3** is reacted with the ester **3.4** to afford the amide **3.5**, and with the ester **3.6** to afford the amide **3.7**. The conversion of esters into amides is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 987. The reactants are combined in a solvent such as toluene or xylene, in the presence of a base such as sodium methoxide under azeotropic conditions, or of a dialkyl aluminum or trialkyl tin derivative of the amine. The use of trimethylaluminum in the conversion of esters to amides is described in *J. Med. Chem. Chim. Ther.*, 34, 1999, 1995, and *Syn. Comm.*, 25, 1401, 1995. The reaction is

conducted in an inert solvent such as dichloromethane or toluene. The conversion of esters such as **3.4** and **3.6**, or the corresponding carboxylic acids, into amides is described in WO 03035077 A1, Optionally, the 5-hydroxyl group of the ester **3.4** and **3.6** is protected, for example as a p-toluenesulfonyl derivative, prior to reaction with the amine component **3.3**.

Scheme 3a. Phosphonates Id and IId.

Method

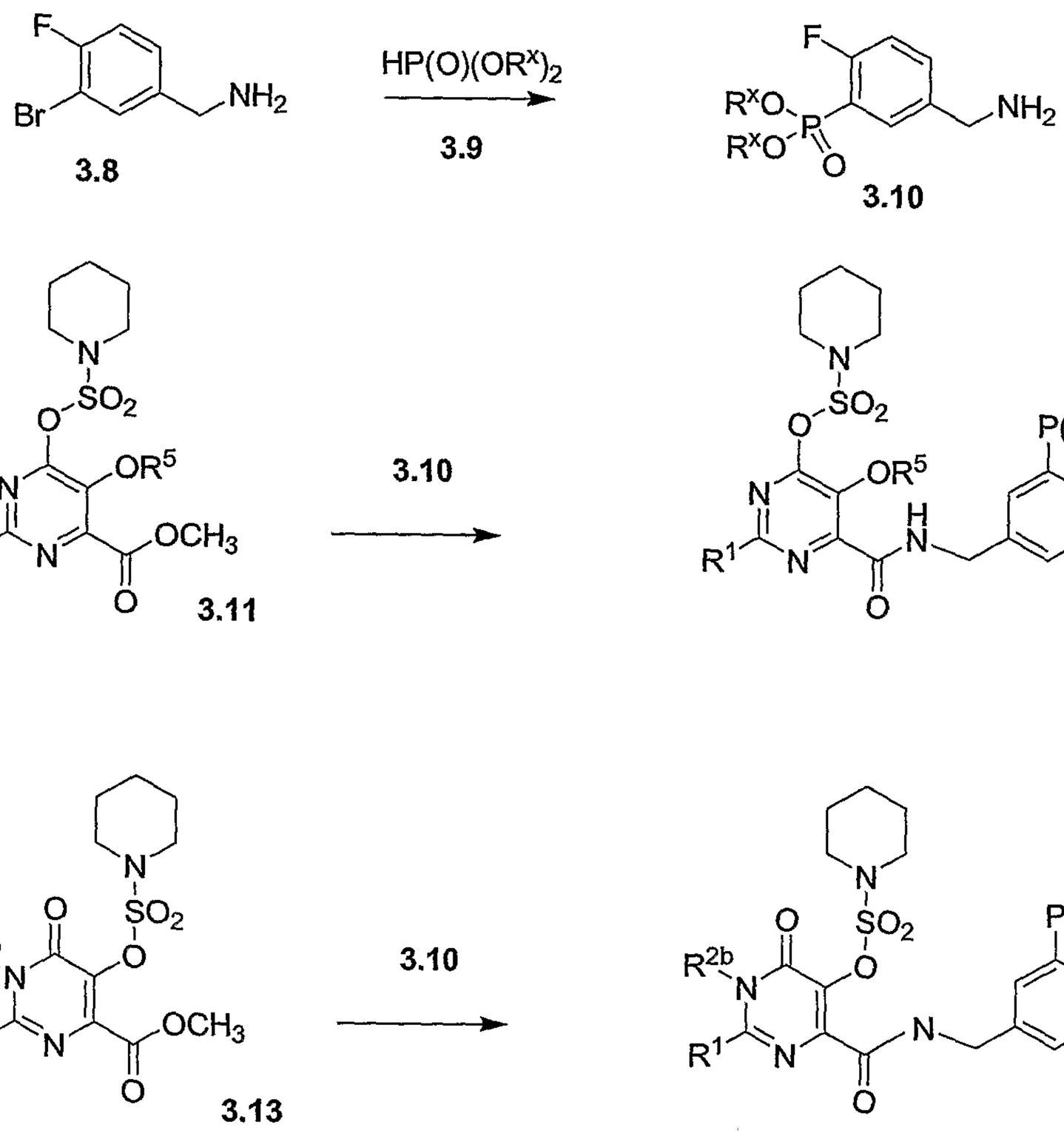


For example, 3-bromo-4-fluorobenzylamine **3.8** (Lancaster) is reacted in toluene solution at ca. 100 °C, with one molar equivalent of a dialkyl phosphite **3.9**, triethylamine and 3 mol % of tetrakis(triphenylphosphine)palladium(0), to give the phosphonate product **3.10** in Scheme 3b. Compound **3.10** is then reacted, in toluene solution at reflux temperature with **3.11** to yield the pyrimidine amide **3.12**. Alternatively, **3.10** is reacted, in toluene solution at reflux temperature with **3.13** to yield the pyrimidinone amide **3.14**

Using the above procedures, but employing, in place of the amine **3.8**, different amines **3.1**, and/or different esters **3.4**, the corresponding amides **3.5** are obtained.

Scheme 3b.

Example



Scheme **4** depicts the preparation of phosphonate esters **1** in which the phosphonate group is attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromo-substituted amine **4.1**, in which Ar is an aryl or heterocycle group, is subjected to a Heck coupling reaction, in the presence of a palladium catalyst, with a dialkyl alkenyl phosphonate **4.2**, in which R^{5a} is a direct bond, a divalent group such as alkylene, alkenylene, alkynylene or cycloalkylene group, optionally incorporating a heteroatom O, S or N, ethyleneoxy, polyethyleneoxy, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heterocycle or aralkyl group, to give the amine **4.3**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in *Acc. Chem. Res.*, 12, 146, 1979. The aryl bromide and

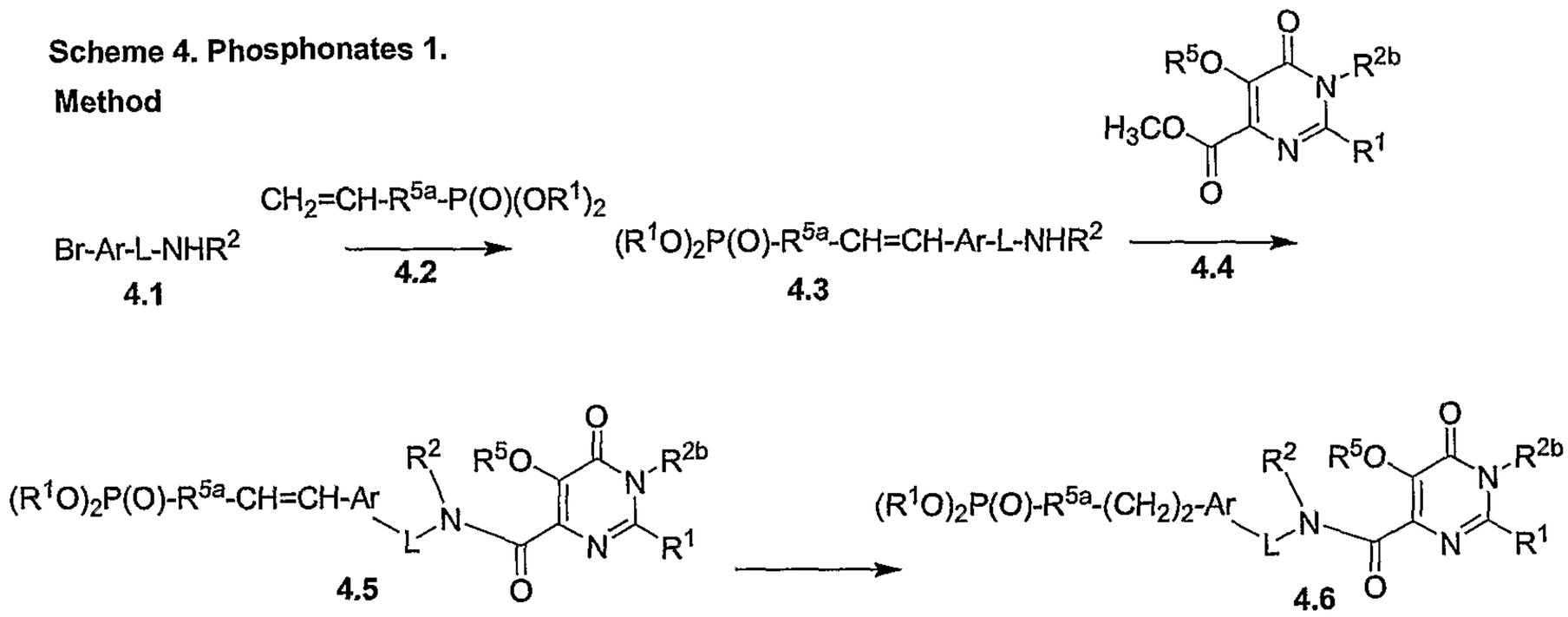
the olefin are coupled in a polar solvent such as dimethylformamide or dioxane, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the amine substituent is protected prior to the coupling reaction, and deprotected afterwards. The phosphonate amine **4.3** is then coupled, as described above, with the ester **4.4**, or the corresponding carboxylic acid, to produce the amide **4.5**. Optionally, the double bond is reduced to give the saturated analog **4.6**. The reduction of olefinic bonds is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

For example, 3-bromo-4-methoxybenzylamine **4.7** (Lancaster) is reacted in dioxane solution with one molar equivalent of a dialkyl vinyl phosphonate **4.8** (Aldrich) and potassium carbonate, to yield the olefinic phosphonate **4.9**. The product is then reacted, as described above, with 6-methyl ester **4.10**, prepared as described in Scheme **1A**, to give the amide **4.11**. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in *Angew. Chem. Int. Ed.*, 4, 271, (1965), to yield the saturated product **4.12**.

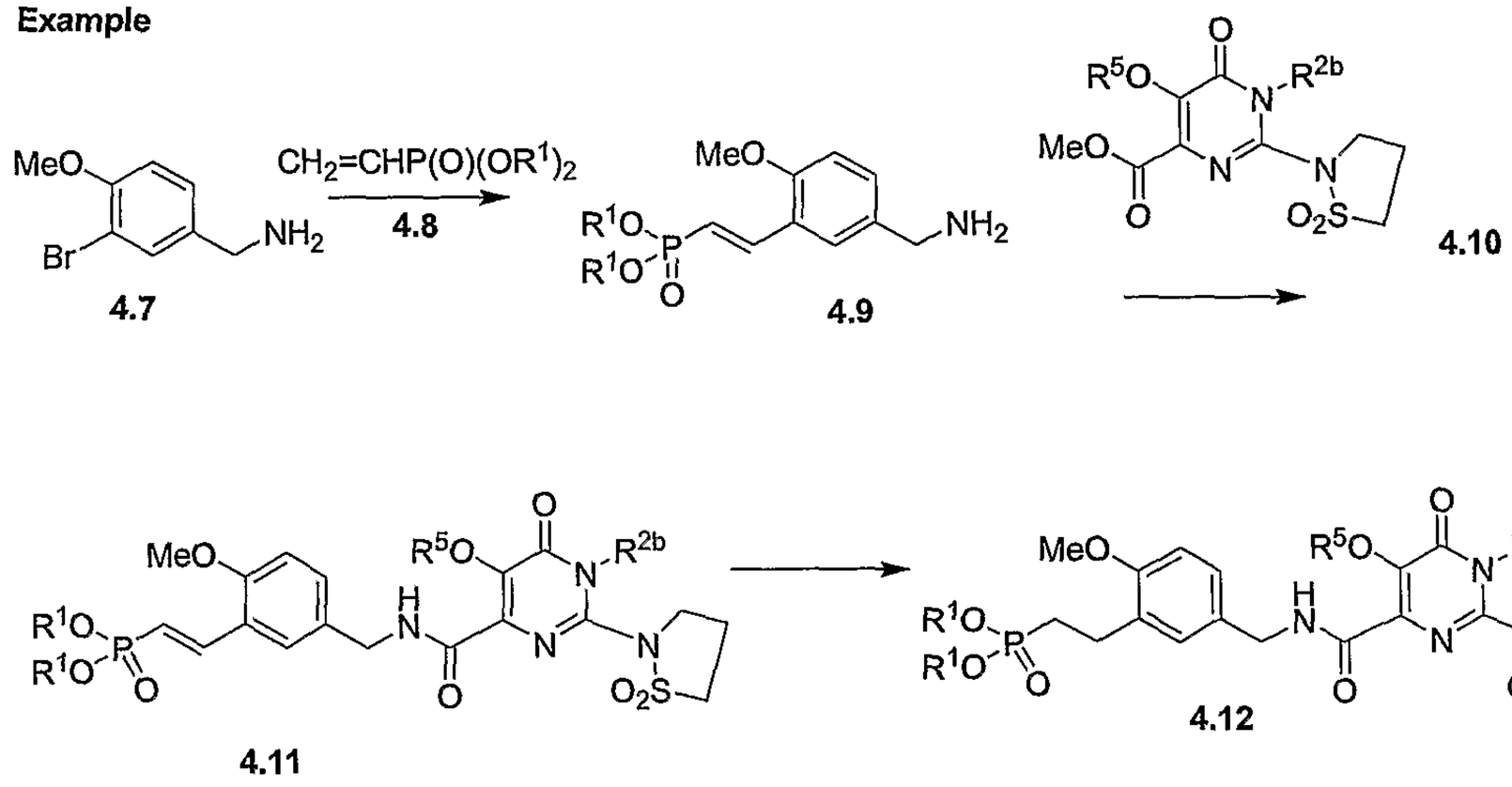
Using the above procedures, but employing, in place of the amine **4.7**, different amines **4.1**, and/or different phosphonates **4.2**, and/or different bicyclic esters **4.4**, the corresponding amides **4.5** and **4.6** are obtained.

Scheme 4. Phosphonates 1.

Method



Example



Scheme **5** depicts the preparation of phosphonate esters **IVd** in which the phosphonate group is attached by means of an amide linkage. In this procedure, the amine group of a carboxy-substituted amine **5.1** is protected to afford the derivative **5.2**. The protection of amino groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 309ff. Amino groups are protected, for example by alkylation, such as by mono or dibenzylation, or by acylation. The conversion of amines into mono or dibenzylamines, for example by treatment with benzyl bromide in a polar solvent such as acetonitrile or aqueous ethanol, in the presence of a base such as triethylamine or sodium carbonate, is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 364. The N-protected carboxylic acid **5.2** is then coupled with an amino-substituted dialkyl phosphonate

5.3, in which the group R^{5a} is as defined in Scheme **4**, to yield the amide **5.4**. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p. 274, and in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenzotriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid is first converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

The amino-protecting group is then removed from the product **5.4** to give the free amine **5.5**. Deprotection of amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 309ff. The amine is then coupled with the carboxylic acid **5.6**, as described above, to produce the amide **5.7**.

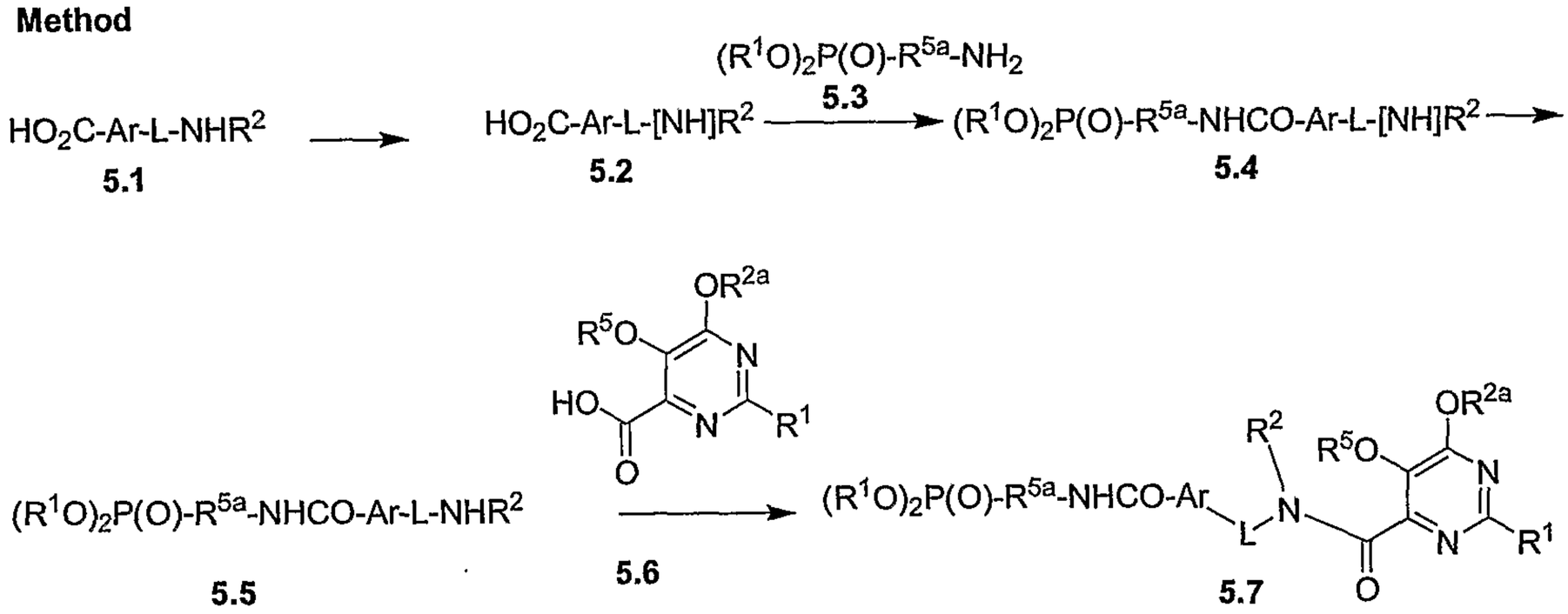
For example, 4-carboxycyclohexylmethylamine **5.8** (Aldrich) is converted into the phthalimido derivative **5.9** (pht = phthalimide). The conversion of amines into phthalimido derivatives is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 358. The conversion is effected by reaction of the amine with an equimolar amount of 2-carbomethoxybenzoyl chloride, N-carboethoxyphthalimide, or preferably, phthalic anhydride. The reaction is performed in an inert solvent such as toluene, dichloromethane or acetonitrile, to prepare the phthalimido derivative **5.9**. This material is then reacted with one molar equivalent of a dialkyl aminoethyl

phosphonate **5.10**, (*J. Org. Chem.*, (2000), 65, 676) and dicyclohexylcarbodiimide in dimethylformamide, to give the amide **5.11**. The phthalimido protecting group is then removed, for example by reaction with ethanolic hydrazine at ambient temperature, as described in *J. Org. Chem.*, 43, 2320, (1978), to afford the amine **5.12**. This compound is coupled in dimethylformamide solution with 6-carboxylic acid **5.13**, to afford the amide **5.14**.

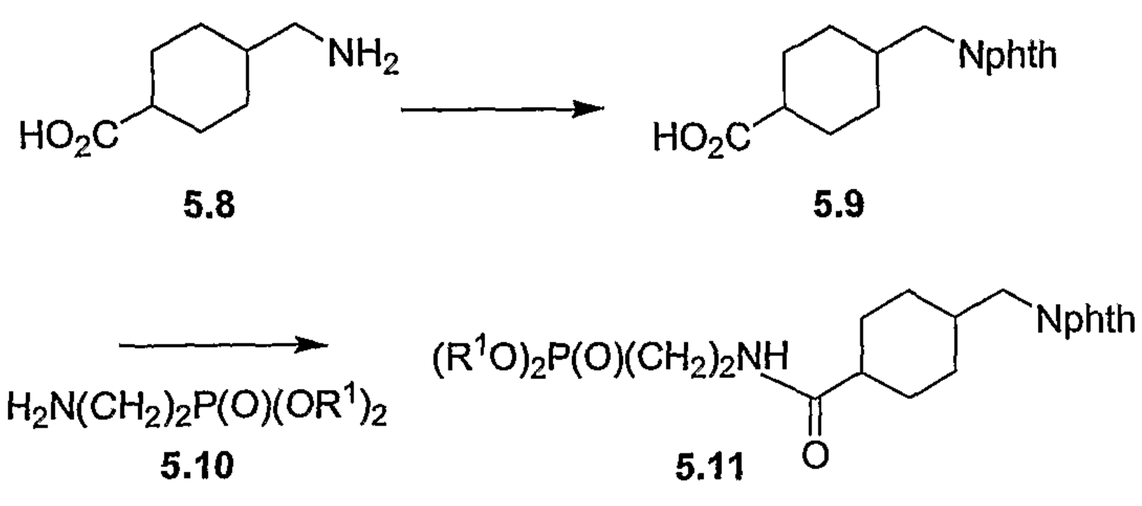
Using the above procedures, but employing, in place of the amine **5.8**, different amines **5.1**, and/or different phosphonates **5.3**, and/or different carboxylic acids **5.6**, the corresponding products **5.7** are obtained.

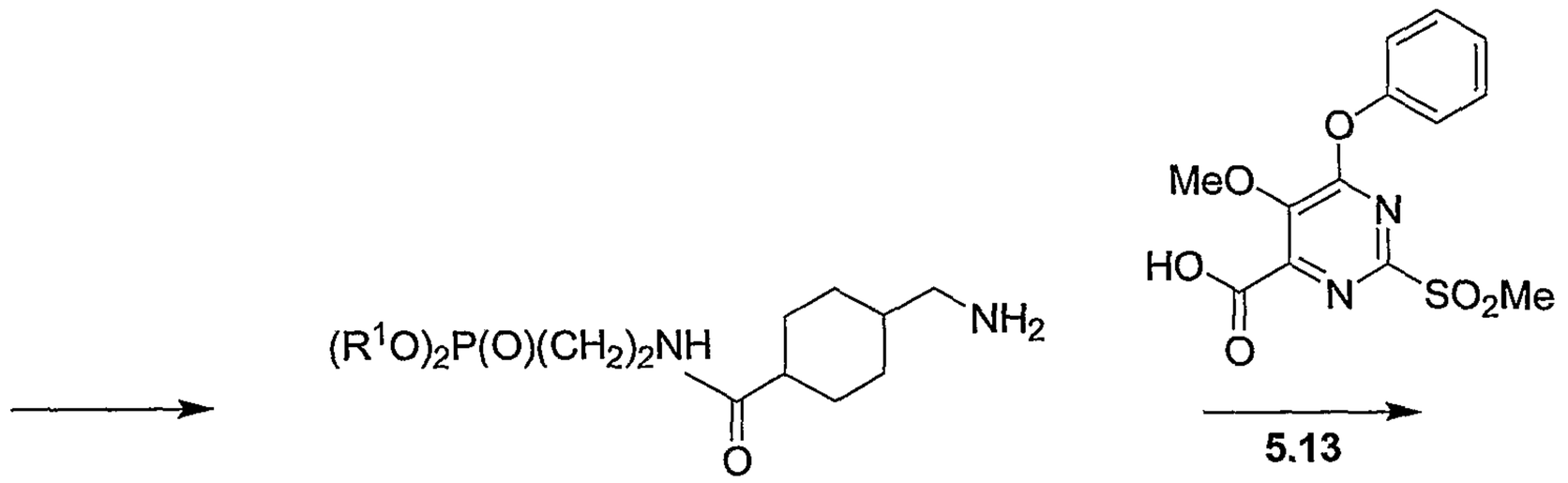
Scheme 5. Phosphonates 1.

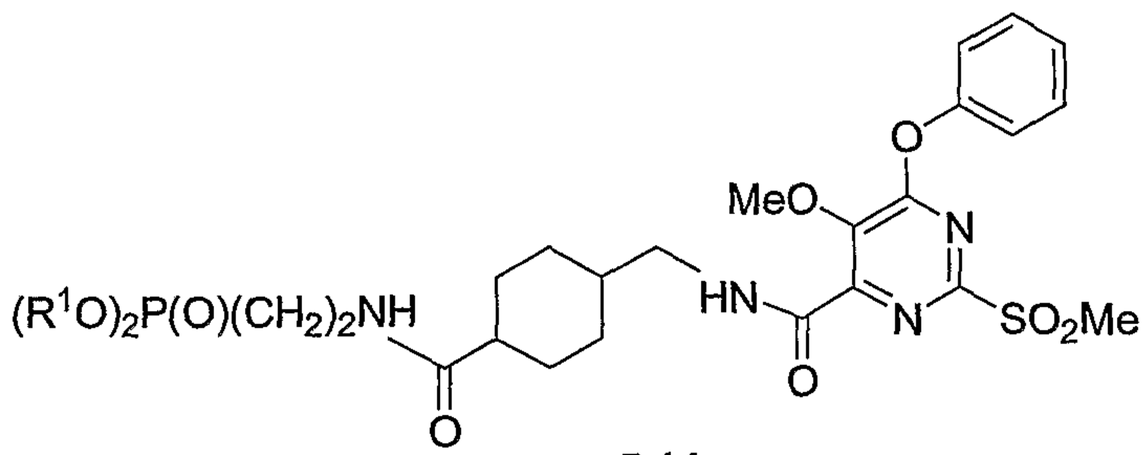
Method



Example







Scheme **6** depicts the preparation of phosphonates **Vd** in which the phosphonate is attached by means of an ether linkage. In this procedure, the amino group of a hydroxy-substituted amine **6.1** may be protected (PG = protecting group), as described above, to give the derivative **6.2**. The alcohol is then reacted, with base catalysis, with a dialkyl bromomethyl phosphonate **6.3**, in which the group R^5 is as defined in Scheme **4**. The reaction is conducted in a polar aprotic solvent such as tetrahydrofuran, dimethylformamide or dimethylsulfoxide, in the presence of a base such as potassium carbonate, for cases in which Ar is an aromatic group, or a strong base such as sodium hydride, for cases in which Ar is an aliphatic group. The amino group of the resulting ether **6.4** is then deprotected, as previously described, to give the amine **6.5**. The amine is then reacted with the ester **6.6**, as described in Scheme **3**, to give the amide **6.7**.

For example, N-methyl 3-hydroxyphenethylamine **6.8** is reacted with one molar equivalent of acetyl chloride in dichloromethane containing pyridine, to give the N-acetyl product **6.9**. The product is then reacted at ca. 60 ˚C in dimethylformamide (DMF) solution with one molar equivalent of a dialkyl 3-bromopropenyl phosphonate **6.10** (Aurora) and cesium carbonate, to produce the ether **6.11**. The N-acetyl group is then removed, for example by treatment with hog kidney acylase, as described in *Tetrahedron*, 44, 5375, (1988), to give the amine **6.12**. The product is then reacted in toluene solution at reflux, **6.13**, to yield the amide **6.14**.

Using the above procedures, but employing, in place of the amine **6.8**, different amines **6.1**, and/or different phosphonates **6.3**, and/or different bicyclic esters **6.6**, the corresponding products **6.7** are obtained.

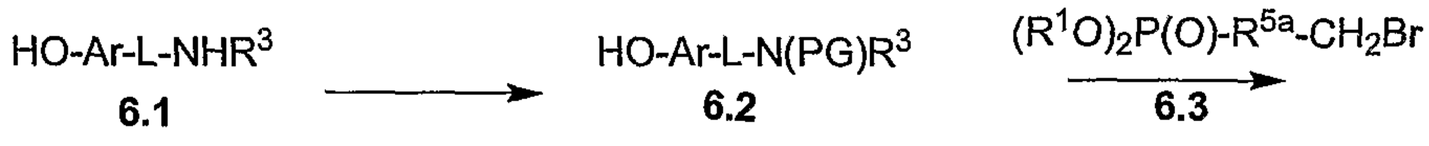
Scheme **7** depicts the preparation of phosphonates **Vd** in which the phosphonate is attached by means of an ether or thioether linkage. In this procedure, a N-protected hydroxyamine **6.2**, in which Ar is an aromatic moiety, is subjected to a Mitsunobu reaction with a hydroxy or mercapto-substituted dialkyl phosphonate **7.1**, in which R^{5a} is as defined in Scheme **4**, to prepare the ether or thioether product **7.2**. The preparation of aromatic ethers and thioethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4 and in *Org. React.*, 1992, 42, 335. The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran or dioxane, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The N-protecting group is then removed and the resultant amine is converted, as described in Scheme **6**, into the amide **7.3**.

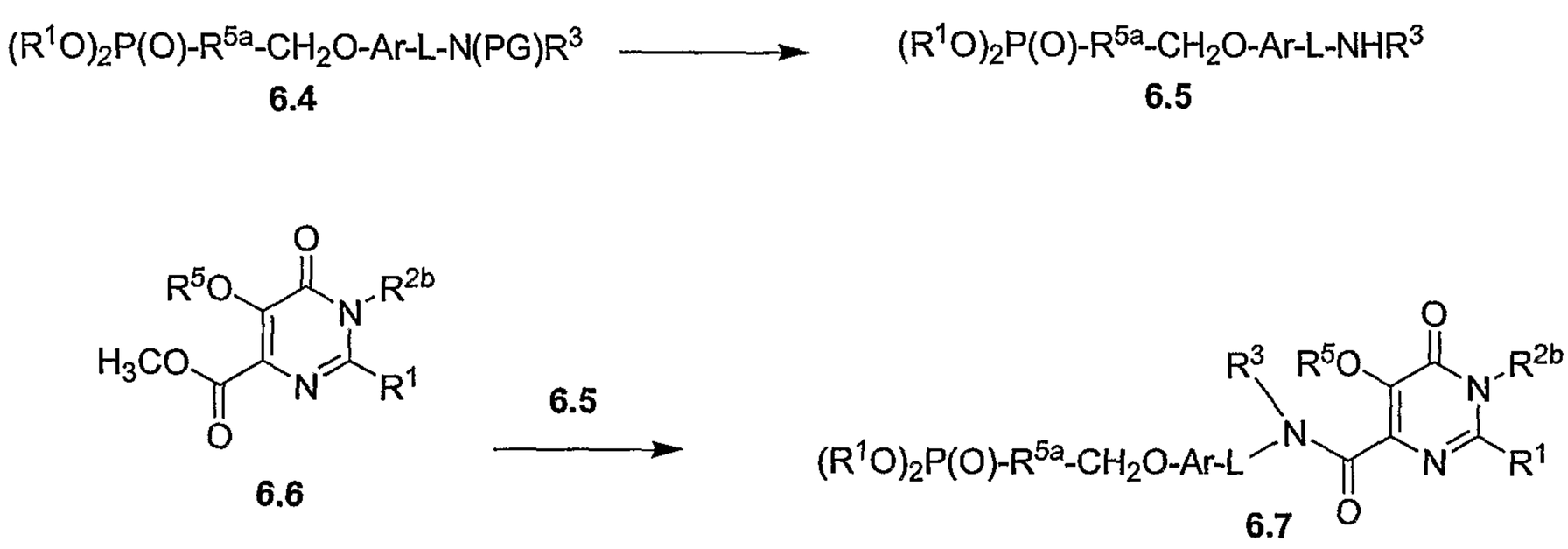
For example, N-acetyl 3,5-dichloro-4-hydroxybenzylamine **7.4** is reacted in a tetrahydrofuran solution with one molar equivalent of a dialkyl mercaptoethyl phosphonate **7.5**, (*Zh. Obschei. Khim.*, 1973, 43, 2364) diethyl azodicarboxylate and tri-o-tolylphosphine, to afford the thioether product **7.6**. The N-acetyl group is removed, as described in Scheme **6**, and the amine **7.7** is then reacted with methyl ester **7.8** (TBDMS = *tert*-butyldimethylsilyl), to afford the amide **7.9**.

Using the above procedures, but employing, in place of the amine **7.4**, different amines **6.2**, and/or different phosphonates **7.2**, the corresponding products **7.3** are obtained.

Scheme 6.

Method





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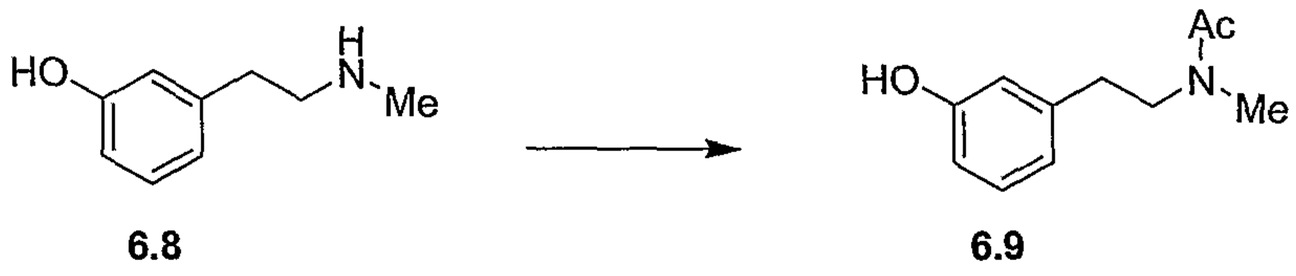
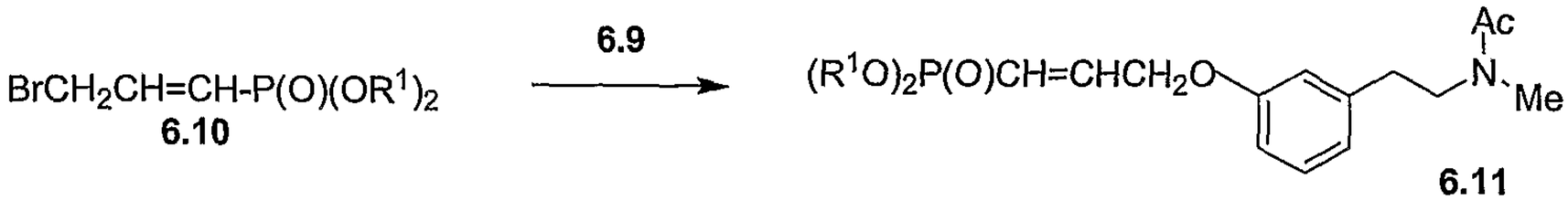
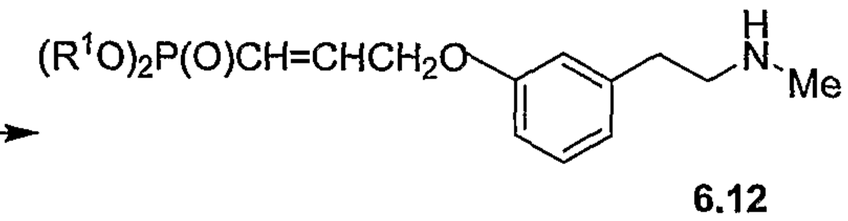
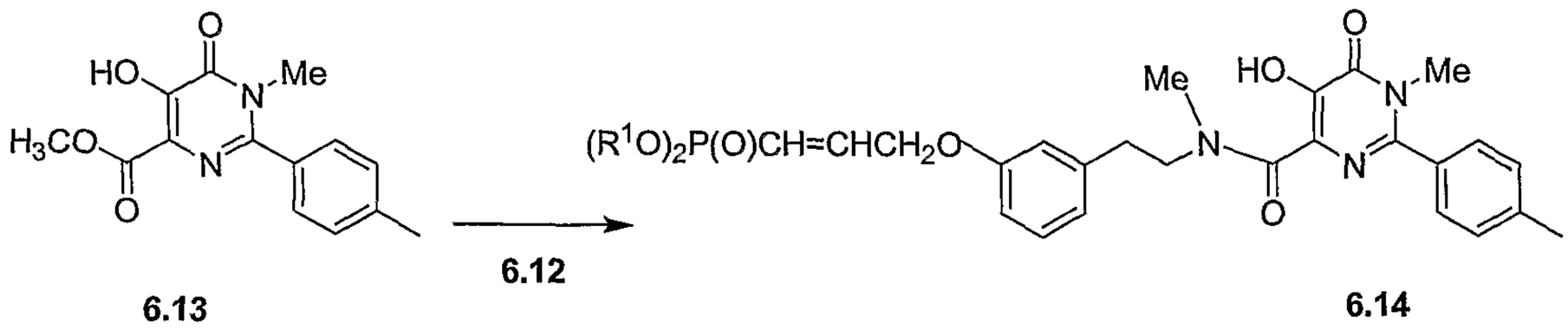


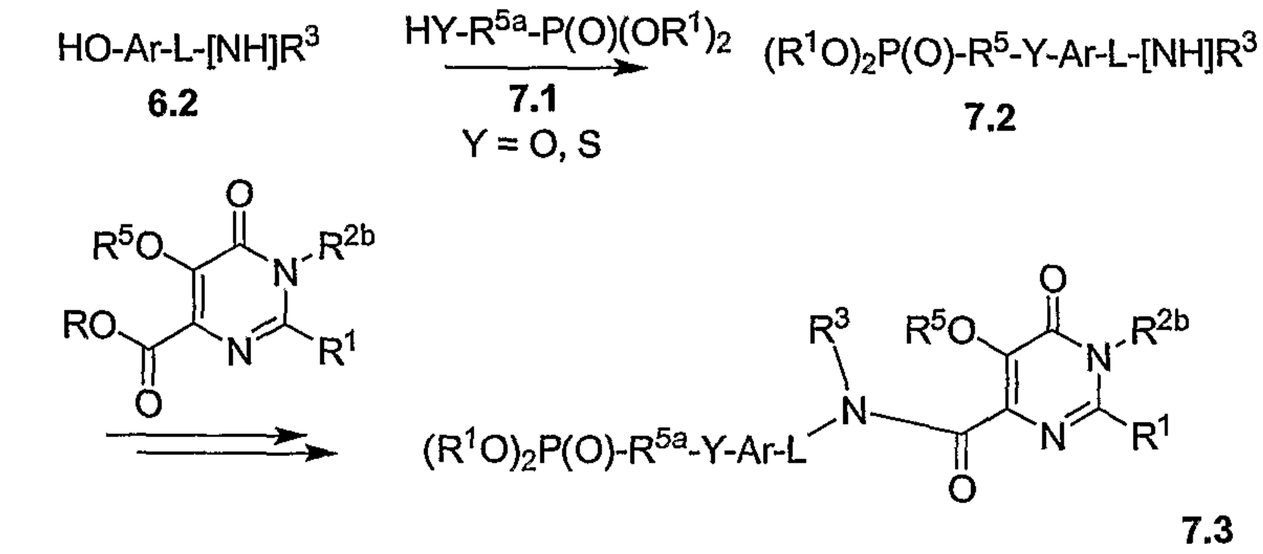




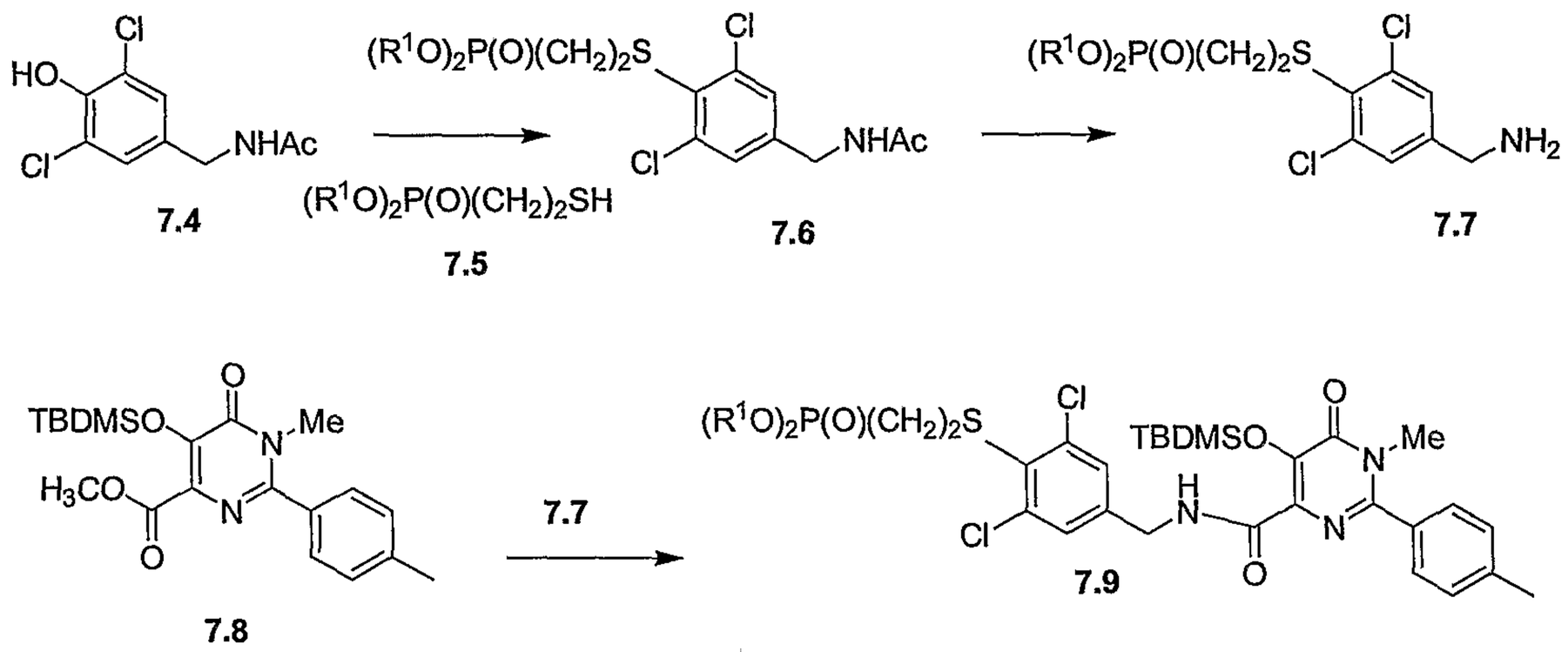


Scheme 7.

Method



Example



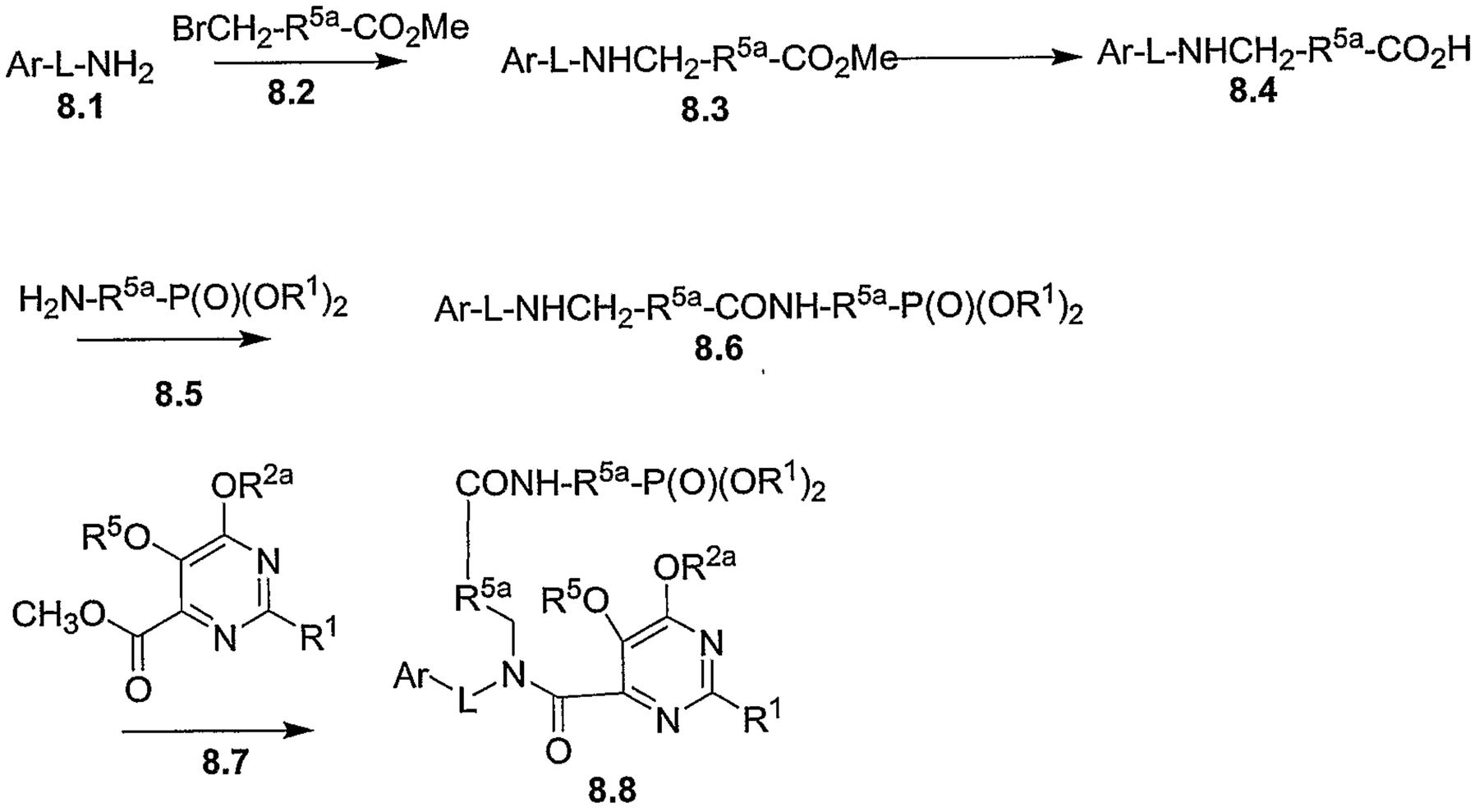
Scheme **8** depicts the preparation of phosphonates **IVd** in which the phosphonate is attached by means of an alkylene chain incorporating an amide linkage. In this procedure, an amine **8.1** is reacted with a bromoalkyl ester **8.2**, in which R^{5a} is as defined in Scheme **4**, to yield the alkylated amine **8.3**. The preparation of substituted amines by the reaction of amines with alkyl halides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 397. Equimolar amounts of the reactants are combined in a polar solvent such as an alkanol or dimethylformamide and the like, in the presence of a base such as cesium carbonate, diazabicyclononene or dimethylaminopyridine, to yield the substituted amine. The ester group is then hydrolyzed to give the carboxylic acid **8.4**, and this compound is then coupled, as described in Scheme **5**, with a dialkyl aminoalkyl phosphonate **8.5**, to produce the aminoamide **8.6**. Optionally, the amino group of the amine **8.4** is protected prior to the coupling reaction, and deprotected afterwards. The product is then reacted with the bicyclic hydroxyester **8.7** to afford the amide **8.8**.

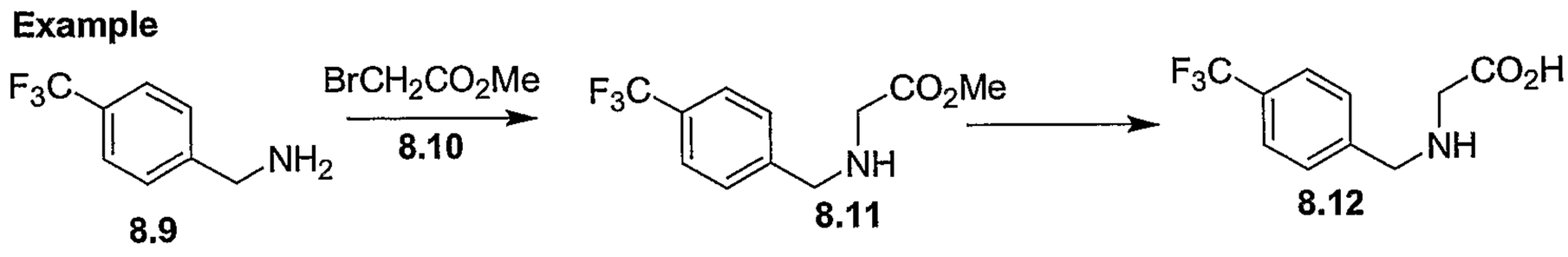
For example, 4-trifluoromethylbenzylamine **8.9** is reacted in dimethylformamide with one molar equivalent of methyl bromoacetate **8.10** and potassium carbonate to give the ester **8.11**. Hydrolysis, employing one molar equivalent of lithium hydroxide in aqueous dimethoxyethane, affords the carboxylic acid **8.12**, and this compound is coupled in tetrahydrofuran solution with a dialkyl aminomethyl phosphonate **8.13** (Aurora), in the presence of dicyclohexylcarbodiimide, to give the aminoamide **8.14**. The product is then reacted with 4-sulfonamide, 6-methyl ester **8.15**, prepared by the methods described above, to yield the amide **8.16**.

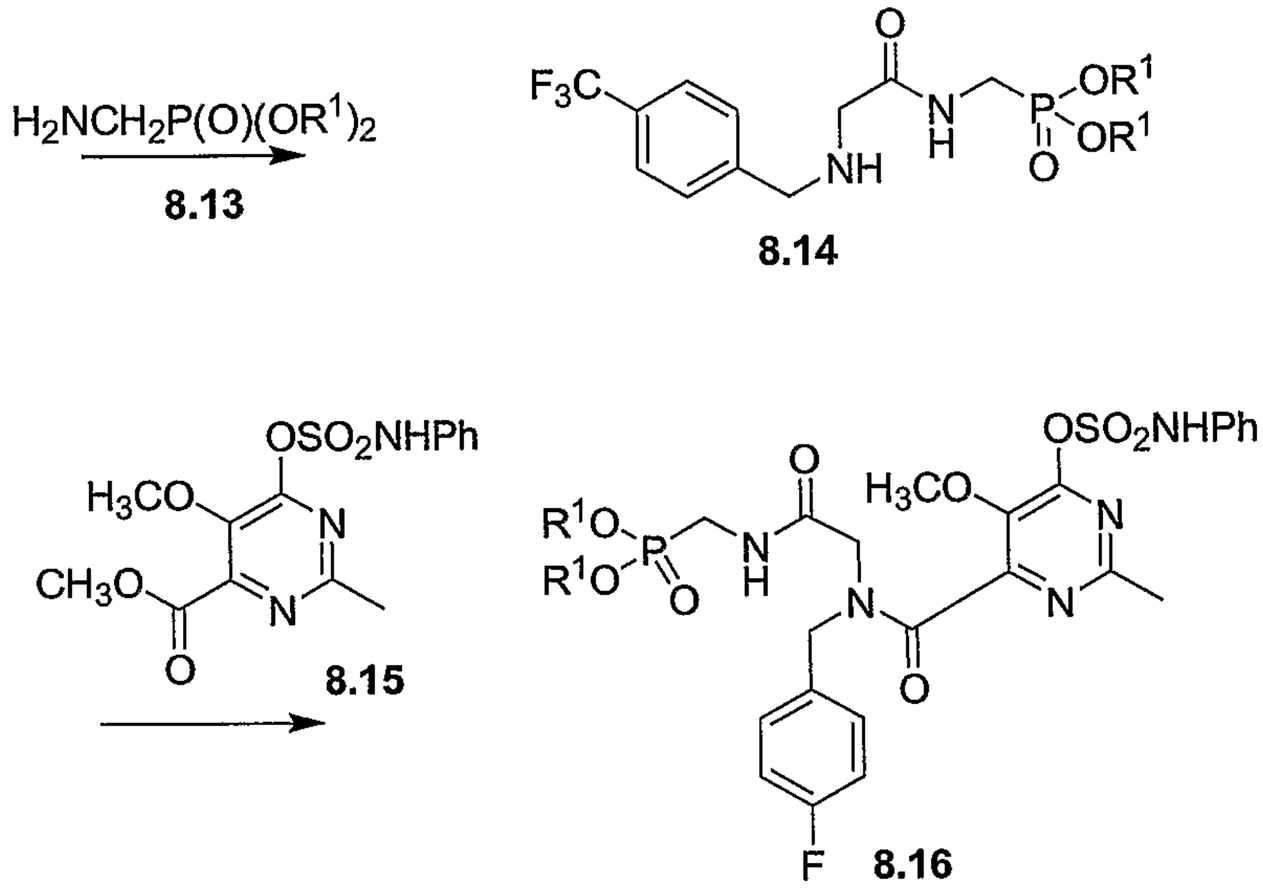
Using the above procedures, but employing, in place of the amine **8.9**, different amines **8.1**, and/or different bromoesters **8.2**, and/or different phosphonates **8.5**, and/or different hydroxyesters **8.7**, the corresponding products **8.8** are obtained.

Scheme 8.

Method







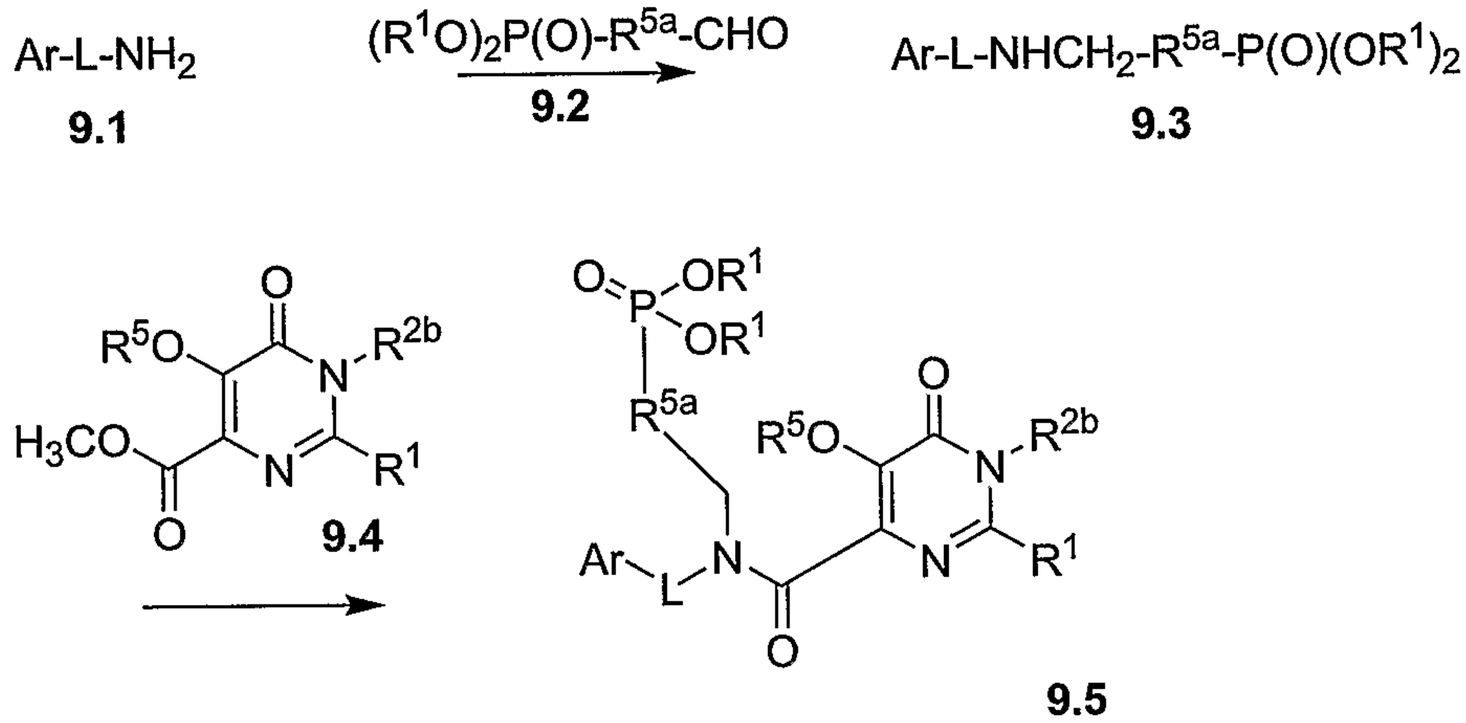
Scheme **9** depicts the preparation of phosphonates **Vd** in which the phosphonate is attached by means of a variable carbon chain. In this procedure, a primary amine **9.1** is subjected to a reductive amination reaction with a dialkyl formyl-substituted phosphonate **9.2**, in which R^5 is as defined in Scheme **4**, to afford the alkylated amine **9.3**. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in a polar solvent in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in *J. Org. Chem.*, 55, 2552, 1990. The product **9.3** is then reacted, as described previously, with the bicyclic ester **9.4** to give the amide **9.5**.

For example, 3,4-dichlorobenzylamine is reacted in methanol solution with one molar equivalent of a dialkyl 3-formylphenyl phosphonate **9.7**, (Epsilon) and sodium cyanoborohydride, to yield the alkylated product **9.8**. This compound is then

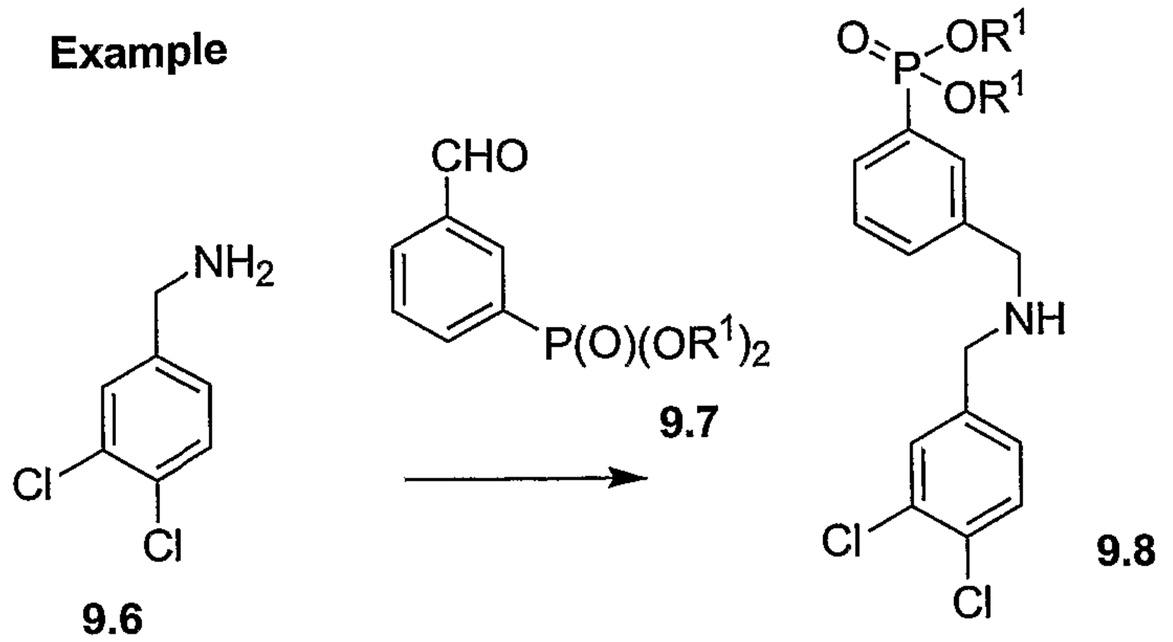
reacted with 2-dimethylcarbamoyl-5,6-dihydroxy-pyrimidine-4-carboxylic acid methyl ester **9.9**, prepared using the methods described above, from the corresponding bromo compound and N-methyl methanesulfonamide, to give the amide **9.10**.

Using the above procedures, but employing, in place of the amine **9.6**, different amines **9.1**, and/or different phosphonates **9.2**, and/or different bicyclic esters **9.4**, the corresponding products **9.5** are obtained.

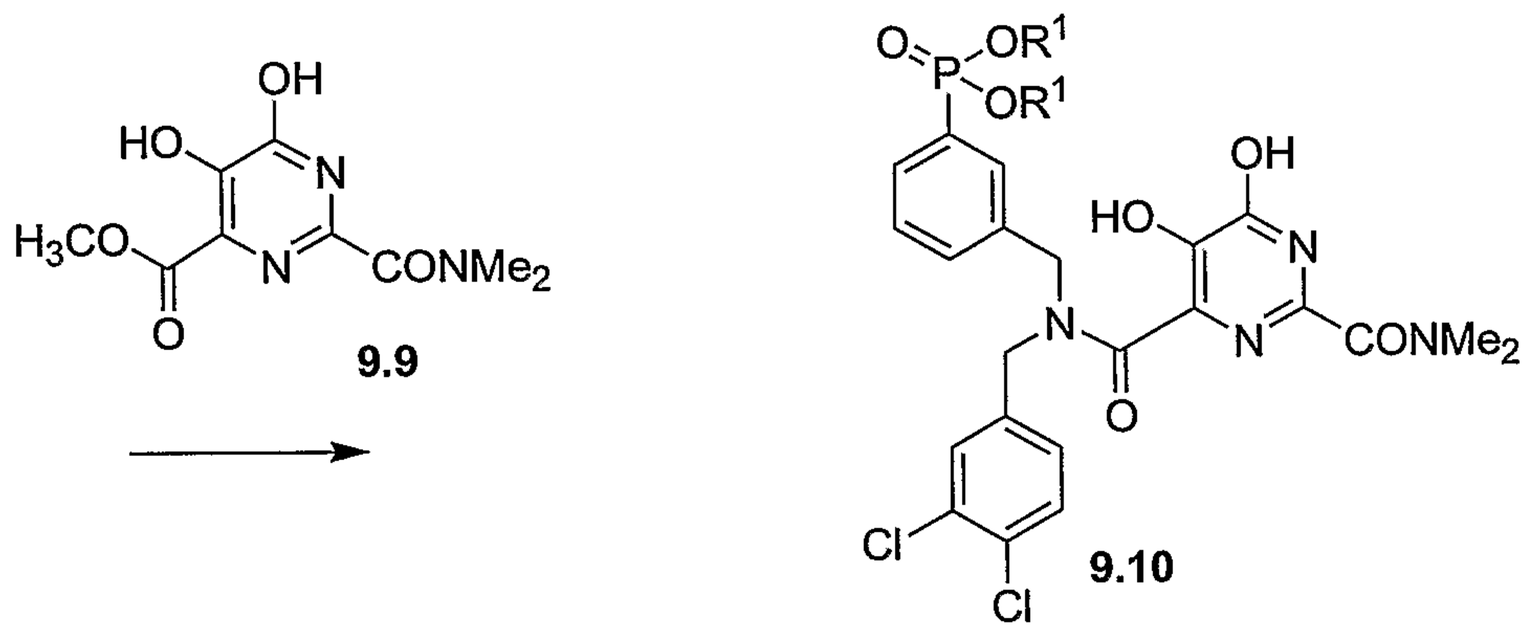
Scheme 9.
Method



Example



9.6 **9.7** **9.8**



9.9 **9.10**

Scheme **10** depicts an alternative method for the preparation of phosphonates **Vd** in which the phosphonate is attached by means of a variable carbon chain. In this procedure, the phenolic group of a bicyclic amide **10.1**, prepared as described above, and in WO 02 30930 A2, is protected to give the product **10.2**. The protection of phenolic hydroxyl groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 10ff. For example, hydroxyl substituents are protected as trialkylsilyloxy ethers. Trialkylsilyl groups are introduced by the reaction of the phenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, phenolic hydroxyl groups are protected as benzyl or substituted benzyl ethers, or as acetal ethers such as methoxymethyl or tetrahydropyranyl. The O-protected amide **10.2** is then reacted with the phosphonate-substituted trifluoromethanesulfonate **10.3**, in which R^{5a} is as defined in Scheme **4**, to produce the alkylated amide **10.4**. The alkylation reaction is conducted between equimolar amounts of the reactants in an aprotic organic solvent such as dimethylformamide or

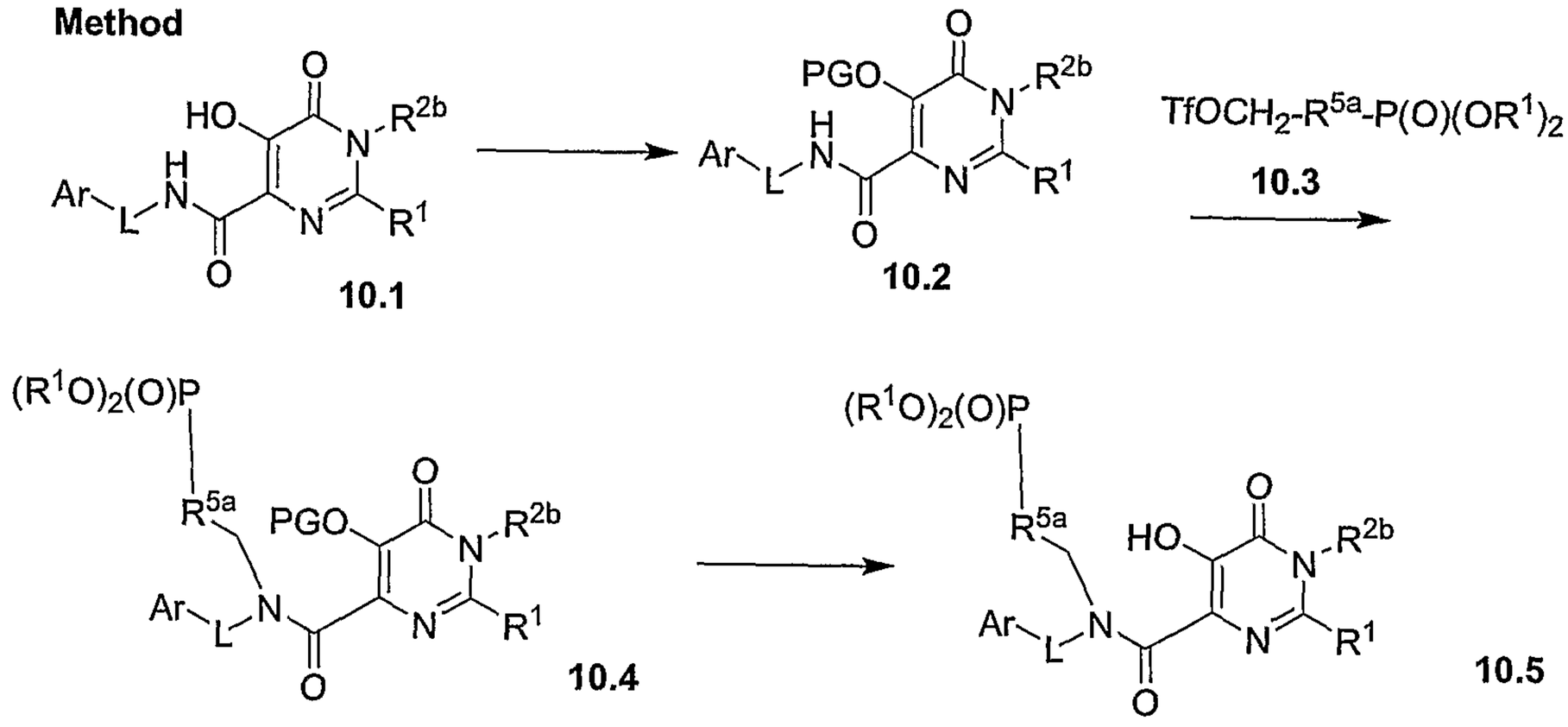
dioxane, in the presence of a strong base such as lithium hexamethyl disilylazide or sodium hydride, at from ambient temperature to about 90 °C. The hydroxyl group is then deprotected to give the phenol **10.5**. Deprotection of phenolic hydroxyl groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p.10ff. For example, silyl protecting groups are removed by reaction with tetrabutylammonium fluoride, benzyl groups are removed by catalytic hydrogenation and acetal ethers are removed by treatment with acids.

Amide **10.7** is reacted with one molar equivalent of tert-butyl chlorodimethylsilane and imidazole in dichloromethane, to give 5-(tert-butyl-dimethyl-silanyloxy)-1-methyl-6-oxo-2-phenyl-1,6-dihydro-pyrimidine-4-carboxylic acid (naphthalen-2-ylmethyl)-amide **10.8**. This compound **10.8** is then reacted at ambient temperature in dioxane solution with one molar equivalent of sodium hydride, followed by the addition of a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **10.9** (*Tet. Lett.*, 1986, 27, 1477), to afford the alkylated product **10.10**. Deprotection, by reaction with tetrabutylammonium fluoride in tetrahydrofuran, then yields the product **10.11**.

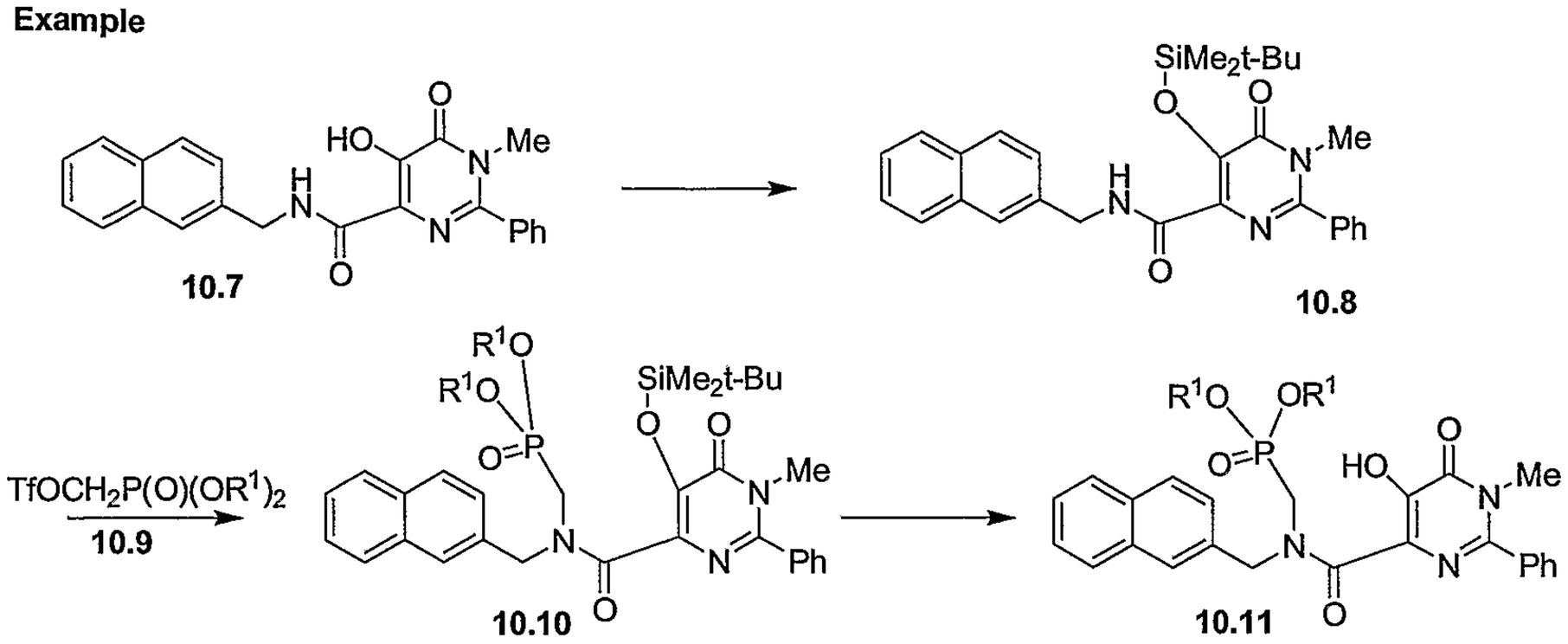
Using the above procedures, but employing, in place of the amide **10.7**, different amides **10.1**, and/or different phosphonates **10.3**, the corresponding products **10.5** are obtained.

Scheme 10.

Method



Example



Schemes **11 - 15** illustrate methods for the preparation of the 2-phosphonate esters **IVa and Va**.

Scheme **11** depicts the preparation of 2-substituted pyrimidyl phosphonates **Va** in which the phosphonate is attached by means of a heteroatom O, S or N, and a variable carbon chain. In this procedure, an amide **11.1**, prepared as previously described, is reacted in an aprotic solvent such as dichloromethane, hexachloroethane or ethyl acetate with a free radical brominating agent such as N-bromosuccinimide or N-bromoacetamide, to yield the 5-bromo product **11.2**. This compound is then reacted with a dialkyl hydroxy, mercapto or amino-substituted phosphonate **11.3**, in which R^5 is as defined as in Scheme **4**, to give the ether, thioether or amine product **11.4**. The displacement reaction is conducted in a polar aprotic organic solvent such as dimethylformamide or DMPU, at from 100 °C to about 150 °C, in the presence of a base such as triethylamine or cesium carbonate, for example as described in WO 0230930A2, Examples 57-69.

Cyclohexylmethyl-amide **11.6** is reacted with one molar equivalent of N-bromosuccinimide in dichloromethane to yield the 5-bromo product **11.7**. This material is then reacted with a dialkyl mercaptoethyl phosphonate **11.8** (*Zh. Obschei. Khim.*, 1973, 43, 2364) and triethylamine at ca 100 °C in a pressure vessel, to produce the thioether **11.9**.

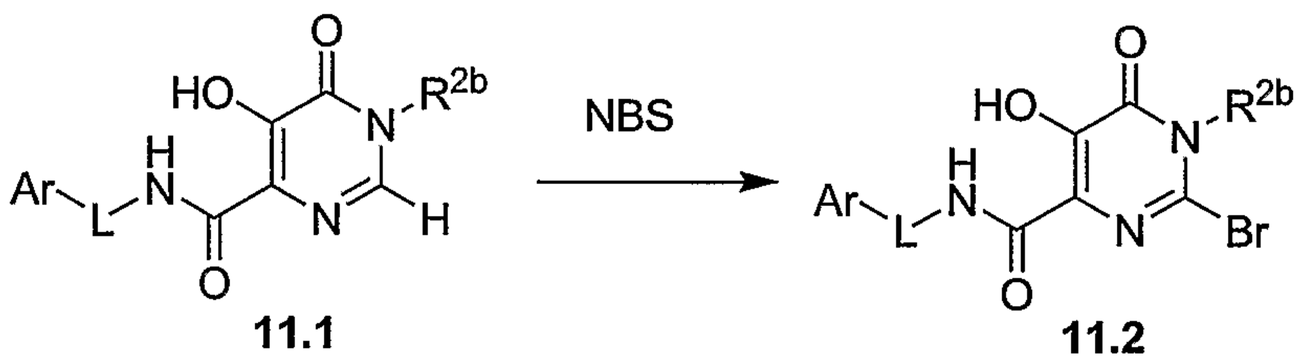
Ketal protected **11.11** is brominated with N-bromosuccinimide in ethyl acetate at reflux temperature to yield the bromo compound **11.12** which is reacted with a dialkyl 3-aminophenyl phosphonate **11.13** (*J. Med. Chem.*, 1984, 27, 654) in dimethylformamide at ca. 130 °C, using the procedure described in WO 0230930 A2

Example 63, to give the phosphonate **11.14**. The product is then reacted with N, N-dimethyloxamide **11.15**, (Japanese Patent 540467 18) and dicyclohexylcarbodiimide in dimethylformamide, to yield the amide product **11.16**.

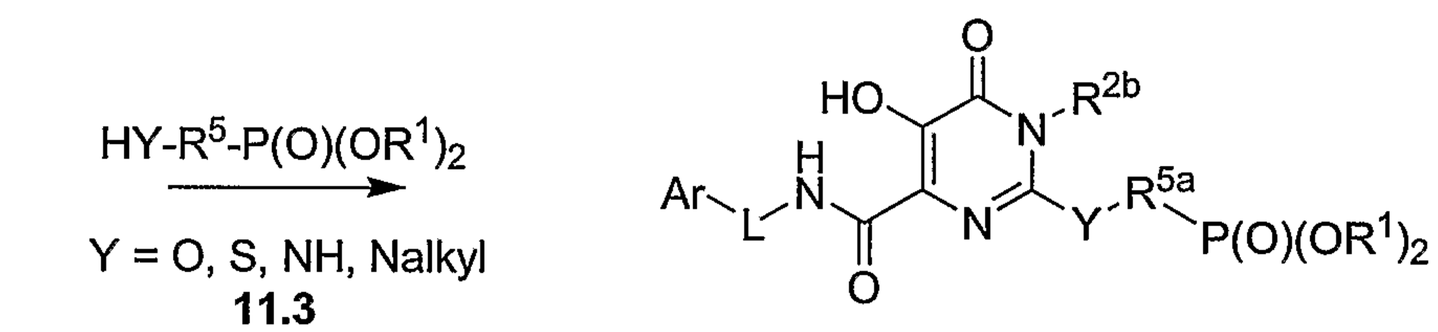
Using the above procedures, but employing, in place of the amides **11.6** or **11.11**, different amides **11.1**, and/or different phosphonates **11.3**, the corresponding products **11.4** are obtained.

Scheme 11.

Method

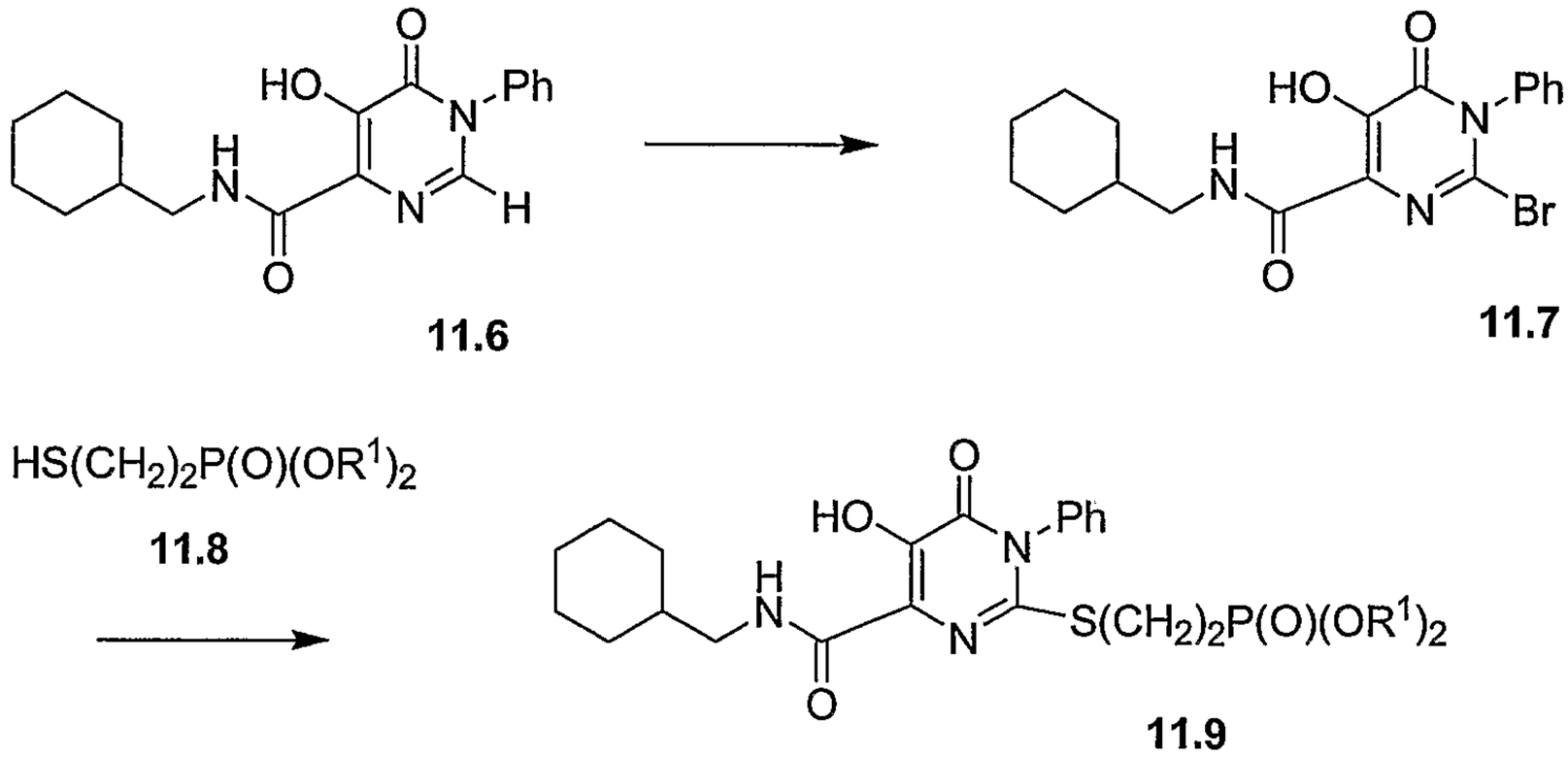


11.1 **11.2**



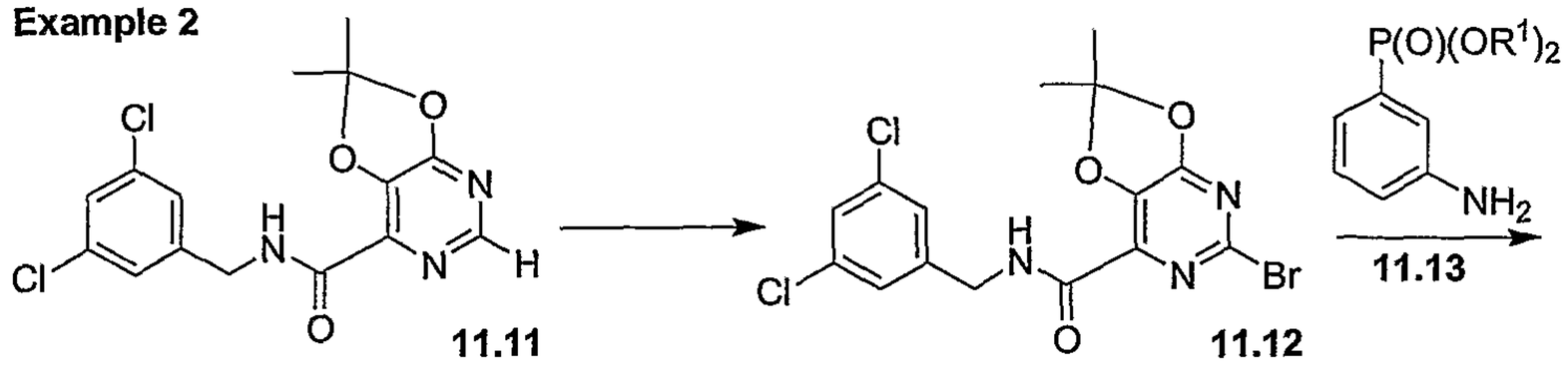
11.3 **11.4**

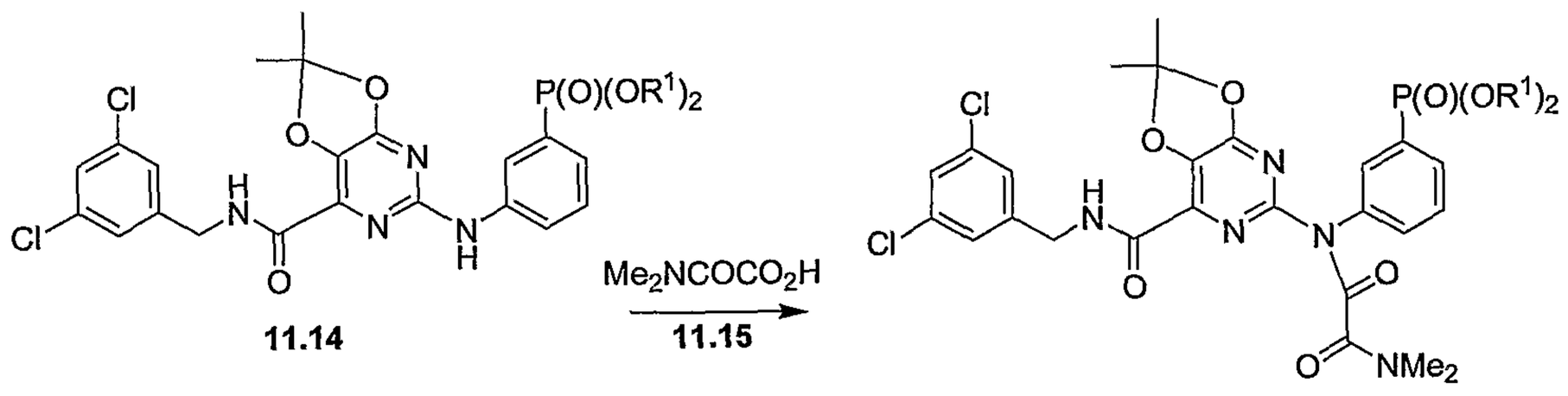
Example 1



11.6 **11.7** **11.8** **11.9**

Example 2





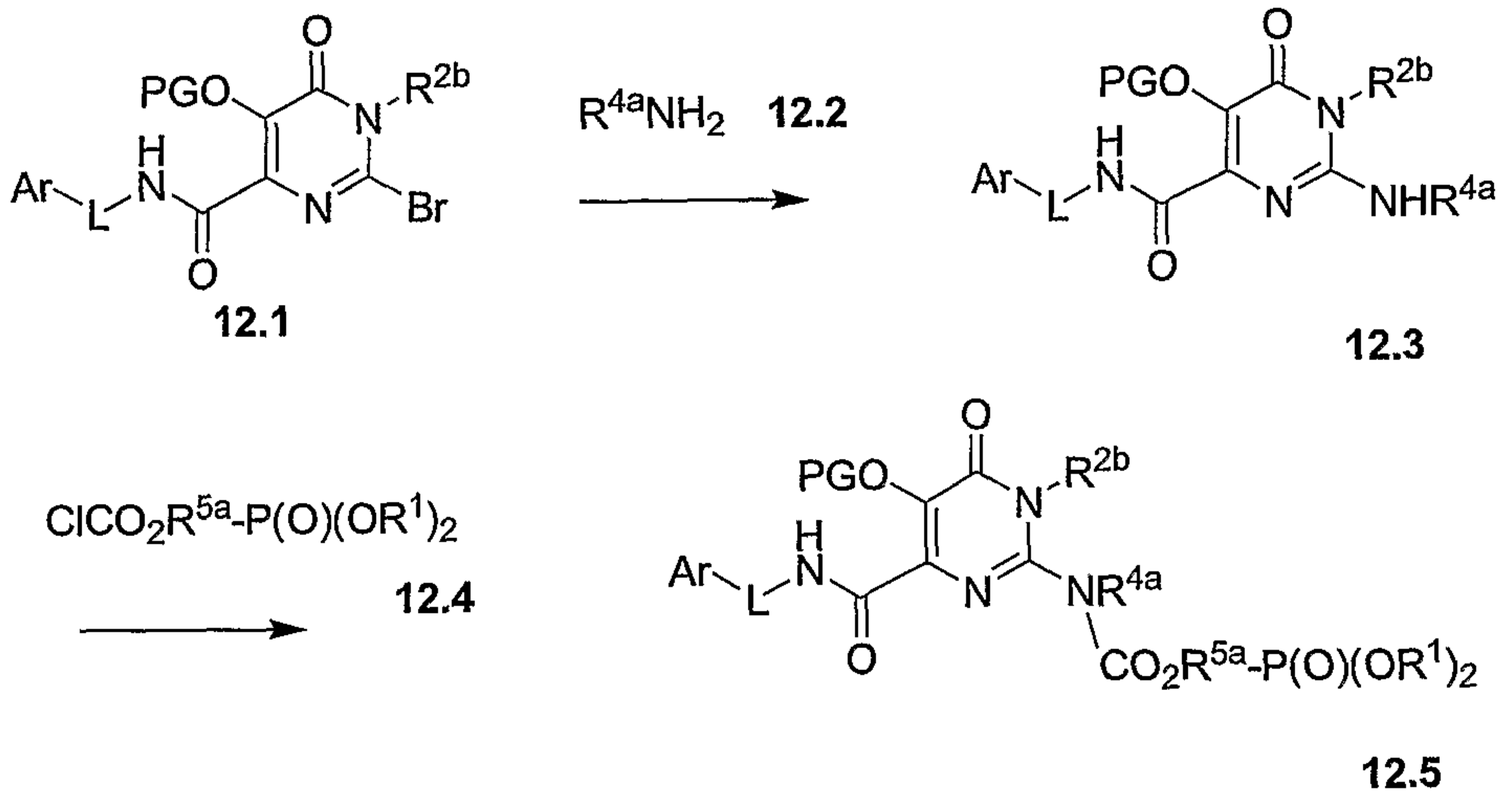
Scheme **12** depicts the preparation of phosphonates **Va** in which the phosphonate is attached by means of a carbamate linkage. In this procedure, a protected bromophenol **12.1** is reacted, as described in Scheme **11**, with an amine **12.2** to give the displacement product **12.3**. This compound is then reacted with phosgene, triphosgene, carbonyl diimidazole or a functional equivalent thereof, and a dialkyl hydroxyalkyl phosphonate **12.4**, in which R^5 is as defined in Scheme **4**, to yield, after deprotection of the phenol, the carbamate **12.5**. Various methods for the preparation of carbamates are described in Scheme **33**.

For example, the hydroxyester **12.6** is converted, as described previously, into the amide **12.7**. This material is then reacted, in dimethylformamide solution at 100°, with ethylamine and cesium carbonate in dimethylformamide, to afford 5-(tert-butyl-dimethyl-silanyloxy)-2-ethylamino-1-methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid [2-(4-fluoro-phenyl)-cyclopropyl]-amide **12.9**. The amine is treated with equimolar amounts of a dialkyl hydroxypropyl phosphonate **12.10** (*Zh. Obschei. Khim.*, 1974, 44, 1834) and carbonyldiimidazole in dichloromethane, to prepare, after desilylation, the carbamate phosphonate **12.11**.

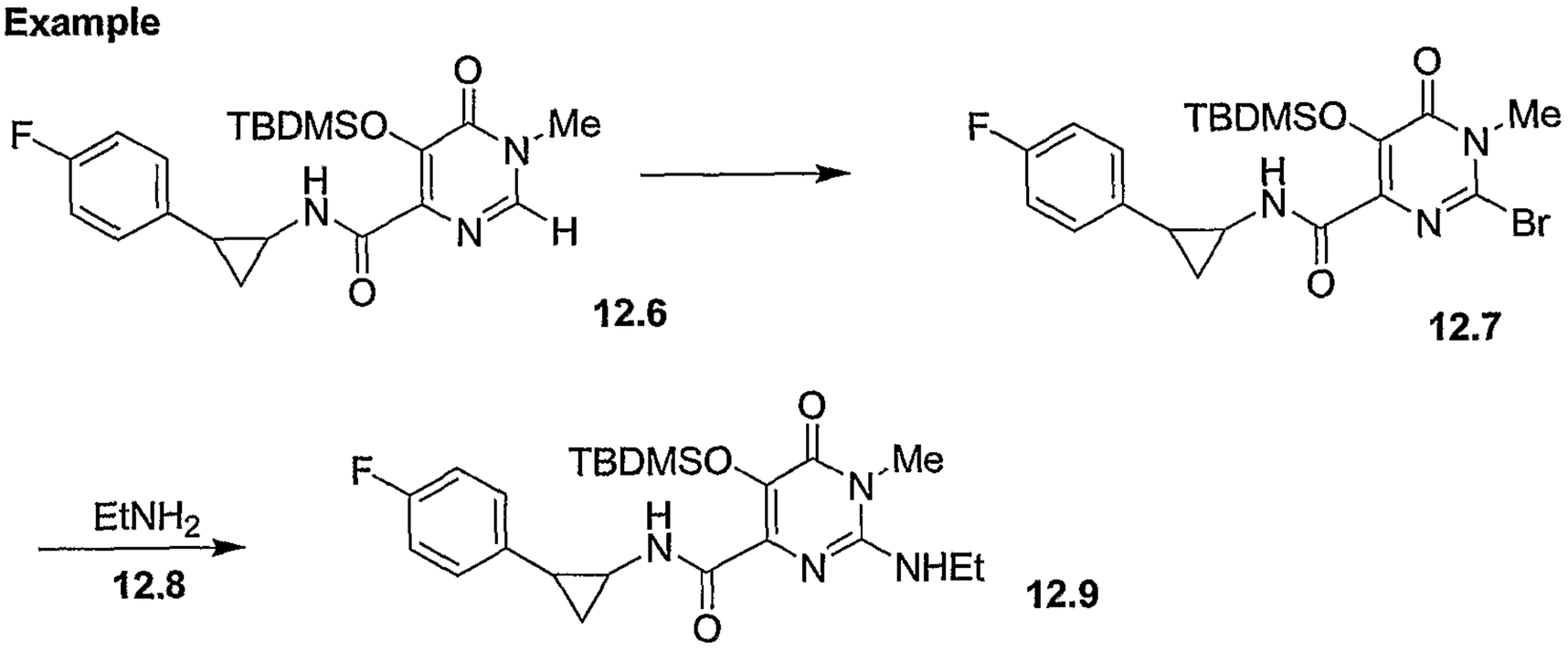
Using the above procedures, but employing, in place of the amide **12.7**, different amides **12.3**, and/or different phosphonates **12.4**, the corresponding products **12.5** are obtained.

Scheme 12.

Method



Example



Scheme **13** depicts the preparation of phosphonates **Va** in which the phosphonate is attached by means of an arylvinyl or arylethyl linkage. In this procedure, a bromophenol **13.1** is protected to give the product **13.2**. This compound is then coupled with tributylvinyltin to yield the 5-vinyl product **13.3**. The coupling reaction is effected in dimethylformamide solution at ca. 80 °C in the presence of a palladium(0) catalyst, such as tris(dibenzylideneacetone)palladium(0), a triarylphosphine such as tri(2-furyl)phosphine and copper(I) iodide, for example as

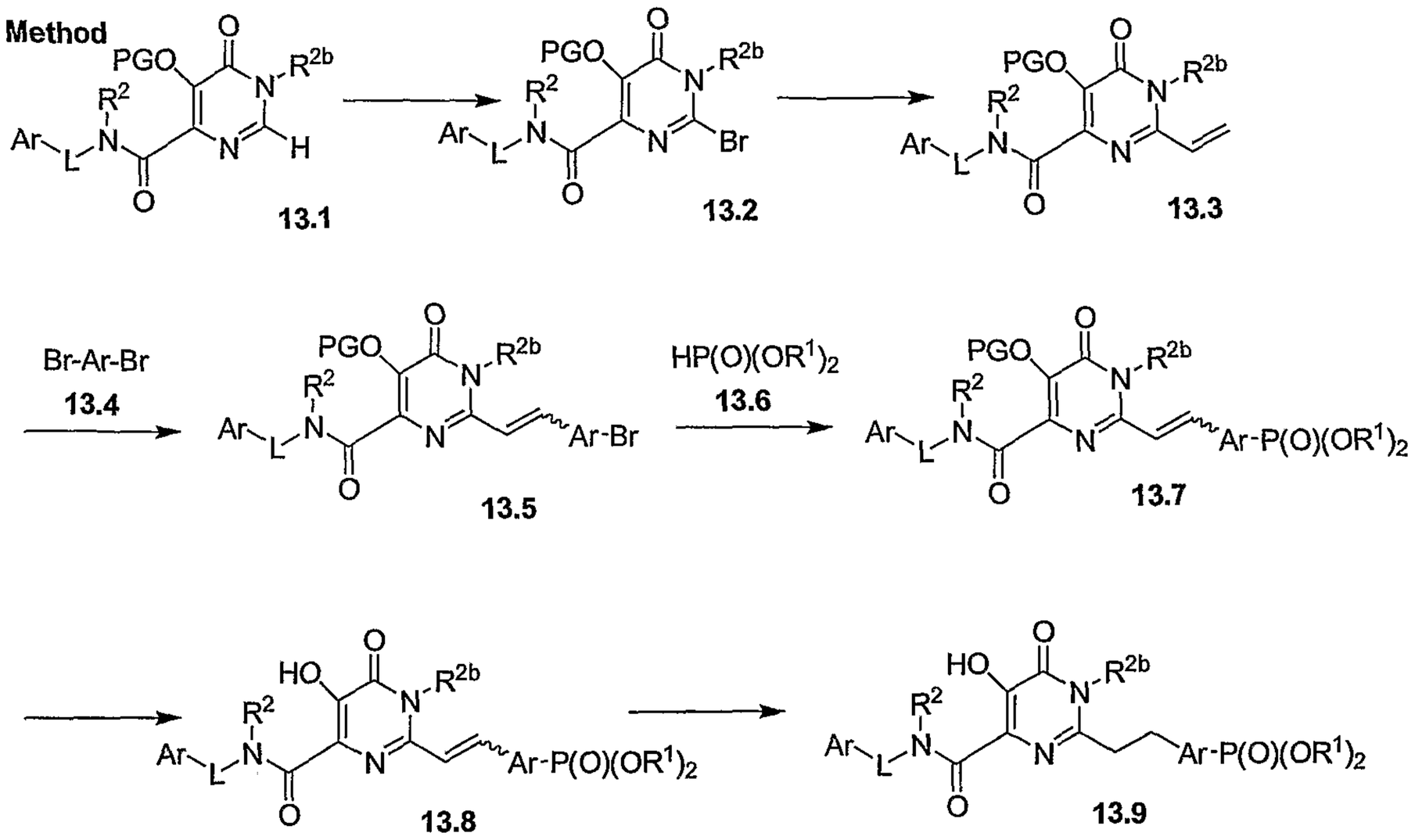
described in WO 0230930A2, Example 176. The vinyl-substituted product is subjected to a palladium-catalyzed Heck coupling reaction, as described in Scheme **4**, with a dibromoaromatic or heteroaromatic compound **13.4**, to give the bromoaryl product **13.5**. The latter compound is then coupled, as described in Scheme **3**, with a dialkyl phosphite **13.6**, in the presence of a palladium catalyst, to give the aryl phosphonate **13.7**. Deprotection then affords the phenol **13.8**. Optionally, the double bond is reduced, for example as described in Scheme **4**, to give the saturated analog **13.9**.

For example, 5-(tert-butyl-dimethyl-silanyloxy)-1-isopropyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid 3,5-dichloro-benzylamide **13.10**, (WO9944992) is converted, using the methods described above, into 2-bromo-5-(tert-butyl-dimethyl-silanyloxy)-1-isopropyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid 3,5-dichloro-benzylamide **13.11**. The product is coupled, as described above, with tri(n-butyl)vinyltin to produce 2-ethylene-5-(tert-butyl-dimethyl-silanyloxy)-1-isopropyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid 3,5-dichloro-benzylamide **13.12**. This material is then coupled, in dimethylformamide solution at 80° with one molar equivalent of 2,5-dibromothiophene **13.13**, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to afford 2-[2-(2-bromothiophene)ethylene, 3-isopropyl, 5-tert-butyldimethylsilyloxy, 6-[3,5-dichloro-benzylamide] pyrimidinone **13.14**. The product **13.14** is coupled, in the presence of a palladium(0) catalyst and triethylamine, with a dialkyl phosphite **13.15**, to afford the phosphonate **13.16**. Deprotection, for example by reaction with tetrabutylammonium fluoride in tetrahydrofuran, then yields the phenol **13.17**, and hydrogenation of the latter compound in methanol, using 5% palladium on carbon as catalyst, produces the saturated analog **13.18**.

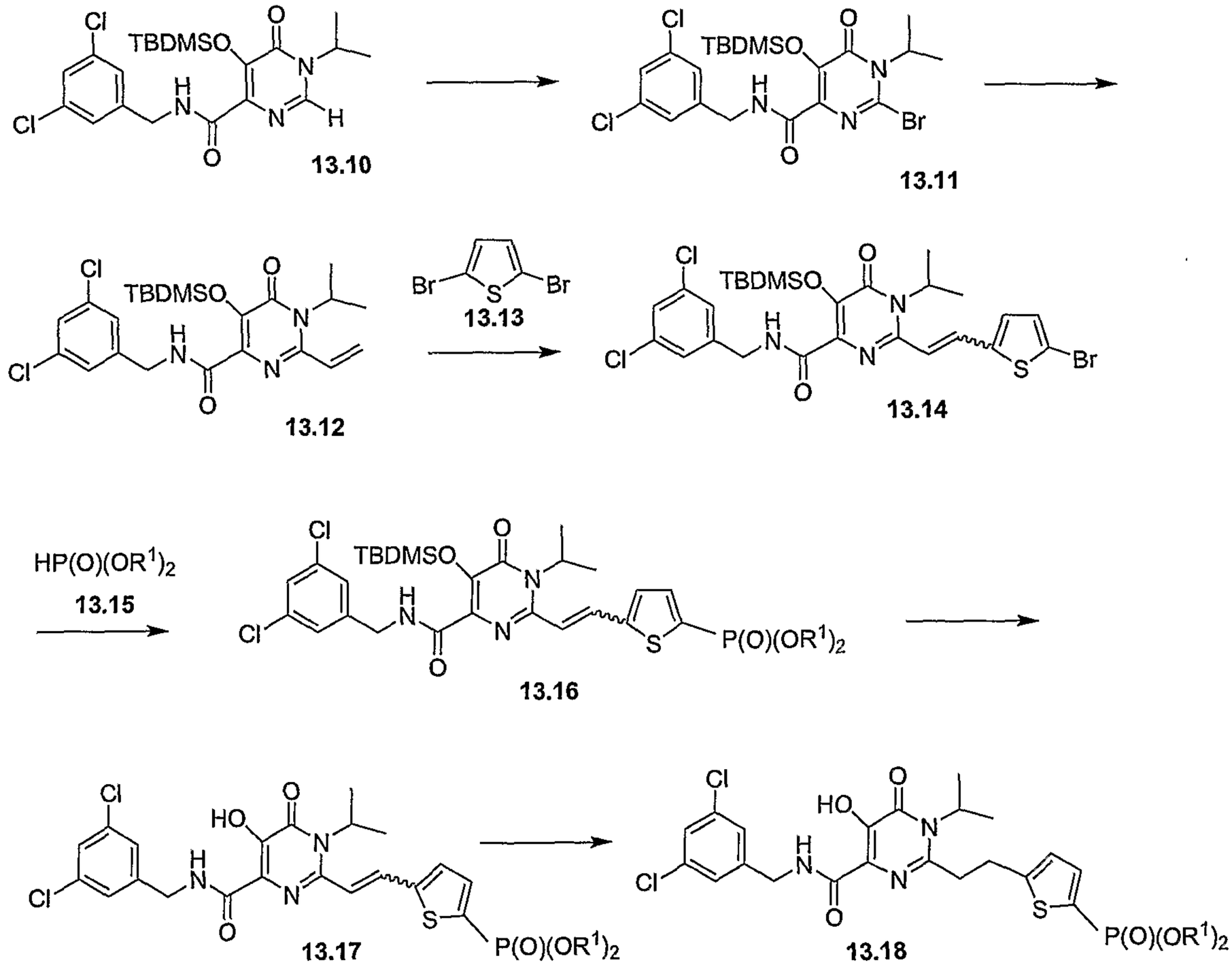
Using the above procedures, but employing, in place of the amide **13.11**, different amides **13.1**, and/or different dibromides **13.4**, the corresponding products **13.8** and **13.9** are obtained.

Scheme 13.

Method



Example



Scheme **14** depicts the preparation of phosphonates **IVa** in which the phosphonate is attached by means of an acetylenic bond. In this procedure, a phenol

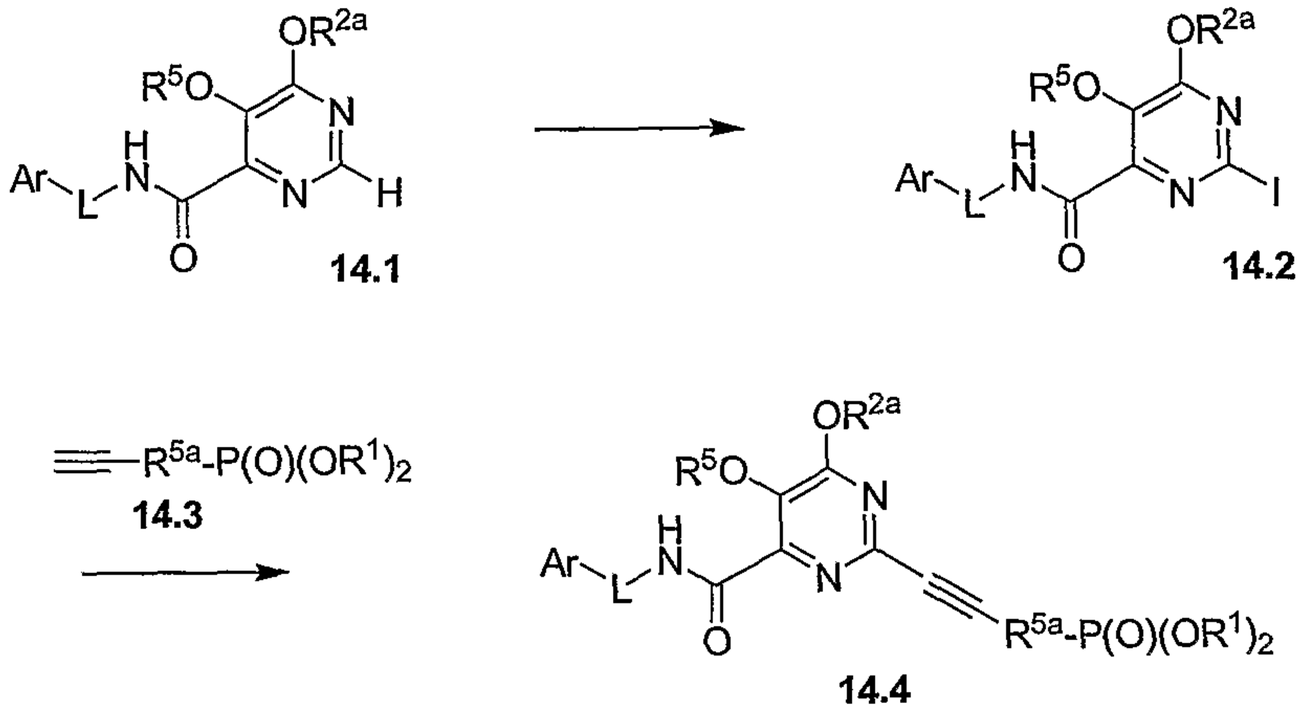
14.1 is reacted, as described in WO 0230930 A2 p. 166 and Example 112, with N-iodosuccinimide in dichloromethane-dimethylformamide, to give the 5-iodo product; protection of the phenolic hydroxyl group then affords the compound **14.2**. This material is coupled, as described in WO 0230930 A2 Example 79, in dimethylformamide solution, in the presence of dichlorobis(triphenylphosphine) palladium (II), copper iodide and triethylamine, with a dialkyl ethynyl phosphonate **14.3**, in which R^{5a} is as defined in Scheme **4**, to give, after deprotection of the phenol, the acetylenic phosphonate **14.4**.

Dibenzoyl amide **14.6** is converted into the 2-iodo compound **14.7**, as described above, and coupled with a dialkyl propynyl phosphonate **14.8**, (*Synthesis*, (1999), 2027) to yield the acetylenic phosphonate **14.9**. After deprotection of the benzoyl groups, the 5,6-dihydroxy-2-methyl-pyrimidine-4-carboxylic acid (cyclopent-3-enylmethyl)-amide phosphonate compound **14.10** is obtained.

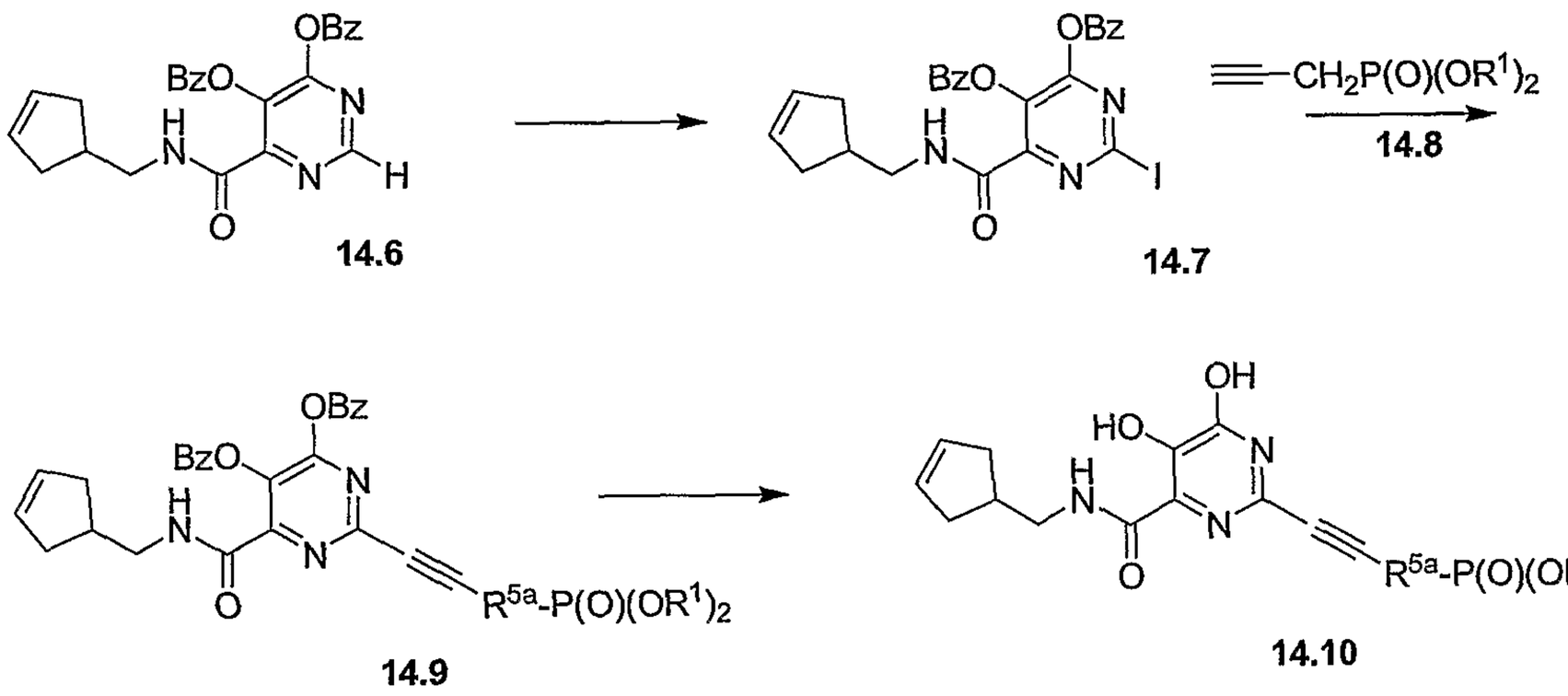
Using the above procedures, but employing, in place of the iodoamide **14.7**, different iodoamides **14.2**, and/or different acetylenic phosphonates **14.3**, the corresponding products **14.4** are obtained.

Scheme 14.

Method



Example



Scheme **15** depicts the preparation of phosphonates **Va** in which the phosphonate is directly attached to pyrimidinone at the 2-position. In this procedure, a protected 2-bromopyrimidyl **15.1** is coupled, in the presence of a palladium catalyst, as described in Scheme **3**, with a dialkyl phosphite **15.2**, to give after deprotection the aryl phosphonate **15.3**.

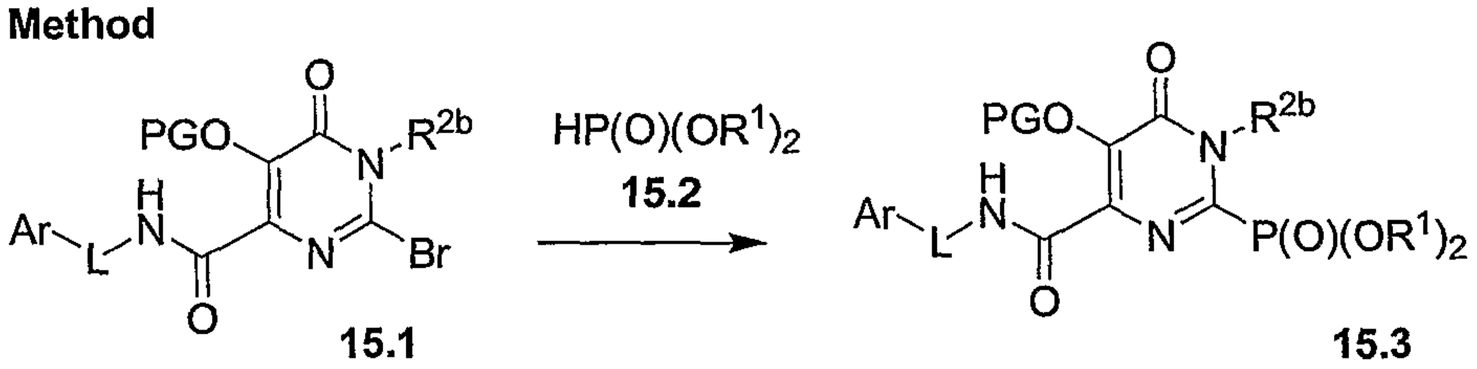
For example, 4-oxo-5-(tetrahydro-pyran-2-yloxy)-3-triisopropylsilanyl-3,4-dihydro-pyrimidine-6-carboxylic acid [1-(3-chloro-4-fluoro-phenyl)-1-methyl-ethyl]-amide **15.4**, is converted, using the procedures described above, is brominated to give 2-bromo-4-oxo-5-(tetrahydro-pyran-2-yloxy)-3-triisopropylsilanyl-3,4-dihydro-pyrimidine-6-carboxylic acid [1-(3-chloro-4-fluoro-phenyl)-1-methyl-ethyl]-amide **15.5**. The product is then coupled, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, as described in Scheme

3, with a dialkyl phosphite **15.6** (for example, R^1 = ethyl), to afford, after desilylation of the phenol, the pyrimidinone 2-phosphonate **15.7** which can be deprotected under acidic conditions to **15.8**.

Using the above procedures, but employing, in place of the bromoamide **15.5**, different bromoamides **15.1**, the corresponding products **15.3** are obtained.

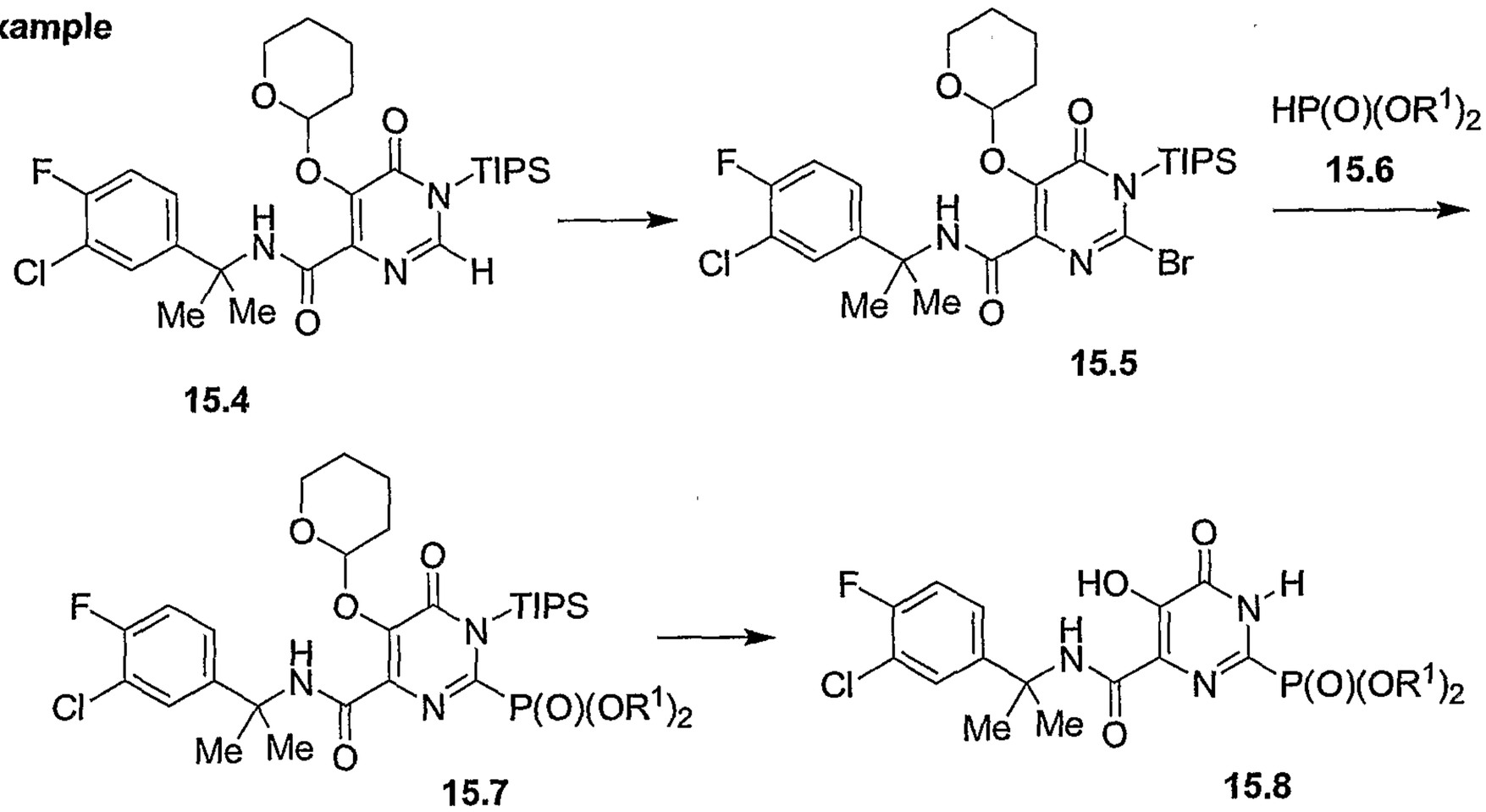
Scheme 15.

Method



15.1 **15.3**

Example



Schemes **16-18** illustrate methods for the preparation of the 2-amino linked phosphonate esters **IVa** and **Va**.

Scheme **16** depicts the N-3 sulfonation of 2-phosphonate compounds. In this procedure, **16.1**, in which the 5-hydroxyl group is protected, prepared as described in Scheme **11**, is reacted with a sulfonyl chloride **16.2** or a sulfonic acid **16.3**, in which R^{4a} can be C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocycle, or C_2–C_{20} substituted heterocycle, to afford sulfonamide **16.4**. The reaction between an amine and a sulfonyl chloride, to produce the

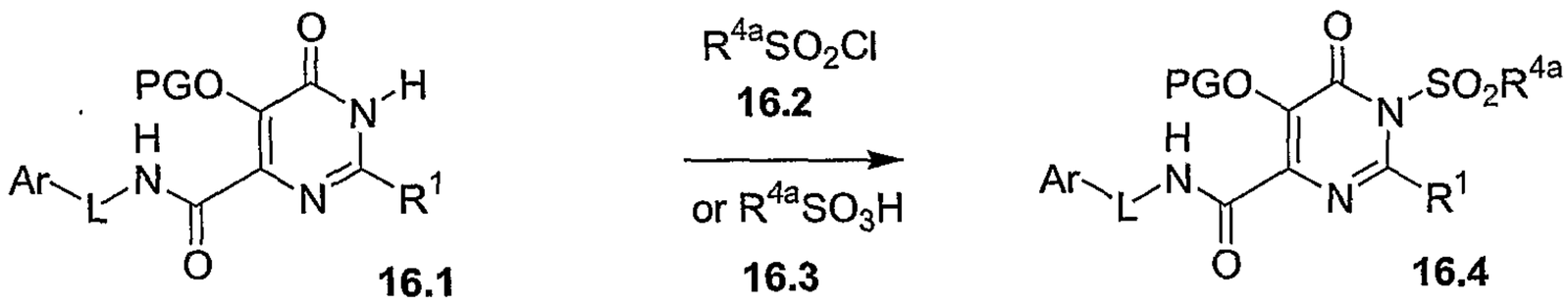
sulfonamide, is conducted at ambient temperature in an inert solvent such as dichloromethane, in the presence of a tertiary base such as triethylamine. The reaction between a sulfonic acid and an amine to afford a sulfonamide is conducted in a polar solvent such as dimethylformamide, in the presence of a carbodiimide such as dicyclohexyl carbodiimide, for example as described in *Synthesis*, (1976), 339.

For example, the 5-protected phosphonate diisobutyl ester **16.5**, prepared by the methods described above, is reacted in dichloromethane solution with one molar equivalent of ethylsulfonyl chloride **16.6** and triethylamine, to produce **16.7**. Desilylation of **16.7** gives {2-[(4-dimethylcarbamoyl-1-ethanesulfonyl-5-hydroxy-6-oxo-1,6-dihydro-pyrimidin-2-yl)-methyl-amino]-ethyl}-phosphonic acid di-sec-butyl ester **16.8**.

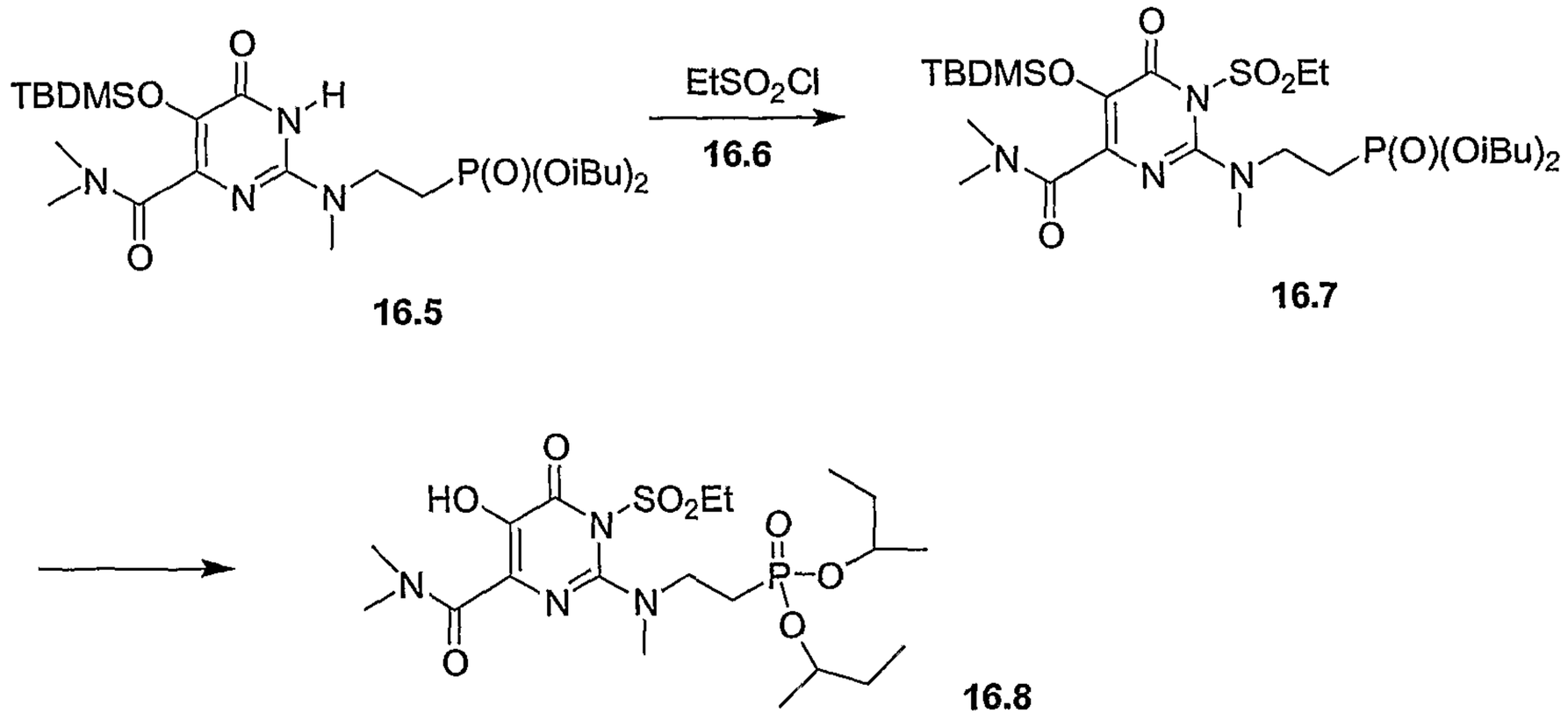
Using the above procedures, but employing, in place of the amine phosphonate **16.5**, different phosphonates **16.1**, and/or different sulfonyl chlorides **16.2** or sulfonic acids **16.3**, the corresponding products **16.4** are obtained.

Scheme 16.

Method



Example



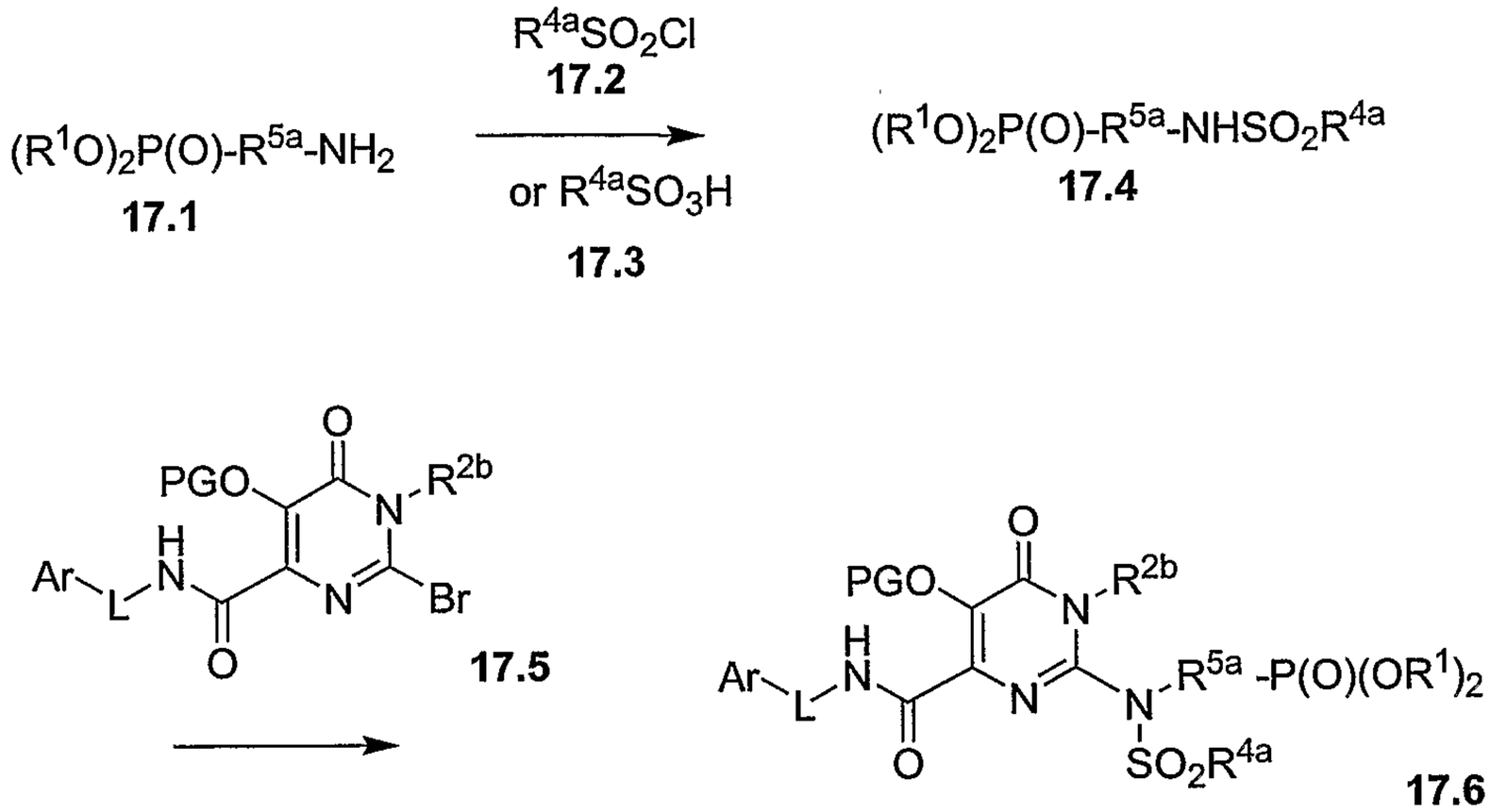
Scheme **17** depicts an alternative method for the preparation of phosphonate esters **Va** in which the phosphonate group is attached by means of a variable carbon chain from a 2-sulfonamido group. In this procedure, a dialkyl amino-substituted phosphonate **17.1**, in which the group R^{5a} is as defined in Scheme **4**, is reacted with a sulfonyl chloride **17.2** or sulfonic acid **17.3**, as described in Scheme **16**, to yield the sulfonamide **17.4**. The product is then reacted with a bromoamide **17.5**, to prepare the displacement product **17.6**. The displacement reaction is performed in a basic solvent such as pyridine or quinoline, at from about 80° to reflux temperature, optionally in the presence of a promoter such as copper oxide, as described in WO 0230930 A2 Example 154.

For example, a dialkyl 4-aminophenyl phosphonate **17.7** (Epsilon) is reacted in dichloromethane solution with one molar equivalent of methanesulfonyl chloride **17.8** and triethylamine, to give the sulfonamide **17.9**. The product is then reacted in pyridine solution at reflux temperature with 2-bromo-6-(4-fluoro-benzylcarbamoyl)-3-methyl-6-benzoyloxy-3,4-dihydro-pyrimidin-5-yl ester **17.10**, prepared by the methods described above, and copper oxide, to yield the sulfonamide **17.11**.

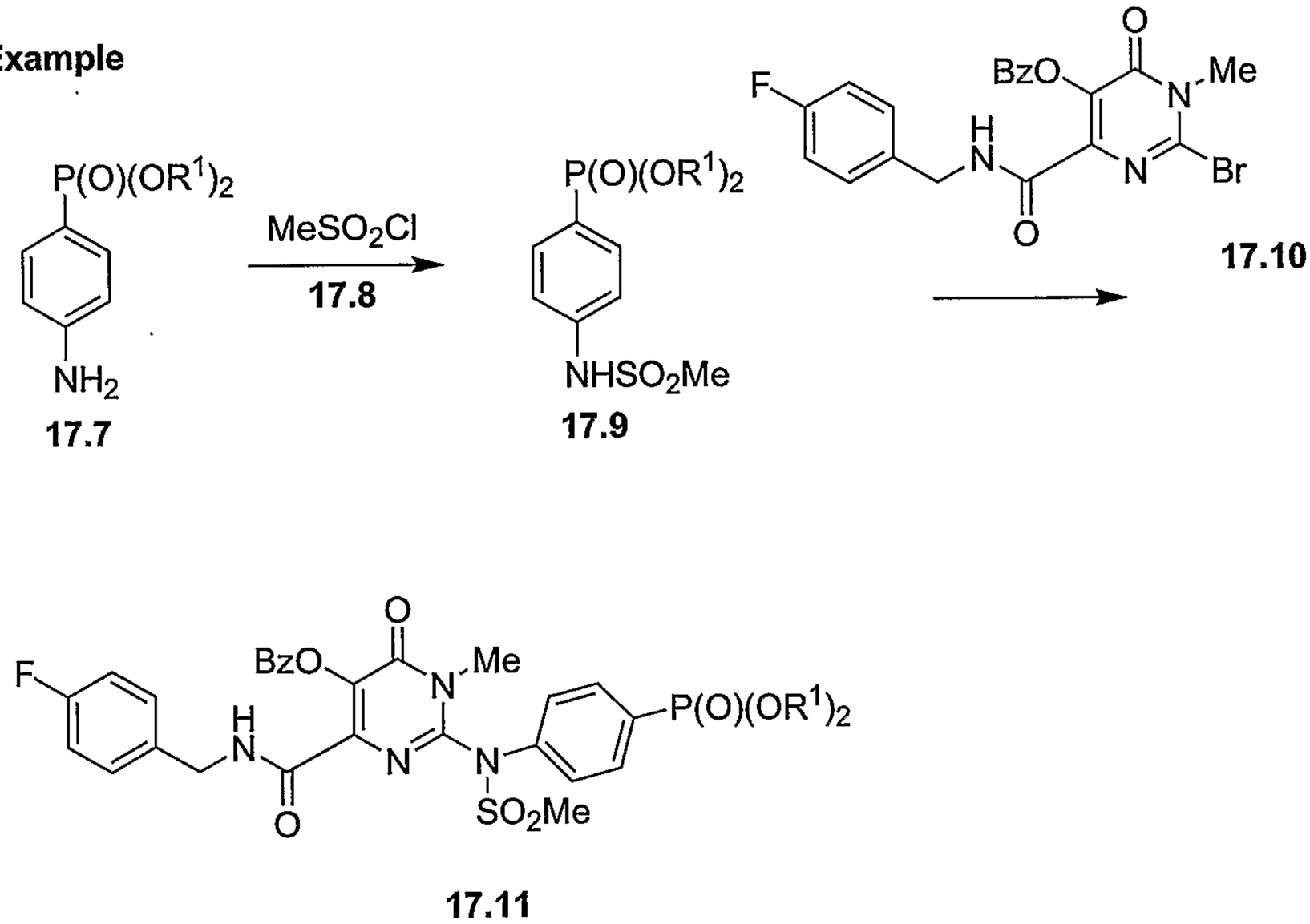
Using the above procedures, but employing, in place of the amine phosphonate **17.7**, different phosphonates **17.1**, and/or different sulfonyl chlorides **17.2** or sulfonic acids **17.3**, the corresponding products **17.6** are obtained.

Scheme 17.

Method



Example



Scheme **18** depicts an alternative method for the preparation of phosphonate esters **IVa** in which the phosphonate group is attached by means of a variable carbon chain. In this procedure, a phenol-protected 5-bromo substituted amide **18.1** is reacted, as described in Scheme **17**, with a sulfonamide **18.2**, to give the displacement product **18.3**. The product is then reacted with a dialkyl bromoalkyl phosphonate **18.4**

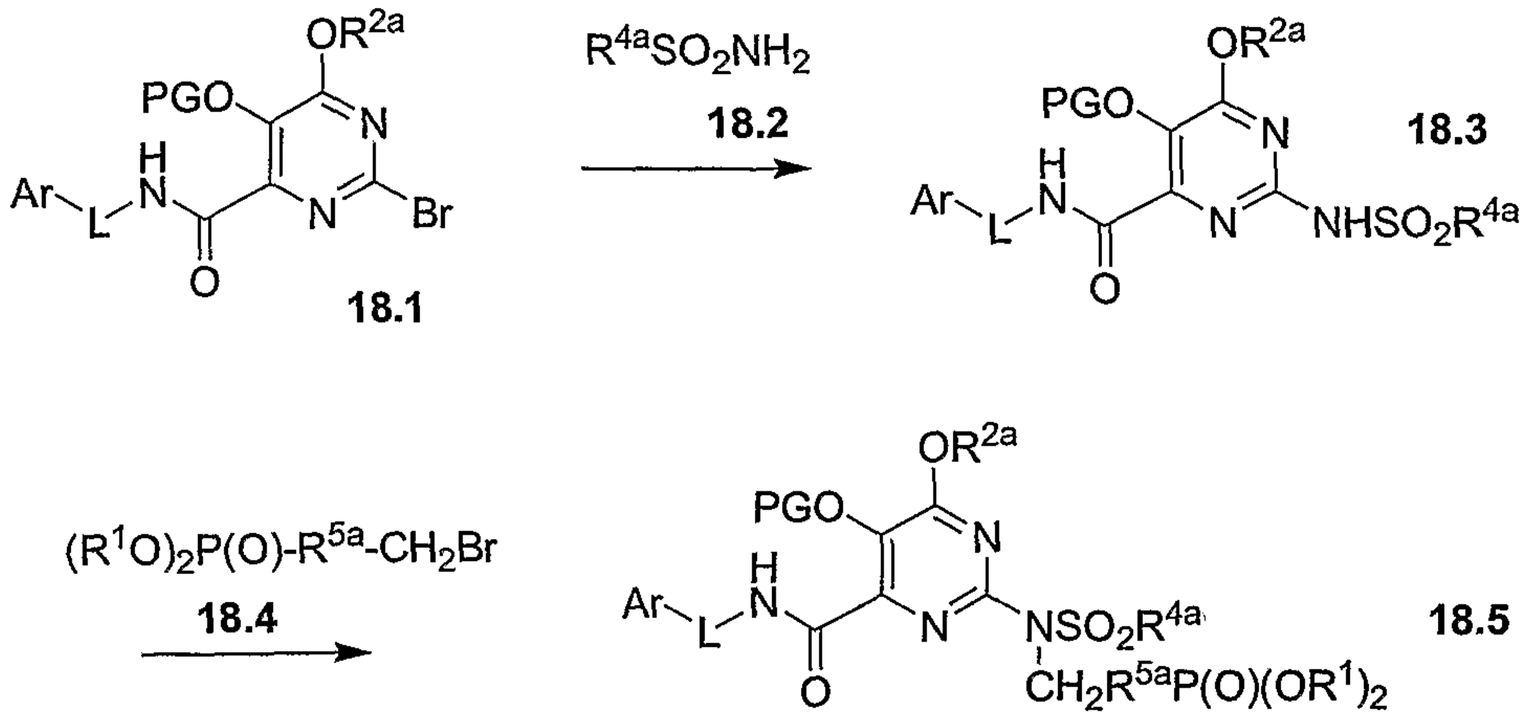
to afford, after deprotection of the phenol, the alkylated compound **18.5**. The alkylation reaction is performed in a polar aprotic solvent such as dimethylformamide or DMPU, at from ambient temperature to about 100 °C, in the presence of a base such as sodium hydride or lithium hexamethyl disilylazide.

For example, benzoic acid 2-bromo-4-hydroxy-6-[1-(3-methoxy-phenyl)-1-methyl-ethylcarbamoyl]-pyrimidin-5-yl ester **18.6**, prepared by the methods described above, is reacted in pyridine solution at reflux temperature with one molar equivalent of propanesulfonamide **18.7** and copper oxide, to afford the sulfonamide **18.8**. The product is then reacted in dimethylformamide solution with one molar equivalent of a dialkyl bromoethyl phosphonate **18.9** (Aldrich) and lithium hexamethyl disilylazide, to give after debenzoylation, the sulfonamide phosphonate **18.10**. The benzoyl protecting group is removed, for example, by reaction with 1% methanolic sodium hydroxide at ambient temperature, as described in *Tetrahedron*, 26, 803, 1970.

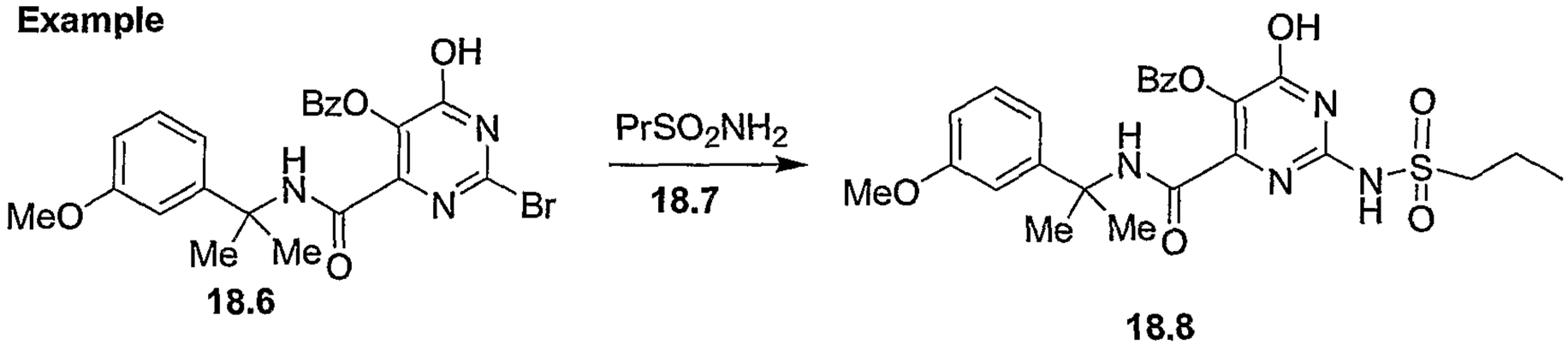
Using the above procedures, but employing, in place of the bromo compound **18.6**, different bromo compounds **18.1**, and/or different sulfonamides **18.2**, and/or different phosphonates **18.4**, the corresponding products **18.5** are obtained.

Scheme 18. Phosphonates 4.

Method



Example



Schemes **19 - 21** illustrate methods for the preparation of 2-amino linked phosphonate esters **IVa** and **Va**.

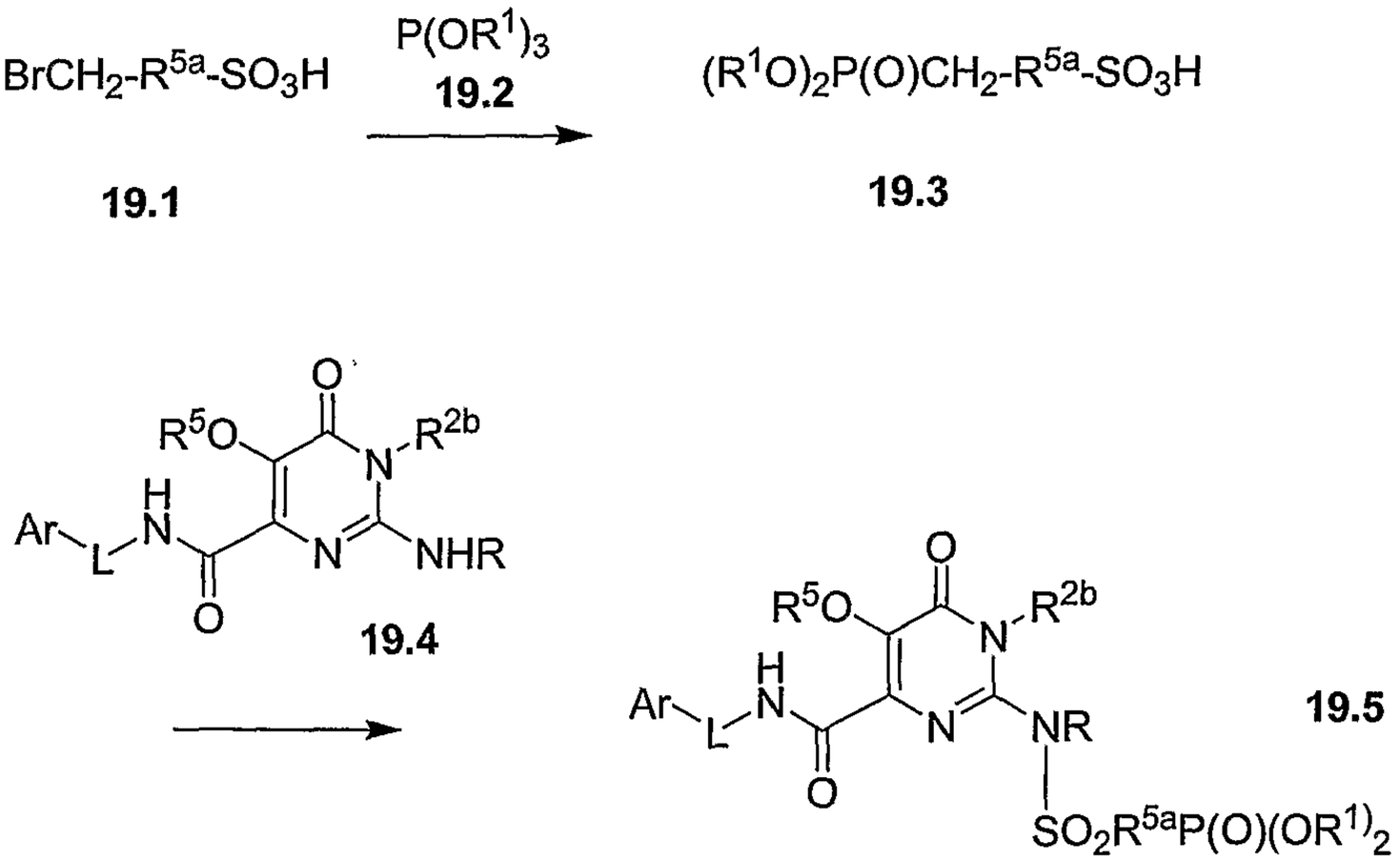
Scheme **19** illustrates the preparation of phosphonates **Va** in which the phosphonate group is attached by means of a variable carbon chain. In this procedure, a bromo-substituted sulfonic acid **19.1** is subjected to an Arbuzov reaction with a trialkyl phosphite **19.2** to give the phosphonate **19.3**. The Arbuzov reaction is performed by heating the bromo compound with an excess of the trialkyl phosphite at from 100 °C to 150 °C, as described in Handbook of Organophosphorus Chem., 1992, 115-72. The resulting phosphonate is then reacted with an amine **19.4**, either directly,

in the presence of a carbodiimide, or by initial conversion to the sulfonyl chloride, as described in Scheme 16, to afford, after deprotection of the phenolic hydroxyl group, the sulfonamide **19.5**.

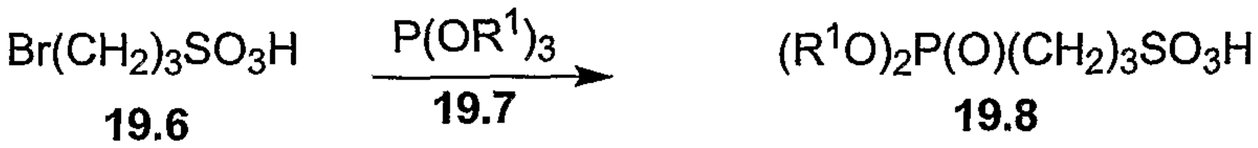
For example, 3-bromopropanesulfonic acid **19.6** (Sigma) is heated at 130 °C with a trialkyl phosphite **19.7** to give the phosphonate **19.8**. The product is then reacted in DMPU solution with **19.9**, prepared by the methods described above, in the presence of dicyclohexylcarbodiimide, to give, after desilylation, by reaction with tetrabutylammonium fluoride in tetrahydrofuran, the sulfonamide **19.10**.

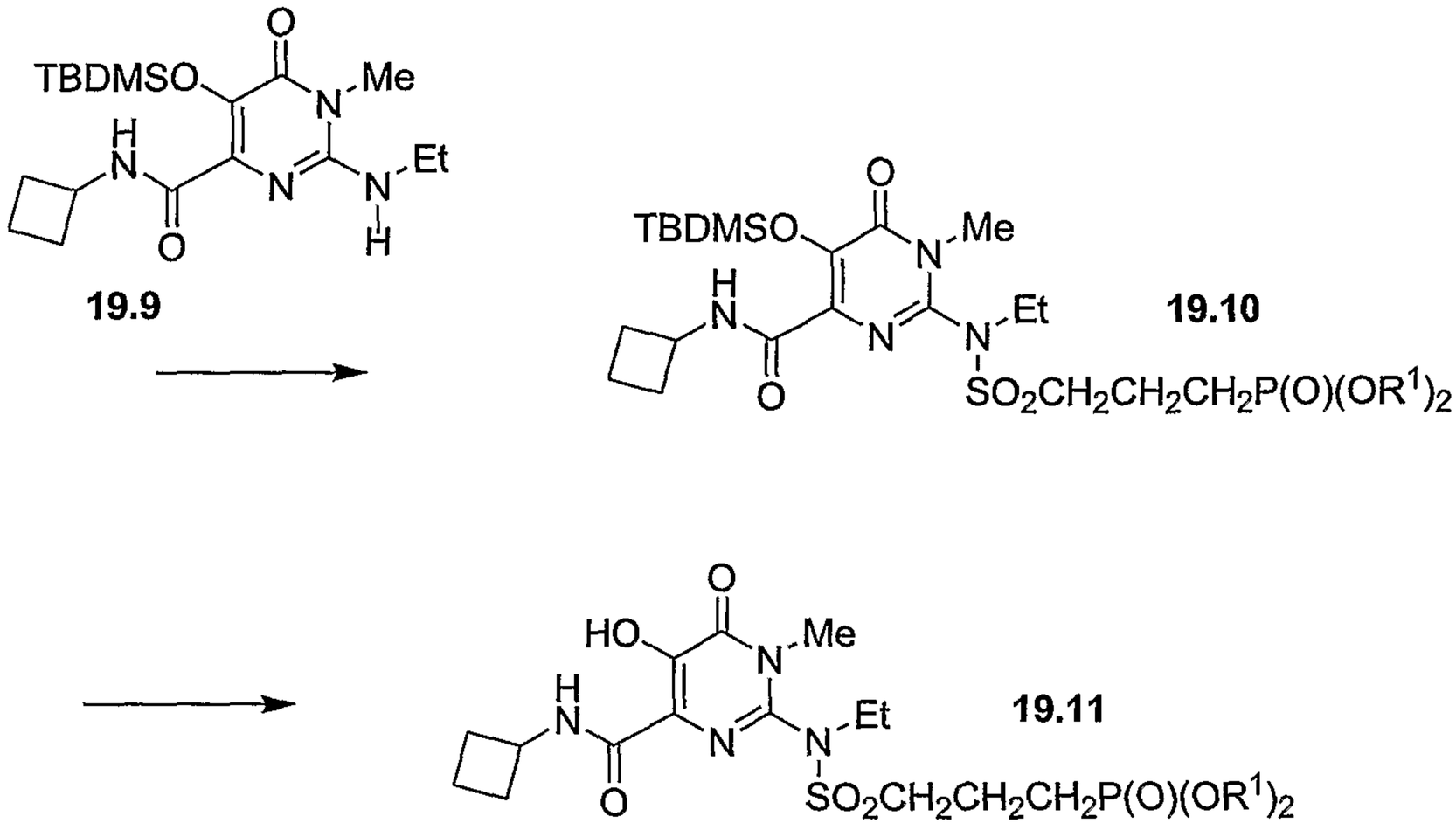
Using the above procedures, but employing, in place of the bromo sulfonic acid **19.6**, different bromosulfonic acids **19.1**, and/or different amines **19.4**, the corresponding products **19.5** are obtained.

Scheme 19.
Method



Example





Scheme **20** illustrates the preparation of phosphonates **Va** in which the phosphonate group is attached by means of a saturated or unsaturated carbon chain and an aromatic or heteroaromatic group. In this procedure, a vinyl-substituted sulfonic acid **20.1** is coupled, in a palladium-catalyzed Heck reaction, as described in Scheme **4**, with a dibromoaromatic or heteroaromatic compound **20.2**, to yield the sulfonic acid **20.3**. The product is then coupled, in the presence of a palladium catalyst, as described in Scheme **3**, with a dialkyl phosphite $HP(O)(OR^1)_2$, to give the phosphonate **20.4**. The latter compound is then reacted, as described above, with an amine **20.5**, either directly, in the presence of a carbodiimide, or by initial conversion to the sulfonyl chloride, as described in Scheme **16**, to afford, after deprotection of the phenolic hydroxyl group, the sulfonamide **20.6**. Optionally, the double bond is reduced, either catalytically or chemically, as described in Scheme **4**, to afford the saturated analog **20.7**.

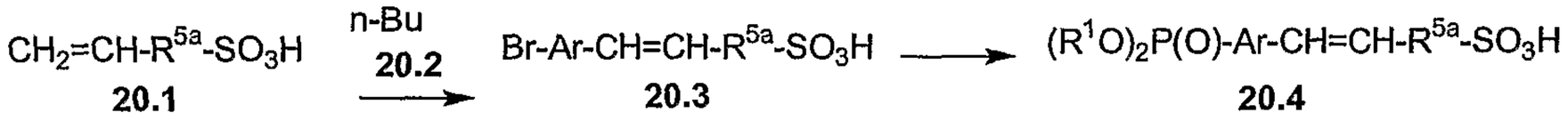
For example, vinylsulfonic acid **20.8** (Sigma) is coupled, in dioxane solution, in the presence of tetrakis(triphenylphosphine)palladium (0) and potassium carbonate, with 2,5-dibromothiophene **20.9**, to form the coupled product **20.10**. The product is then reacted in toluene solution at 100 °C with a dialkyl phosphite **20.11**,

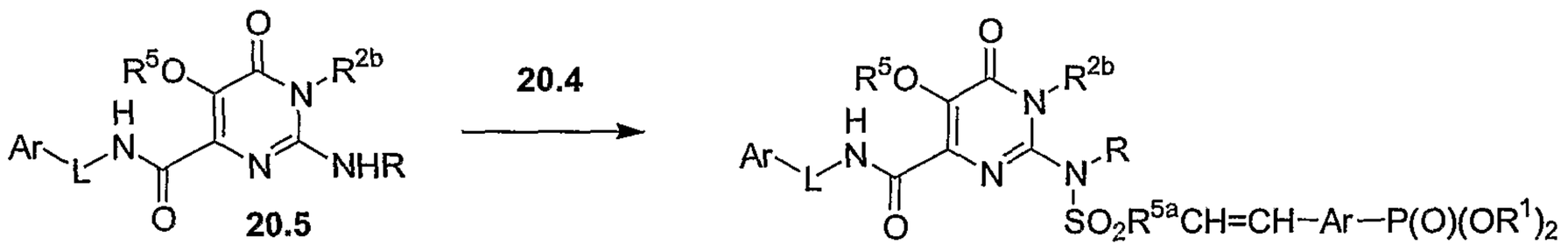
triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium (0), to produce the phosphonate **20.12**. This material is then reacted, in dimethylformamide solution at ambient temperature, as described above, with 4-fluoro-benzylamide **20.13**, prepared by the methods described above, in the presence of dicyclohexylcarbodiimide, to give, after desilylation, using tetrabutylammonium fluoride, the sulfonamide **20.14**. Hydrogenation of the double bond, for example using 5% palladium on carbon as catalyst, then yields the saturated analog **20.15**.

Using the above procedures, but employing, in place of the sulfonic acid **20.8**, different sulfonic acids **20.1**, and/or different dibromoaromatic compounds **20.2**, and/or different amines **20.5**, the corresponding products **20.6** and **20.7** are obtained.

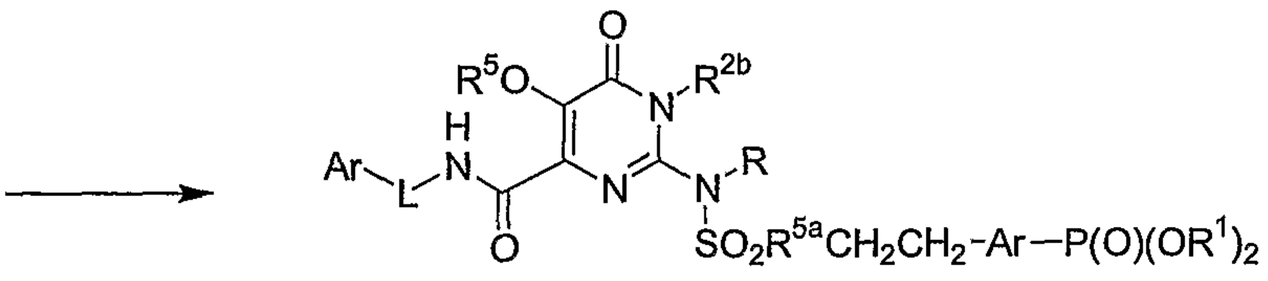
Scheme 20.

Method

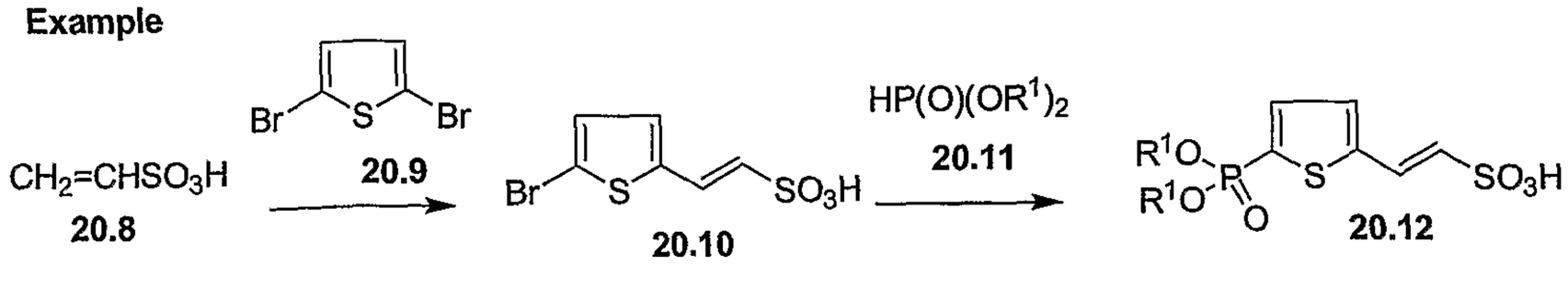


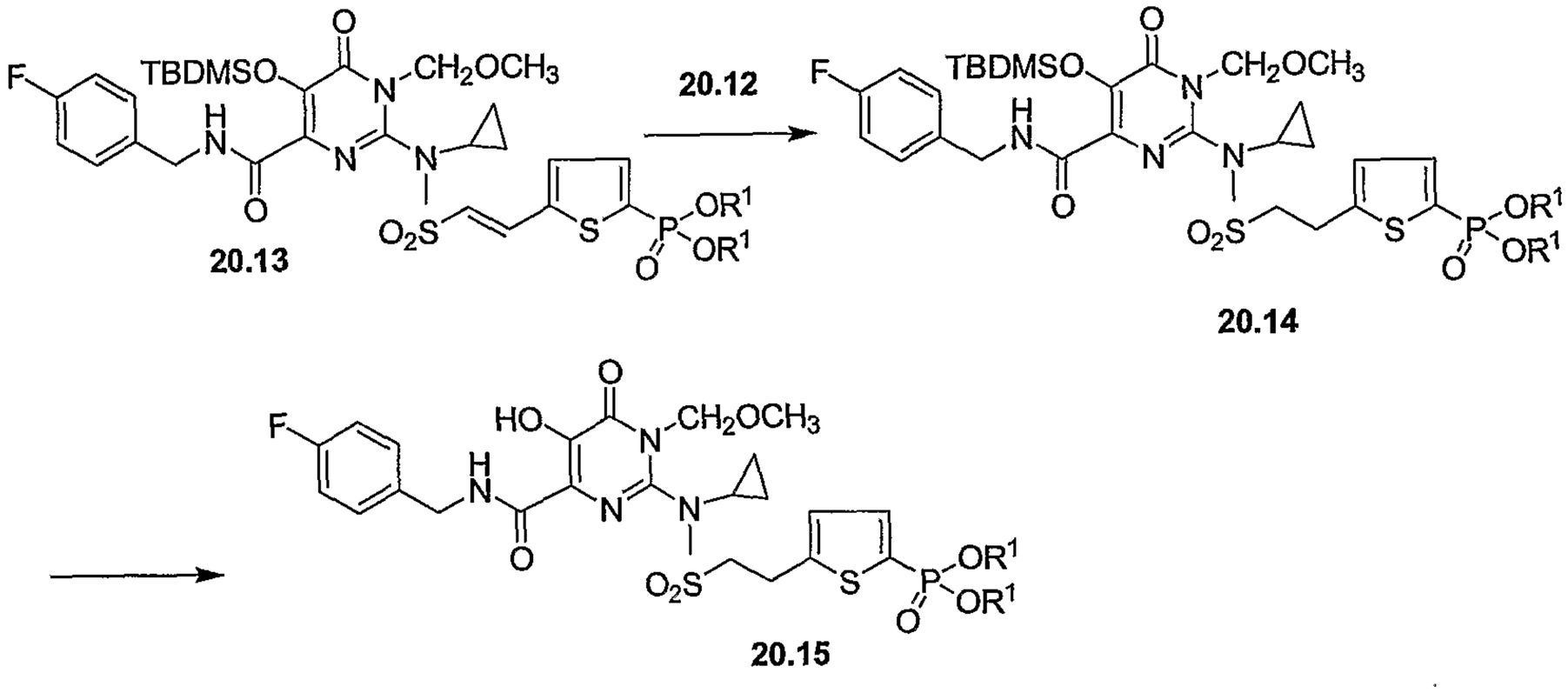


20.6



20.7





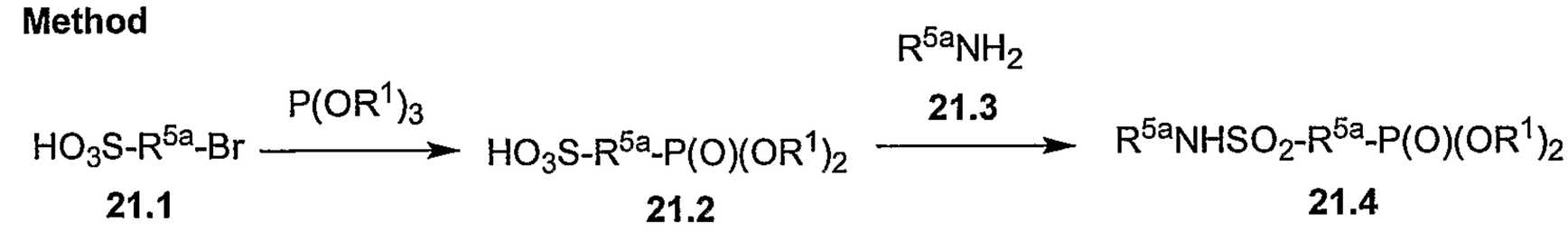
Scheme **21** illustrates the preparation of phosphonates **IVa** in which the phosphonate group is attached by means of a variable carbon chain. In this procedure, an aliphatic bromo-substituted sulfonic acid **21.1** is subjected to an Arbuzov reaction with a trialkyl phosphite, as described in Scheme **19**, to give the phosphonate **21.2**. Alternatively, an aryl bromosulfonic acid **21.1** is coupled, as described in Scheme **3**, with a dialkyl phosphite, to give the phosphonate **21.2**. The product is then reacted with an amine **21.3** to afford the sulfonamide **21.4**. The latter compound is then reacted, as described in Scheme **17**, with a bromoamide **21.5**, to give the displacement product **21.6**.

For example, 4-bromobenzenesulfonic acid **21.7** is reacted, as described in Scheme **20**, with a dialkyl phosphite to form the phosphonate **21.8**. The product is then reacted with phosphoryl chloride to afford the corresponding sulfonyl chloride, and the latter compound is reacted, in dichloromethane solution, in the presence of triethylamine, with 2-methoxyethylamine **21.9**, to yield the sulfonamide **21.10**. This material is then reacted, in pyridine solution at reflux temperature, with 2-bromo-4,5-dimethoxy-pyrimidine-6-carboxylic acid 4-fluoro-benzylamide **21.11**, prepared by the methods described above, and copper oxide, to give the 2-sulfonamide phosphonate **21.12**.

Using the above procedures, but employing, in place of the sulfonic acid **21.7**, different sulfonic acids **21.1**, and/or different amines **21.3**, and/or different bromo compounds **21.5**, the corresponding products **21.6** are obtained.

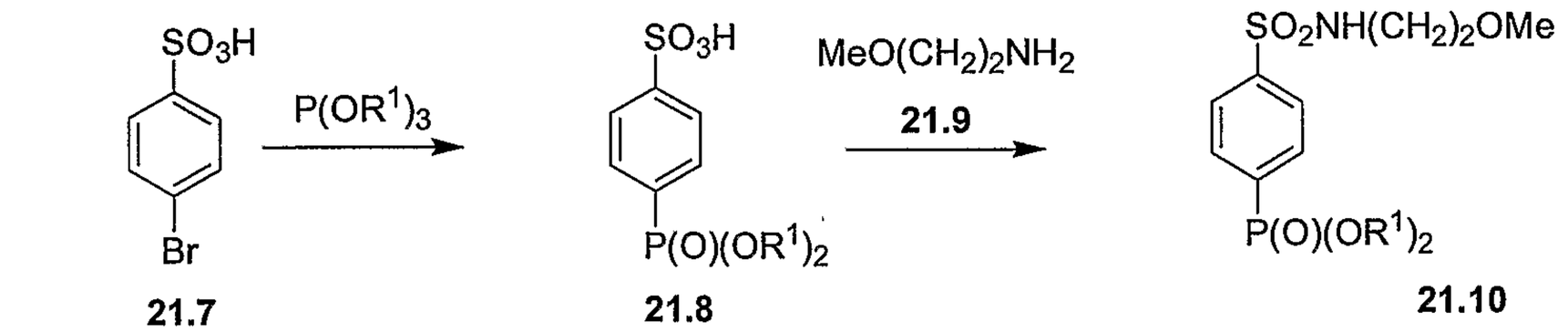
Scheme 21.

Method



21.1 **21.2** **21.3** **21.4** **21.5** **21.6**

Example



21.7 **21.8** **21.9** **21.10** **21.11** **21.12**

Preparation of phosphonate esters IVa and Va.

Scheme **22** depicts the preparation of phosphonate esters **IVa** in which the phosphonate group is attached by means of an cyclic sulfonamide group at the 2-amino position. In this procedure, a cyclic sulfonamide **22.1**, where m and n are independently 1, 2, 3, 4, 5, or 6, and incorporating a secondary amine, is coupled, as

described in Scheme **5**, with a dialkyl carboxy-substituted phosphonate **22.2** to produce the amide **22.3**. The product is then reacted with a bromoamide **22.4** to afford the displacement product **22.5**.

Alternatively, the cyclic sulfonamide **22.1** is protected to give the analog **22.6**. Sulfonamides are protected, for example, by conversion into the N-acyloxymethyl derivatives, such as the pivalyloxymethyl derivative or the benzoyloxymethyl derivative, by reaction with the corresponding acyloxymethyl chloride in the presence of dimethylaminopyridine, as described in *Bioorg. Med. Chem. Lett.*, 1995, 5, 937, or by conversion into the carbamate derivative, for example the tert. butyl carbamate, by reaction with an alkyl, aryl or aralkyl chloroformate, in the presence of a base such as triethylamine, as described in *Tet. Lett.*, 1994, 35, 379. The protected sulfonamide is reacted with a dialkyl bromoalkyl phosphonate **22.7** to form the alkylated product **22.8**. The alkylation reaction is effected as described in Scheme **8**. The product is then deprotected to yield the sulfonamide **22.9**. Deprotection of pivalyloxymethyl amides is effected by treatment with trifluoroacetic acid; deprotection of benzyloxymethyl amides is effected by catalytic hydrogenation, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 398. Sulfonamide carbamates, for example the tert. butyl carbamate, are deprotected by treatment with trifluoroacetic acid. The sulfonamide **22.9** is then reacted with the bromoamide **22.10** to give the displacement product **22.11**.

For example, [1,2,5]thiadiazepane 1,1-dioxide **22.11A** (WO 0230930A2 p.321) is reacted in dioxane solution with equimolar amounts of a dialkyl 3-carboxypropyl phosphonate **23.12**, (Epsilon) and dicyclohexylcarbodiimide, to produce the amide **22.13**. This material is reacted in pyridine solution at reflux temperature with 2-bromo-3-methyl-4-oxo-5-triisopropylsilanyloxy-3,4-dihydro-pyrimidine-6-carboxylic acid 4-fluoro-benzylamide **22.14**, prepared by the methods described above, and copper oxide, to afford the displacement product **22.15**.

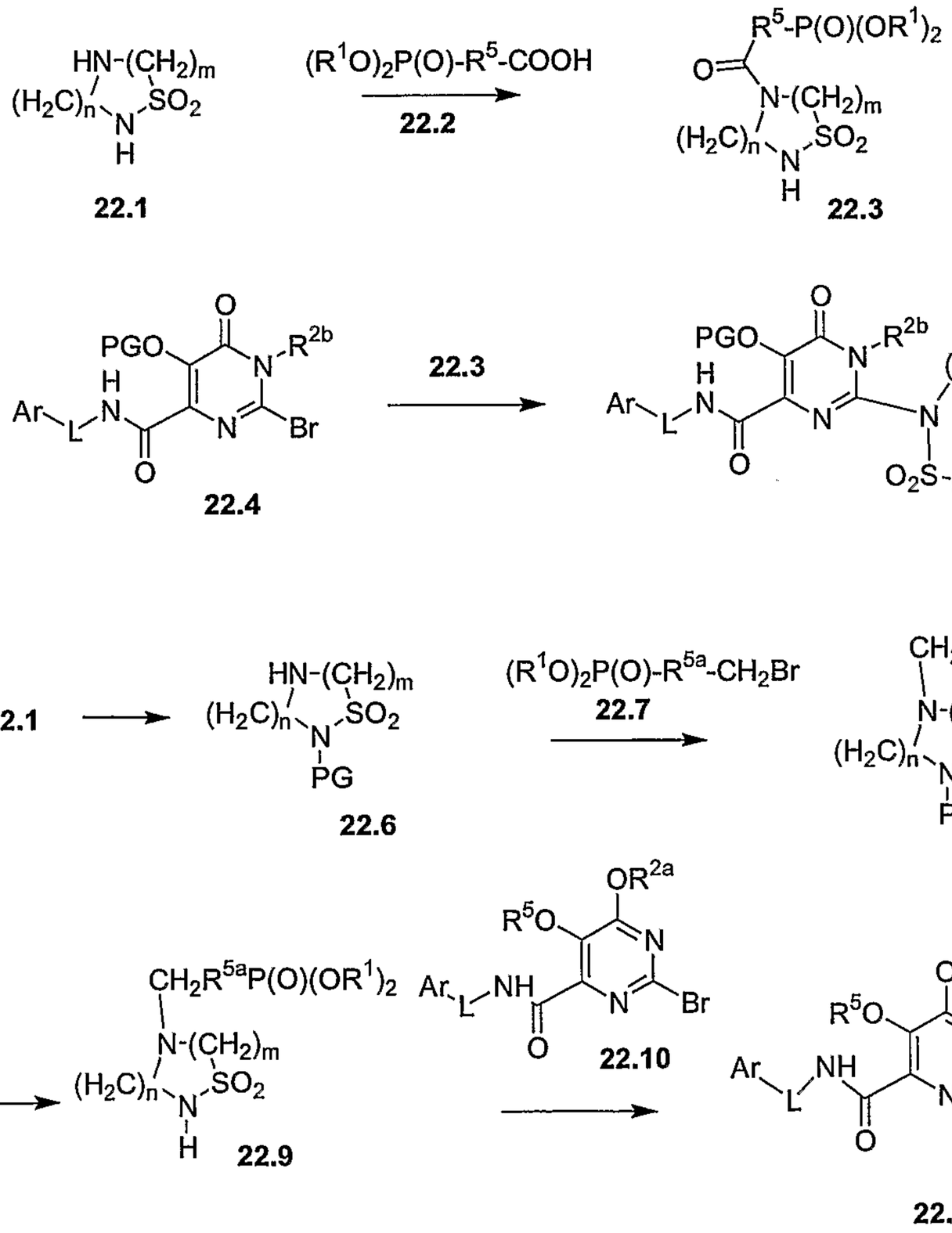
As a further example, the sulfonamide **22.11A** is reacted in dichloromethane with one molar equivalent of t-Boc anhydride, triethylamine and dimethylaminopyridine, to give 1,1-dioxo-[1,2,5]thiadiazepane-2-carboxylic acid tert-7butyl ester **22.16**. The product is then reacted at ambient temperature in dimethylformamide solution with a dialkyl 4-bromomethyl benzyl phosphonate **22.17**,

(*Tetrahedron*, 1998, 54, 9341) and potassium carbonate, to yield the alkylation product **22.18**. The BOC group is removed by treatment with trifluoroacetic acid to give the sulfonamide **22.19**, and this material is reacted, as described above, with 2-bromo-3,4-dihydroxy-pyrimidine-6-carboxylic acid 3-fluoro-benzylamide **22.20**, prepared by the methods described above, to afford the displacement product **22.21**.

Using the above procedures, but employing, in place of the sulfonamide **22.11A**, different sulfonamides **22.1**, and/or different carboxylic acids **22.2** or alkyl bromides **22.7**, and/or different bromides **22.4**, the corresponding products **22.5** and **22.11** are obtained.

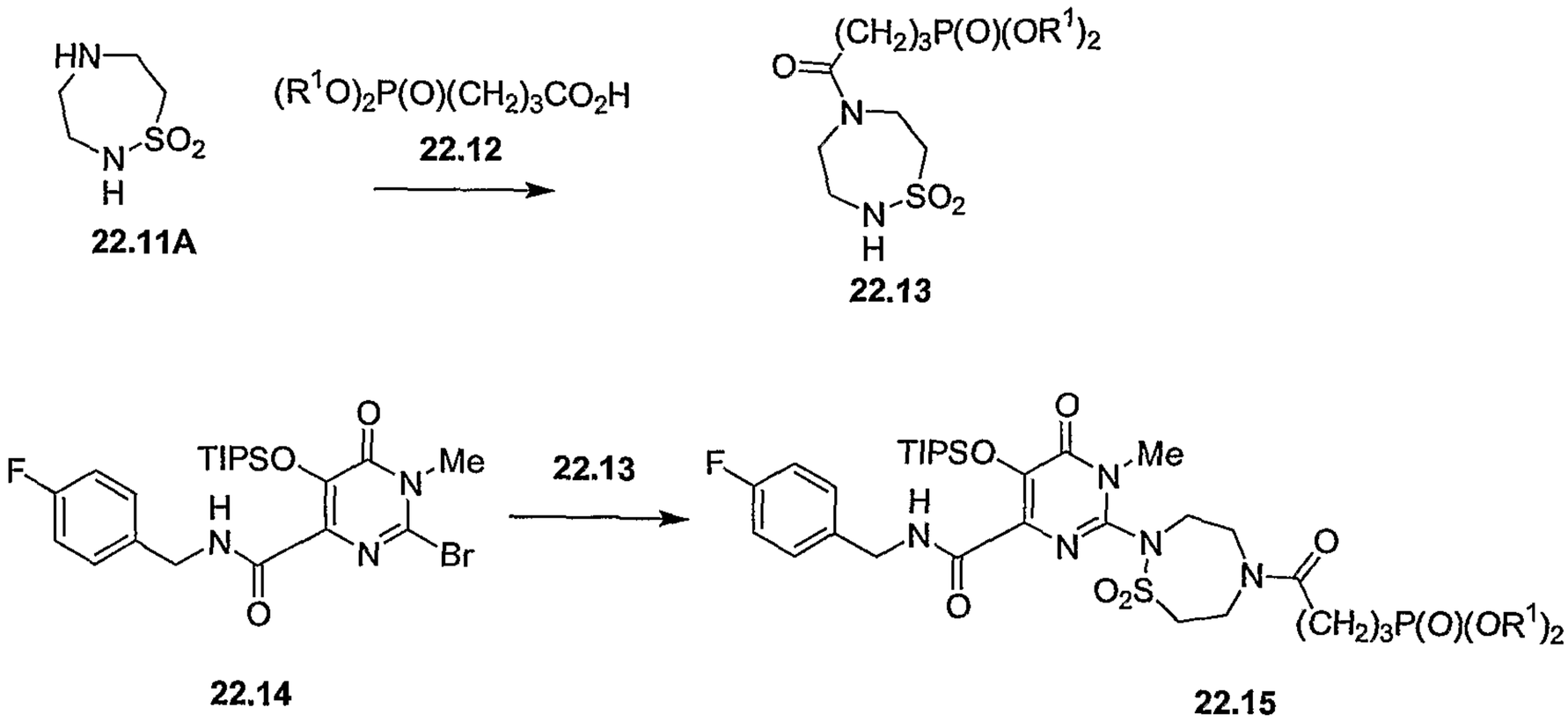
Scheme 22.

Method

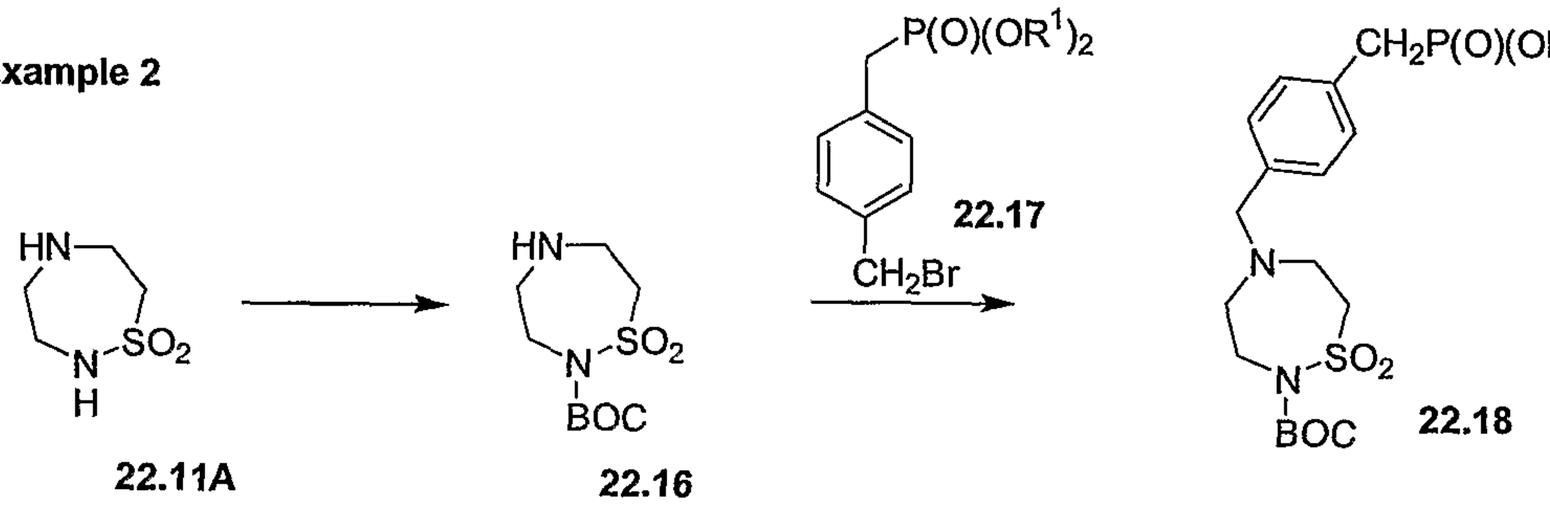


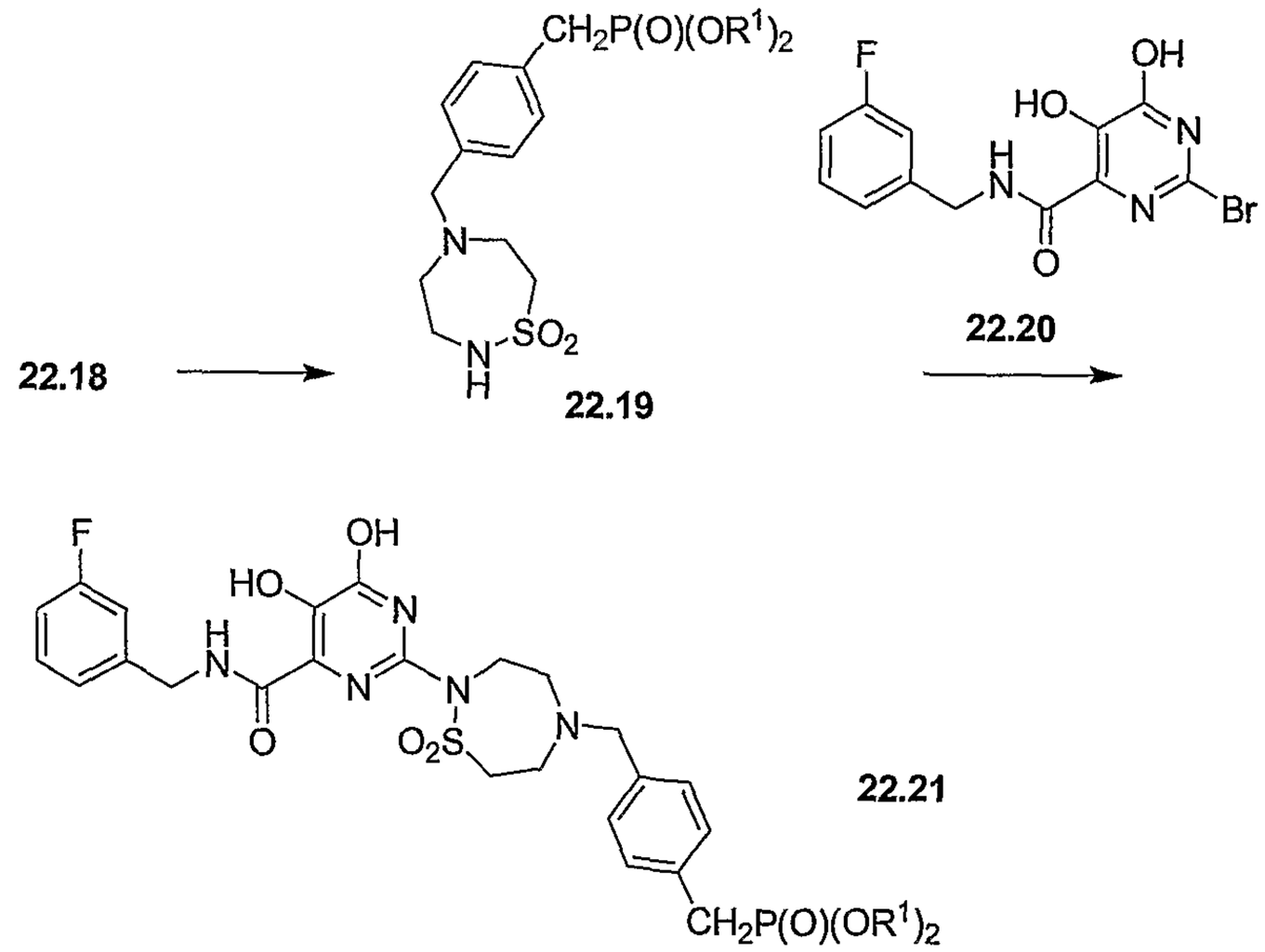
Scheme 22.

Example 1



Example 2





Scheme **23** depicts the preparation of phosphonates **Va** in which the phosphonate group is attached by means of an aryl or heterocycle group. In this

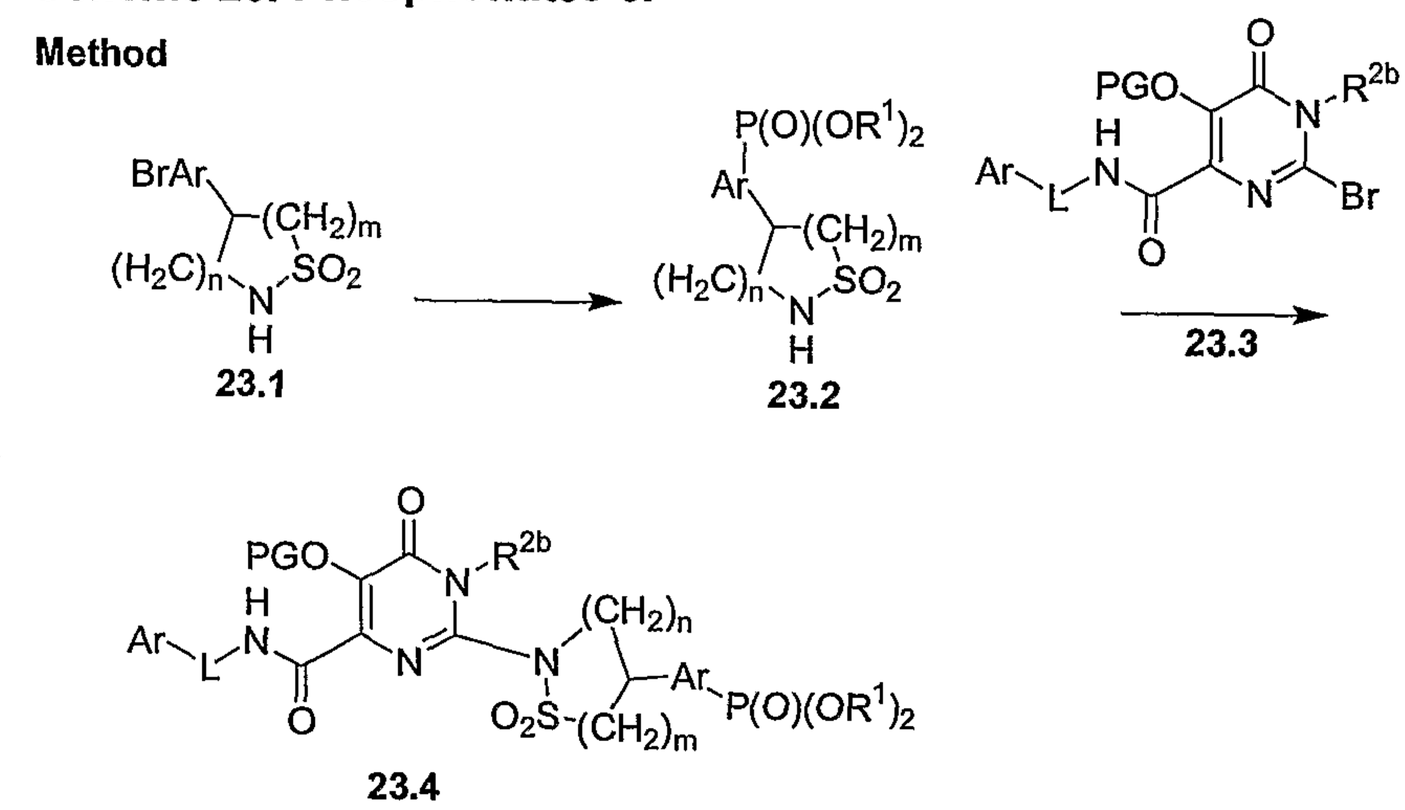
procedure, a bromoaryl-substituted cyclic sulfonamide, prepared as described in *J. Org. Chem.*, (1991), 56, 3549, from the corresponding bromoaryl or bromoheterocycle acetic acid and a vinyl sulfonic ester, is coupled, as described in Scheme **3**, with a dialkyl phosphite to afford the phosphonate **23.2**. The product is then reacted, as described above, with a bromoamide **23.3** to yield the displacement product **23.4**.

For example, 4-(4-bromo-phenyl)-[1,2]thiazinane 1,1-dioxide **23.5** (*J. Org. Chem.*, 1991, 56:3549) is reacted in dimethylformamide solution with a dialkyl phosphite **23.6** and tetrakis(triphenylphosphine)palladium(0), to give the phosphonate **23.7**. The product is then reacted with 2-bromo-3-(2-methoxy-ethyl)-4-oxo-5-triisopropylsilanyloxy-3,4-dihydro-pyrimidine-6-carboxylic acid (5-fluoro-indan-1-yl)-amide **23.8**, prepared by the methods described above, to give the phosphonate **23.9**.

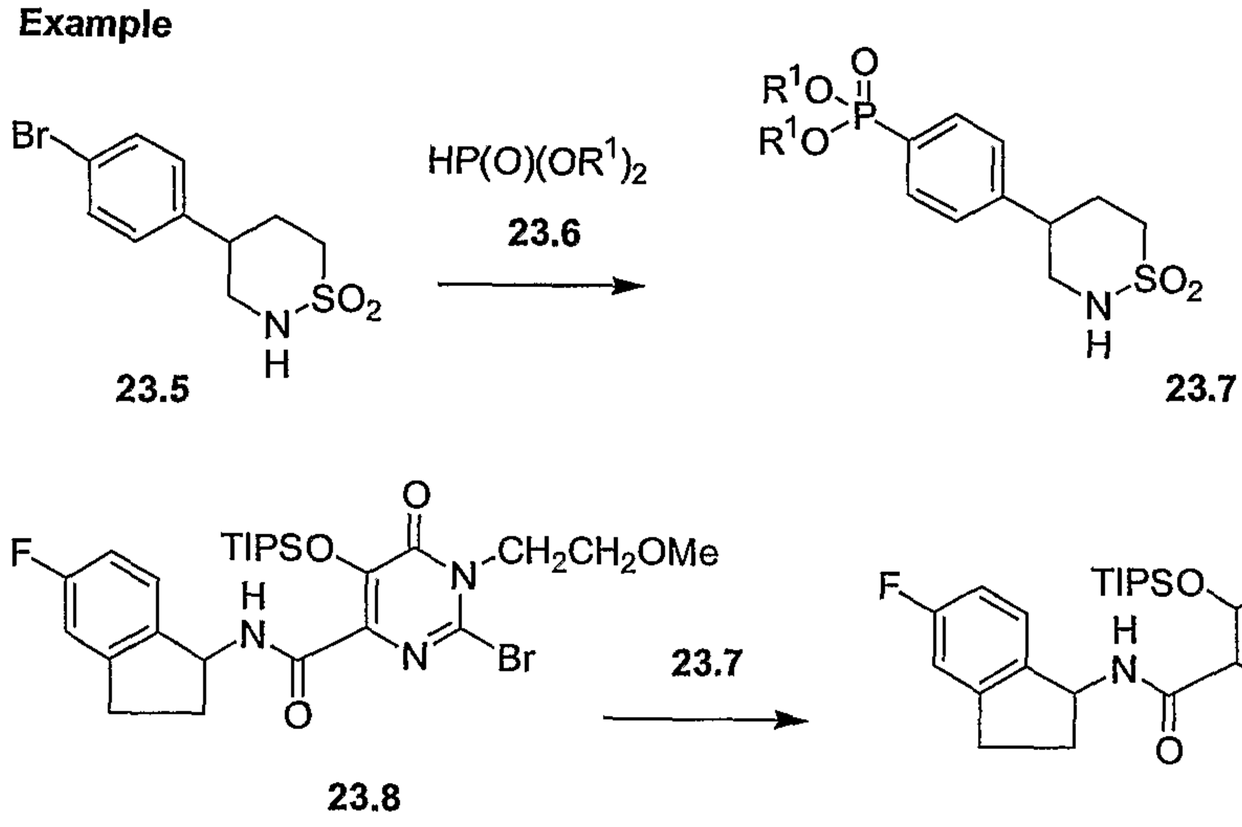
Using the above procedures, but employing, in place of the sulfonamide **23.5**, different sulfonamides **23.1**, and/or different bromo compounds **23.3**, the corresponding products **23.4** are obtained.

Scheme 23. Phosphonates 6.

Method



Example



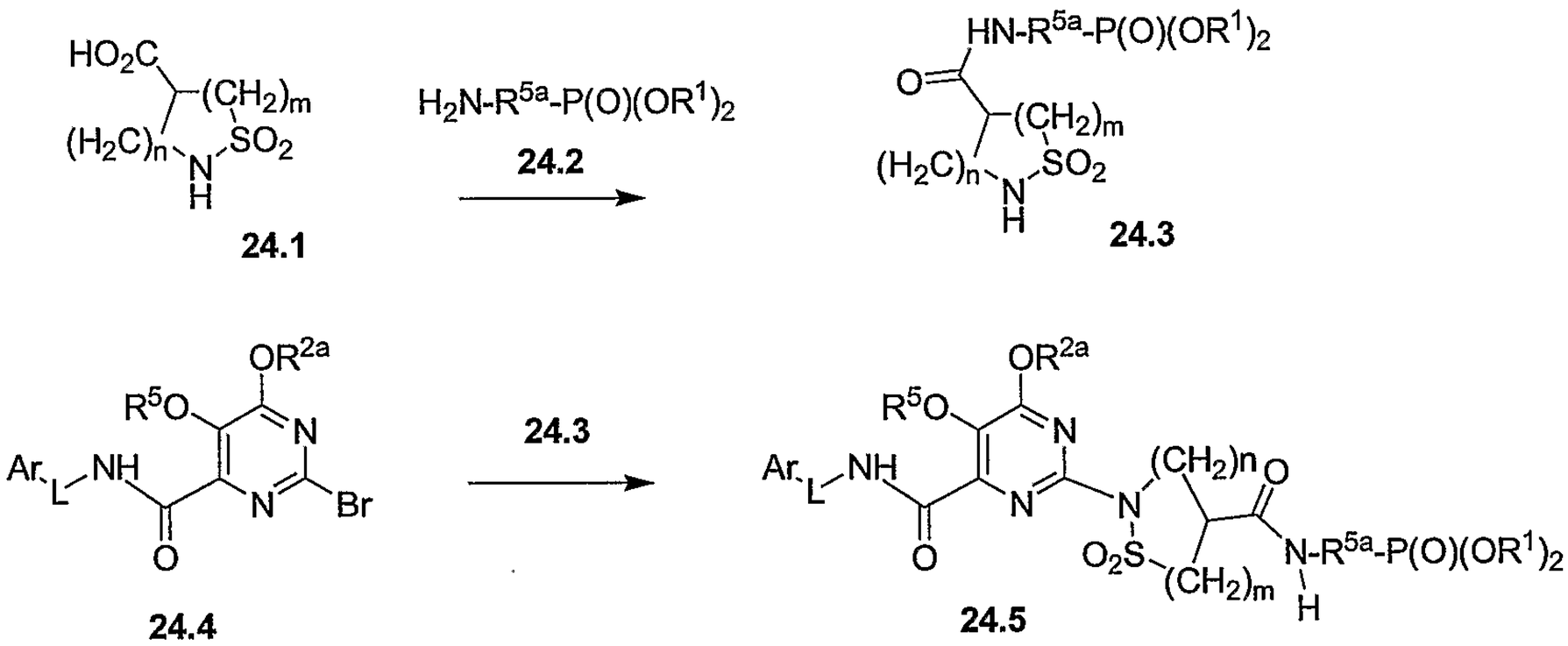
Scheme **24** depicts the preparation of phosphonates **IVa** in which the phosphonate group is attached by means of an amide linkage. In this procedure, a carboxy-substituted cyclic sulfonamide **24.1** is coupled with an amino-substituted dialkyl phosphonate **24.2**, as described in Scheme **5**, to give the amide **24.3**. The product is then reacted with the bromoamide **24.4** to afford the displacement product **24.5**.

For example, 1,1-dioxo-[1,2]thiazinane-3-carboxylic acid **24.6** (*Izvest. Akad. Nauk. SSSR Ser. Khim.*, 1964, 9, 1615) is reacted in dimethylformamide solution with equimolar amounts of an amino-substituted butyl phosphonate **24.7** (Acros) and dicyclohexylcarbodiimide, to afford the amide **24.8**. The latter compound is then condensed with 2-bromo-5,6,7,8,8a,10a-hexahydro-9,10-dioxa-1,3-diaza-anthracene-6-carboxylic acid [1-(3-chloro-4-fluoro-phenyl)-ethyl]-amide **24.9**, prepared by the methods described above, to give the product **24.10**.

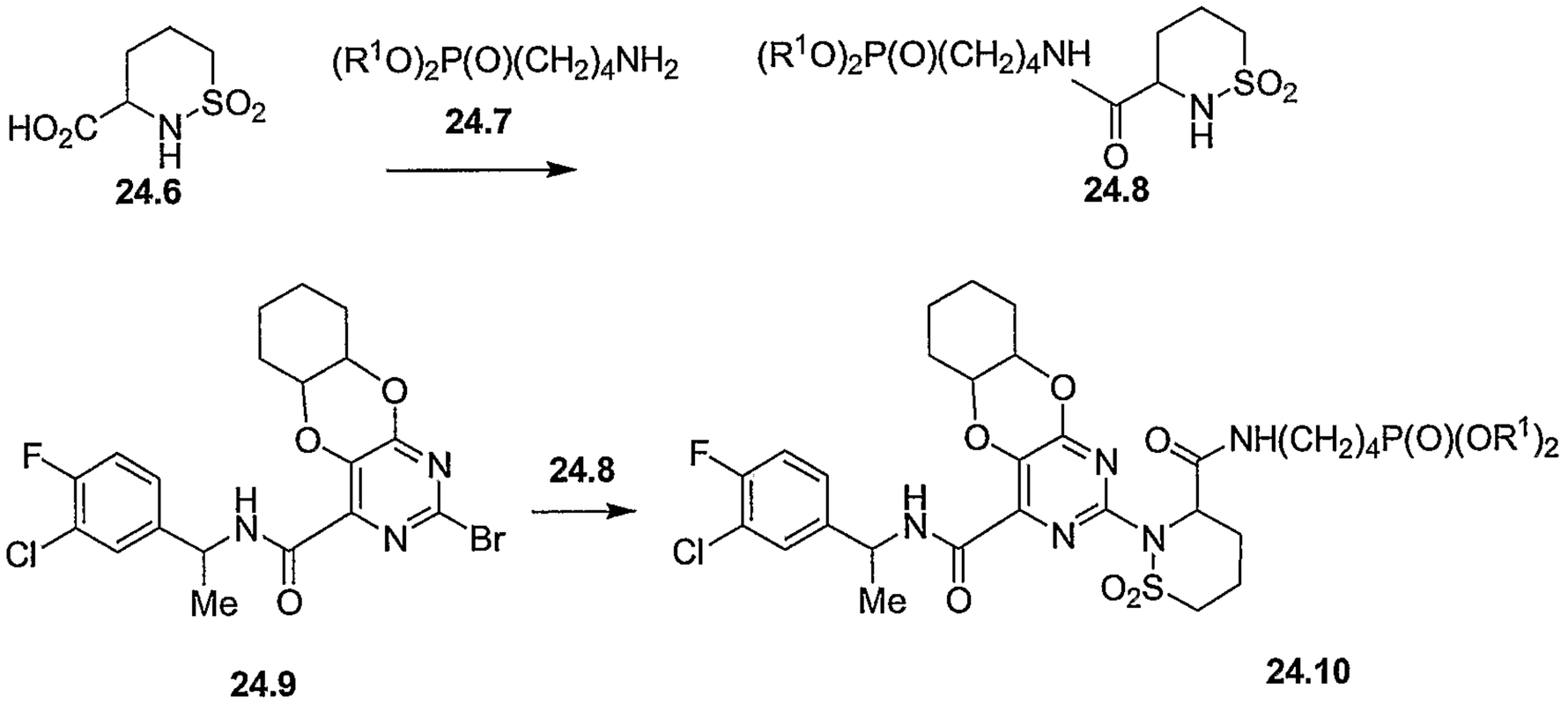
Using the above procedures, but employing, in place of the sulfonamide **24.6**, different sulfonamides **24.1**, and/or different bromo compounds **24.4**, the corresponding products **24.5** are obtained.

Scheme 24.

Method



Example



Schemes **25-27** illustrate methods for the preparation of the phosphonate esters **IVa** and **Va** in which the phosphonate is attached by means of a carbon link or a variable carbon chain incorporating a heteroatom. In these procedures, for example, a tolyl-substituted pyrimidine **25.1** is reacted with a free radical brominating agent such as N-bromosuccinimide to prepare the bromomethyl derivative **25.3**. The benzylic bromination reaction is performed at reflux temperature in an inert organic solvent such as hexachloroethane or ethyl acetate, optionally in the presence of an initiator

such as dibenzoyl peroxide. The bromomethyl compound **25.3** is then reacted with a trialkyl phosphite in an Arbuzov reaction, as described in Scheme **19**, to give, after deprotection of the phenolic hydroxyl group, the phosphonate **25.4**.

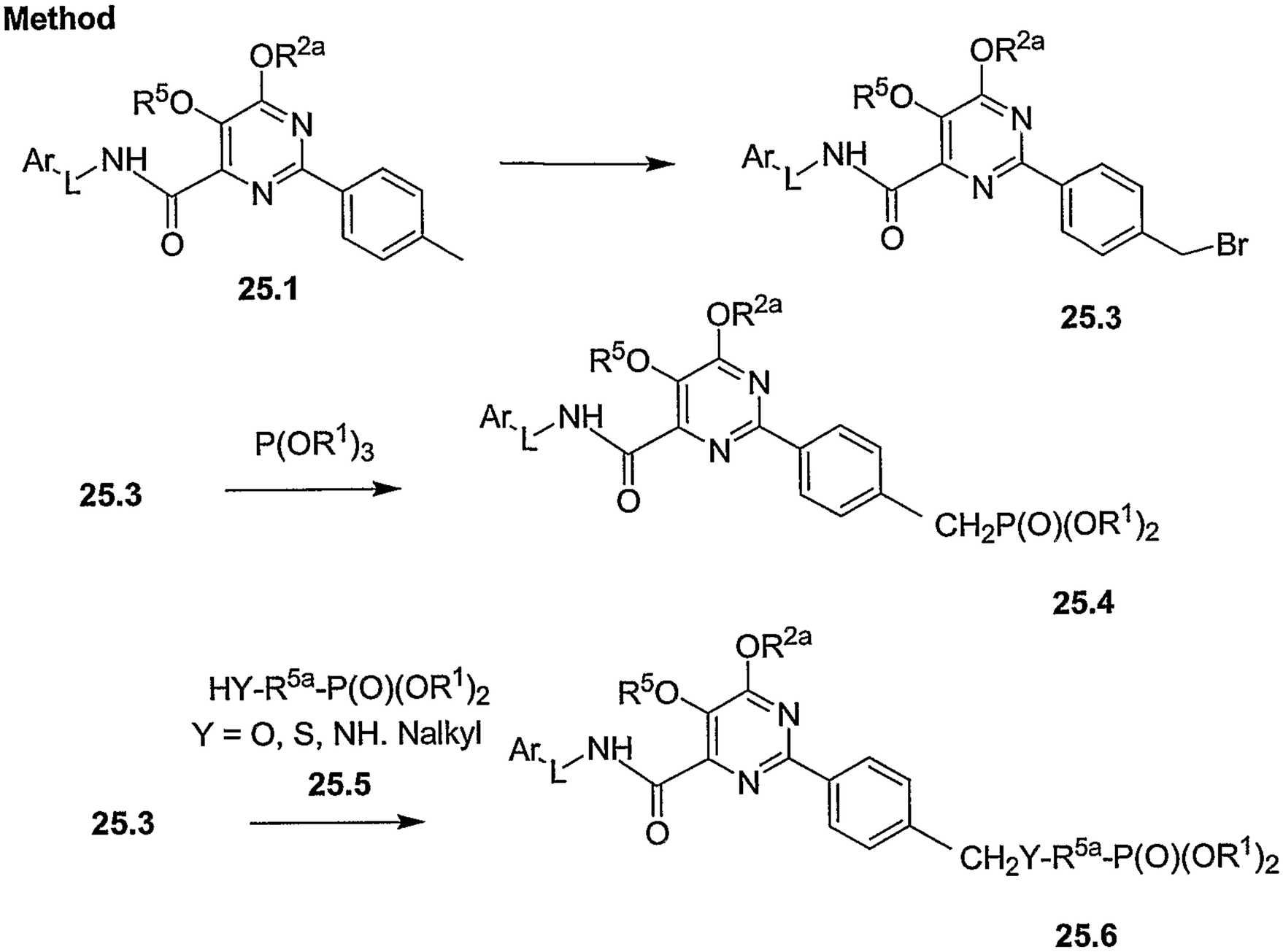
Alternatively, the benzylic bromide **25.3** is reacted with a dialkyl hydroxy, mercapto or amino-substituted phosphonate **25.5**, to afford, after deprotection of the phenolic hydroxyl group, the displacement product **25.6**. The displacement reaction is effected at from ambient temperature to about 100 °C, in a polar organic solvent such as dimethylformamide or DMPU, in the presence of a suitable base such as sodium hydride or lithium hexamethyldisilazide, for instances in which Y is O, or cesium carbonate or triethylamine for instances in which Y is S or N.

For example 6-p-tolyl-2,3,3a,9a-tetrahydro-1H-4,9-dioxa-5,7-diaza-cyclopenta[b]naphthalene-8-carboxylic acid 4-fluoro-benzylamide **25.8** is reacted with one molar equivalent of N-bromosuccinimide in ethyl acetate at reflux, to afford the bromomethyl analog **25.9**. This product is reacted with a dialkyl hydroxyethyl phosphonate **25.11** (Epsilon) and sodium hydride in dimethylformamide at 80°, to yield, after desilylation, the phosphonate **25.12**. Alternatively, the bromomethyl compound **25.9** is reacted at 120 °C with a trialkyl phosphite, to obtain, after desilylation, the phosphonate **25.10**.

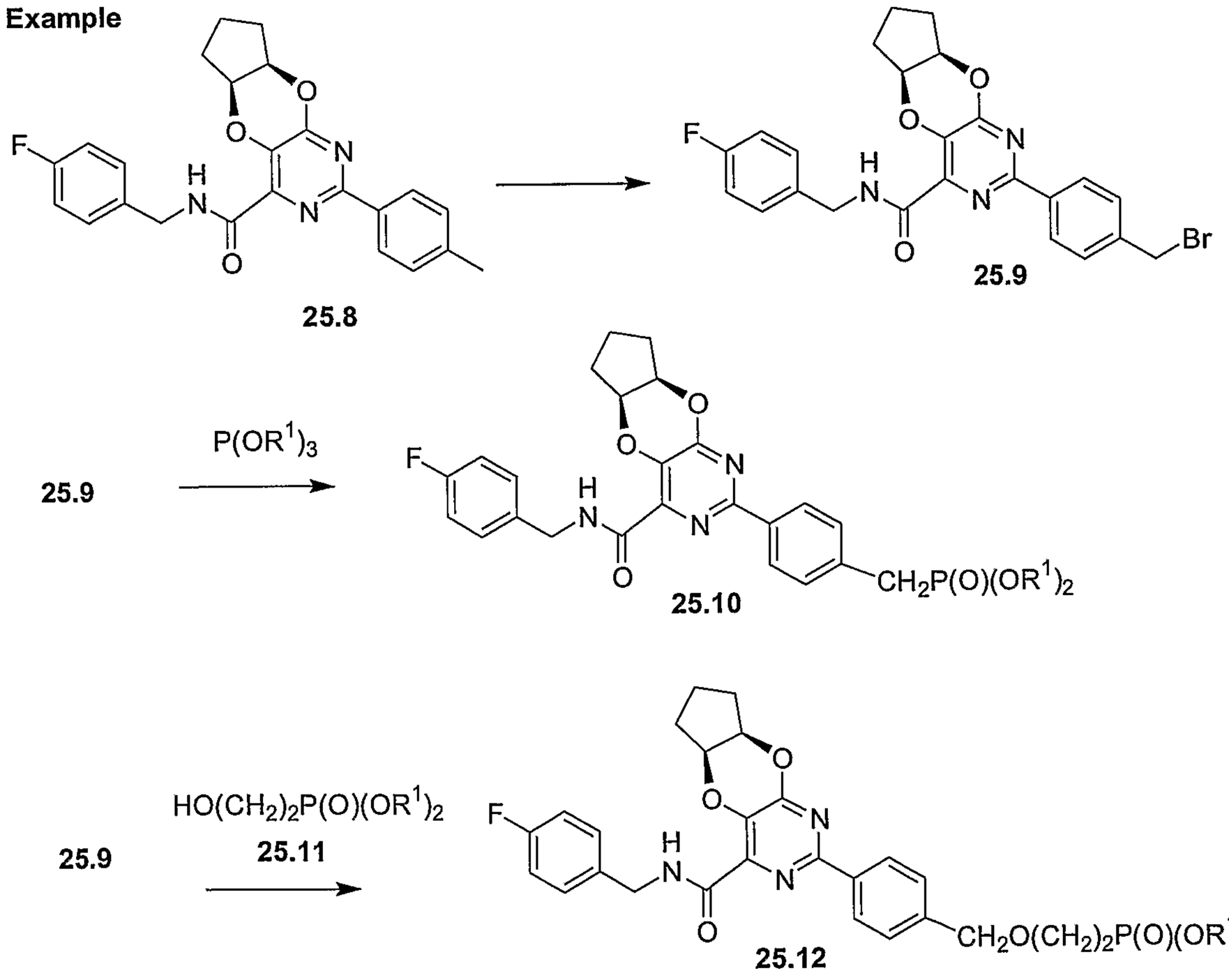
Using the above procedures, but employing, in place of the anhydride **25.7**, different anhydrides **25.1**, and/or different phosphonates **25.5**, the corresponding products **25.4** and **25.6** are obtained.

Scheme 25.

Method



Example



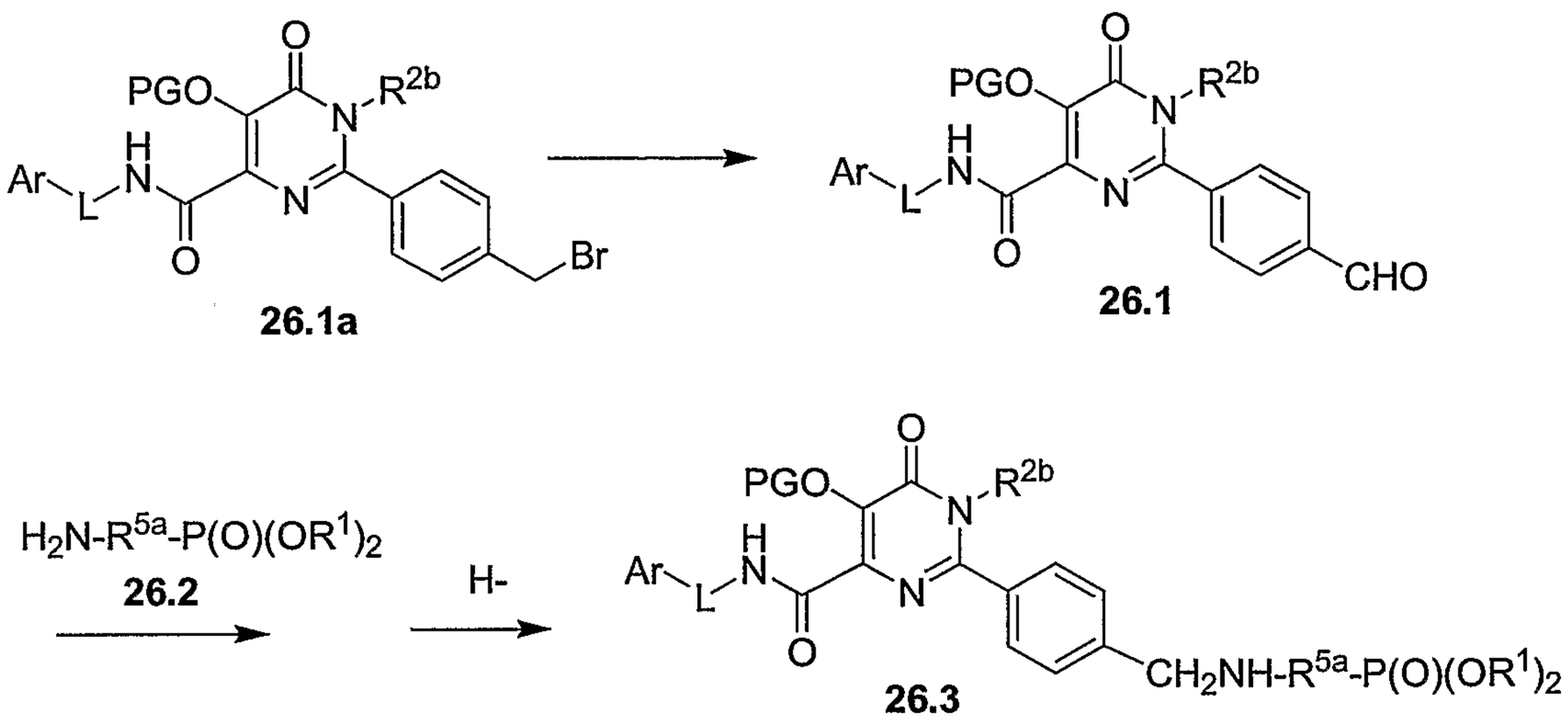
Scheme **26** illustrates the preparation of phosphonate esters **Va** in which the phosphonate is attached by means of an aminomethyl linkage through the 2-position. In this procedure, a bromomethyl-substituted bicyclic amide **26.1a**, prepared as described in Scheme **25**, is oxidized to the corresponding aldehyde **26.1**. The oxidation of halomethyl compounds to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 599ff. The transformation is effected by treatment with dimethylsulfoxide and base, optionally in the presence of a silver salt, or by reaction with trimethylamine N-oxide or hexamethylene tetramine. The aldehyde **26.1** is then reacted with a dialkyl amino-substituted phosphonate **26.2** in a reductive amination reaction (H- = reducing agent), as described in Scheme **9**, to yield, after deprotection of the phenolic hydroxyl group, the aminomethyl product **26.3**.

For example, 5-benzyloxymethoxy-2-(4-bromomethyl-phenyl)-4-oxo-3,4-dihydro-pyrimidine-6-carboxylic acid 3,5-dichloro-benzylamide **26.4**, prepared from the anhydride **25.7**, using the methods described in Scheme **25**, is reacted with dimethylsulfoxide and 2,4,6-collidine at 90°, as described in *J. Org. Chem.* (1986) 51:1264, , to afford the aldehyde **26.5**. The product is then reacted with one molar equivalent of a dialkyl aminoethyl phosphonate **26.6** (Epsilon) and sodium triacetoxyborohydride to produce, after desilylation, the phosphonate **26.7**.

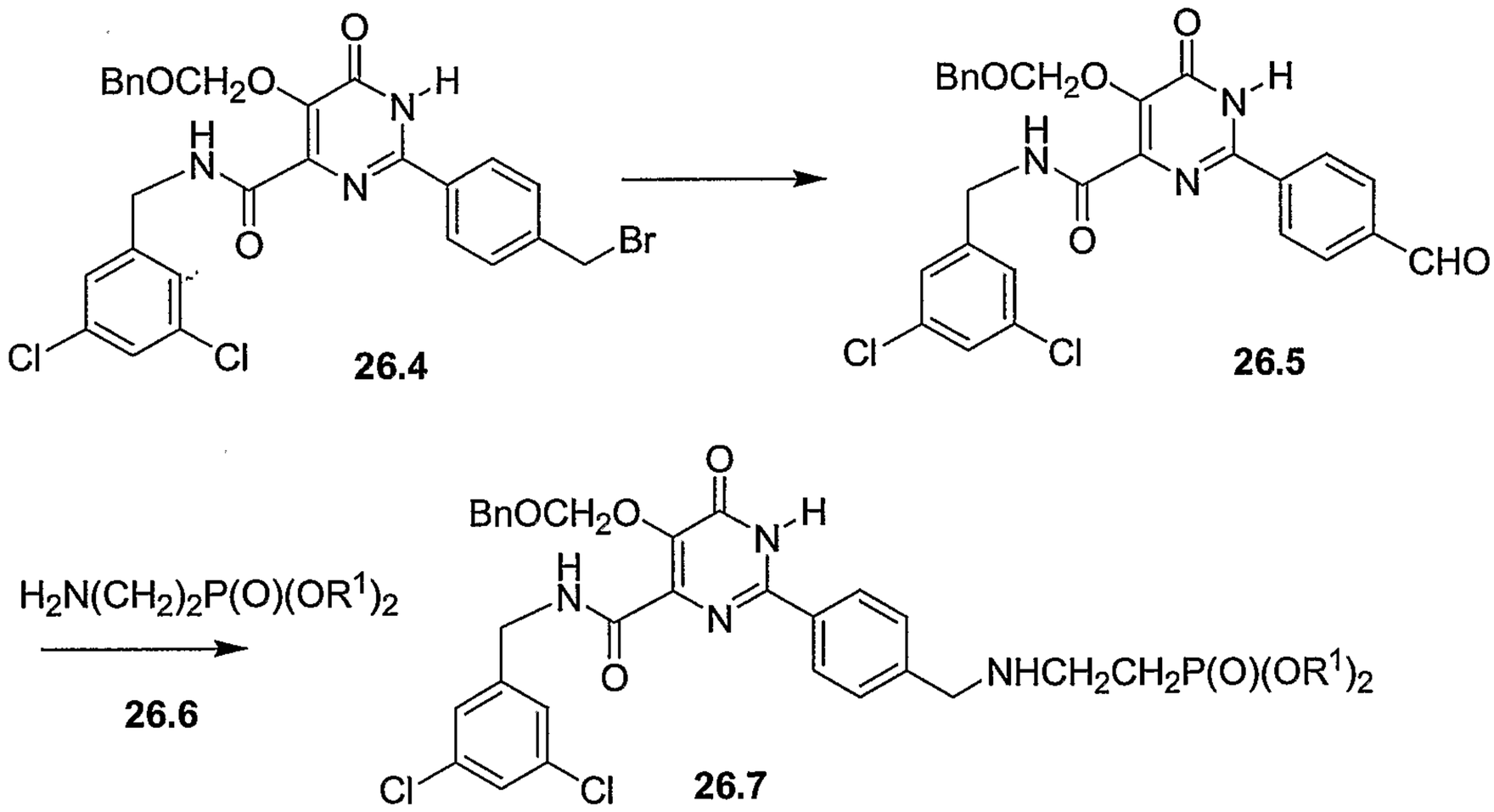
Using the above procedures, but employing, in place of the bromomethyl compound **26.4**, different bromomethyl compounds **25.3**, and/or different phosphonates **26.2**, the corresponding products **26.3** are obtained.

Scheme 26.

Method



Example



A reductive amination procedure can also be employed to attach a phosphonate ester through an amino linker. 1-Methyl-6-oxo-2-(2-oxo-ethyl)-5-triisopropylsilanyloxy-1,6-dihydro-pyrimidine-4-carboxylic acid 4-fluoro-benzylamide **26.8**, prepared by the method of WO 03/03577 at page 96 can be reductively aminated by amino phosphonate reagents, **26.9, 26.10,** and **26.11** to give **26.12**, **26.13**, and **26.14**, respectively, after desilylation with tetrabutylammonium fluoride (TBAF) (Scheme **26a**). As with the previous examples herein, R^1 may be further converted to other phosphorus substituents, e.g. X and Y. Embodiments of

phosphonate substituent X include OPh, OAr, OCH_2CF_3, and NHR, where R is the residue of an amino acid. Embodiments of phosphonate substituent Y include a lactate ester or a phosphonamidate.

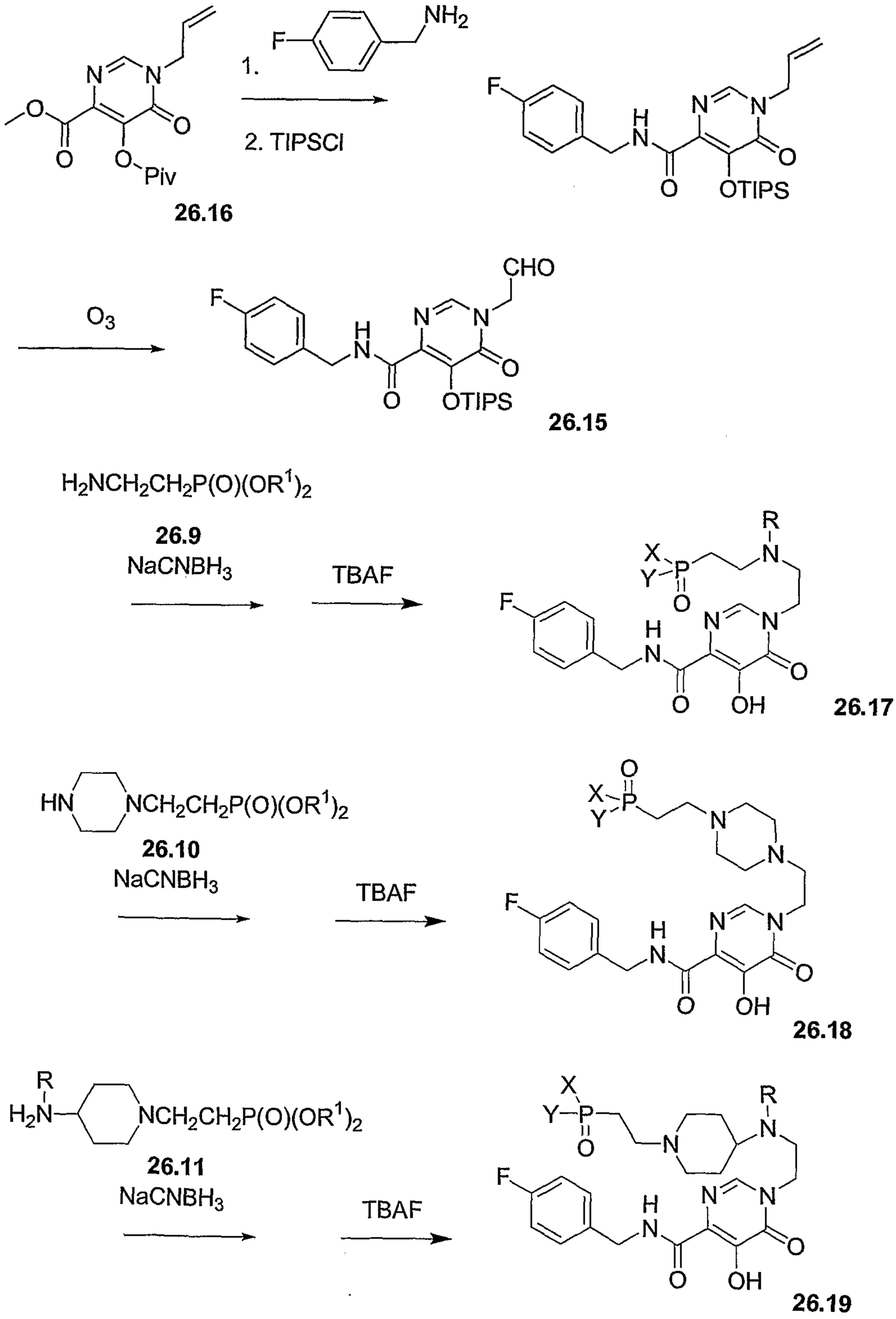
Scheme 26a.

Example

6-Oxo-1-(2-oxo-ethyl)-5-triisopropylsilanyloxy-1,6-dihydro-pyrimidine-4-carboxylic acid 4-fluoro-benzylamide **26.15**, prepared from 1-allyl-5-(2,2-dimethyl-propionyloxy)-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid methyl ester **26.16** (piv = pivalate, $(CH_3)_3CC(O)$-) by the method of WO 03/03577 at page 110 can be reductively aminated by amino phosphonate reagents, **26.9, 26.10,** and **26.11** to give **26.17**, **26.18**, and **26.19**, respectively after desilylation with TBAF (Scheme **26b**).

Scheme 26b.

Example



Scheme **27** illustrates the preparation of phosphonate esters **IVa** in which the phosphonate is attached by coupling a carboxylic acid with an amino phosphonate

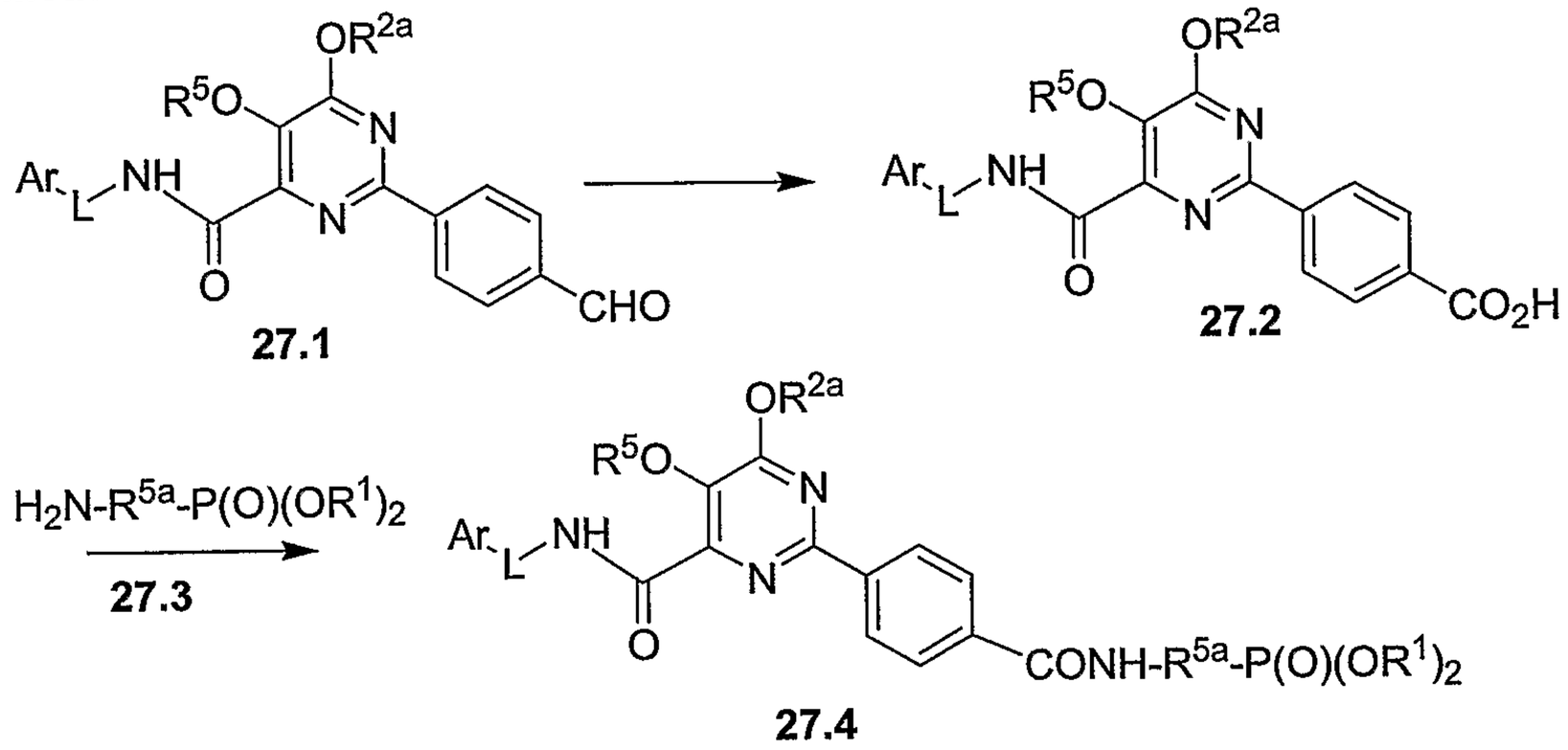
reagent to form an amide linkage. In this procedure, an aldehyde **27.1**, or **26.1** from Scheme **26**, is oxidized to the corresponding carboxylic acid **27.2**. The conversion of aldehydes to the corresponding carboxylic acids is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 838. The reaction is effected by the use of various oxidizing agents such as, for example, potassium permanganate, ruthenium tetroxide, silver oxide or sodium chlorite. The resultant carboxylic acid **27.2** is then coupled, as described in Scheme **5**, with a dialkyl amino-substituted phosphonate **27.3**, to yield the amide **27.4**.

For example, 2-(4-formyl-phenyl)-4-methoxy-5-triisopropylsilanyloxy-pyrimidine-6-carboxylic acid (cyclohex-3-enylmethyl)-amide **27.5** is reacted with silver oxide in aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 4, 919, 1963, to afford the carboxylic acid **27.6**. The latter compound is then reacted in dioxane solution at ambient temperature with equimolar amounts of a dialkyl aminomethyl phosphonate **27.7** (Interchim) and dicyclohexylcarbodiimide, to give, after desilylation, the amide phosphonate **27.8**.

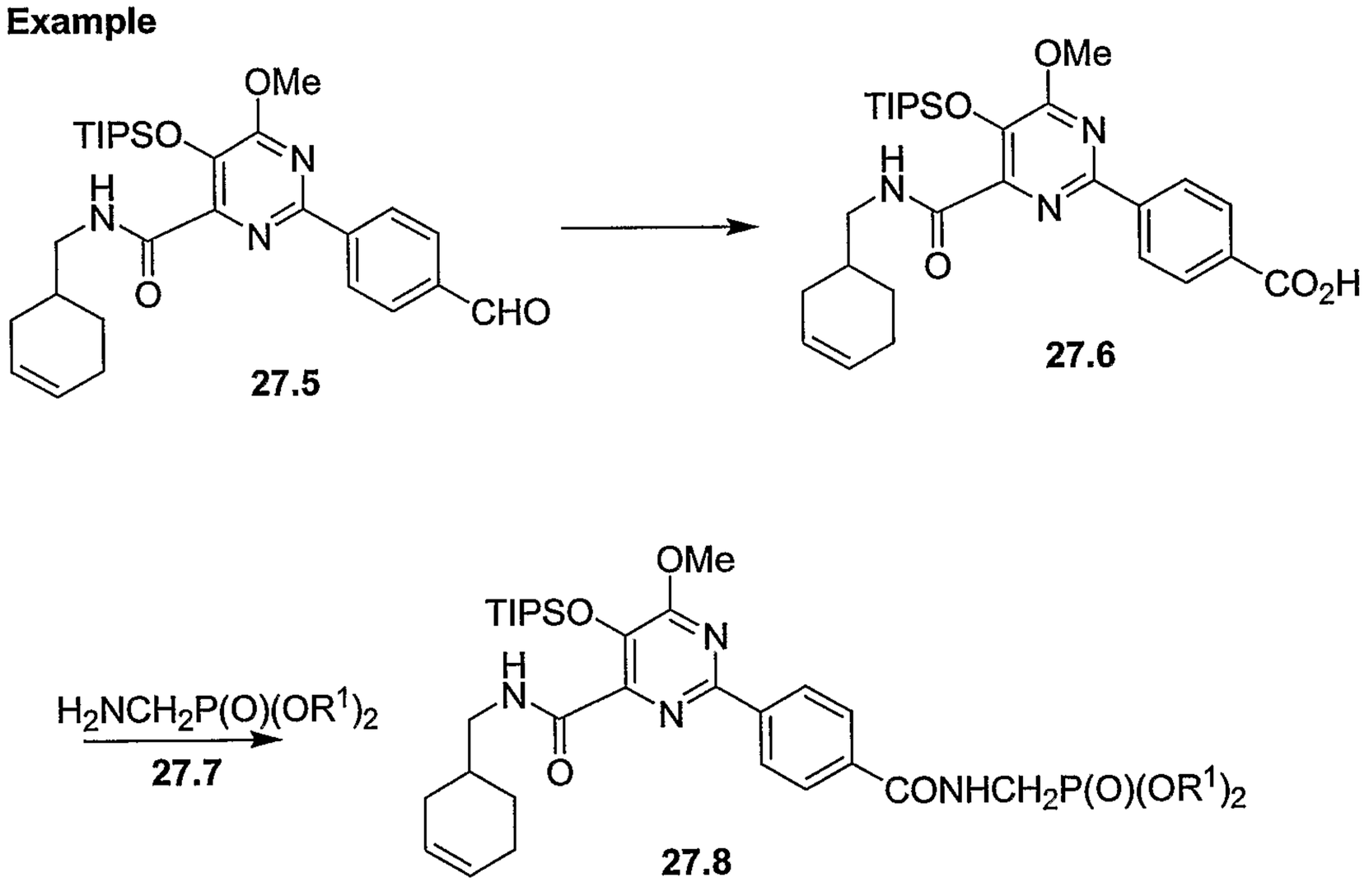
Using the above procedures, but employing, in place of the aldehyde **27.5**, different aldehydes **26.1**, and/or different phosphonates **27.3**, the corresponding amides **27.4** are obtained. For example, 5,6-dihydroxy-pyrimidine-2,4-dicarboxylic acid 4-methyl ester **27.9**, prepared by the method of WO 03/035077, p.85, may be converted to the 4-fluorobenzyl amide **27.10** with 4-fluorobenzylamine (Scheme **27a**), and the carboxylic acid group coupled with a plethora of amines, including **26.9**, **26.10**, and **26.11** to give **27.11**, **27.12**, and **27.13**, respectively (Scheme **27b**).

Scheme 27.

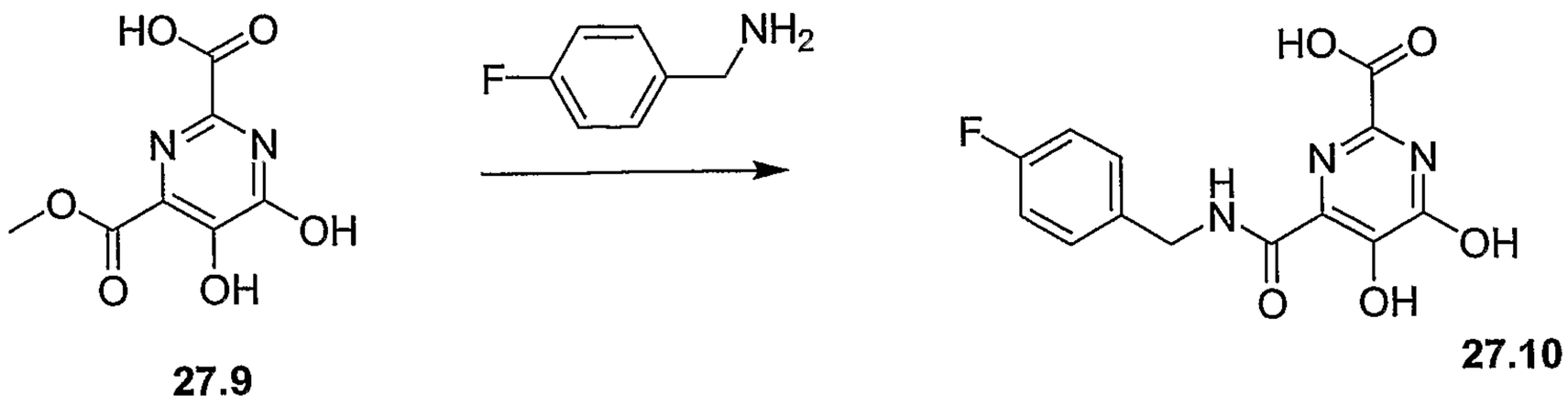
Method



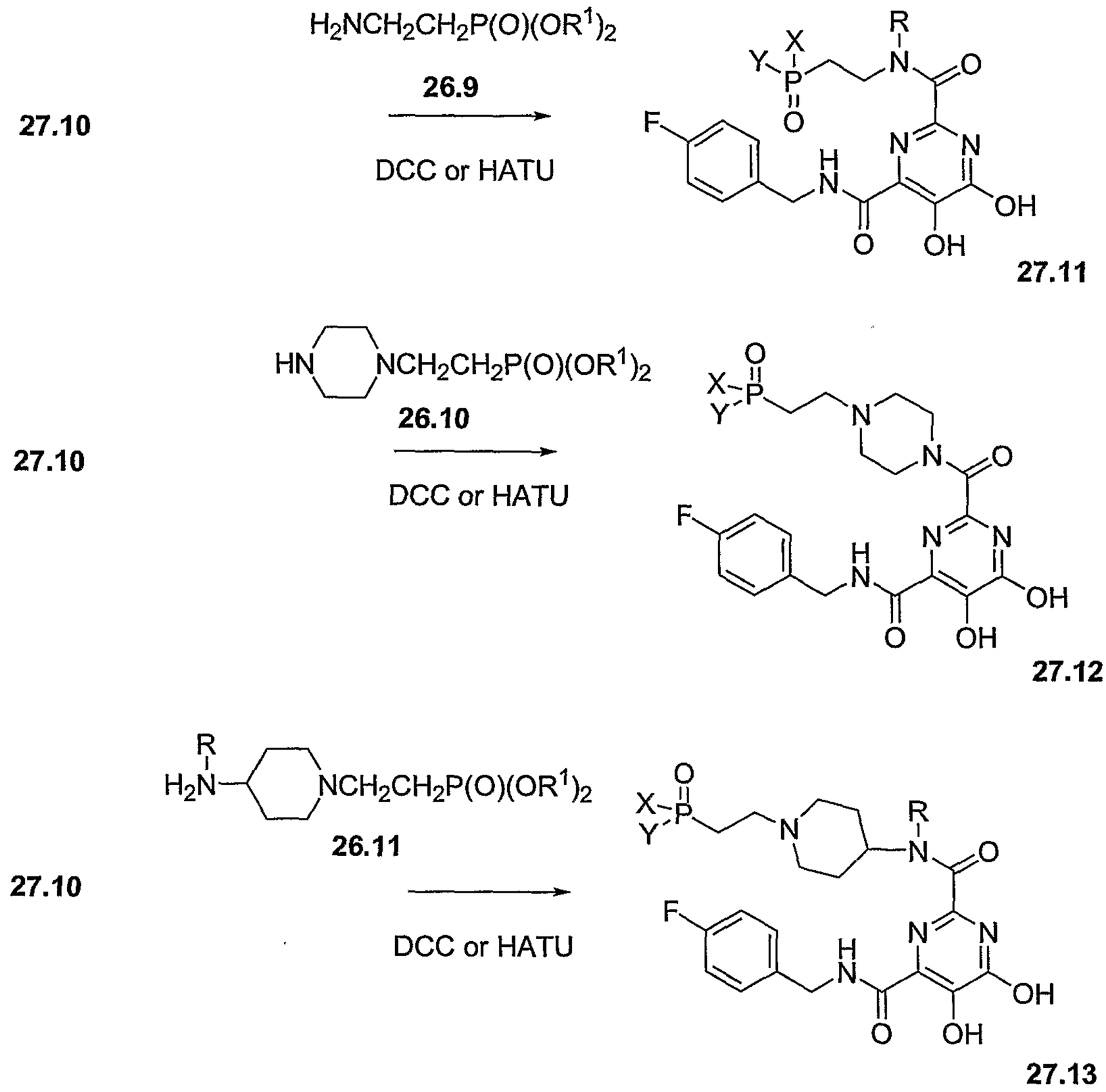
Example



Scheme 27a.



Scheme 27b.



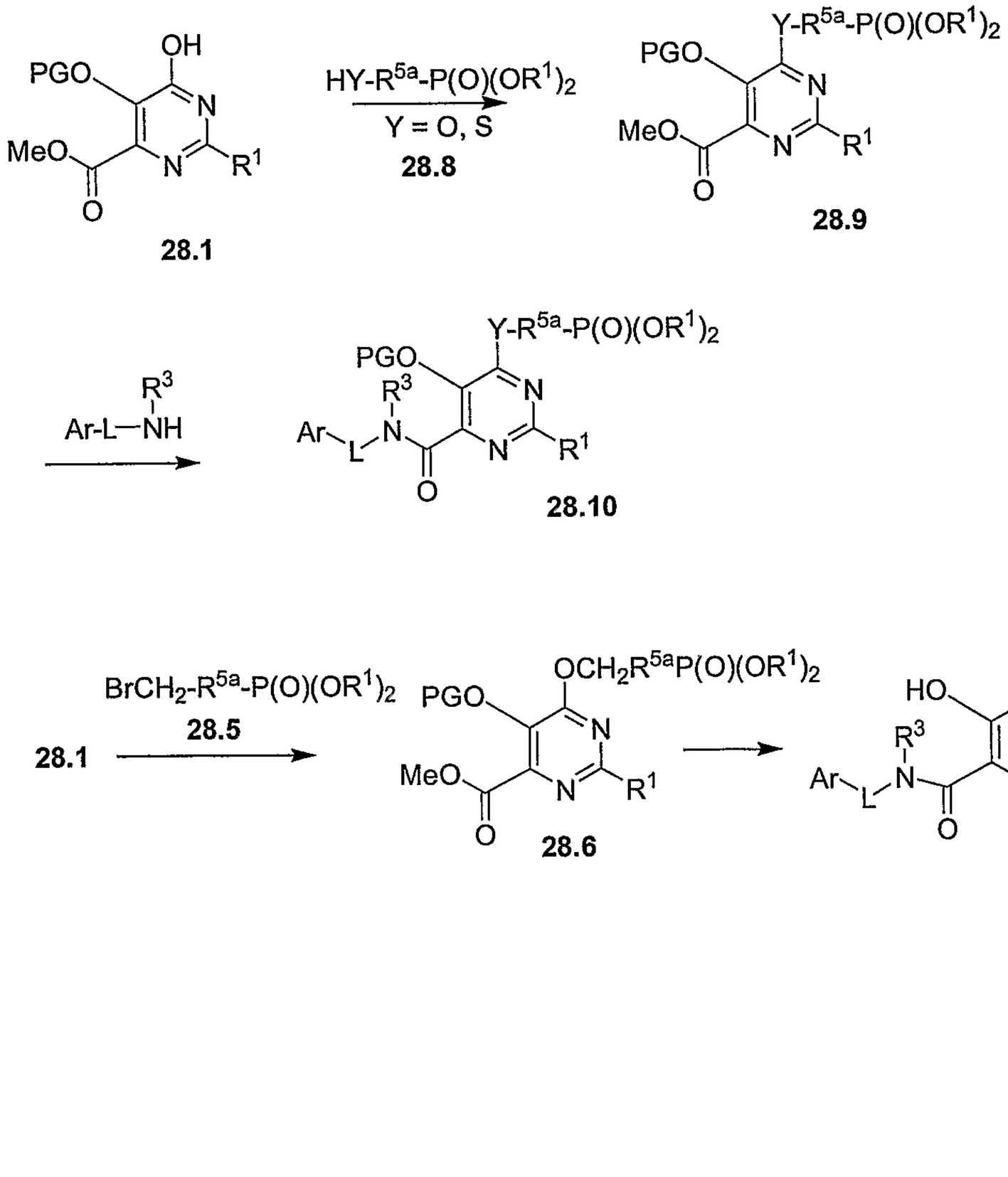
Scheme **28** illustrates the preparation of phosphonate esters **IVb** in which the phosphonate is attached by means of a heteroatom O or S and a variable carbon link at the 4-position. In this procedure, the 5-hydroxyl protected methyl ester **28.1** is subjected to a Mitsunobu reaction, as described in Scheme **7**, with a dialkyl hydroxy or mercapto-substituted phosphonate **28.8**, to produce the ether or thioether phosphonate **28.9**. This compound is then reacted, as described in Scheme **3**, with the amine Ar-L-NR^3H, to give amide **28.10**. Alternatively, **28.1** is reacted with a dialkyl bromoalkyl-substituted phosphonate **28.5**, as described in Scheme **6**, to yield the ether **28.6**. The latter compound is then transformed, as described above, into the amide **28.7**.

In other embodiments, Scheme **28a** shows 5-hydroxy-3-methyl-4-oxo-2-p-tolyl-1,6-dihydro-pyrimidine-6-carboxylic acid benzylamide **28.11** reacting with a

dialkyl 2-mercaptoethyl phosphonate **28.18** (*Zh. Obschei. Khim.*, (1973), 43, 2364), diethylazodicarboxylate and triphenylphosphine to give thioether **28.12.** 3-Ethyl-5-hydroxy-4-oxo-2-p-tolyl-3,4-dihydro-pyrimidine-6-carboxylic acid [1-(4-fluoro-phenyl)-cyclopropyl]-amide **28.13** is reacted with a dialkyl bromomethyl phosphonate **28.15** (Lancaster) and potassium carbonate, to produce the phosphonate **28.16**. 5-Hydroxy-4-oxo-3-propyl-2-p-tolyl-3,4-dihydro-pyrimidine-6-carboxylic acid (5-sulfamoyl-naphthalen-2-ylmethyl)-amide **28.17** is alkylated with 2-chloroethyl dialkylphosphonate reagent **28.19** to give phosphonate pyrimidinone **28.20**.

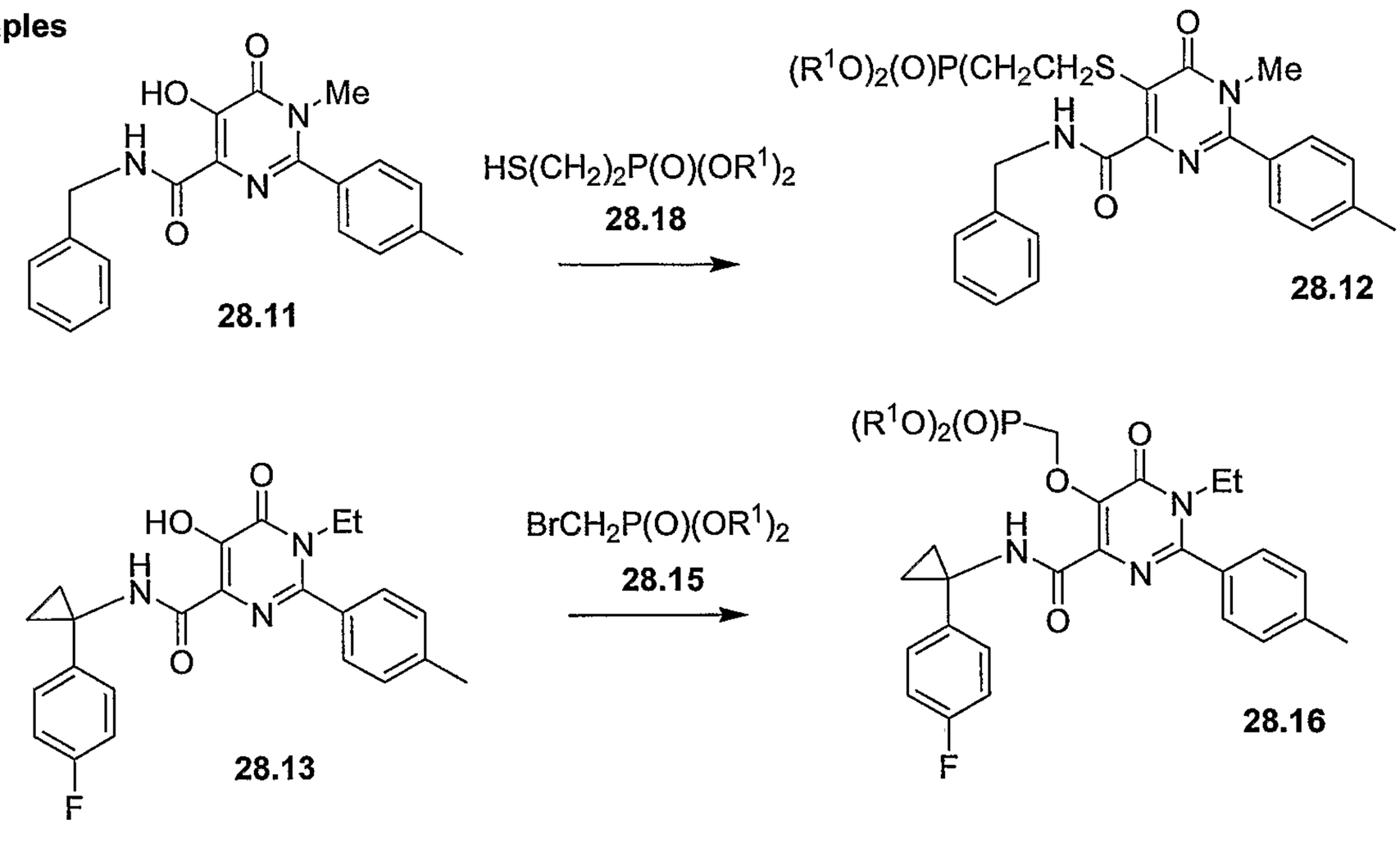
Scheme 28.

Method



Scheme 28a.

Examples



Scheme **29** illustrates the preparation of phosphonate esters **IVa** in which the phosphonate is attached either directly, or by means of a saturated or unsaturated carbon chain at the 2-position. In this procedure, a bromo-substituted anhydride **29.1** is converted, as described above, into the phenol-protected amide **29.2**. The product is then subjected to a Heck coupling reaction, in the presence of a palladium (0) catalyst, as described in Scheme **4**, with a dialkyl alkenyl phosphonate **29.3**, to afford the phosphonate **29.4**. Optionally, the olefinic bond is reduced, as described in Scheme **4**, to yield the saturated analog **29.5**.

Alternatively, the bromo-substituted amide **29.1** is coupled, as described in Scheme **3**, with a dialkyl phosphite, in the presence of a palladium (0) catalyst, to

generate, after deprotection of the phenolic hydroxyl group, the amide phosphonate **29.6**.

For example, 2-bromo-4,5-dihydroxy-pyrimidine-6-carboxylic acid 4-trifluoromethyl-benzylamide **29.8**. This compound is then reacted, in dimethylformamide solution at 80 °C, with one molar equivalent of a dialkyl vinyl phosphonate **29.9**, (Aldrich), triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) to yield, after desilylation, the unsaturated phosphonate **29.10**. The product is then reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in *Angew. Chem. Int. Ed.*, 4, 271, 1965, to yield the saturated product **29.11**.

Alternatively, **29.8** is reacted in toluene solution at ca. 100 °C, with one molar equivalent of a dialkyl phosphite **29.2**, triethylamine and 3 mol % tetrakis(triphenylphosphine)palladium(0), to give, after desilylation, the phosphonate product **29.12**.

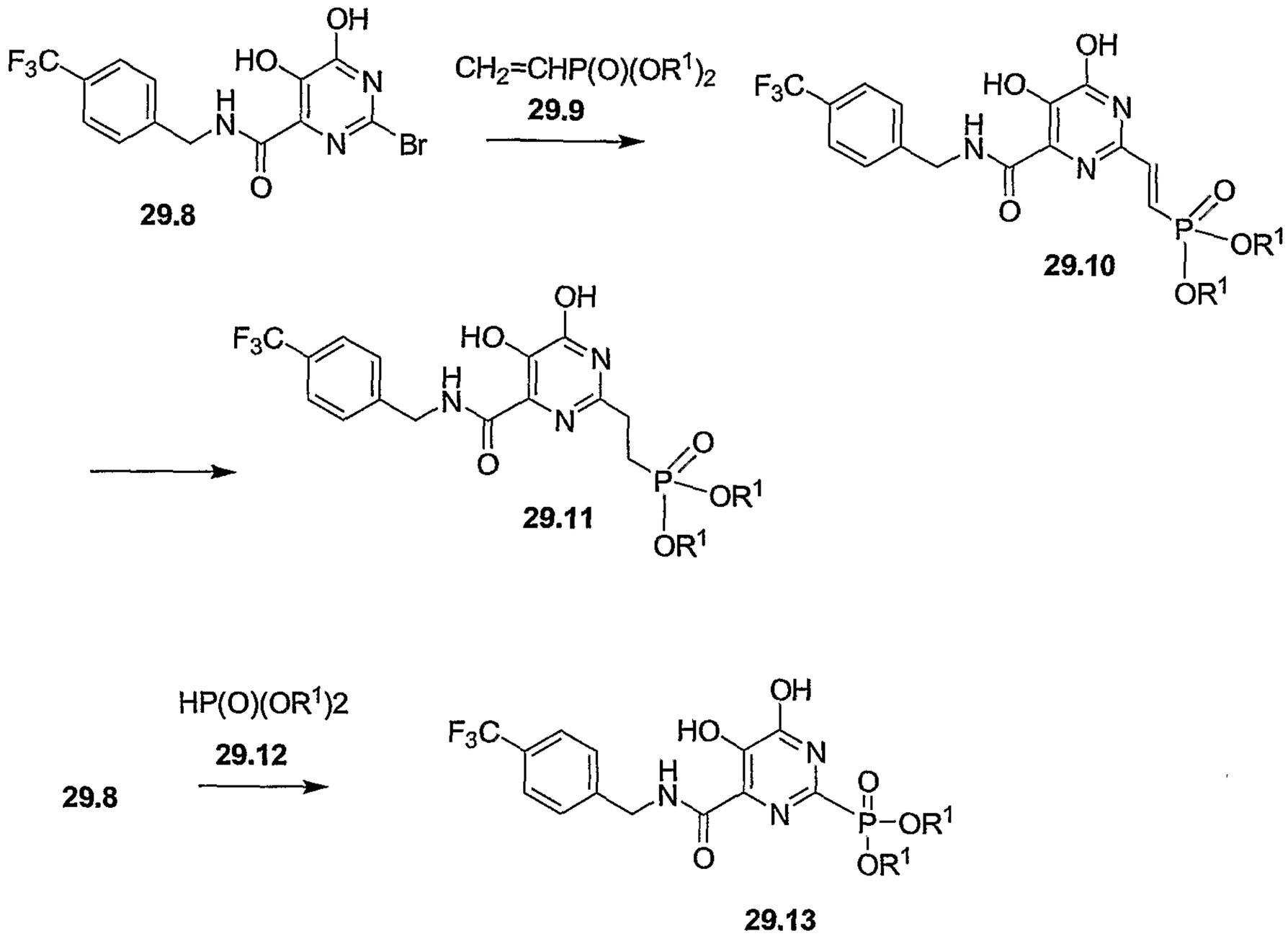
Using the above procedures, but employing, in place of the anhydride **29.7**, different anhydrides **29.1**, and/or different phosphonates **29.3**, the corresponding products **29.4**, **29.5** and **29.6** are obtained.

Scheme 29.

Method

Scheme 29.

Example



Scheme **30** illustrates the preparation of phosphonate esters **Va** in which the phosphonate is attached by means of a saturated or unsaturated carbon link at the 2-position. In this procedure, the amide **30.2** is condensed, under basic conditions, with a dialkyl formyl-substituted phosphonate **30.3**, to afford the unsaturated phosphonate **30.4**. The reaction is conducted at from ambient temperature to about 100 °C, in a polar aprotic solvent such as dimethylformamide or dioxane, in the presence of a base such as sodium hydride, potassium tert. butoxide or lithium hexamethyldisilazide. Optionally, the product **30.4** is reduced, as described in Scheme **4**, to afford the saturated analog **30.5**.

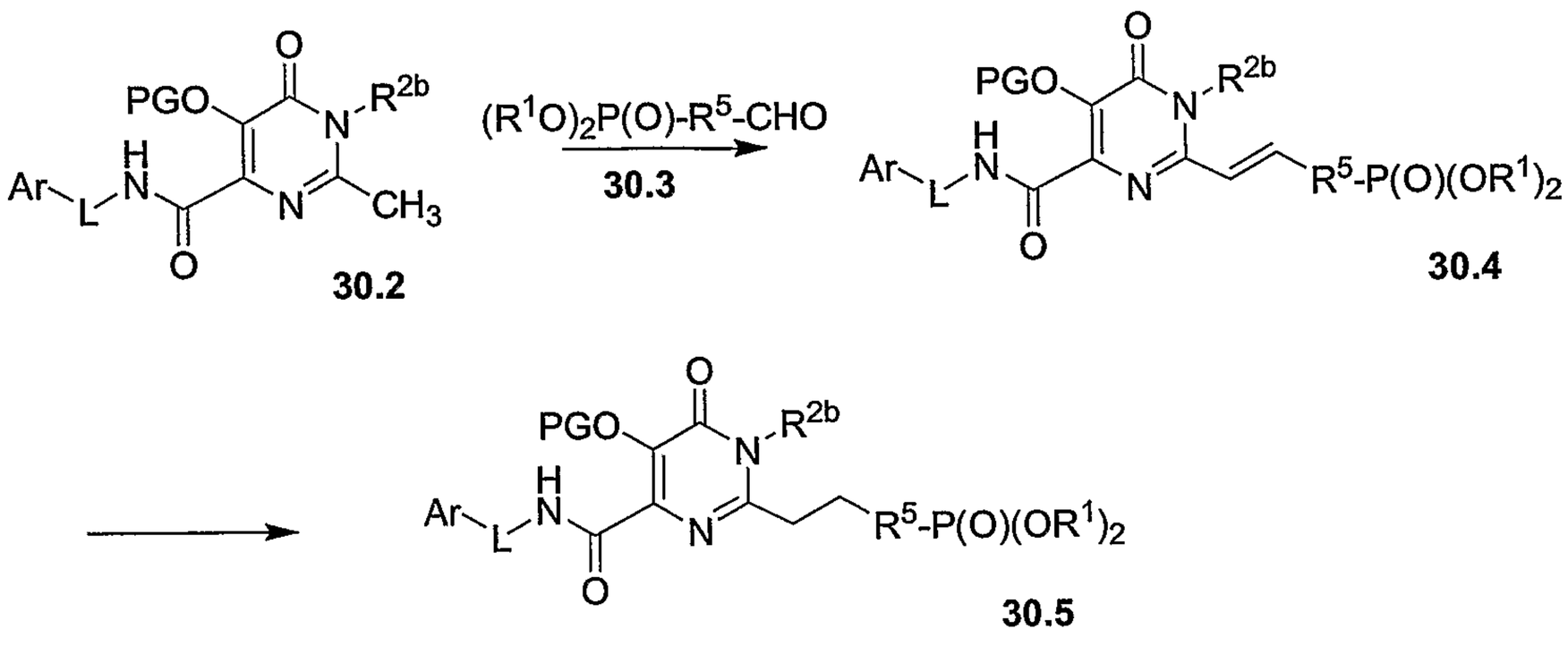
For example, 3-(4-methoxy-benzyl)-2-methyl-4-oxo-5-triisopropylsilanyloxy-3,4-dihydro-pyrimidine-6-carboxylic acid (3,5-dichloro-benzyl)-ethyl-amide **30.7** is reacted, in dimethylformamide solution at 60 °C, with one molar equivalent of a dialkyl formylmethyl phosphonate **30.8** (Aurora) and sodium hydride, to give, after desilylation, the unsaturated phosphonate **30.9**. The product is then reacted with

diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in *Angew. Chem. Int. Ed.*, 4, 271, 1965, to yield the saturated phosphonate **30.10**.

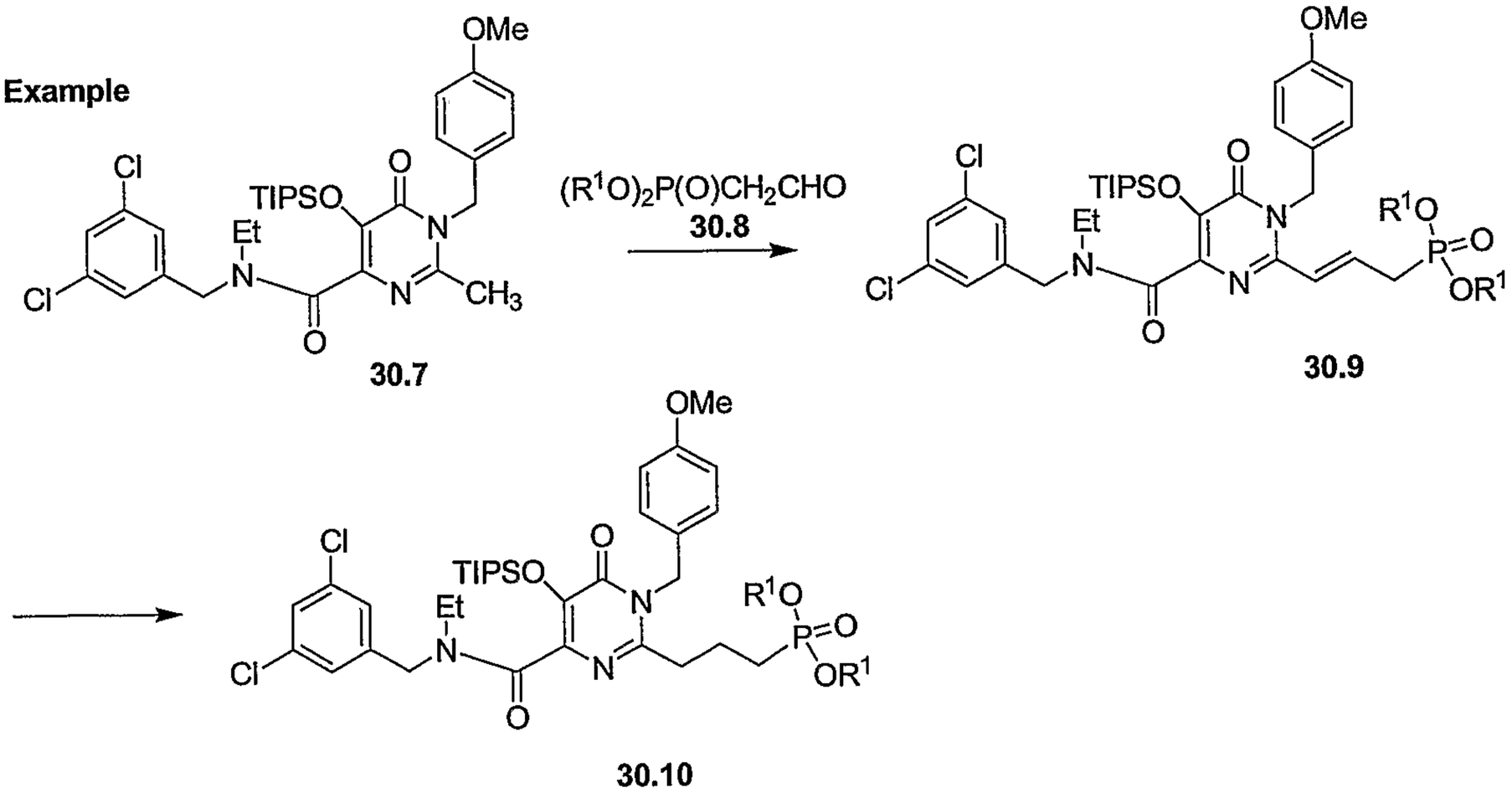
Using the above procedures, but employing, in place of the anhydride **30.6**, different anhydrides **30.1**, and/or different phosphonates **30.3**, the corresponding products **30.4**, and **30.5** are obtained.

Scheme 30.

Method



Example



30.10

Scheme **31** illustrates the preparation of phosphonate esters **IVa** in which the phosphonate is attached by means of an oxime linkage at the 2-position. In this procedure, a 2-methyl, 6-amide **31.2** is brominated to give the 2-bromomethyl compound **31.3**. Oxidation, as described in Scheme **26,** of **31.3** affords the corresponding aldehyde **31.4**. The aldehyde **31.4** is then converted, by reaction with hydroxylamine, into the oxime **31.5**. The latter compound is then reacted, in a polar

solvent such as tetrahydrofuran or dimethylformamide, in the presence of a base such as sodium hydroxide or potassium carbonate, with a dialkyl bromomethyl-substituted phosphonate **31.6**, to prepare, after deprotection of the phenolic hydroxyl group, the oxime derivative **31.7**.

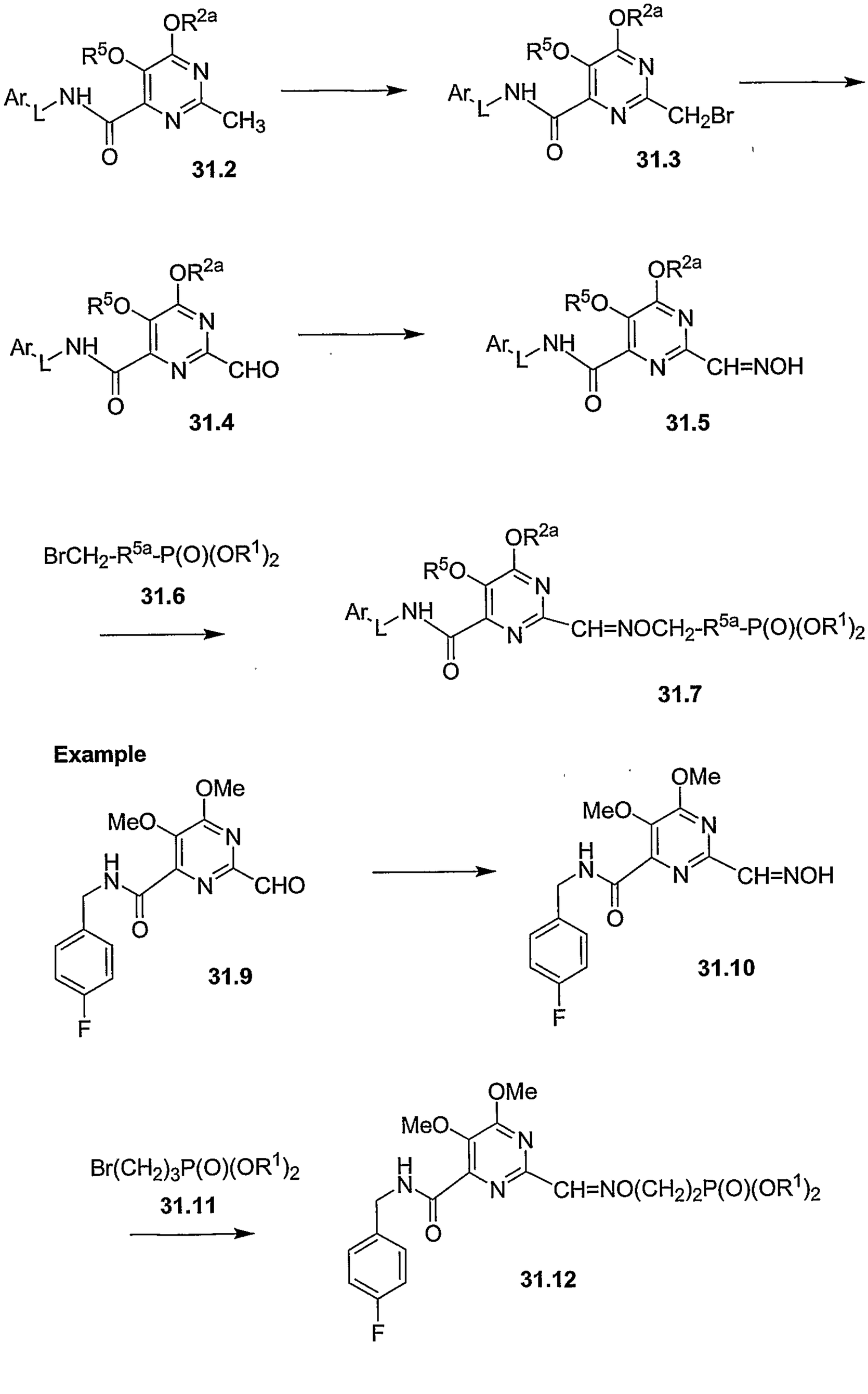
For example, 2-formyl-4,5-dimethoxy-pyrimidine-6-carboxylic acid 4-fluoro-benzylamide **31.9** is reacted in tetrahydrofuran solution with three molar equivalents of hydroxylamine hydrochloride and sodium acetate, to produce 2-(hydroxyimino-methyl)-4,5-dimethoxy-pyrimidine-6-carboxylic acid 4-fluoro-benzylamide **31.10**, which is then reacted in dioxane solution at ambient temperature, with one molar equivalent of a dialkyl bromopropyl phosphonate **31.11** (Synthelec) and potassium carbonate, to yield, after desilylation of the phenolic hydroxyl group, the oxime ether **31.12**.

Also for example, a 2-phosphonate Formula IVa compound can be prepared with a morpholino linkage. The 5-hydroxyl of 3-[4-(4-Fluoro-benzylcarbamoyl)-5-hydroxy-3-methyl-4-oxo-3,4-dihydro-pyrimidin-2-yl]-morpholine-4-carboxylic acid tert-butyl ester **31.13** can be esterified as the 2-iodobenzoate to give **31.14**. The Boc group can be removed under acidic conditions from **31.14** and the amino group of 2-iodo-benzoic acid 4-(4-fluoro-benzylcarbamoyl)-1-methyl-2-morpholin-3-yl-6-oxo-1,6-dihydro-pyrimidin-5-yl ester **31.15** may be condensed with aldehyde **31.16** to give **31.17** by reductive amination with sodium cyanoborohydride. The 2-iodobenzoate group may be removed under mild oxidative conditions, following the methods of R. Moss et al, *Tetrahedron Letters*, 28, 5005 (1989), to give morpholino phosphonate **31.18**.

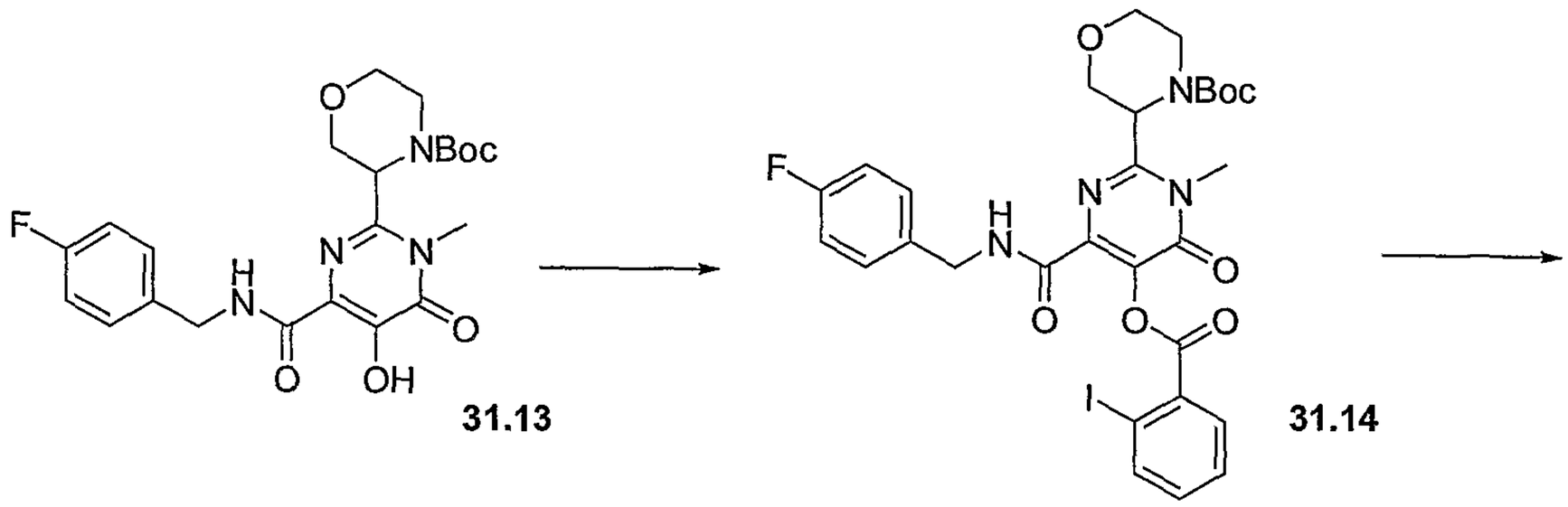
Using the above procedures, but employing, in place of the anhydride **31.8**, different anhydrides **31.1**, and/or different phosphonates **31.6**, the corresponding products **31.7** are obtained.

Scheme 31.

Method

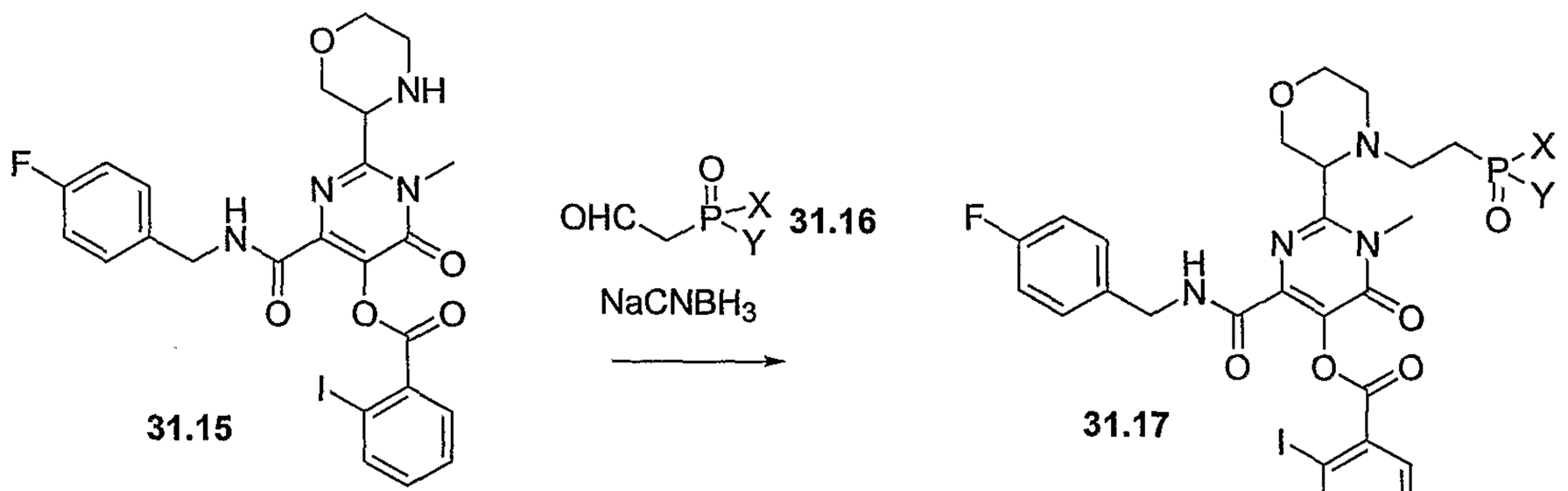


Example



31.13

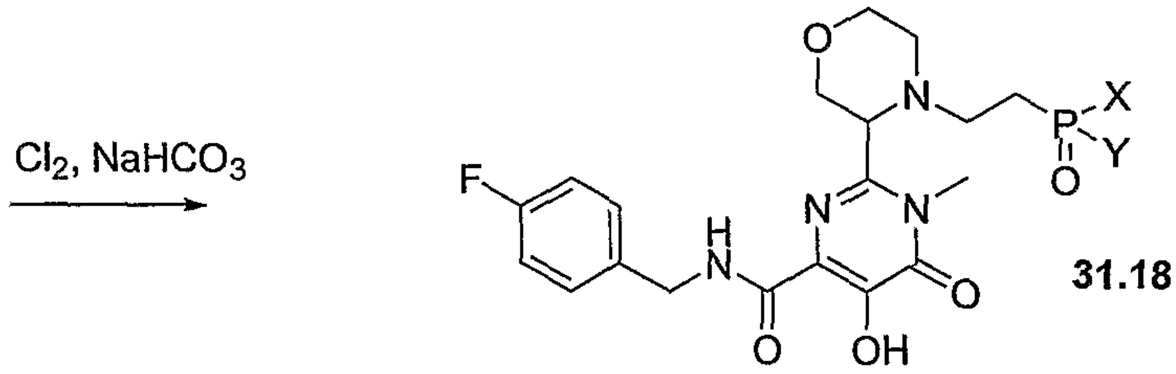
31.14



31.15

31.16

31.17



31.18

The preparation of phosphonate esters and the interconversion of such esters to other phosphonate analogs of the invention can be carried out as described in WO 2004/096237 A2 pages 110-144.

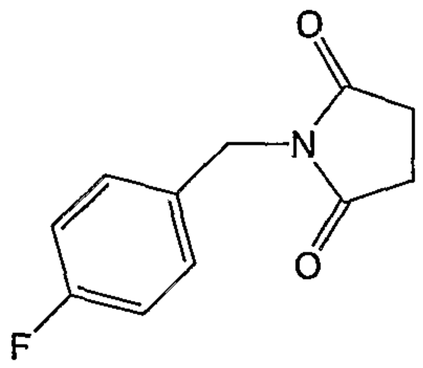
EXAMPLES GENERAL SECTION

Some Examples have been performed multiple times. In repeated Examples, reaction conditions such as time, temperature, concentration, and the like, and yields were within normal experimental ranges. In repeated Examples where significant modifications were made, these have been noted where the results varied significantly from those described. In Examples where different starting materials were used, these are noted. When the repeated Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl ester", this intends that an otherwise present group, in this case typically a methyl ester, is taken to be the same group modified as indicated.

SYNTHESIS OF HIV-INTEGRASE INHIBITOR COMPOUNDS

EXAMPLES

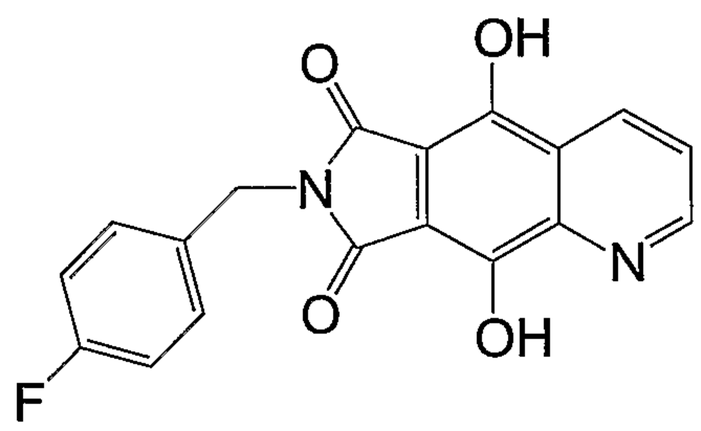
Example 1 N-4-fluorobenzyl-succinimide **1**



1

Freshly ground potassium carbonate, K_2CO_3 (31 g, 225 mmol) was added to dry acetone (200ml) in a 3-necked flask equipped with drying tube, condenser, and mechanical stirrer. Succinimide (7.43 g, 75mmol) and 4-fluorobenzylbromide (11.21 mL, 90 mmol) were added. The mixture was refluxed for 19 hours and filtered through Celite. Acetone was removed under vacuum, diluted with EtOAc, washed with saturated aqueous sodium bicarbonate and also with brine, dried ($MgSO_4$), filtered and concentrated to give crude. Crude product was chromatographed (EtOAc/Hexane) on silica gel to give N-4-fluorobenzyl-succinimide **1** as white solid (13.22 g, 85%). ^{1}H NMR ($CDCl_3$) δ 7.4 (dd, 2H), 7.0 (t, 2H), 4.6 (s, 1H), 2.7 (s, 4 H).

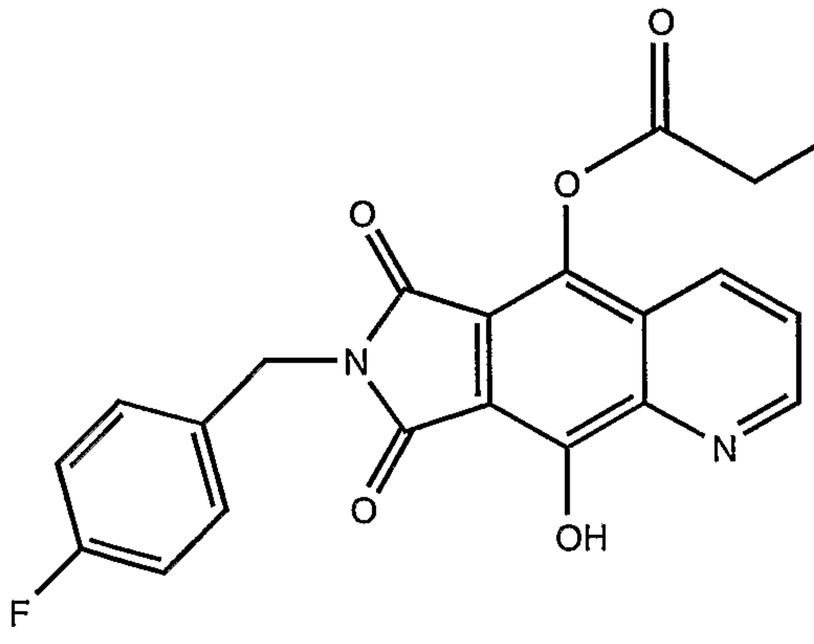
Example 2 5,8-Dihydroxy-[6,7]-N-(4-fluorobenzyl)-succinimido-quinoline **2**



2

N-4-fluorobenzyl-succinimide **1** (8 g, 38.6 mmol) and 2,3-pyridine carboxylic acid dimethyl ester (7.9 g, 40.6 mmol) were dissolved in dry tetrahydrofuran (THF, 78 mL) and dry methanol (MeOH, 1.17 mL) in a 3-necked flask with mechanical stirrer and condenser. Sodium hydride (NaH, 60% in mineral oil, 3.4g, 85 mmol) was added slowly in four portions. The mixture was stirred until bubbling ceased, then refluxed for 24 hours. HCl (30 mL 6 M) was then added to the mixture while in an ice bath, with stirring for 15 minutes. Diethylether (100 mL) was added. The precipitate was filtered, washed with diethylether and H_2O, and dried under vacuum at 100 °C. Crude product was then recrystallized from 1 L refluxing dioxane and dried under vacuum at 100 ° C to give solid 5,8-Dihydroxy-[6,7]-N-(4-fluorobenzyl)-succinimido-quinoline **2** (8.6 g, 66%). ^{1}H NMR (CD_3SOCD_3) δ 9.05 (d, 1H), 8.75 (d, 1H), 7.79 (dd, 1 H), 7.37 (dd, 2 H), 7.17 (t, 2H), 4.73 (s, 2 H). mp: 281.9-284.0.

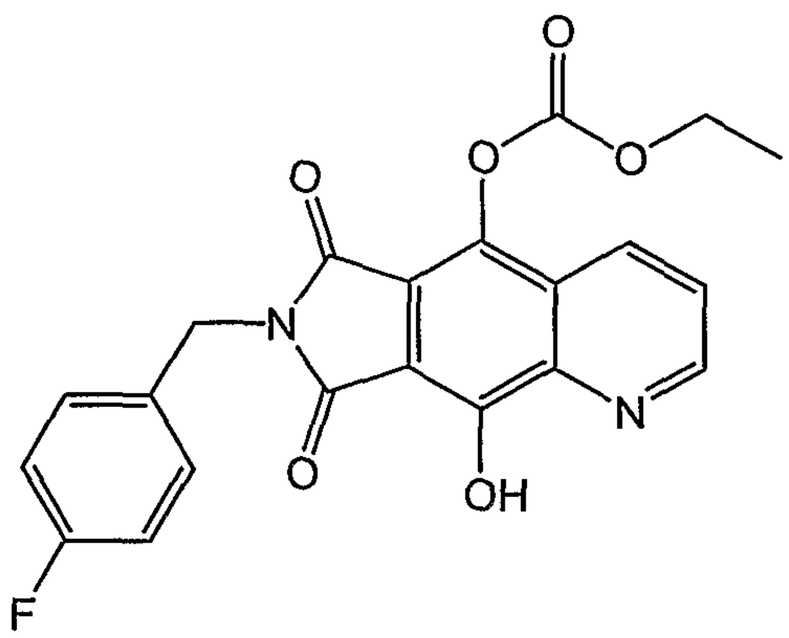
Example 3 5-O-Propanoate, 8-hydroxy-[6,7]-N-(4-fluorobenzyl)-succinimido-quinoline **3**



3

5,8-Dihydroxy-[6,7]-N-(4-fluorobenzyl)-succinimido-quinoline **2** is acylated with propanoyl chloride to give 5-O-propanoate, 8-hydroxy-[6,7]-N-(4-fluorobenzyl)-succinimido-quinoline **3**.

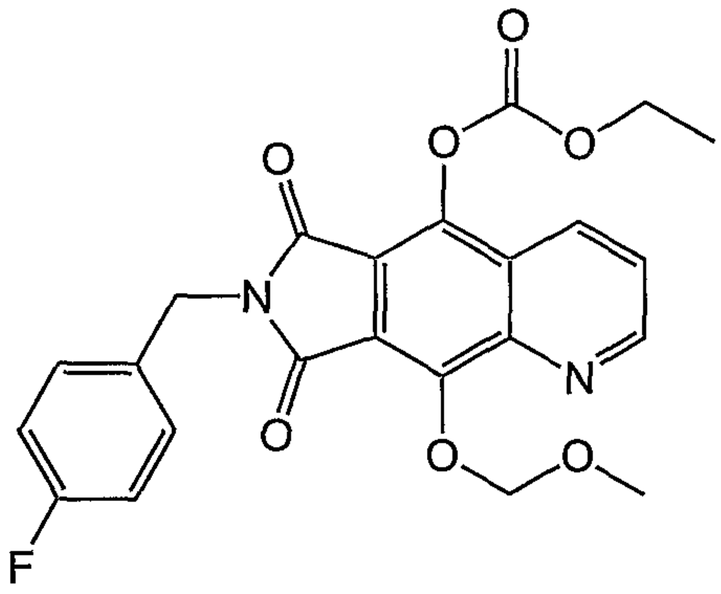
Example 4 Carbonic acid ethyl ester 7-(4-fluoro-benzyl)-9-hydroxy-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **4**



4

5,8-Dihydroxy-[6,7]-N-(4-fluorobenzyl)-succinimido-quinoline (300mg, 0.887 mmol) **2** was suspended in 1,4 dioxane (5 mL) and water (20 mL). An aqueous solution of NaOH (0.567 M, 3.1 mL) was added slowly to form red solution which was then cooled in an ice-water bath. Ethyl chloroformate (0.093 mL, 0.975 mmol) was added and the mixture was stirred at room temperature for 30 minutes. Dichloromethane and 1N aqueous HCl were added to the mixture in a separate. The aqueous layer was extracted with dichloromethane two more times. The combined organic solution was washed with brine, dried (MgSO4) and concentrated. The crude product was crystallized from EtOAc to give carbonic acid ethyl ester 7-(4-fluoro-benzyl)-9-hydroxy-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **4** (136 mg, 37%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.5 (d, 1H), 7.7 (dd, 1H),7.5 (t, 2H), 7.4 (t, 2 H), 7.0 (t, 2 H), 4.8 (s, 2H), 4.5 (q, 2 H), 1.5 (t, 3H); MS: 409 (M-1)

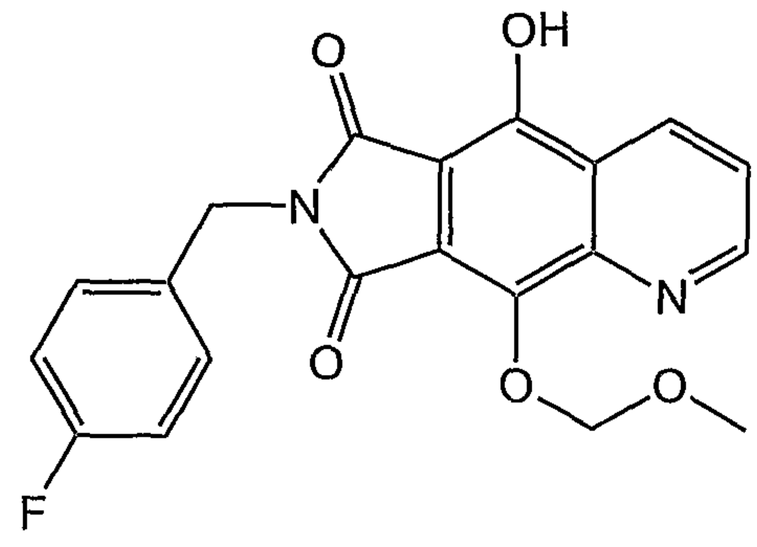
Example 5 Carbonic acid ethyl ester 7-(4-fluoro-benzyl)-9-methoxymethoxy-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **5**



5

Carbonate (23.6 mg, 0.08 mmol) **4** was dissolved in acetonitrile (2mL). Chloromethyl methyl ether (0.013mL, 0.17 mmol) and Cs_2CO_3 (74 mg , 0.23 mmol) were added consecutively. The mixture was stirred at room temperature for 30 minutes when most of the starting material was consumed as indicated by TLC. Dichloromethane was added and the solution was washed with 1N HCl and brine, dried ($MgSO_4$) and concentrated. The crude product was chromatographed on silica gel column, eluting with EtOAc/hexanes to give the product, carbonic acid ethyl ester 7-(4-fluoro-benzyl)-9-methoxymethoxy-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **5** as a white solid (18 mg, 70%). ^1H NMR ($CDCl_3$) δ 9.1 (dd, 1H), 8.5 (dd, 1H), 7.7 (dd, 1H), 7.4 (dd, 2H), 7.0 (t, 2H), 5.9 (s, 2H), 4.8 (s, 2H), 4.5 (q, 2H), 3.7 (s, 1H), 1.5 (t, 3H).

Example 6 7-(4-Fluoro-benzyl)-5-hydroxy-9-methoxymethoxy-pyrrolo[3,4-g]quinoline-6,8-dione **6**

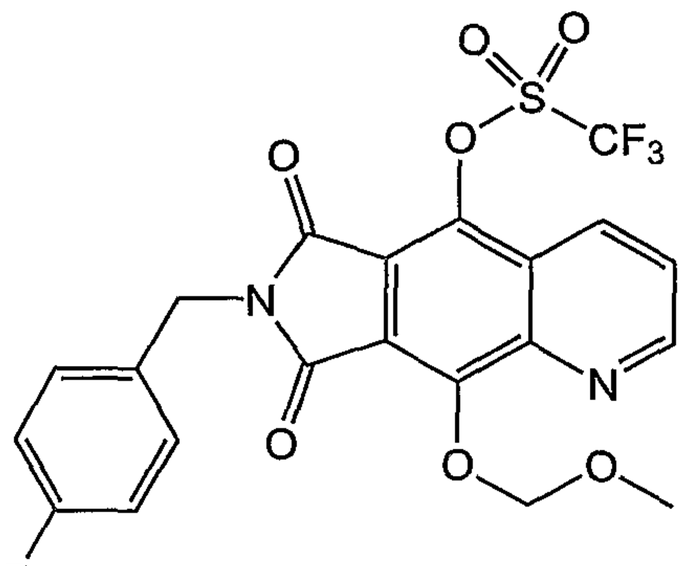


6

To the ethyl carbonate methoxymethyl ether **5** (70.9 mg, 0.156 mmol) in THF (7.6 mL) at room temperature was added a solution (5 mL) of K_2CO_3 (215 mg, 1.56 mmol) in water and 4-dimethylaminopyridine (3.8 mg, 0.03 mmol). The yellow solution was stirred at room temperature under nitrogen atmosphere overnight. Most

of THF was removed under reduced pressure at 30-40°C and the remaining solution was diluted with dichloromethane, washed with 1N HCl and brine, dried ($MgSO_4$) and concentrated to give solid crude product (51 mg, 85%), which is triturated in diethylether/hexane to afford the product, 7-(4-fluoro-benzyl)-5-hydroxy-9-methoxymethoxy-pyrrolo[3,4-g]quinoline-6,8-dione **6** as a yellow solid (34 mg). ^1H NMR ($CDCl_3$) δ 9.1 (dd, 1H), 8.7 (dd, 1H), 7.6 (dd, 1H), 7.4 (dd, 2H), 7.0 (t, 2H), 5.8 (s, 2H), 4.8 (s, 2H), 3.7 (s, 1H). MS: 383 (M+1); 381 (M-1).

Example 7 Trifluoro-methanesulfonic acid 7-(4-fluoro-benzyl)-9-methoxymethoxy-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **7**



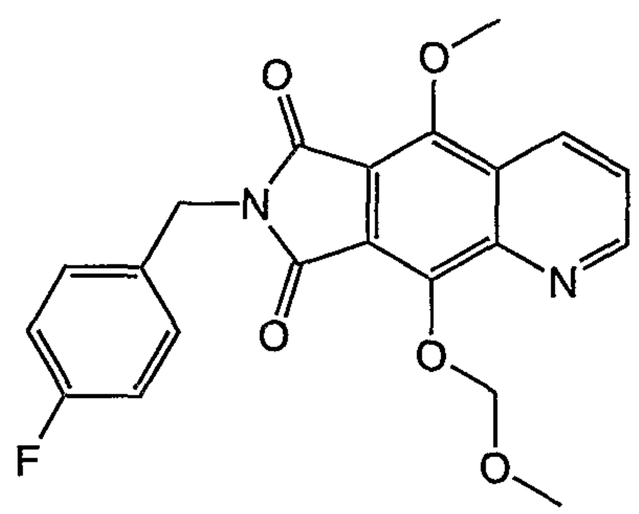
7

To the methoxymethyl ether **6** (13.7 mg, 0.036 mmol) in dichloromethane (1 mL) at -78°C were added N,N-diisopropylethylamine (0.019 mL, 0.1 mmol) and trifluoromethanesulfonic anhydride (0.012 mL, 0.054 mmol) successively. The solution was stirred at the same temperature for 30 minutes and diluted with dichloromethane, washed with water and brine, dried ($MgSO_4$) and concentrated, The mixture was chromatographed on a silica gel column, eluting with EtOAc/hexanes to afford the product, trifluoro-methanesulfonic acid 7-(4-fluoro-benzyl)-9-methoxymethoxy-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **7** (6 mg, 33%). ^1H NMR ($CDCl_3$) δ 9.1 (dd, 1H), 8.5 (dd, 1H), 7.8 (dd, 1H), 7.5 (dd, 2H), 7.0 (t, 2H), 5.9 (s, 2H), 4.9 (s, 2H), 3.7 (s, 1H). ^{19}F NMR ($CDCl_3$) δ -72.8.

The reaction was repeated, where monophenol **6** (0.0444 g, 0.116 mmol) was dissolved in 2 mL dry dichloromethane. To this was added diisopropylethylamine (0.06 mL, 0.348 mmol.) After cooling to –78 °C, triflic anhydride was added (0.029 mL, 0.342 mmol) and was stirred at this temperature for thirty minutes. Reaction was then complete by TLC, diluted with dichloromethane, washed with 1M HCl, saturated

$NaHCO_3$ solution, dried ($MgSO_4$) and organics concentrated to give product, trifluoro-methanesulfonic acid 7-(4-fluoro-benzyl)-9-methoxymethoxy-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **7** (0.06 g, 0.116 mmol, 100%) which was used as crude for the next reaction. ^1H NMR ($CDCl_3$) δ 9.15 (dd, 1H), 8.46 (d, 1H), 7.47 (dd, 1H), 7.01 (t, 2H), 5.92 (s, 2H), 4.87 (s, 2H.), 3.67 (s, 3H); MS: 537 (M+Na).

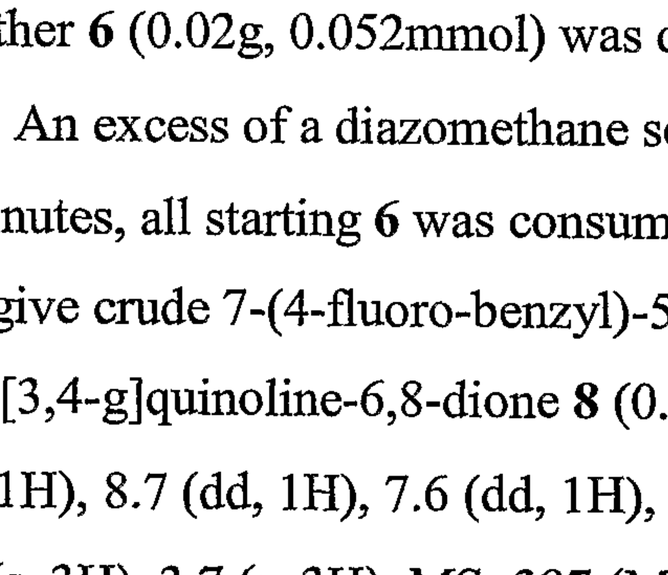
Example 8 7-(4-Fluoro-benzyl)-5-methoxy-9-methoxymethoxy-pyrrolo[3,4-g]quinoline-6,8-dione **8**



8

Methoxymethyl ether **6** (0.02g, 0.052mmol) was dissolved in 2 mL dry dichloromethane at 0 °C. An excess of a diazomethane solution in diethylether was added. After about 20 minutes, all starting **6** was consumed. The mixture was concentrated *in vacuo* to give crude 7-(4-fluoro-benzyl)-5-methoxy-9-methoxymethoxy-pyrrolo[3,4-g]quinoline-6,8-dione **8** (0.0223g, 0.0527mmol). ^1H NMR ($CDCl_3$) δ 9.1 (dd, 1H), 8.7 (dd, 1H), 7.6 (dd, 1H), 7.5 (t, 2H), 7.0 (t, 2H), 5.8 (s, 2 H), 4.8 (s, 2 H), 4.4 (s, 3H), 3.7 (s, 3H). MS: 397 (M+1); 419 (M+23).

Example 9 7-(4-Fluoro-benzyl)-9-hydroxy-5-methoxy-pyrrolo[3,4-g]quinoline-6,8-dione **9**

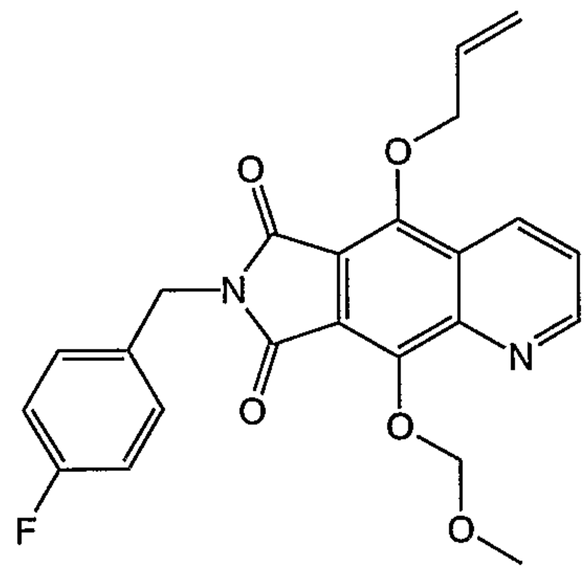


9

Crude diether **8** (0.0223g, 0.0527mmol) was dissolved in 1mL dichloromethane. Ten equivalents of trifluoroacetic acid was added. the mixture was

stirred at room temperature for 45 minutes. The reaction mixture was concentrated and azeotroped with toluene (2x) to give crude 7-(4-fluoro-benzyl)-9-hydroxy-5-methoxy-pyrrolo[3,4-g]quinoline-6,8-dione **9** which was triturated with 8 mL of 1:1 diethylether/hexane and filtered to give **9** (0.0161g, 0.0456mmol, 83% for two steps). ^{1}H NMR ($CDCl_3$) δ 9.0 (br s, 1 H), 8.7 (d, 1 H), 7.7 (d, 1 H), 7.5 (m, 2 H), 7.0 (t, 2 H), 4.8 (s, 2H), 4.4 (s, 3H). MS: 353 (M+1).

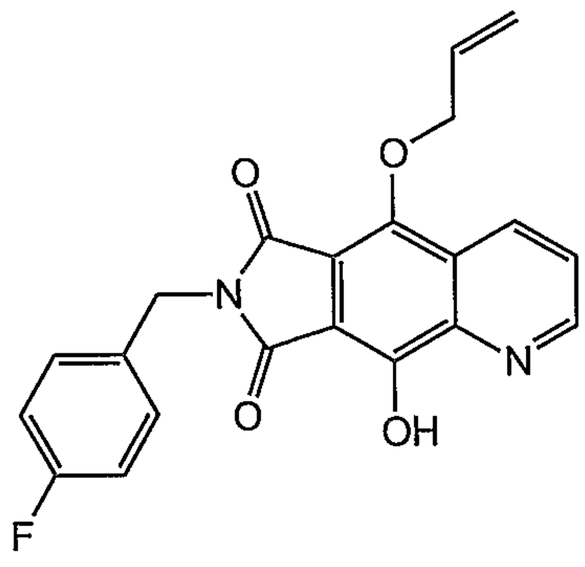
Example 10 5-Allyloxy-7-(4-fluoro-benzyl)-9-methoxymethoxy-pyrrolo[3,4-g]quinoline-6,8-dione **10**



10

Methoxymethyl ether **6** (0.0172g, 0.045mmol) was dissolved in 1.5 mL dry dimethylformamide (DMF). Ground K_2CO_3 (0.0186g, 0.135 mmol) was added, followed by allyl bromide (0.0077 mL, 0.09 mmol). The mixture was stirred at room temperature overnight, then diluted with 100 mL of ethylacetate, washed with saturated NH_4Cl solution, dried ($MgSO_4$), and concentrated to give crude **10**. The crude product **10** was chromatographed on silica gel, eluting with ethylacetate and hexanes to give white solid allyl, methoxymethyl diether **10**: (0.0063g, 33%). ^{1}H NMR ($CDCl_3$) δ 9.1 (dd, 1H), 8.8 (dd, 1H), 7.6 (dd, 1H), 7.5 (dd, 2H), 7.0 (t, 2H), 6.1 (m, 1H), 5.8 (s, 2H), 5.5 (d, 1H), 5.3 (d, 1H), 5.1 (d, 2H), 4.8 (s, 2H). MS: 423 (M+1); 445 (M+23).

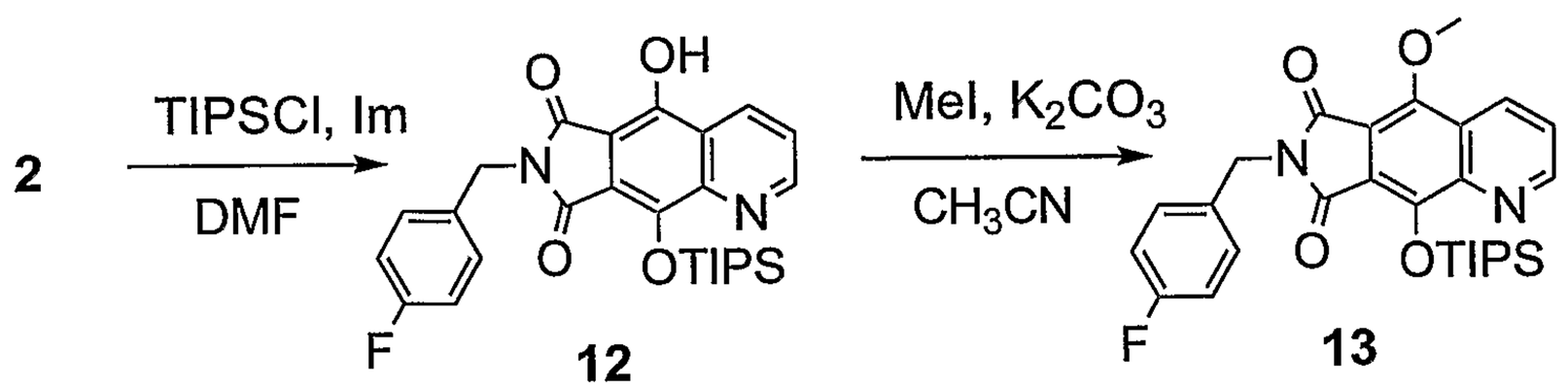
Example 11 5-Allyloxy-7-(4-fluoro-benzyl)-9-hydroxy-pyrrolo[3,4-g]quinoline-6,8-dione **11**



11

5-Allyloxy-7-(4-fluoro-benzyl)-9-methoxymethoxy-pyrrolo[3,4-g]quinoline-6,8-dione **10** was dissolved in 1 mL dichloromethane. Ten equivalents of trifluoroacetic acid was added and the mixture was stirred at room temperature. After one hour another 10 equivalents of trifluoroacetic acid was added. The mixture was then stirred overnight, concentrated *in vacuo*, and azeotroped with toluene (2x), to give crude **11** which was triturated with 2 mL of 1:1 diethylether/hexane two times to give allyl ether **11** (0.0025g, 0.0066mmol, 44%). ^{1}H NMR ($CDCl_3$) δ 9.0 (s, 1H), 8.7 (d, 1H), 7.7 (m, 1H), 7.5 (m, 2H), 7.0 (t, 2H), 6.1 (m, 1H), 5.4 (d, 1H), 5.3 (d, 1H), 5.1 (d, 2H), 4.8 (s, 2H). MS: 379 (M+1).

Example 12 7-(4-Fluoro-benzyl)-5-hydroxy-9-triisopropylsilanyloxy-pyrrolo[3,4-g]quinoline-6,8-dione **12**

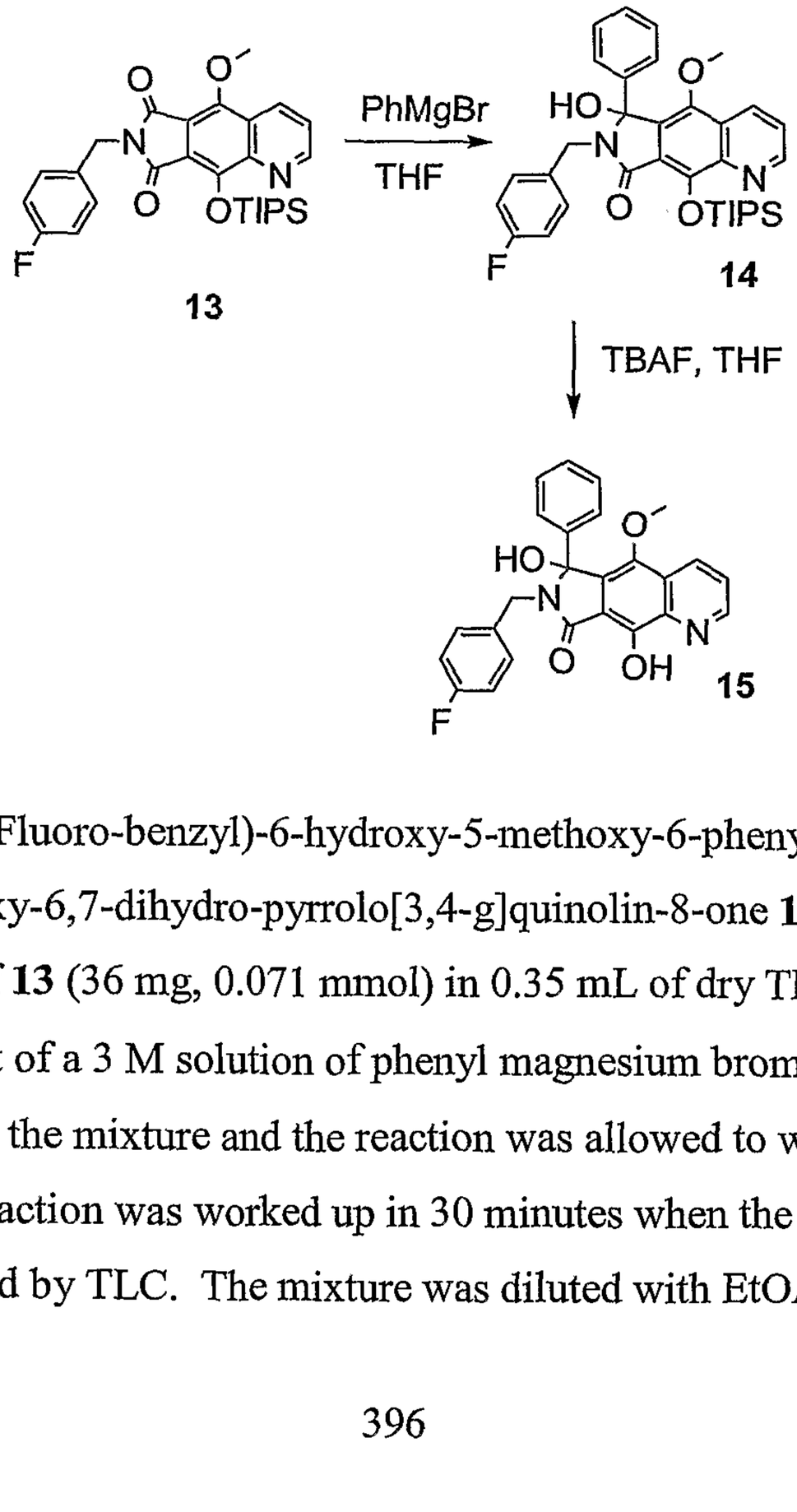


A solution of 7-(4-fluoro-benzyl)-5,9-dihydroxy-pyrrolo[3,4-g]quinoline-6,8-dione **2** (1.039 g, 3.07 mmol) in 31 mL of DMF was stirred with imidazole (314 mg, 4.62 mmol) and triisopropylsilylchloride (TIPSCl, 0.723 mL, 3.38 mmol) under a N_2 atmosphere for 1.5 days when most of the starting materials was converted to the regiospecific mono TIPS (triisopropylsilyl) protected compound. The solid bisphenol left in the reaction was filtered and recycled. The mother liquor was dried and the residue was suspended in EtOAc. The organic layer was washed with water and

dried. The resulted solid **12** was carried to the next step. EI MS (*m/z*) 495.6 [MH^+], 517.4 [M+Na].

Example 13 7-(4-Fluoro-benzyl)-5-methoxy-9-triisopropylsilanyloxy-pyrrolo[3,4-g]quinoline-6,8-dione **13**

A mixture of **12** from the monosilylation reaction was heated at 40 °C in anhydrous acetonitrile with K_2CO_3 (1.64 g, 11.8 mmol) and methyl iodide (4.2 g, 29.6 mmol) for 5 hours. The reaction mixture was worked up by addition of H_2O and EtOAc. The organic layer was washed with H_2O and the solvent was removed *in vacuo*. The residue was purified by column chromatography using a gradient of 10% EtOAc-Hex to elute the product **13** as a yellow solid (72% for two steps). ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, 18H, *J*= 8 Hz), 1.53 (septet, 3H, *J*= 7 Hz), 4.29 (s, 3H), 4.84 (s, 2H), 7.00 (t, 2H, *J*= 8 Hz), 7.48 (dd, 2H, *J*= 5, 8 Hz), 7.58 (dd, 1H, *J*= 4, 8 Hz), 8.65 (dd, 1H, *J*= 2, 8 Hz), 8.93 (dd, 1H, *J*= 2, 4 Hz); EI MS (*m/z*) 509.7 [MH^+], 531.4 [M+Na].



13 **14** **15**

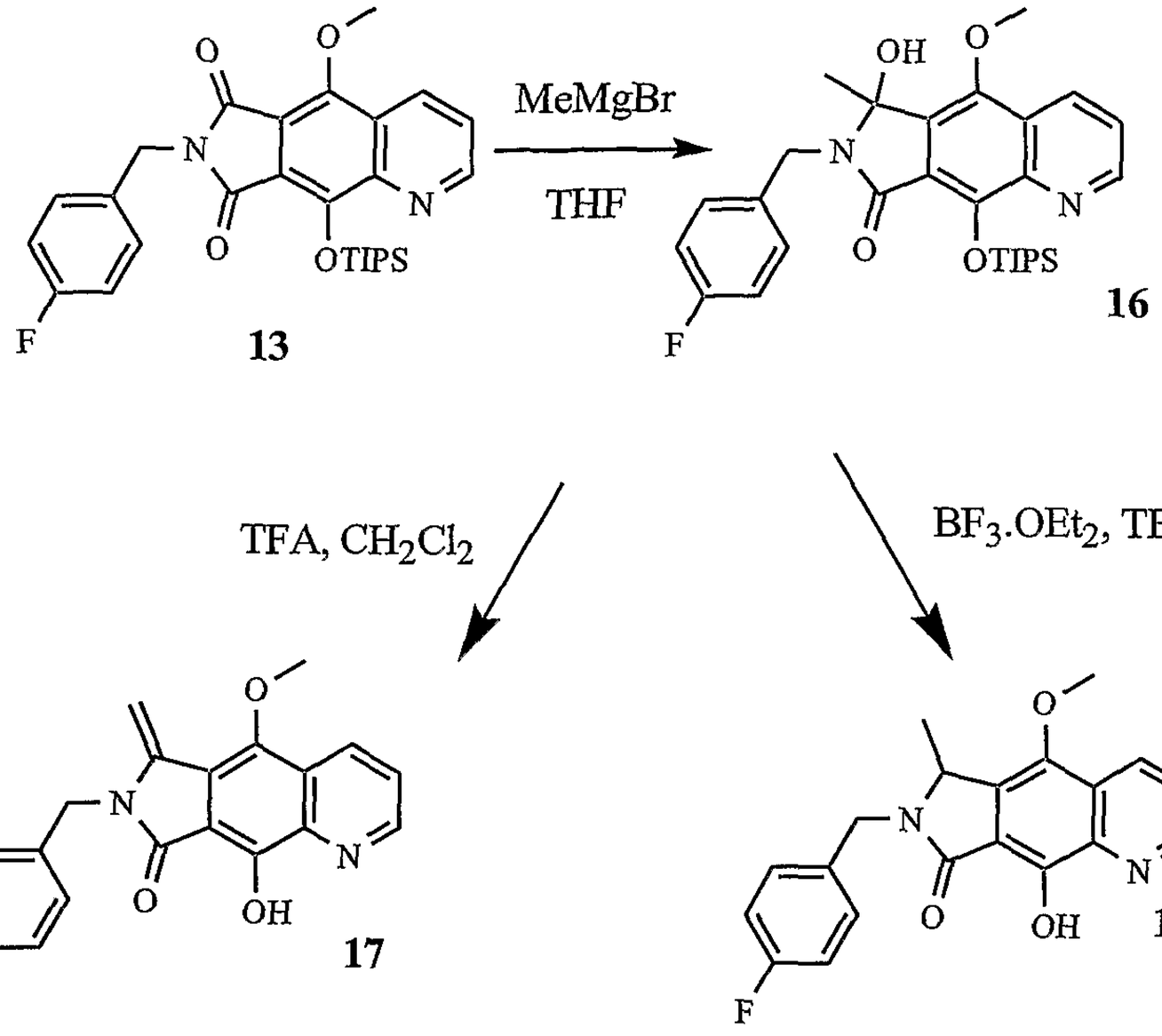
Example 14 7-(4-Fluoro-benzyl)-6-hydroxy-5-methoxy-6-phenyl-9-triisopropylsilanyloxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **14**

A mixture of **13** (36 mg, 0.071 mmol) in 0.35 mL of dry THF was cooled to 0 °C. A 26 μL aliquot of a 3 M solution of phenyl magnesium bromide in ether (0.078 mmol) was added to the mixture and the reaction was allowed to warm up to room temperature. The reaction was worked up in 30 minutes when the reaction was complete as indicated by TLC. The mixture was diluted with EtOAc and washed with

water. The product **14** was purified by column chromatography using 20% EtOAc-Hex solvent system to provide 33 mg (80%) of the product as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 18H), 1.52-1.68 (m, 3H), 2.95 (s, 1H), 3.93 (s, 3H), 4.08 (d, 1H, *J*= 15 Hz), 4.77 (d, 1H, *J*= 15 Hz), 6.85 (t, 2H, *J*= 9 Hz), 7.19- 7.25 (m, 2H), 7.25- 7.35 (m, 3H), 7.39- 7.49 (m, 3H), 8.26 (d, 1H, *J*= 8 Hz), 8.84 (br d, 1H, *J*= 4 Hz); ^{19}F NMR (282.6 MHz, $CDCl_3$) δ -76.2, 60.7; EI MS (*m/z*) 587.5 [MH^+], 609.4 [M+Na].

Example 15 7-(4-Fluoro-benzyl)-6,9-dihydroxy-5-methoxy-6-phenyl-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **15**

A mixture of **14** (27 mg, 0.046 mmol) in THF (0.46 mL) and tetrabutyl ammonium fluoride (50 μL, 0.050 mmol) was stirred at room temperature under a N_2 atmosphere for 2 hours when reaction was complete as demonstrated by LCMS analysis. The organic solvent was removed *in vacuo* and the residue was suspended in EtOAc. The organic layer was washed with water and dried. The solid was washed with hexane and dried to provide 15 mg (76%) of the product **15** as a light orange solid. ^{1}H NMR (300 MHz, CD_3OD) δ 3.54 (s, 3H), 4.36 (d, 1H, *J*= 15 Hz), 4.48 (d, 1H, *J*= 15 Hz), 6.84 (t, 2H, *J*= 9 Hz), 7.17- 7.23 (m, 2H), 7.24- 7.26 (m, 3H), 7.35-7.46 (m, 2H), 7.62 (dd, 1H, *J*= 4, 9 Hz), 8.44 (d, 1H, *J*= 9 Hz), 8.89 (d, 1H, *J*= 3 Hz); ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 58.5; EI MS (*m/z*) 431.2 [MH^+], 453.2 [M+Na].



Example 16 7-(4-Fluoro-benzyl)-6-hydroxy-5-methoxy-6-methyl-9-triisopropylsilanyloxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **16**

Under a nitrogen atmosphere, a solution of **13** (90 mg, 0.18 mmol) was dissolved in 0.885 mL of dry THF. A solution of 3 M of methylmagnesium bromide in ether (71 μL, 0.213 mmol) was added. The solution was allowed to stir at ambient temperature for 2 hours when TLC indicated complete consumption of starting materials. The reaction mixture was diluted with EtOAc and washed with water and saturated aqueous NH_4Cl. The organic layer was reduced *in vacuo* to 1 mL and cooled to get the product **16** to crystallize from the solvent (92 mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, 18H, *J*= 8 Hz), 1.55 (septet, 3H, *J*= 8 Hz), 1.78 (s, 3H), 2.29 (s, 1H), 4.04 (s, 3H), 4.72 (ABqt, 2H, *J*= 13 Hz), 6.99 (t, 2H, *J*= 9 Hz), 7.38 (dd, 2H, *J*= 6, 9 Hz), 7.52 (dd, 1H, *J*= 4, 9 Hz), 8.42 (dd, 1H, *J*= 2, 8 Hz), 8.87 (dd, 1H, *J*= 2, 4 Hz); ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 60.8.

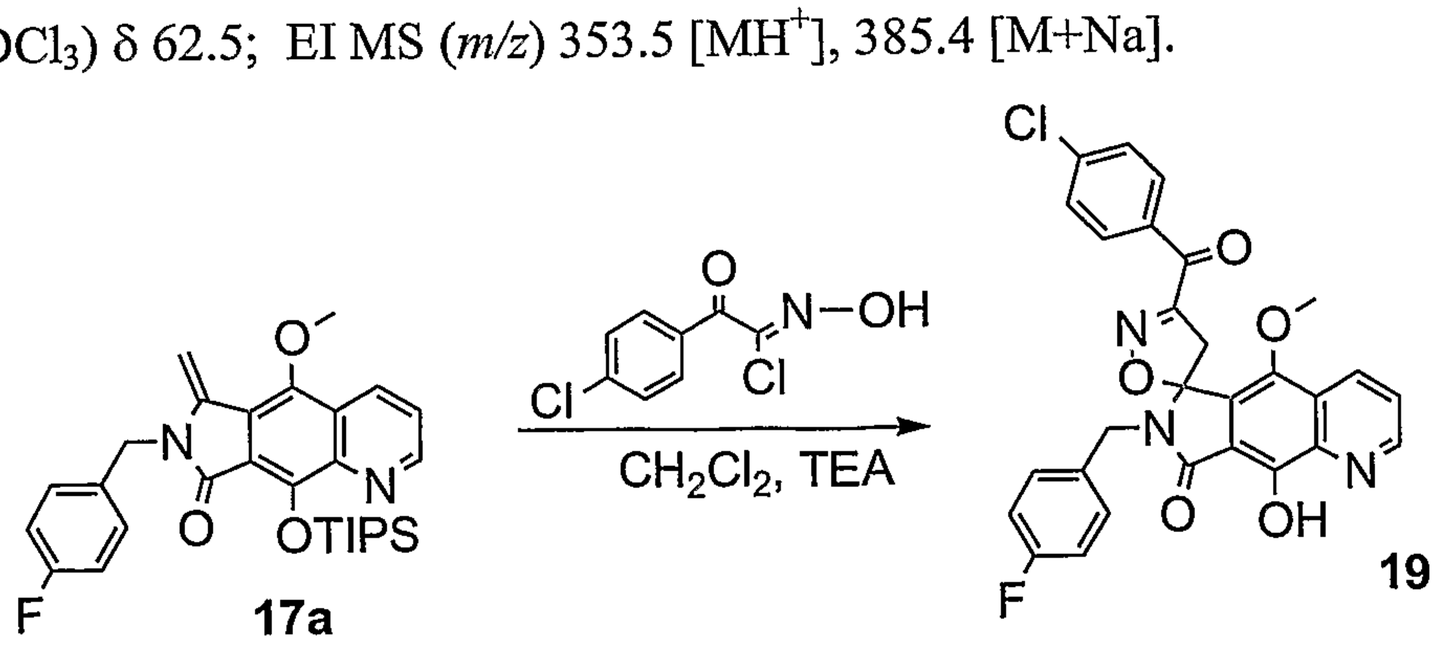
Example 17 7-(4-Fluoro-benzyl)-9-hydroxy-5-methoxy-6-methylene-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **17**

A solution of **16** (10 mg, 0.019 mmol) in 3 mL of CH_2Cl_2 and TFA (30 μL, 0.389 mmol) was aged for 18 hours. Analysis of the reaction demonstrated complete

conversion of starting materials to the product. The solvents were removed under reduced pressure. The residue was dissolved in EtOAc and precipitated with hexanes. The mother liquor was removed and the solid residue was washed with hexanes and subsequently with Et_2O to yield the product **17** as a solid. ^1H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 3H), 4.99 (s, 2H), 5.04 (d, 1H, *J*= 2 Hz), 5.63 (d, 1H, *J*= 2 Hz), 6.90 (br s, 1H), 7.04 (t, 2H, *J*= 8 Hz), 7.31 (dd, 2H, *J*= 5, 8 Hz), 7.71 (dd, 1H, *J*= 4, 8 Hz), 8.64 (dd, 1H, *J*= 2, 9 Hz), 9.11 (d, 1H, *J*= 3 Hz); ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 62.1; EI MS (*m/z*) 351.5 [MH^+], 383.3 [M+Na].

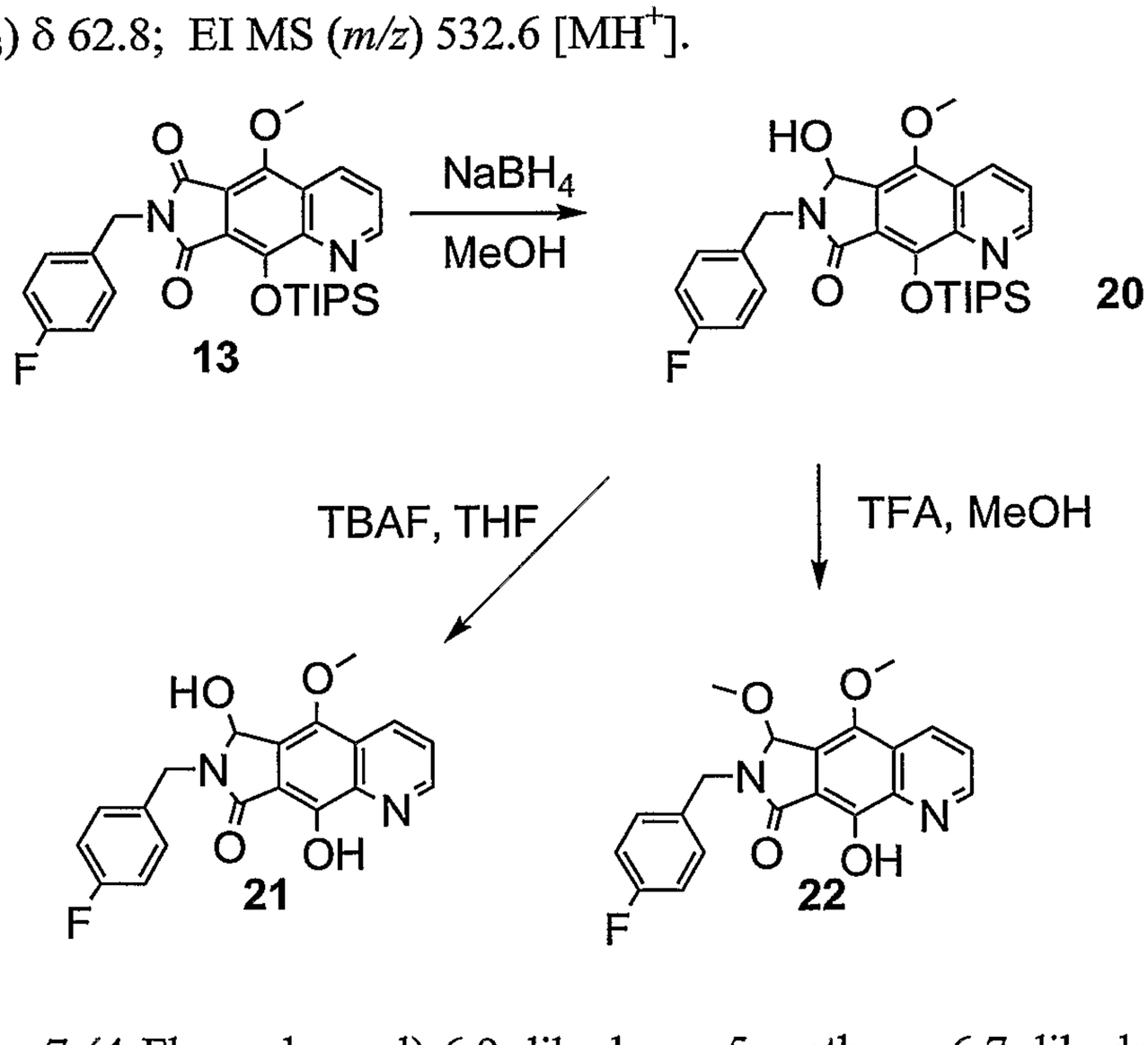
Example 18 7-(4-Fluoro-benzyl)-9-hydroxy-5-methoxy-6-methyl-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **18**

To a solution of **16** (52 mg, 0.099 mmol) in 1.4 mL of dry CH_2Cl_2 under a N_2 atmosphere, was added BF_3•OEt_2 (49 μL, 0.397 mmol) followed by triethylsilane (63 μL, 0.397 mmol). The solution was allowed to stir at ambient temperature for 1 day when LCMS indicated a clean conversion of starting materials to the desired product. The reaction was worked up by removing the solvent and dissolving the residue in EtOAc. The organic layer was washed with water and the solvent removed under reduced pressure. The residue was dissolved in 1 mL of EtOAc and triturated by addition of hexanes to provide the product **18**. ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (d, 3H, *J*= 7 Hz), 3.93 (s, 3H), 4.28 (d, 1H, *J*= 15 Hz), 4.65 (q, 1H, *J*= 7 Hz), 5.25 (d, 1H, *J*= 15 Hz), 7.06 (t, 2H, *J*= 8 Hz), 7.32 (dd, 2H, *J*= 6, 8 Hz), 7.67 (dd, 1H, *J*= 4, 8 Hz), 8.59 (br s, 1H), 8.61 (d, 1H, *J*= 8 Hz), 9.11 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 42.8, 54.5, 61.9, 113.9, 115.7, 116.0, 122.7, 126.6, 129.8, 129.9, 130.8, 132.1, 133.1, 136.7, 142.4, 147.8, 148.3, 162.3 (d, *J*= 245 Hz), 168.1; ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 62.5; EI MS (*m/z*) 353.5 [MH^+], 385.4 [M+Na].



Example 19 Isoxazole **19**

The exocyclic olefin in **17** can be utilized toward a cycloaddition reaction. Under a nitrogen atmosphere, a TIPS protected analog **17a** (17 mg, 0.033 mmol) was suspended in 0.17 mL of dry CH_2Cl_2. To this solution was added 4-chlorophenylglyoxyl-O-hydroxamyl chloride (7.3 mg, 0.034 mmol) and TEA (4.7 μL, 0.034 mmol). The solution was stirred at room temperature for 12 hours. The reaction was worked up by diluting the solution with EtOAc and washing the organic layer with water. The organic layer was removed under reduced pressure. The residue was dissolved in EtOAc and diluted with hexanes. The solution was filtered and the mother liquor was dried to provide 18 mg (100%) of the product **19** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.31 (d, 1H, *J*= 19 Hz), 3.94 (s, 3H), 4.01 (d, 1H, *J*= 19 Hz), 4.36 (d, 1H, *J*= 16 Hz), 4.96 (d, 1H, *J*= 15 Hz), 6.95 (t, 2H, *J*= 9 Hz), 7.29 (dd, 2H, *J*= 5, 9 Hz), 7.55 (d, 2H, *J*= 9 Hz), 7.65 (dd, 1H, *J*= 4, 8 Hz), 8.29 (d, 2H, *J*= 9 Hz), 8.45 (dd, 1H, *J*= 2, 9 Hz), 8.99 (dd, 1H, *J*= 2, 4 Hz); ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 62.8; EI MS (*m/z*) 532.6 [MH^+].



Example 20 7-(4-Fluoro-benzyl)-6,9-dihydroxy-5-methoxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **20**

To a solution of **13** (0.699 g, 1.38 mmol) in 14 mL of a 1:1 solution of dry MeOH: CH_2Cl_2 under a N_2 atmosphere was added sodium borohydride ($NaBH_4$, 156 mg, 4.13 mmol). The reaction mixture was dried after 5 hours and the residue was loaded onto a silica column. The product was eluted with a 10% EtOAc-Hex to

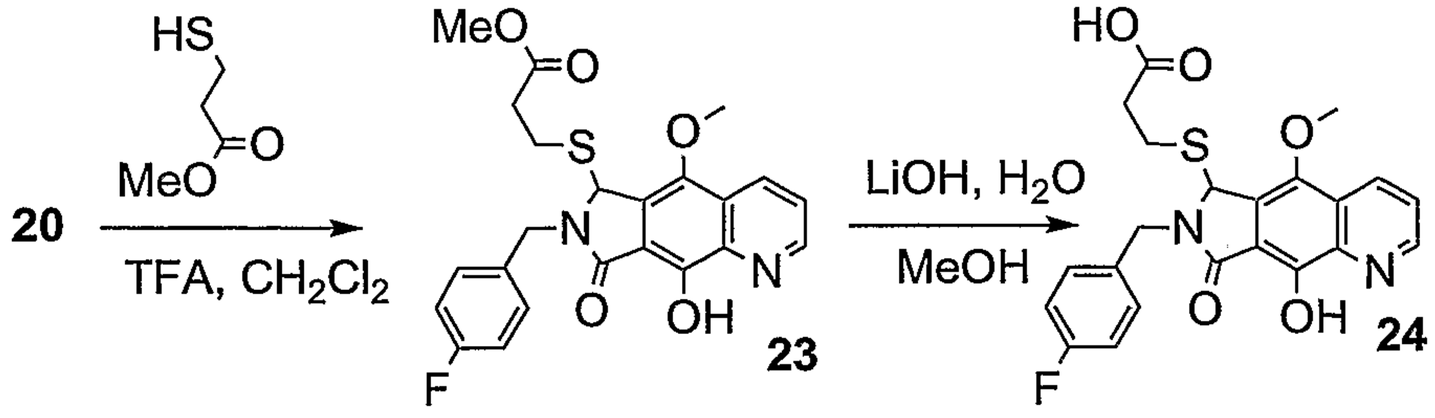
provide the product **20**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, 9H, *J*= 8 Hz), 1.16 (d, 9H, *J*= 7 Hz), 1.52 (septet, 3H, *J*= 8 Hz), 3.72 (d, 1H, *J*= 11 Hz), 4.11 (s, 3H), 4.23 (d, 1H, *J*= 15 Hz), 4.85 (d, 1H, *J*= 15 Hz), 5.79 (d, 1H, *J*= 11 Hz), 6.97 (t, 2H, *J*= 9 Hz), 7.27 (dd, 2H, *J*= 6, 9 Hz), 7.43 (dd, 1H, *J*= 4, 8 Hz), 8.43 (dd, 1H, *J*= 2, 8 Hz), 8.81 (dd, 1H, *J*= 2, 4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8. 18.2, 41.3, 61.6, 78.6, 115.3, 115.6, 116.6, 122.3, 126.0, 126.8, 130.1, 130.2, 131.1, 132.8, 143.1, 143.8, 148.3, 162.1 (d, *J*= 244 Hz), 165.2; EI MS (*m/z*) 511.5 [MH^+], 533.4 [M+Na].

Example 21 7-(4-Fluoro-benzyl)-6,9-dihydroxy-5-methoxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **21**

A solution of **20** (35 mg, 0.069 mmol) was stirred in 0.69 mL of dry THF and 75 μL of a 1 M solution of tetra-butylammonium fluoride (TBAF, 0.075 mmol) under a N_2 atmosphere for 2 hours at ambient temperature. The solution was diluted with EtOAc and the organic layer was washed with water. The organic layer was removed *in vacuo* to leave a yellow residue. The solid was washed with hexanes and dried to give 27 mg (100%) of the product **21**. ^{1}H NMR (300 MHz, CD_3OD) δ 4.13 (s, 3H), 4.46 (d, 1H, *J*= 15 Hz), 5.04 (d, 1H, *J*= 15 Hz), 6.01 (s, 1H), 7.09 (t, 2H, *J*= 9 Hz), 7.42-7.47 (m, 2H), 7.65 (dd, 1H, *J*= 4, 9 Hz), 8.61 (d, 1H, *J*= 8 Hz), 8.89 (d, 1H, *J*= 3Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 41.1, 79.3, 60.0, 111.6, 115.0, 115.4, 122.4, 125.1, 125.9, 129.6, 130.0, 131.5, 132.9, 139.5, 142.8, 148.8, 161.8 (d, *J*= 245 Hz), 166.7; ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 59.4; EI MS (*m/z*) 355.4 [MH^+].

Example 22 7-(4-Fluoro-benzyl)-9-hydroxy-5,6-dimethoxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **22**

A solution of **21** (6.7 mg, 0.019 mmol) in a 1:1 solution of CH_2Cl_2: MeOH was stirred with TFA (3 μL, 0.038 mmol) at room temperature for 2 hours when complete conversion was observed by LCMS. The solution was dried *in vacuo* and the residue was washed with hexanes to yield 7 mg of the product **22**. EI MS (*m/z*) 355.4 [MH^+].



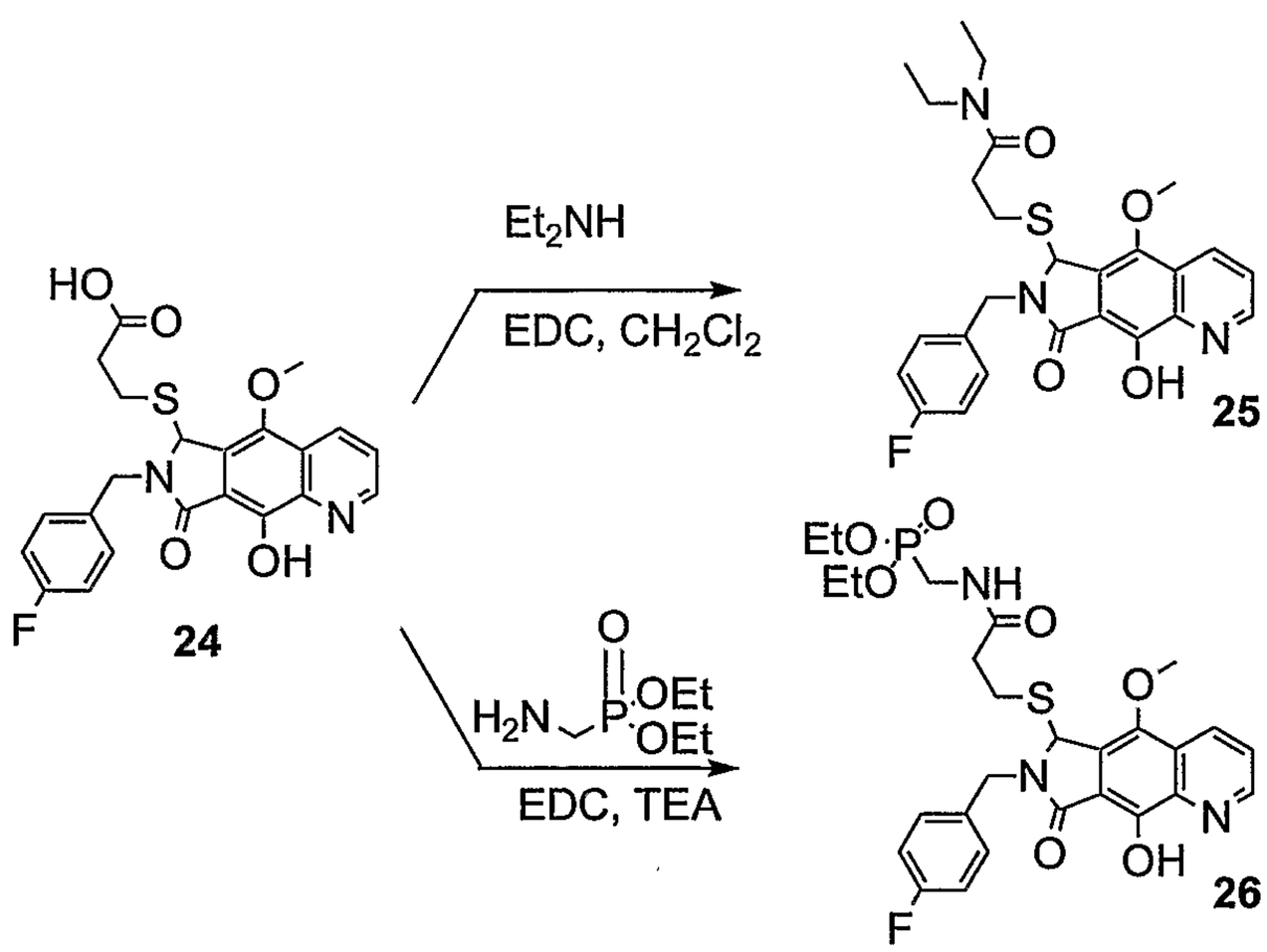
Example 23 3-[7-(4-Fluoro-benzyl)-9-hydroxy-5-methoxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-6-ylsulfanyl]-propionic acid methyl ester **23**

To a solution of **20** (215 mg, 0.422 mmol) in CH_2Cl_2 (4.2 mL) and TFA (98 μL, 1.26 mmol) was added methyl-3-mercaptopropionate (56 μL, 0.506 mmol). The solution was stirred at ambient temperature for 5 hours when LCMS analysis indicated complete conversion of the starting materials to the products. The solution was dried under reduced pressure and azeotroped with CH_2Cl_2 three times to provide the product **23** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30-2.38 (m, 4H), 3.63 (s, 3H), 4.04 (s, 3H), 4.42 (d, 1H, *J*= 15 Hz), 5.33 (d, 1H, *J*= 15 Hz), 5.49 (s, 1H), 7.05 (t, 2H, *J*= 9 Hz), 7.38 (dd, 2H, *J*= 5, 8 Hz), 7.59 (dd, 1H, *J*= 4, 9 Hz), 8.53 (d, 1H, *J*= 8 Hz), 8.91- 9.01 (m, 1H); ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 62.6; EI MS (*m/z*) 457.3 [MH^+], 479.2 [M+Na].

Example 24 3-[7-(4-Fluoro-benzyl)-9-hydroxy-5-methoxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-6-ylsulfanyl]-propionic acid **24**

A solution of **23** (150 mg, 0.329 mmol) in 3.29 mL of a 1:2:3 solution of H_2O: MeOH: THF was stirred with LiOH. H_2O (69 mg, 1.65 mmol) for 1 hour when LCMS demonstrated complete conversion of starting materials to product. The reaction mixture was dried under reduced pressure and the residue was suspended in water and the pH was adjusted to 11 with aqueous 1N NaOH solution. The aqueous layer was washed with EtOAc twice. The pH of the aqueous layer was then adjusted to 5 using 1N HCl and the product was extracted with CH_2Cl_2 under continuous extraction conditions. The organic layer was dried *in vacuo* to yield the product **24** as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.1 (s, 1H), 2.25- 2.45 (m, 4H), 4.04 (s, 3H), 4.43 (d, 1H, *J*= 15 Hz), 5.32 (dd, 1H, *J*= 3, 14 Hz), 5.49 (s, 1H), 7.03 (t, 2H, *J*= 9 Hz), 7.35 (dd, 2H, *J*= 5, 8 Hz), 7.57 (dd, 1H, *J*= 4, 8 Hz), 8.52 (dd, 1H, *J*= 2, 8 Hz), 8.98 (dd, 1H, *J*= 2, 5 H); ^{13}C NMR (75 MHz, CD_3OD) δ 21.4, 33.6, 41.9, 61.8, 61.9,

112.3, 115.7, 116.0, 123.1, 125.0, 126.5, 130.4, 130.5, 131.8, 131.8, 139.3, 142.6, 148.3, 149.6, 162.4 (d, *J*= 245 Hz), 167.2, 175.3; ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 62.6; EI MS (*m/z*) 441.4 $[M-H]^-$, 883.1 $[2M-2H]^-$.



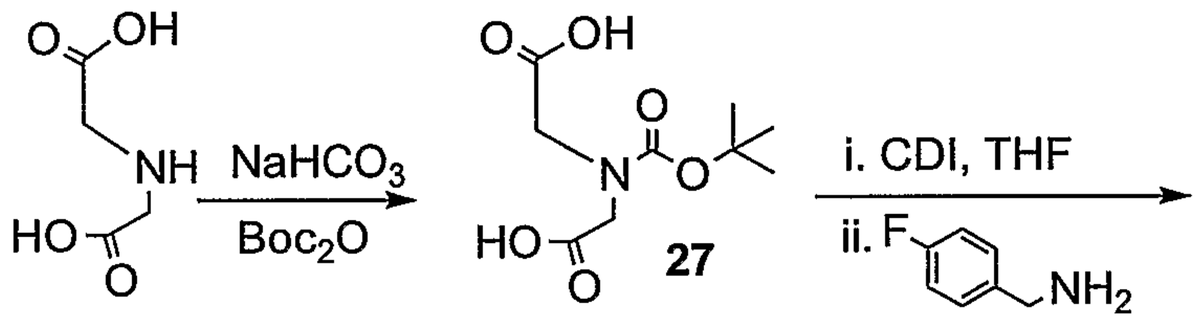
Example 25 N,N-Diethyl-3-[7-(4-fluoro-benzyl)-9-hydroxy-5-methoxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-6-ylsulfanyl]-propionamide **25**

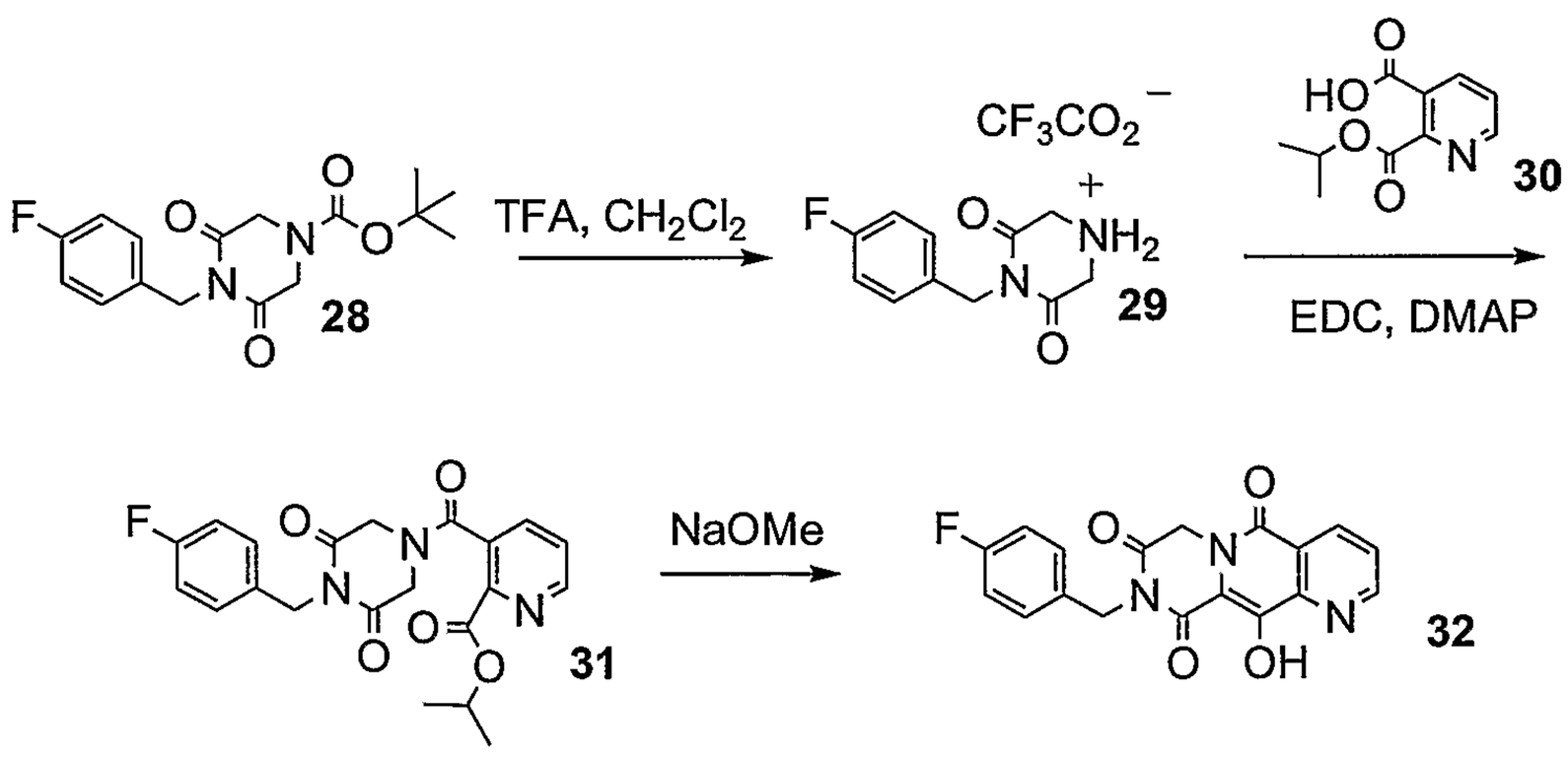
A solution of **24** (10.7 mg, 0.024 mmol) in CH_2Cl_2 (0.24 mL) was stirred with EDC (14 mg, 0.73 mmol) and diethyl amine (10 μL, 0.097 mmol) for 1 day at ambient temperature. The product **25** was purified by reverse phase HPLC using 5-95% A. Buffer A contained CH_3CN- 1% HOAc and B contained H_2O- 1% HOAc. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.984 (t, 3H, *J*= 6 Hz), 1.05 (t, 3H, *J*= 7 Hz), 2.23-2.45 (m, 4H), 3.04 (q, 2H, *J*= 7 Hz), 3.29 (q, 2H, *J*= 8 Hz), 4.06 (s, 3H), 4.47 (d, 1H, *J*= 14 Hz), 5.31 (d, 1H, *J*= 15 Hz), 5.50 (s, 1H), 7.05 (t, 2H, *J*= 9 Hz), 7.36- 7.44 (m, 2H), 7.55- 7.62 (m, 1H), 8.53 (d, 1H, *J*= 9 Hz), 8.95- 9.00 (m, 1H); EI MS (*m/z*) 520.2 $[MH^+]$, 1016.9 [2M+Na].

Example 26 ({3-[7-(4-Fluoro-benzyl)-9-hydroxy-5-methoxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-6-ylsulfanyl]-propionylamino}-methyl)-phosphonic acid diethyl ester **26**

To a solution of **24** (15 mg, 0.035 mmol) in 0.35 mL of CH2Cl2 (0.35 mL) was added diethyl(aminomethyl)phosphonate oxalate (27 mg, 0.105 mmol), EDC (20

mg, 0.105 mmol) and TEA (15 μL, 0.105 mmol). The solution was stirred at room temperature for 1 day when the same amount of the aminomethyl phosphonate, EDC and TEA were added. The reaction was stirred for another day when complete conversion of starting materials to the desired product was observed by LCMS. The product **26** was purified by reverse phase HPLC using 5- 95% A. Buffer A contained CH_3CN-1% HOAc and buffer B was H_2O-1% HOAc. ^1H NMR (300 MHz, $CDCl_3$) δ 1.33- 1.40 (m, 6H), 2.37- 2.45 (m, 4H), 3.60- 3.72 (m, 2H), 4.05 (s, 3H), 4.06- 4.18 (m, 4H), 4.44 (d, 1H, *J*= 15 Hz), 5.33 (d, 1H, *J*= 14 Hz), 5.49 (s, 1H), 6.17 (br s, 1H), 6.98- 7.08 (m, 2H), 7.33-7.43 (m, 2H), 7.55- 7.63 (m, 1H), 8.50- 8.57 (br d, 1H), 8.97 (br s, 1H); ^{31}P (121.4 MHz, $CDCl_3$) δ 22.7; ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 62.6; EI MS (*m/z*) 590.4 $[M-H]^-$, 614.2 [M+Na].





Example 27 (tert-Butoxycarbonyl-carboxymethyl-amino)-acetic acid **27**

A mixture of iminodiacetic acid (5.1 g, 38.3 mmol) and sodium hydrogen carbonate ($NaHCO_3$, 12.9 g, 153 mmol) were dissolved in 50 mL of water. Once the bubbling subsided, 50 mL of THF was added followed by 10.0 g (46.0 mmol) of BOC_2O. The mixture was stirred at ambient temperature for 2 days when starting materials were completely consumed as detected by ESI. The reaction was worked up by removing THF and washing the aqueous layer with Et_2O twice. The pH of the aqueous layer was then adjusted to 1 using conc. HCl. The product was extracted

with EtOAc and solvent removed *in vacuo* to provide the product as a white solid. The product was purified by crystallization from EtOAc to give 8.04 g (90%) of clear crystals of **27**. ES MS $[M-H]^-$ 232.1.

Example 28 4-(4-Fluoro-benzyl)-3,5-dioxo-piperazine-1-carboxylic acid tert-butyl ester **28**

A solution of **27** (547 mg, 2.35 mmol) and carbonyl diimidazole (837 mg, 5.16 mmol) in 4.7 mL of dry THF under a N_2 atmosphere was refluxed for 5 minutes. Once the reaction cooled down to room temperature 4-fluorobenzyl amine (0.295 mL, 2.58 mmol) was added and the mixture was heated to reflux overnight. The reaction mixture was then concentrated and re-dissolved in EtOAc. The organic layer was washed with an aqueous 0.5 N HCl solution and the solvent was removed *in vacuo*. The product was purified by column chromatography eluting with CH_2Cl_2 to provide clean product **28** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 4.39 (s, 4H), 4.92 (s, 2H), 6.99 (t, 2H, *J*= 9 Hz), 7.40 (dd, 2H, *J*= 5, 9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1, 42.0, 47.1, 82.3, 115.2, 115.5, 131.1, 131.2, 132.0, 153.0, 162.7 (d, *J*= 245 Hz), 168.0; ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 62.5; EI MS (*m/z*) 340.5 [M+Na].

Example 29 4-(4-Fluoro-benzyl)-3,5-dioxo-piperazin-1-ium; trifluoro-acetate **29**

A solution of **28** (26 mg, 0.080 mmol) in 2 mL of CH_2Cl_2 was stirred with 1 mL of TFA for 1.5 hours when TLC indicated complete conversion to the product. The solution was dried *in vacuo* to yield a white solid. The product was purified by crystallization using CH_2Cl_2. ^{1}H NMR (300 MHz, CD_3OD) δ 4.18 (s, 4H), 4.95 (s, 2H), 5.01 (s, 2H), 7.01 (dt, 2H, *J*= 2, 9 Hz), 7.41 (ddd, 2H, *J*= 2, 5, 9 Hz); ^{19}F NMR (282.6 MHz, $CDCl_3$) δ -77.5, 60.0.

Example 30 Pyridine-2,3-dicarboxylic acid 2-isopropyl ester **30**

A mixture of 2,3-pyridine carboxylic anhydride (100 g, 0.67 mol) in 500 mL of *i*-PrOH was heated at reflux for 1 day according to the procedure of Ornstein, P. *et al. J. Med. Chem.* (1989) *32*, 4, 827. The reaction mixture was then dried *in vacuo* to provide the product **30** as a white solid. ^{1}H NMR (300 MHz, CD_3OD) δ 1.37 (d, 6H,

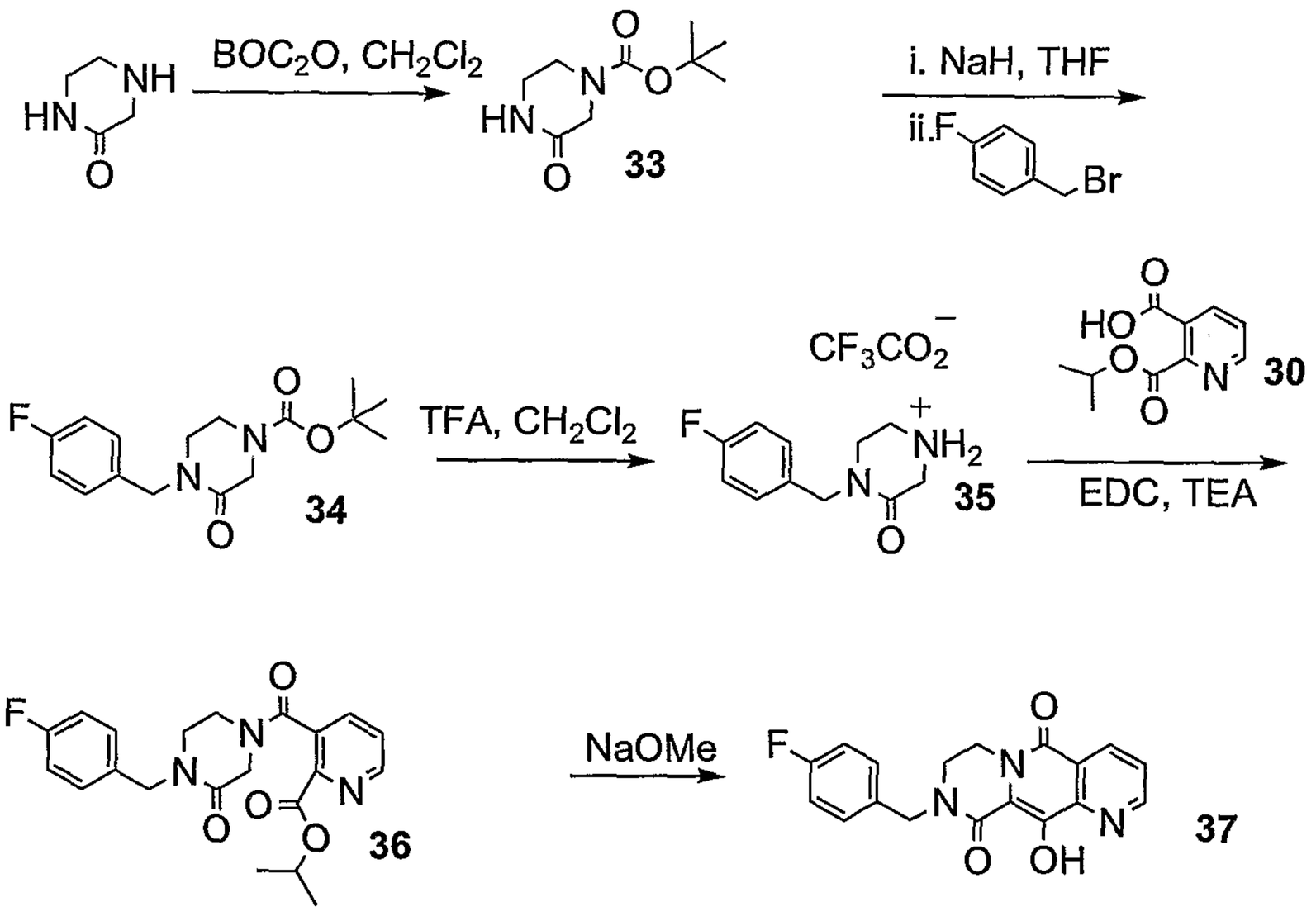
J= 7 Hz), 5.27 (septet, 1H, *J*= 6 Hz), 7.63 (dd, 1H, *J*= 5, 8 Hz), 8.34 (dd, 1H, *J*= 1, 8 Hz), 8.71 (d, 1H, *J*= 5 Hz); EI MS (*m/z*) 210.0 [MH^+].

Example 31 3-[4-(4-Fluoro-benzyl)-3,5-dioxo-piperazine-1-carbonyl]-pyridine-2-carboxylic acid isopropyl ester **31**

A solution of **29** (54 mg, 0.16 mmol), **30** (34 mg, 0.16 mmol), EDC (92 mg, 0.48 mmol), dimethylaminopyridine (20 mg, 0.16 mmol), triethylamine (67 µL, 0.48 mmol) in 1.6 mL of a 1:1 mixture of CH_2Cl_2:DMF was stirred for 1 day at ambient temperature. The reaction mixture was directly loaded onto a silica column and the product was eluted with a gradient of 1:1 Hex-EtOAc to EtOAc followed by 10% MeOH-EtOAc. The product **31** was obtained as a clear oil. EI MS (*m/z*) 414.7 [MH^+], 436.4 [M+Na].

Example 32 7-(4-Fluoro-benzyl)-9-hydroxy-1,7,10a-triaza-anthracene-6,8,10-trione **32**

A solution of **31** (5 mg, 0.01 mmol) in 0.3 mL of dry 0.5 M NaOMe was stirred at ambient temperature for 15 minutes when a yellow precipitate formed. The solvent was removed *in vacuo* and the solid was dissolved in a mixture of CH_2Cl_2- 1N HCl. The layers were separated and the aqueous layer was washed with CH_2Cl_2. The organic solvent was removed to provide an off-white solid. The product **32** was purified by trituration using CH_2Cl_2 and hexane. ^1H NMR (300 MHz, $CDCl_3$) δ 5.01 (s, 2H), 5.16 (s, 2H), 7.02 (dt, 2H, *J*= 2, 9 Hz), 7.51 (ddd, 2H, *J*= 2, 5, 9 Hz), 7.79 (dd, 1H, *J*= 8, 5 Hz), 8.61 (dd, 1H, *J*= 8, 2 Hz), 9.13 (dd, 1H, *J*= 4, 2 Hz), 12.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.4, 46.1, 107.0, 115.5, 115.8, 126.7, 127.1, 130.8, 131.4, 131.5, 132.5, 143.2, 148.4, 153.7, 156.0, 162.2 (d, *J*= 249 Hz), 163.9, 164.0; EI MS (*m/z*) 354.6 [MH^+].



Example 33 3-Oxo-piperazine-1-carboxylic acid *tert*-butyl ester **33**

To a mixture of piperazine-2-one (1.037 g, 10.4 mmol) in 52 mL of CH_2Cl_2, was added BOC_2O (2.5 g, 11.4 mmol). The reaction became homogeneous after 3 hours when the starting material was completely consumed. The reaction was diluted with CH_2Cl_2 and the organic layer was washed with water. The solvent was removed *in vacuo* to yield quantitative amount of product **33** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H), 3.35-3.44 (m, 2H), 3.64 (t, 2H, *J*= 5 Hz), 4.10 (s, 2H), 6.41 (br s, 1H).

Example 34 4-(4-Fluoro-benzyl)-3-oxo-piperazine-1-carboxylic acid tert-butyl ester **34**

To a heterogeneous solution of **33** (1.6 g, 8.1 mmol) in 16.2 mL of dry THF under a N_2 atmosphere was added 0.211 g (8.80 mmol) of 95% NaH. Once the bubbling subsided, 4-fluorobenzylbromide (1.2 mL, 9.7 mmol) was added dropwise to the solution. After 1 hour, when the reaction was complete as judged by TLC, the reaction was quenched by addition of water and the organic layer was diluted with EtOAc. The organic layer was washed with water and the solvent removed *in vacuo*. The product was purified by column chromatography using 1:1 EtOAc-Hex solvent system to provide 2.3 g (93%) of the product **34** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 3.24 (t, 2H, *J*= 5 Hz), 3.60 (t, 2H, *J*= 5 Hz), 4.16 (s, 2H),

4.59 (s, 2H), 7.03 (t, 2H, *J*= 9 Hz), 7.26 (dd, 2H, *J*= 5. 8 Hz); ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 62.2.Example 35 4-(4-Fluoro-benzyl)-3-oxo-piperazin-1-ium trifluoroacetate salt **35**

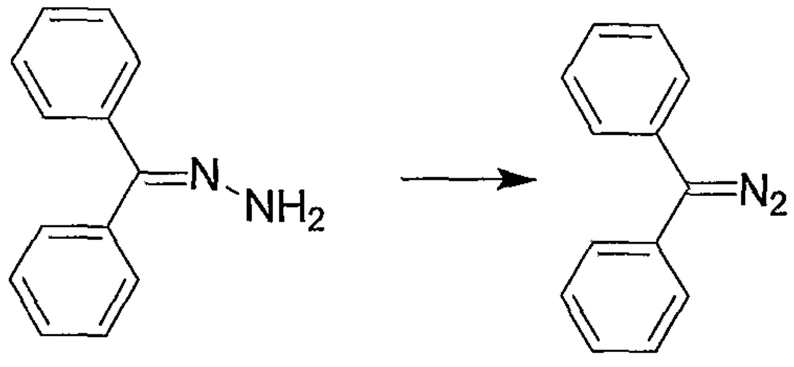
A solution of **34** (1.4 g, 4.5 mmol) in 6 mL of a 1:1 solution of CH_2Cl_2: TFA was stirred at ambient temperature for 2 hours when all of the starting materials were consumed as judged by TLC. The reaction mixtures were dried *in vacuo* to yield 1.5 g of **35** as a thick oil which was used in the next reaction without purification.

Example 36 3-[4-(4-Fluoro-benzyl)-3-oxo-piperazine-1-carbonyl]-pyridine-2-carboxylic acid isopropyl ester **36**

A solution of **35** (1.46 g, 4.55 mmol) was dissolved in 20 mL of a 1:1 solution of CH_2Cl_2:DMF. To this solution was added 0.95 g (4.55 mmol) of **30**, EDC (1.74 g, 9.10 mmol) and triethylamine (1.90 mL, 13.7 mmol). The solution was stirred at room temperature for 4 hours when the reaction was complete. The solution was diluted with CH_2Cl_2 and washed with water. The organic layer was subsequently washed with aq. saturated solution of NH_4Cl and the solvent was removed. The yellow residue was purified by column chromatography using EtOAc-10% MeOH gradient to yield 1.8 g (100%) of the product **36** as a clear oil. EI MS (*m/z*) 400.5 [MH^+], 422.3 [M+Na].

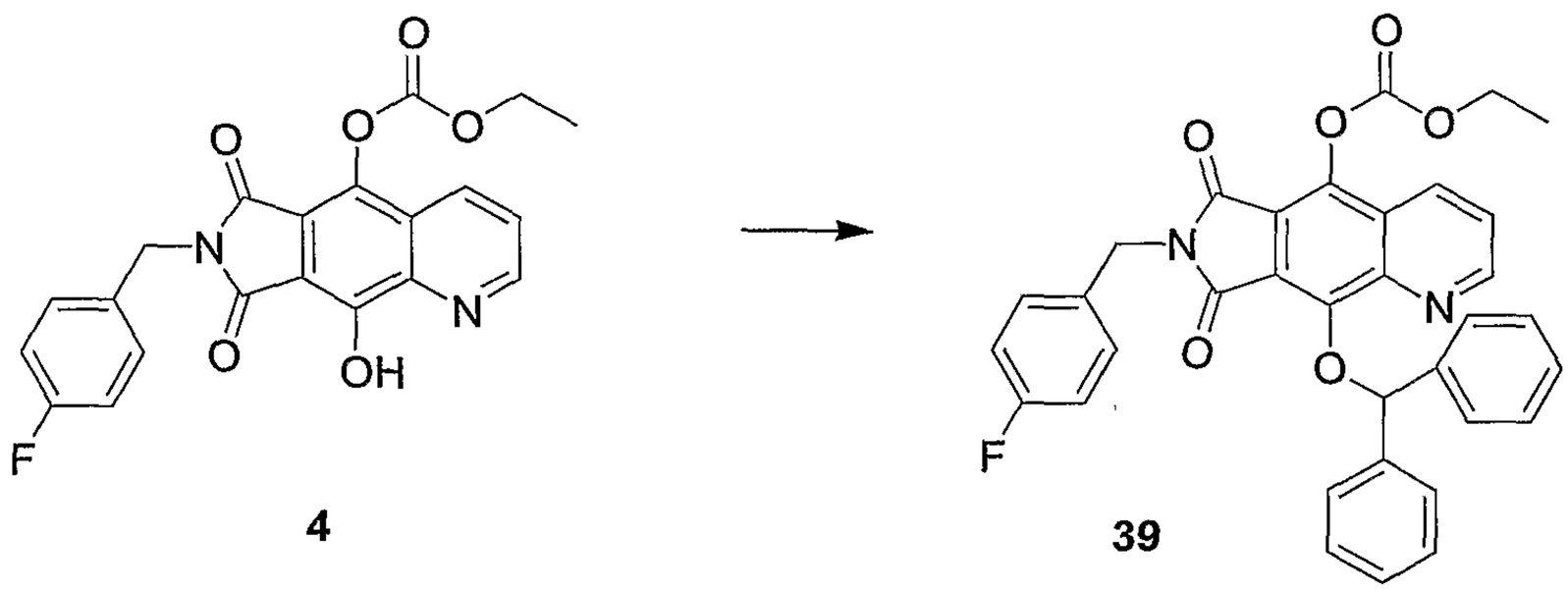
Example 37 7-(4-Fluoro-benzyl)-9-hydroxy-6,7-dihydro-5H-1,7,10a-triaza-anthracene-8,10-dione **37**

To a solution of **36** (0.900 g, 2.26 mmol) in 12 mL of dry MeOH under a N_2 atmosphere was added 12.5 mL of a 0.5 M sodium methoxide (NaOMe). The solution was stirred at ambient temperature for 2.5 hours. The reaction was worked up by removing the solvent and dissolving the residue in CH_2Cl_2. The organic layer was washed with a saturated aqueous solution of NH_4Cl and dried to provide 610 mg of the product **37** as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.58 (t, 2H, *J*= 6 Hz), 4.308 (t, 2H, *J*= 5 Hz), 4.77 (s, 2H), 7.09 (t, 2H, *J*= 8 Hz), 7.34 (t, 2H, *J*= 8 Hz), 7.61 (dd, 1H, *J*= 5, 8 Hz), 8.73 (d, 1H, *J*= 8 Hz), 9.12 (d, 1H, *J*= 3 Hz), 13.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.8, 43.9, 49.5, 111.9, 115.9, 116.2, 124.7, 130.0, 130.1, 131.0, 136.4, 146.8, 147.2, 154.7, 157.3, 163.0 (d, *J*= 245 Hz), 163.7; ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 63.2; EI MS (*m/z*) 340.5 [MH^+], 362.3 [M+Na].



Example 38 Diphenyldiazomethane **38**

Benzophenone hydrazone (25 g, 122.3 mmol) and sodium sulfate (anhydrous) (26 g, 183.5 mmol) were suspended in ether (anhydrous, 400 mL). To this mixture, a potassium hydroxy (powder) saturated ethanol solution (10 mL) was added, followed by mercury oxide (66.2g, 305.8 mmol) to form a red solution. This solution was shaken at RT for 1.5 hours. The solid was filtered off. The filtrate was concentrated to a residue, which was redissolved in 200 mL of hexane and placed in a cold room overnight. The solidified solution was evaporated to dryness, which gave diphenyldiazomethane **38** as a red solid (24.7 g, 99.7 %).

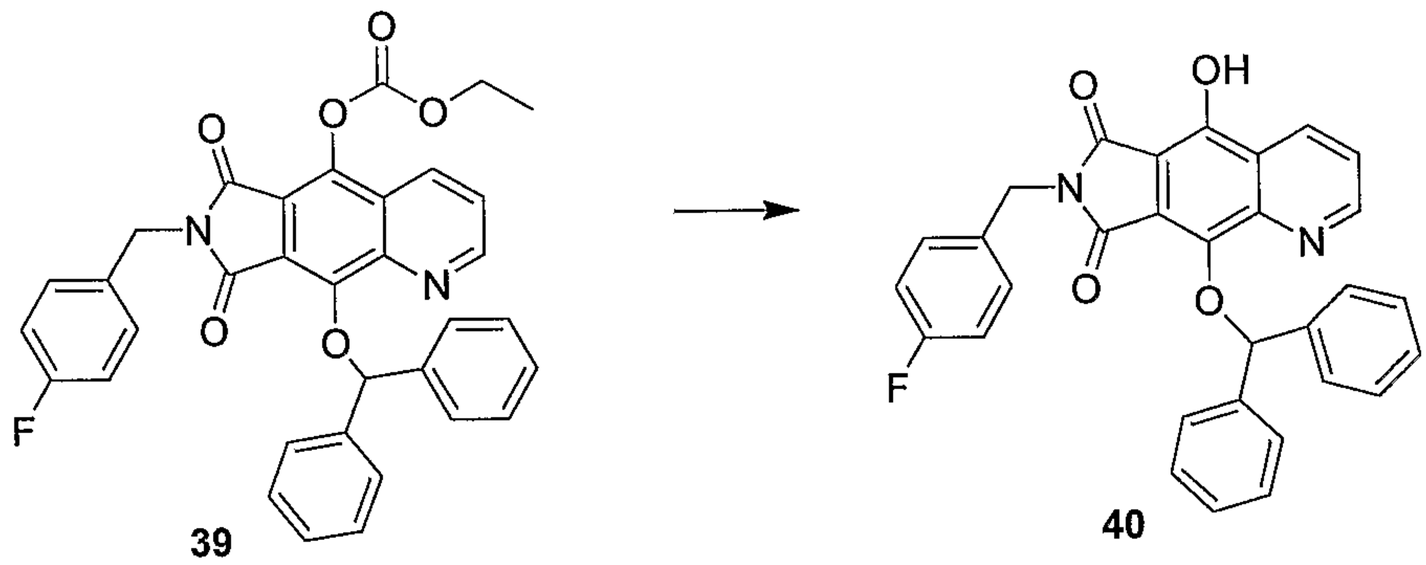


4 **39**

Example 39

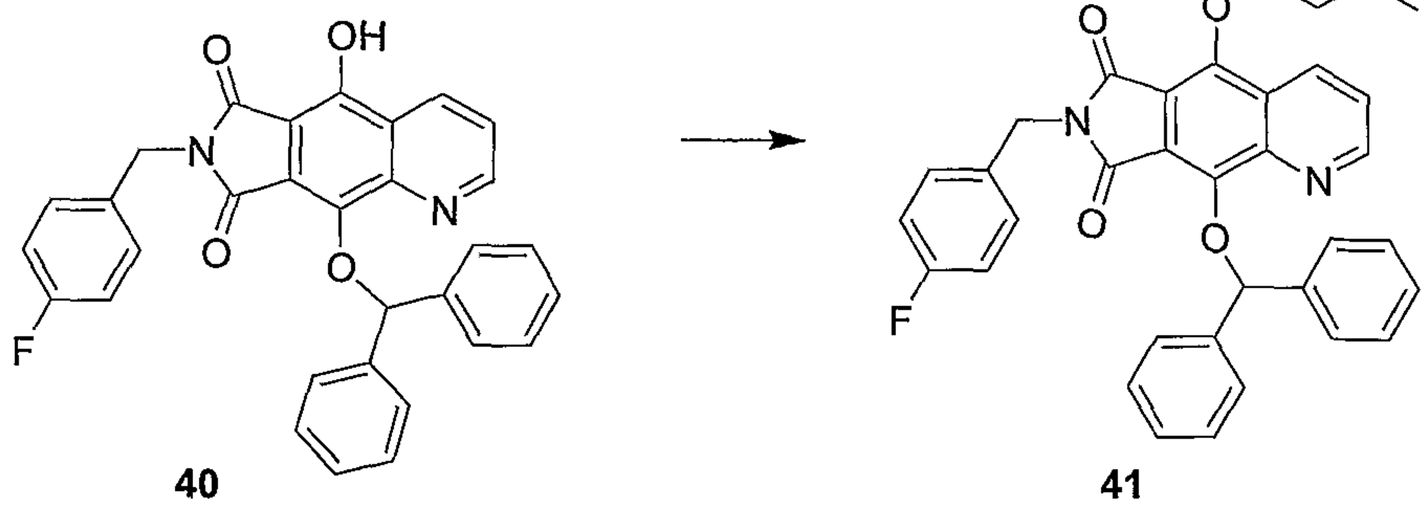
Mono carbonate **4** (8.9 g, 21.7 mmol) was dissolved in 1,2-dichloroethane (400 mL). Diphenyldiazomethane **38** (8.4g, 43.4 mmol) was added in one portion. The mixture was stirred at 70°C for 3 hours. The reaction was monitored by TLC (EtOAc/Hexane = 3/7). After completion of the reaction, the solution was cooled down to room temperature. The solvent was evaporated. The crude product is chromatographed on a silica gel column, eluting with EtOAc/hexane to give the product **39** as a white solid (10.1g, 80%). ^{1}H NMR ($CDCl_3$): δ 9.1 (d, 1H), 8.4 (d, 1H), 8.0 (s, 1H), 7.6 (dd, 1H), 7.6 (d, 4H), 7.4 (dd, 2H), 7.2-7.3 (m, 6H), 7.0 (t, 2H), 4.8 (s, 2H), 4.4 (q, 2H), 1.4 (t, 3H). MS: 577 (M+1), 599 (M+23).

The reaction was repeated, where mono-carbonate **4** (.2 g, 0.4878 mmol) was dissolved in 9 mL of dichloroethane. To this was added diphenyldiazomethane (0.189 g, 0.9756 mmol) and stirred at 70 °C for two hours. After starting material consumed, concentrated off some solvent, and chromatographed (25% ethylacetate/hexanes) to give product **39** (0.2653 g, .4598 mmol, 94%.) ^{1}H NMR ($CDCl_3$) δ 9.14 (d, 1H), 8.47 (d, 1H), 7.99 (s, 1H), 7.61 (m, 5H), 7.43 (dd, 2H), 7.27 (m, 6H), 7.02 (dd, 2H), 4.82 (s, 2H), 4.45 (q, 2H), 1.47 (t, 3H.) MS: 577 (M+1)



Example 40

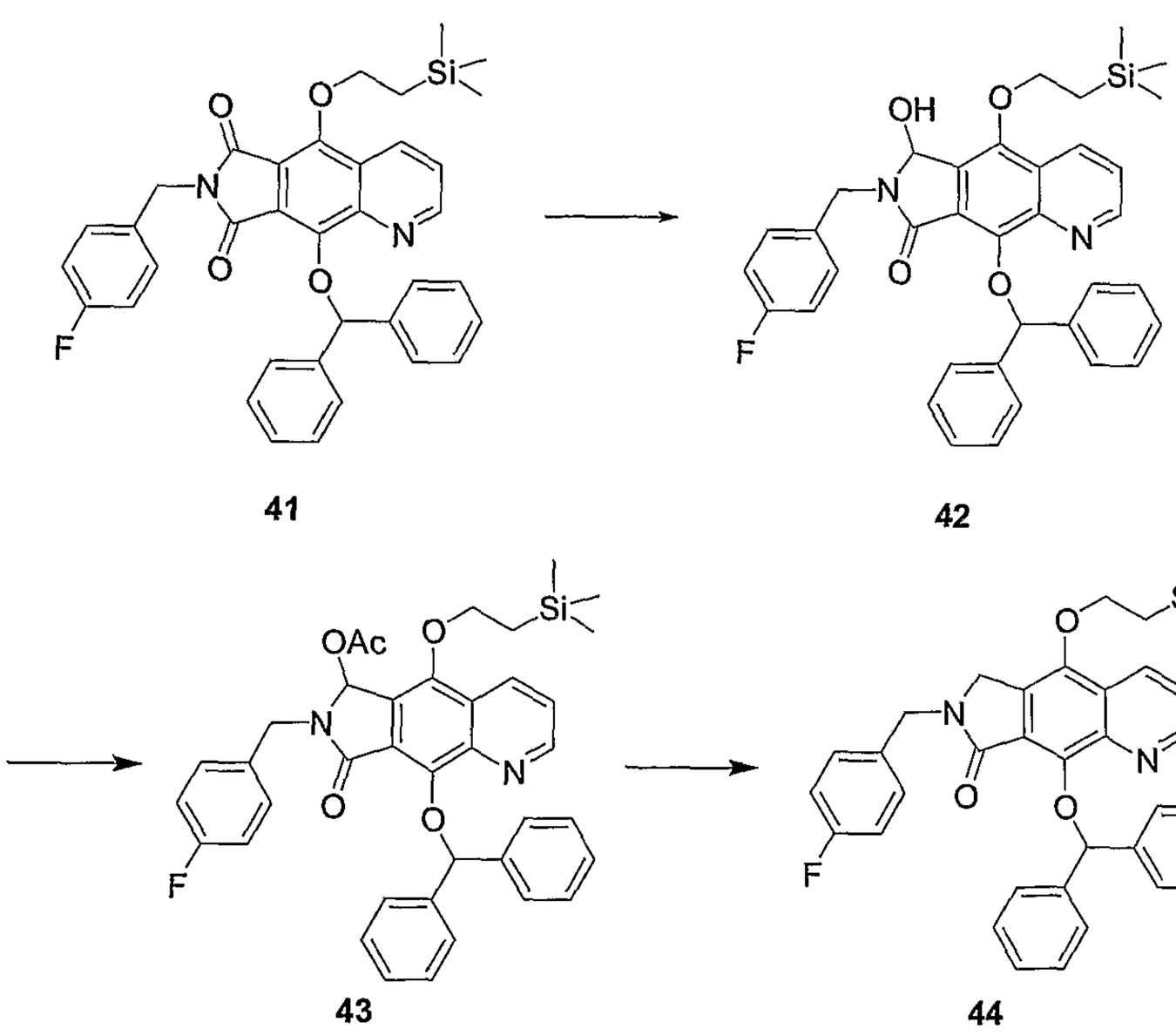
A solution of K_2CO_3 (24.2 g, 175.2 mmol) in water (120 mL) and 4-dimethylaminopyridine (4.24 g, 35.0 mmol) was added to the ethyl carbonate **39** (10.1 g, 17.5 mmol) in THF (180 mL). The mixture is stirred at room temperature under nitrogen atmosphere overnight. Most of THF is removed under reduced pressure at 30-40°C and the remaining solution is diluted with dichloromethane. To this, it is acidified with 1N HCl to pH about 4. The organic phase was separated and washed with brine, dried ($MgSO_4$) and concentrated to give a yellow solid crude product **40** (9.9 g, 100%). ^{1}H NMR ($CDCl_3$): δ 9.1 (d, 1H), 8.6 (d, 1H), 8.4 (s, 1H, (OH)), 7.8 (s, 1H), 7.6 (dd, 1H), 7.6 (dd, 4H), 7.4 (d, 2H), 7.2-7.3 (m, 6H), 7.0 (t, 2H), 4.8 (s, 2H). LC/MS: 527 (M+23).



40 41

Example 41

2-(Trimethylsilyl) ethanol (2.4 mL, 16.7 mmol), triphenylphosphine (3.5 g, 13.4 mmol) and diethyl azodicarboxylate (92.1 mL, 13.4 mmol) was added to the phenol **40** (3.37 g, 6.7 mmol) in anhydrous THF (70 mL). The solution was stirred at room temperature for 3 hours under nitrogen. TLC indicated the completion of the reaction. The solvent was evaporated and the residue oil was purified by silica gel chromatography, eluting with EtOAc/hexane to afford the product **41** (3.3 g, 82%). ^{1}H NMR ($CDCl_3$): δ 9.1 (d, 1H), 8.6 (d, 1H), 7.9 (s, 1H), 7.6 (dd, 1H), 7.6 (d, 4H), 7.4 (d, 2H), 7.2-7.3 (m, 6H), 7.0 (t, 2H), 4.8 (s, 2H), 4.6 (t, 2H), 1.2 (t, 2H). MS: 605 (M+1), 627 (M+23).



41 42

43 44

Example 42

Compound **41** (3.3 g, 5.46 mmol) was dissolved in the mixture of THF (40 mL), isopropanol (20 mL) and water (10 mL) and chilled to 0 °C in an ice-bath. To this was added lithium borohydride (373.0 mg, 16.4 mmol) slowly. The mixture was stirred at 0°C for 1 hour and at room temperature for 1 hour under nitrogen. TLC indicated the completion of the reaction. A solution of 1N HCl (30 mL) was added and the mixture was extracted twice with CH_2Cl_2 (2x50 mL). The organic layer was washed with saturated $NaHCO_3$ and dried over Mg_2SO_4 and evaporated to dryness to give **42** as an oil (3.3 g).

Example 43

Crude product **42** was dissolved in anhydrous dichloromethane (50mL). *N*-dimethylaminopyridine (66.7 mg, 0.546 mmol), *N, N*-diisopropylethylamine (2.85 mL, 16.4 mmol) and acetic anhydride (1.03 mL, 109 mmol) were added. The mixture was stirred at room temperature under nitrogen overnight. TLC indicated the completion of the reaction. The reaction was quenched with 1N HCl (30 mL) and extracted with CH_2Cl_2 twice (2x50 mL). The organic layer was washed with saturated$NaHCO_3$, dried (Mg_2SO_4) and concentrated. The residue was chromatographed on a silica gel column, eluting with EtOAc/Hexane to afford **44** (1.4 g, 43.4% in 3 steps from **41**). ^1H NMR ($CDCl_3$): δ 9.0 (d, 1H), 8.4 (d, 1H), 8.0 (s, 1H), 7.7 (d, 4H), 7.4 (dd, 1H), 7.1-7.3 (m, 8H), 7.0 (t, 2H), 4.8 (s, 2H), 4.2 (s, 2H), 4.1 (t, 2H), 1.1 (t, 2H), 0.1 (s, 9H). MS: 591 (M+1).

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 412

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JUMBO APPLICATIONS/PATENTS

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THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 412

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

We claim:

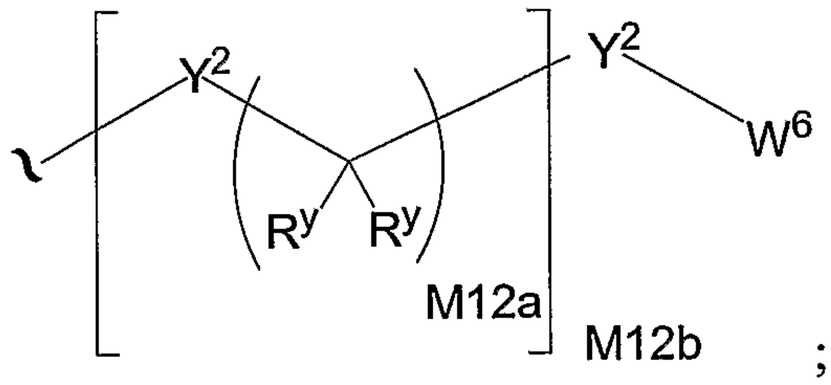
1. An HIV integrase inhibitor compound comprising a phosphonate group.

2. An HIV integrase inhibitor compound of claim 1 comprising one or more covalently attached A^0 groups;

wherein:

A^0 is A^1, A^2 or W^3;

A^1 is:



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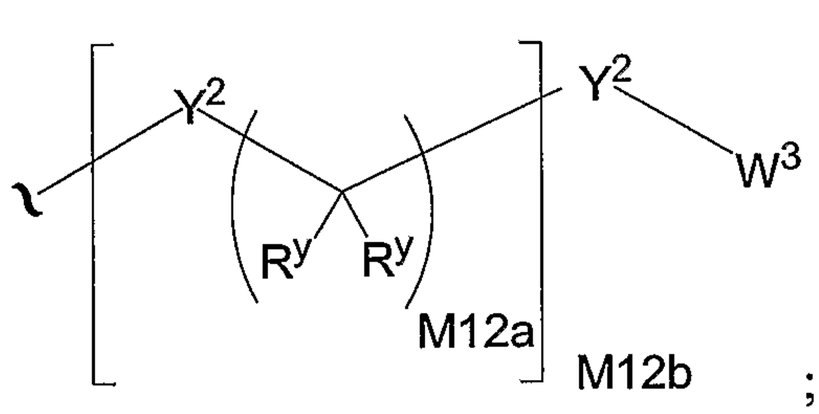
A^2 is:



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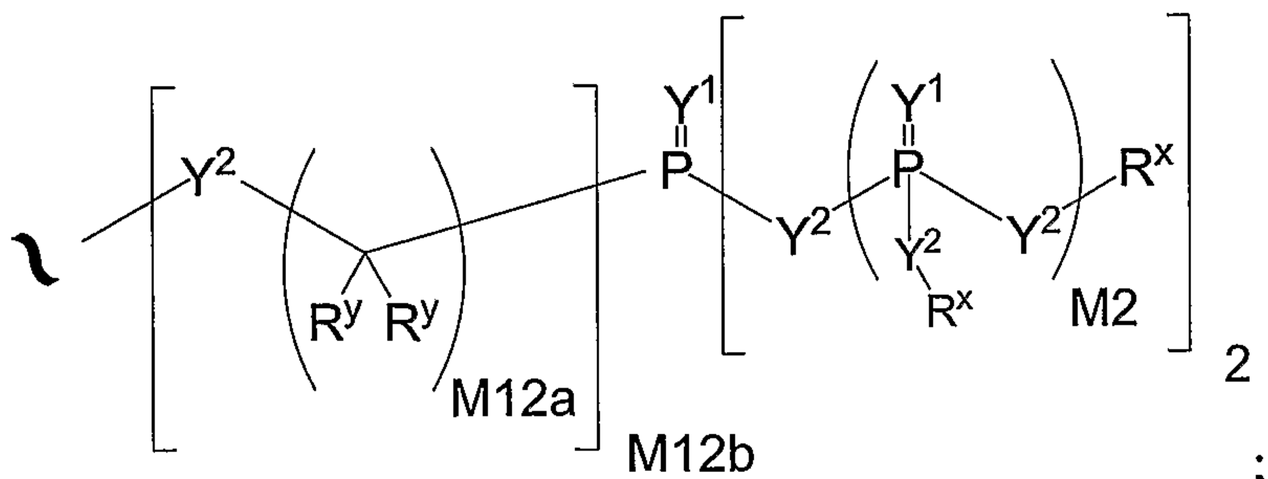
A^3 is:



.

where:

Y^1 is independently O, S, NR^x, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)_2)$;

Y^2 is independently a bond, O, NR^x, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)_2)$, S(O) (sulfoxide), $S(O)_2$ (sulfone), S (sulfide), or S-S (disulfide);

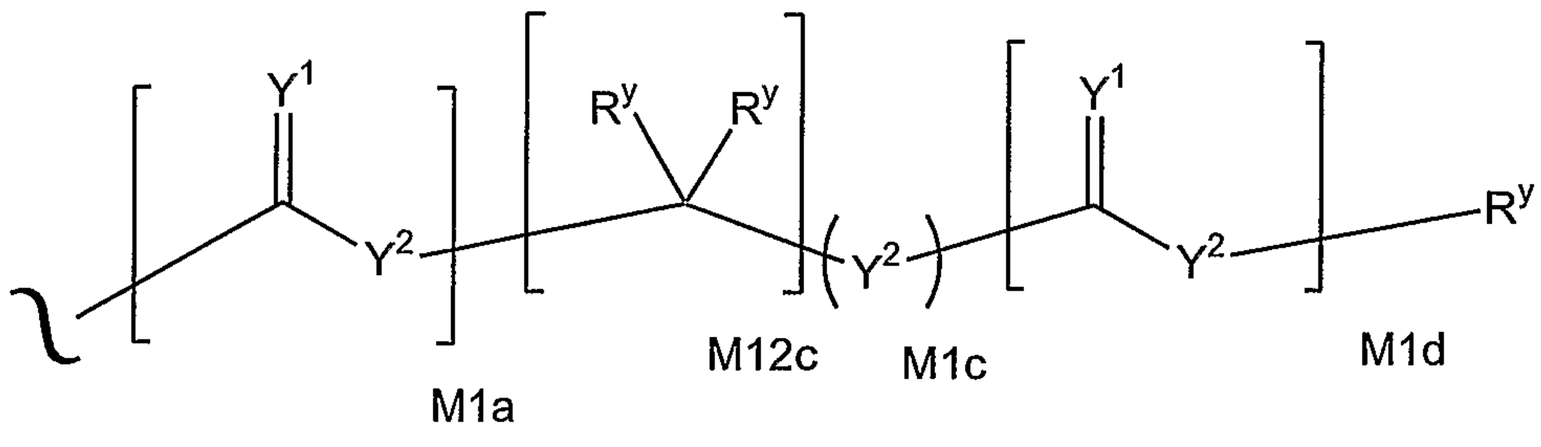
M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12; and

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

R^y is independently H, C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, or a protecting group, or where taken together at a carbon atom, two vicinal R^y groups form a carbocycle or a heterocycle; or taken together at a carbon atom, two vicinal R^y groups form a ring; such as, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; or the ring may contain one or more heteroatoms forming a heterocyclic ring such as, piperazinyl, piperidinyl, pyranyl, or tetrahydrofuryl;

R^x is independently H, C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, or a protecting group, or the formula:



;

where M1a, M1c, and M1d are independently 0 or 1, and M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is a carbocycle or a heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^{3a} is W^{4a} or W^{5a};

W^{4a} is R^{5a}, $-C(Y^1)R^{5a}$, $-C(Y^1)W^{5a}$, $-SO_2R^{5a}$, or $-SO_2W^{5a}$;

W^{5a} is a multivalent substituted carbocycle or heterocycle wherein W^{5a} is independently substituted with 0 to 3 R^2 groups;

W^6 is W^{3a} independently substituted with 1, 2, or 3 A^3 groups;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups; or taken together at a carbon atom, two R^2 groups form a ring; such as, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; optionally, the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)_2$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)N(R^x)_2$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)N(R^x)_2$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)N(R^x)_2$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)N(R^x)_2$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups; and

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;

R is independently selected from H, C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocycle, C_2–C_{20} substituted heterocycle, phosphonate, phosphate, polyethyleneoxy, a protecting group, L–A^3, and a prodrug moiety;

Substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, and substituted heterocycle are independently substituted with one or more substituents selected from F, Cl, Br, I, OH, amino (–NH_2), ammonium (–NH_3^+), alkylamino (–NHR), dialkylamino (–NR_2), trialkylammonium (–NR_3^+), C_1–C_8 alkyl, C_1–C_8 alkylhalide, carboxylate, thiol (–SH), sulfate (–OSO_3R), sulfamate, sulfonate (–SO_3R), 5-7 membered ring sultam, C_1–C_8 alkylsulfonate, C_1–C_8 alkylamino, 4-dialkylaminopyridinium, C_1–C_8

alkylhydroxyl, C_1–C_8 alkylthiol, alkylsulfone (–SO_2R), arylsulfone (–SO_2Ar), arylsulfoxide (–SOAr), arylthio (–SAr), sulfonamide (–SO_2NR_2), alkylsulfoxide (–SOR), ester (–COOR), amido (–C(=O)NR_2), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile (–CN), azido (–N_3), nitro (–NO_2), C_1–C_8 alkoxy (–OR), C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocycle, and C_2–C_{20} substituted heterocycle, phosphonate, phosphate, polyethyleneoxy, and a prodrug moiety; and

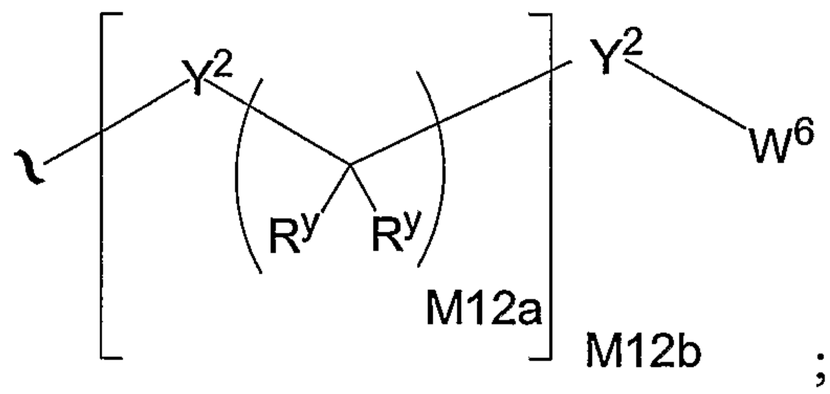
L is a bond, O, S, S–S (disulfide), S(=O) (sulfoxide), $S(=O)_2$ (sulfone), –$S(=O)_2N(R)$– (sulfonamide), NR, N–OR, C_1–C_{12} alkylene, C_1–C_{12} substituted alkylene, C_2–C_{12} alkenylene, C_2–C_{12} substituted alkenylene, C_2–C_{12} alkynylene, C_2–C_{12} substituted alkynylene, –$(CR_2)_nO(CR_2)_n$–, –C(=O)NH–, –OC(=O)NH–, –NHC(=O)NH–, C(=O), –C(=O)$NH(CH_2)_n$–, or –$(CH_2CH_2O)_n$–, where n may be 1, 2, 3, 4, 5, or 6;

wherein at least one A^0 group is an A^1 group.

3. An HIV integrase inhibitor compound of claim 1 comprising one or more covalently attached A^1 groups;

wherein:

A^1 is:



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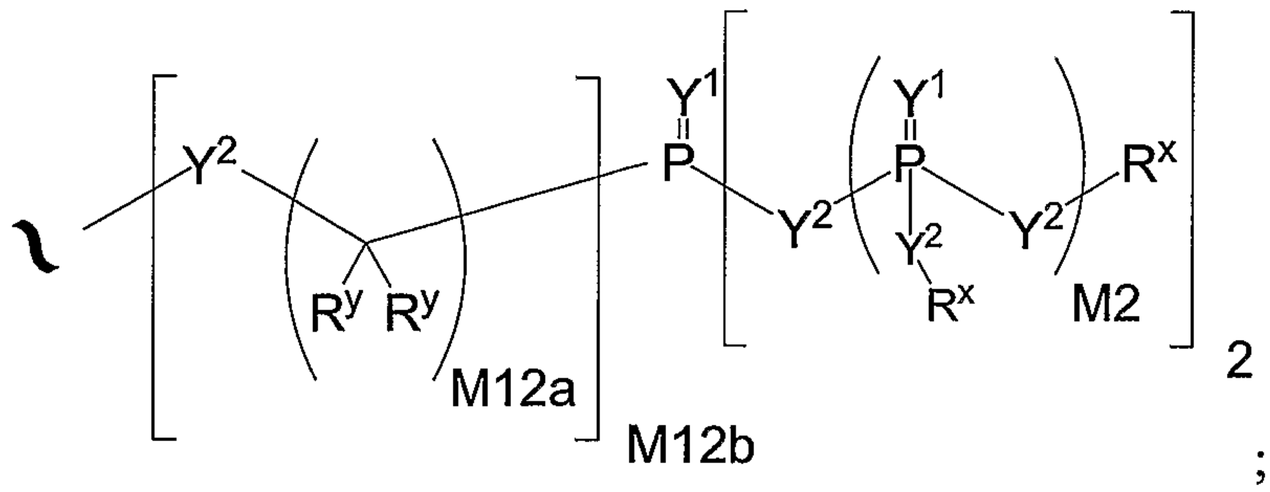
A^3 is:



;

where:

Y^1 is independently O, S, NR^x, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)_2)$;

Y^2 is independently a bond, O, NR^x, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)_2)$, S(O) (sulfoxide), $S(O)_2$ (sulfone), S (sulfide), or S-S (disulfide);

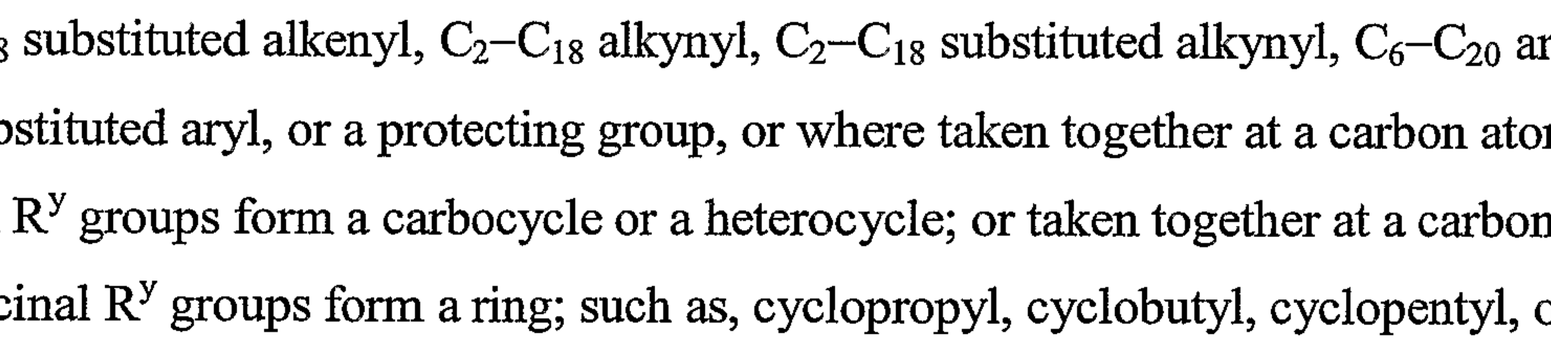
M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12; and

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12;

R^y is independently H, C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, or a protecting group, or where taken together at a carbon atom, two vicinal R^y groups form a carbocycle or a heterocycle; or taken together at a carbon atom, two vicinal R^y groups form a ring; such as, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; or the ring may contain one or more heteroatoms forming a heterocyclic ring such as, piperazinyl, piperidinyl, pyranyl, or tetrahydrofuryl;

R^x is independently H, C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, or a protecting group, or the formula:



;

where M1a, M1c, and M1d are independently 0 or 1, and M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

W^{3a} is W^{4a} or W^{5a};

W^{4a} is R^{5a}, $-C(Y^1)R^{5a}$, $-C(Y^1)W^{5a}$, $-SO_2R^{5a}$, or $-SO_2W^{5a}$;

W^{5a} is a multivalent substituted carbocycle or heterocycle wherein W^{5a} is independently substituted with 0 to 3 R^2 groups;

W^6 is W^{3a} independently substituted with 1, 2, or 3 A^3 groups;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups; or taken together at a carbon atom, two R^2 groups form a ring; such as, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; optionally, the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)_2$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)N(R^x)_2$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)N(R^x)_2$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)N(R^x)_2$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)N(R^x)_2$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups; and

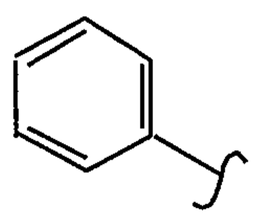
R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;

R is independently selected from the group consisting of H, C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocycle, C_2–C_{20} substituted heterocycle, phosphonate, phosphate, polyethyleneoxy, a protecting group, L–A^3, and a prodrug moiety;

substituted alkyl, substituted alkenyl, substituted alkynyl, substituted aryl, and substituted heterocycle are independently substituted with one or more substituents selected from F, Cl, Br, I, OH, amino ($-NH_2$), ammonium ($-NH_3^+$), alkylamino (–NHR), dialkylamino ($-NR_2$), trialkylammonium ($-NR_3^+$), C_1-C_8 alkyl, C_1-C_8 alkylhalide, carboxylate, thiol (–SH), sulfate ($-OSO_3R$), sulfamate, sulfonate ($-SO_3R$), 5-7 membered ring sultam, C_1-C_8 alkylsulfonate, C_1-C_8 alkylamino, 4-dialkylaminopyridinium, C_1-C_8 alkylhydroxyl, C_1-C_8 alkylthiol, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide (–SOAr), arylthio (–SAr), sulfonamide ($-SO_2NR_2$), alkylsulfoxide (–SOR), ester (–COOR), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile (–CN), azido ($-N_3$), nitro ($-NO_2$), C_1-C_8 alkoxy (–OR), C_1-C_8 alkyl, C_1-C_8 substituted alkyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heterocycle, and C_2-C_{20} substituted heterocycle, phosphonate, phosphate, polyethyleneoxy, and a prodrug moiety; and

L is a bond, O, S, S–S (disulfide), S(=O) (sulfoxide), $S(=O)_2$ (sulfone), $-S(=O)_2N(R)-$ (sulfonamide), NR, N–OR, C_1-C_{12} alkylene, C_1-C_{12} substituted alkylene, C_2-C_{12} alkenylene, C_2-C_{12} substituted alkenylene, C_2-C_{12} alkynylene, C_2-C_{12} substituted alkynylene, $-(CR_2)_nO(CR_2)_n-$, –C(=O)NH–, –OC(=O)NH–, –NHC(=O)NH–, C(=O), $-C(=O)NH(CH_2)_n-$, or $-(CH_2CH_2O)_n-$, where n may be 1, 2, 3, 4, 5, or 6.

4. An HIV integrase inhibitor compound of claim 2 wherein a carbocycle and a heterocycle is independently selected from: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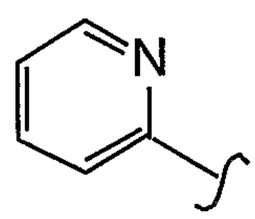
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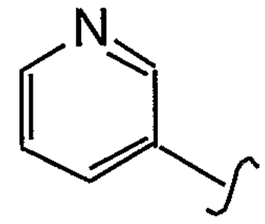
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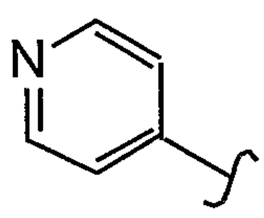
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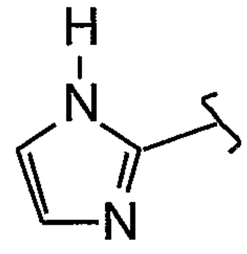
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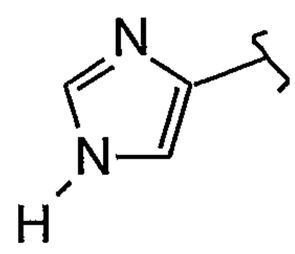
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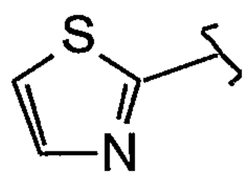
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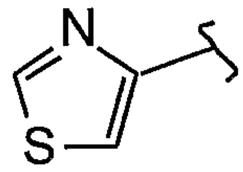
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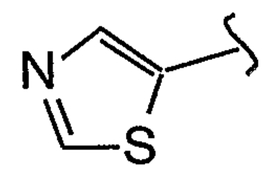
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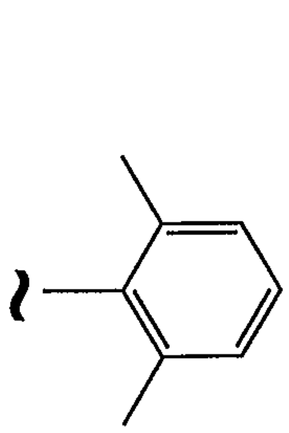
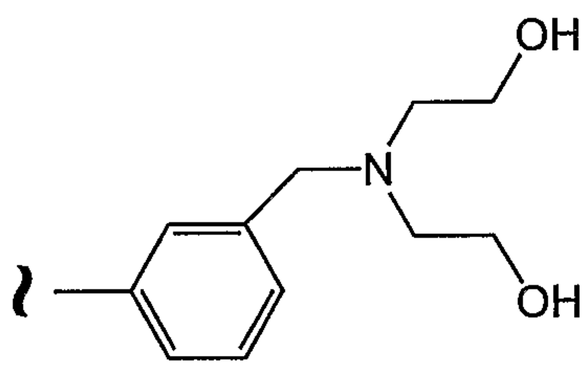
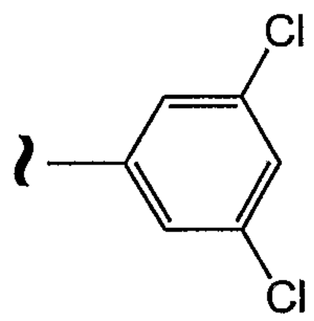
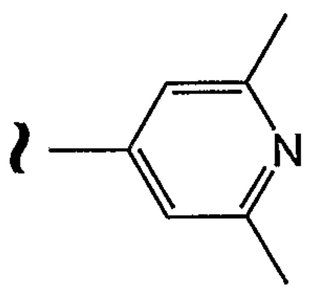
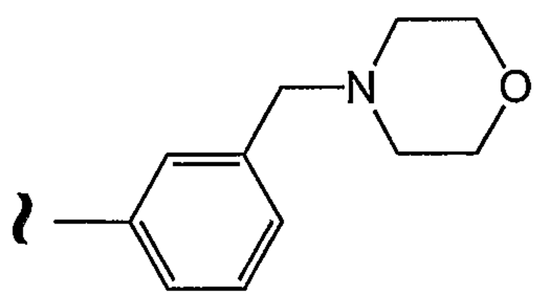
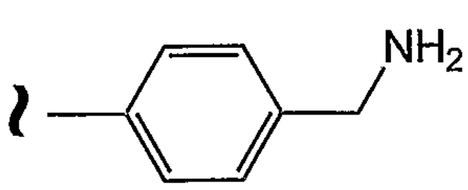
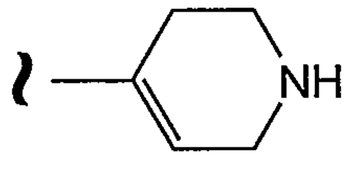
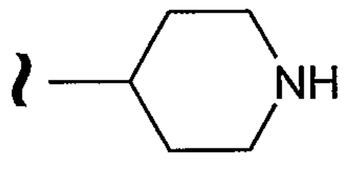
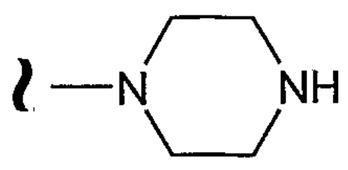
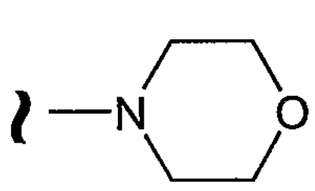
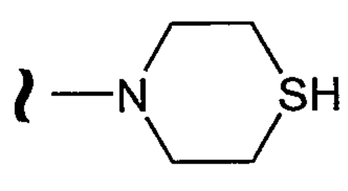
5. An HIV integrase inhibitor compound of claim 2 wherein a carbocycle is selected from: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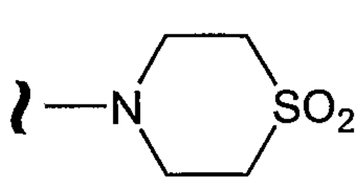
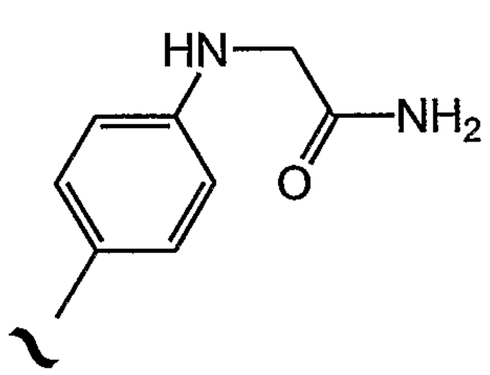
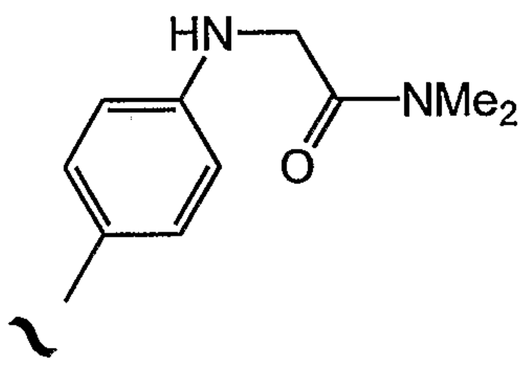
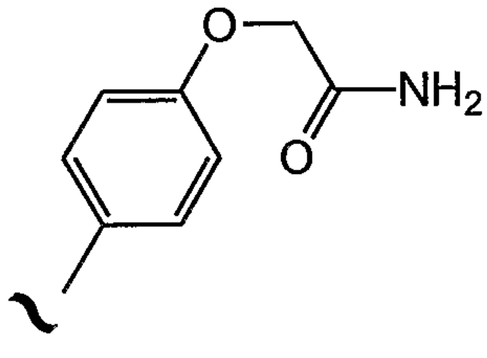
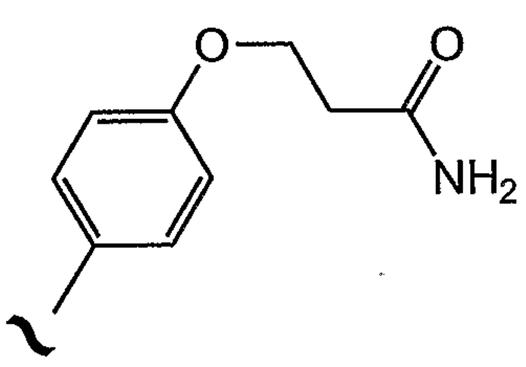
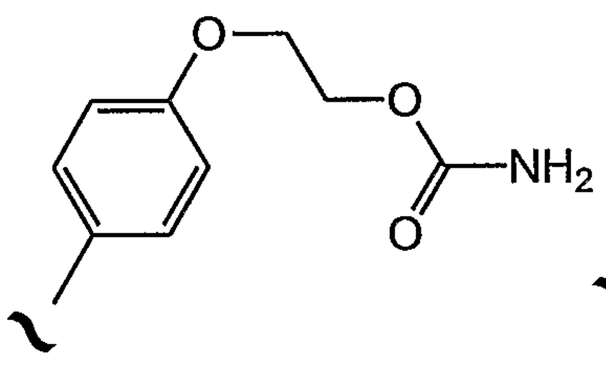
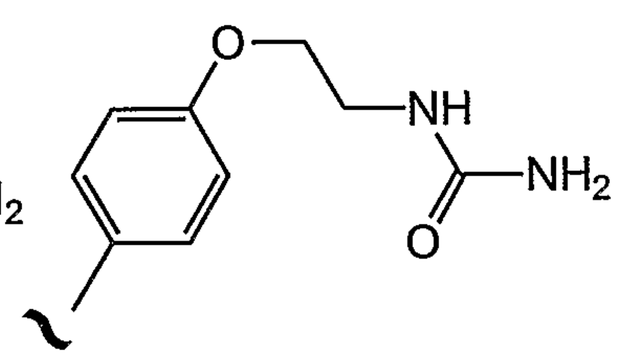


6. An HIV integrase inhibitor compound of claim 2 wherein a substituted aryl is selected from:

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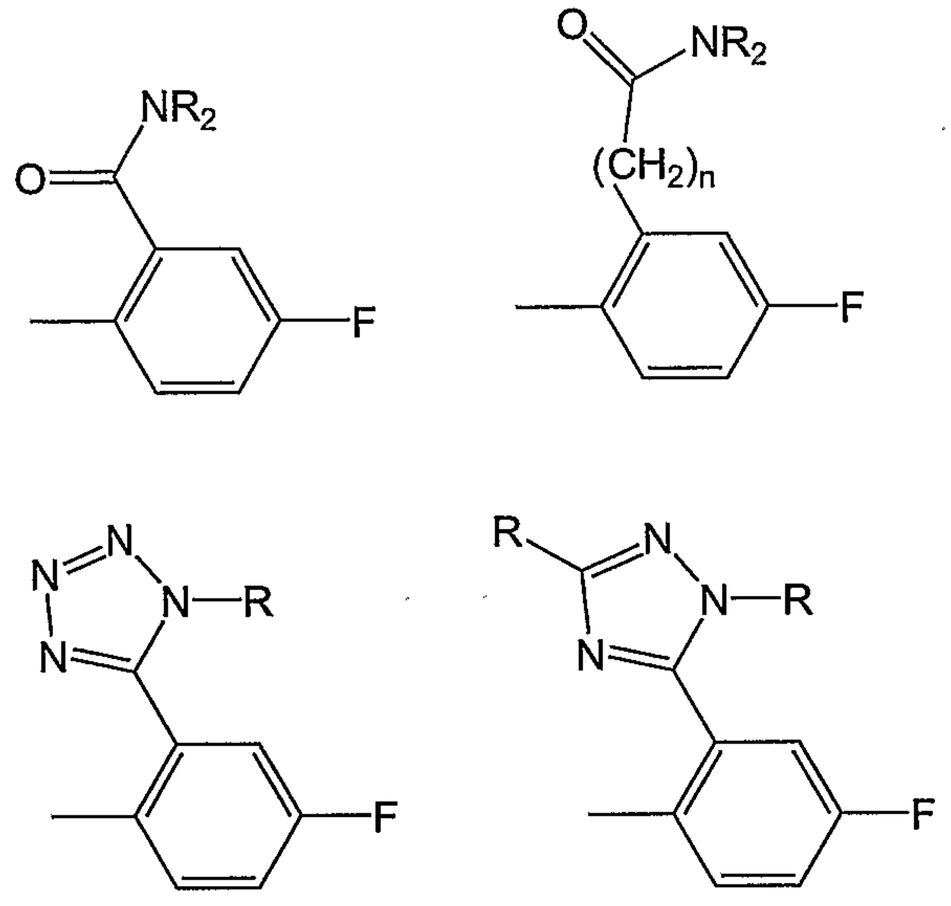
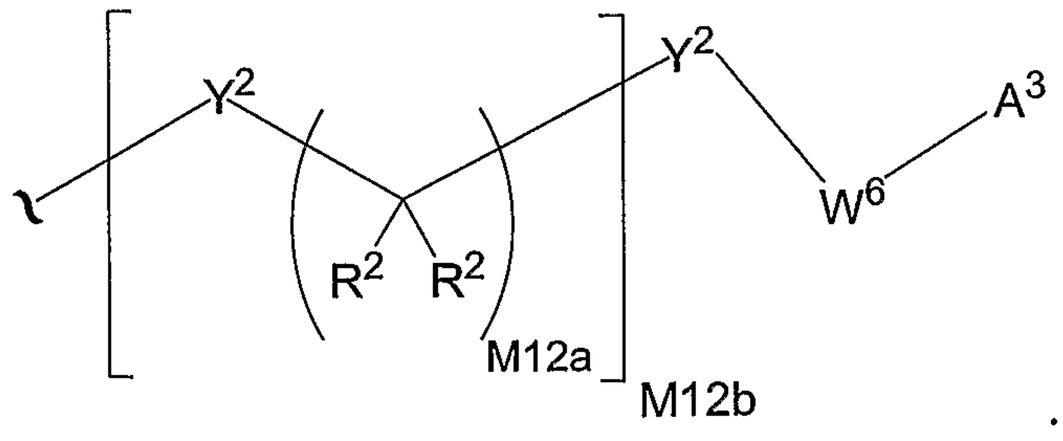
7. An HIV integrase inhibitor compound of claim 2 wherein a substituted aryl is selected from:

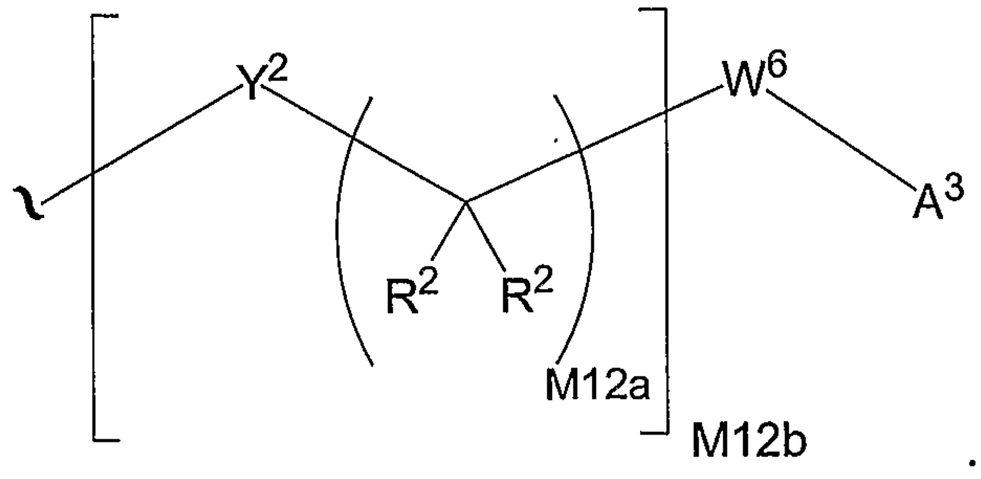


where n is 1 to 6.

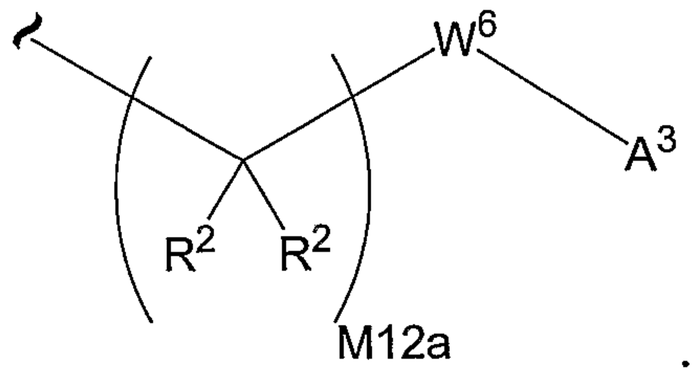
8. An HIV integrase inhibitor compound of claim 2 wherein A^1 is of the formula:



9. An HIV integrase inhibitor compound of claim 8 wherein A^1 is of the formula:

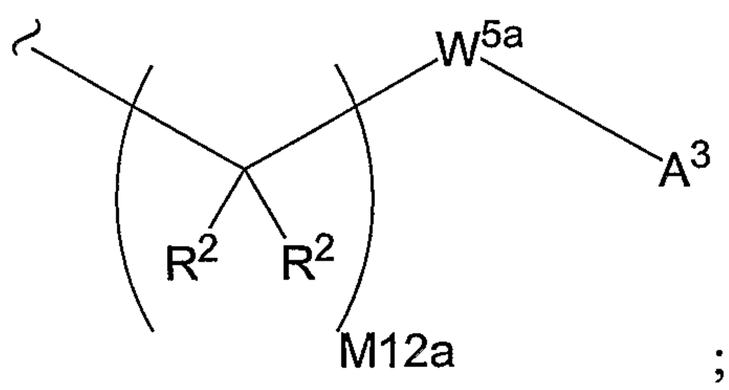


10. An HIV integrase inhibitor compound of claim 9 wherein A^1 is of the formula:



.

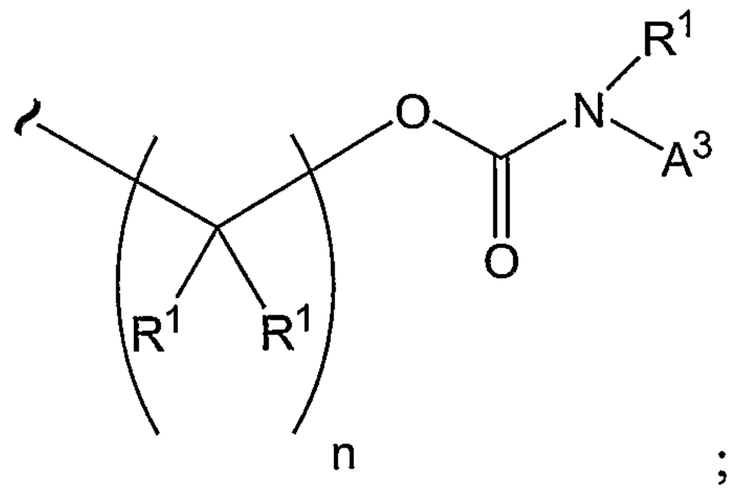
11. An HIV integrase inhibitor compound of claim 10 wherein A^1 is of the formula:



;

where W^{5a} is a carbocycle or a heterocycle and W^{5a} is independently substituted with 0 or 1 R^2 groups.

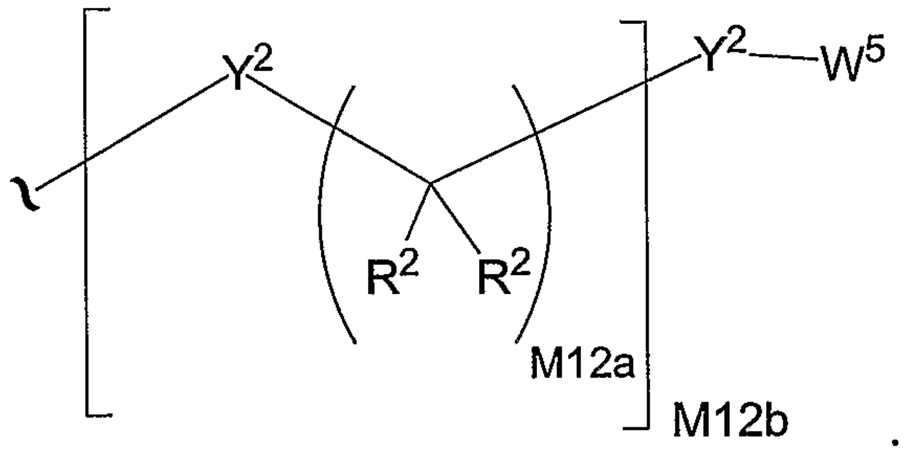
12. An HIV integrase inhibitor compound of claim 2 wherein A^1 is of the formula:



;

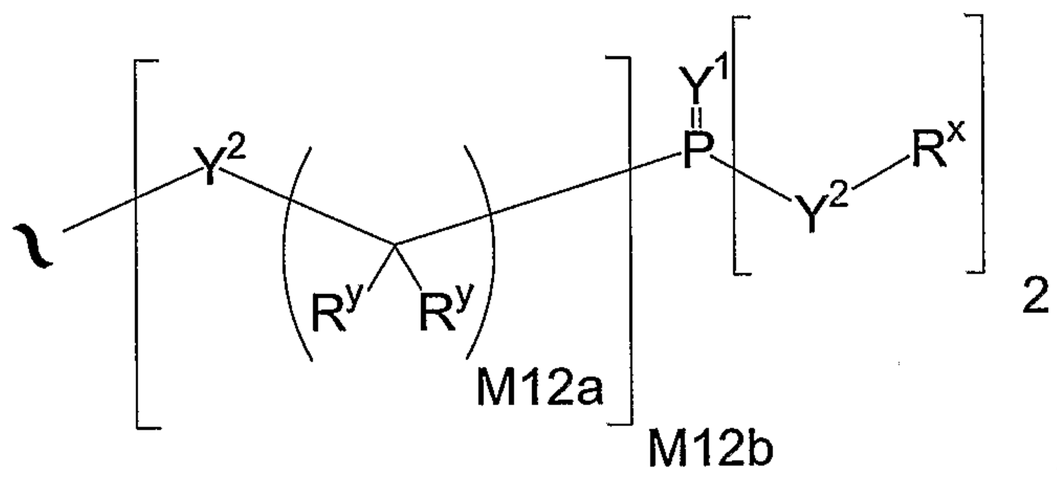
where n is an integer from 1 to 18.

13. An HIV integrase inhibitor compound of claim 2 wherein A^2 is of the formula:

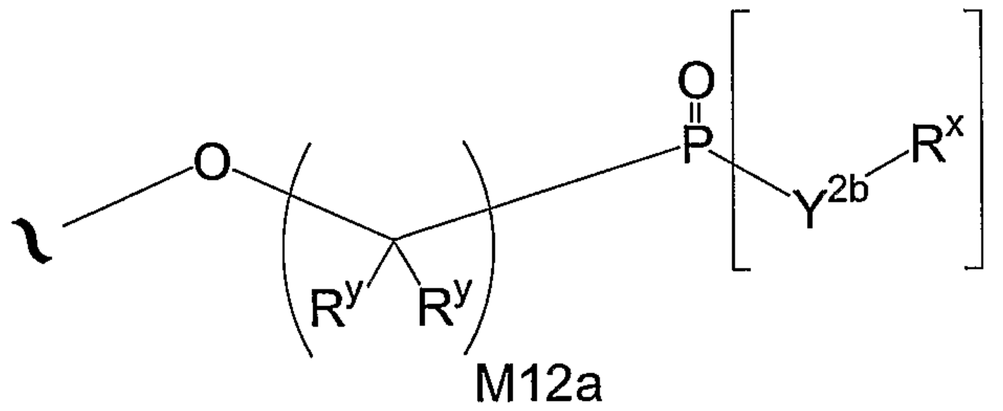


14. An HIV integrase inhibitor compound of claim 13 wherein A^2 is phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl or substituted pyridyl.

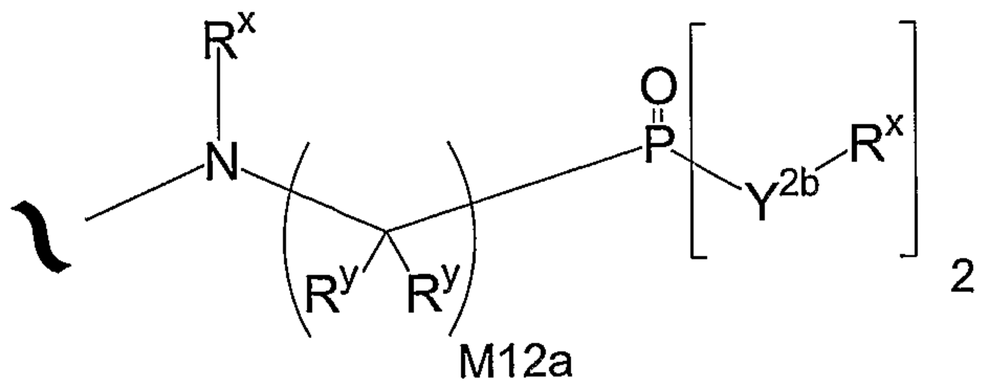
15. An HIV integrase inhibitor compound of claim 2 wherein A^3 is of the formula:



16. An HIV integrase inhibitor compound of claim 15 wherein A^3 is of the formula:

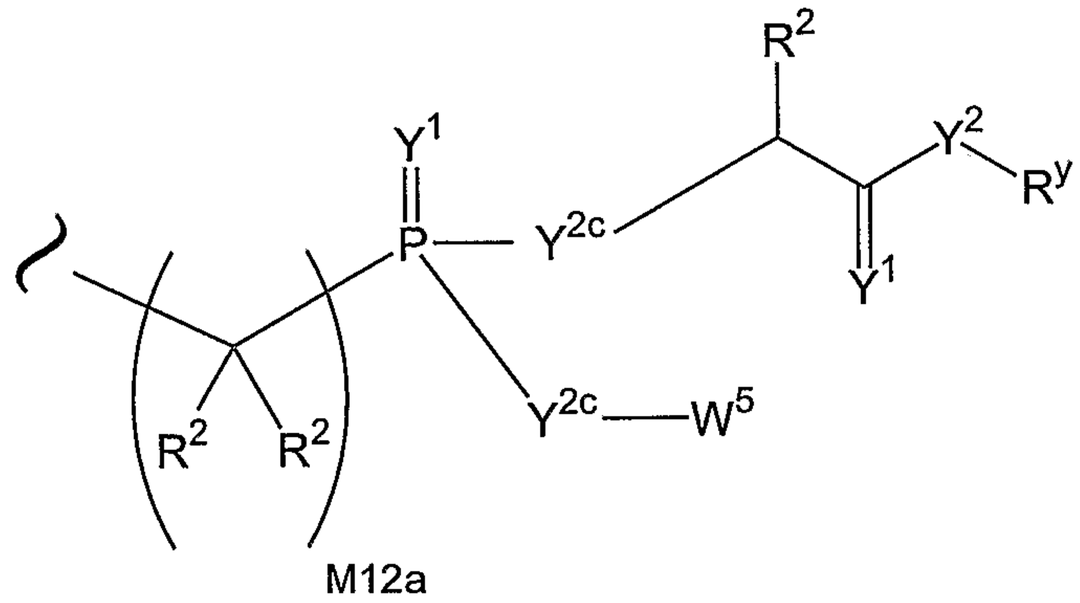


, or



where Y^{2b} is independently oxygen (O) or nitrogen ($N(R^x)$).

17. An HIV integrase inhibitor compound of claim 2 wherein A^3 is of the formula:

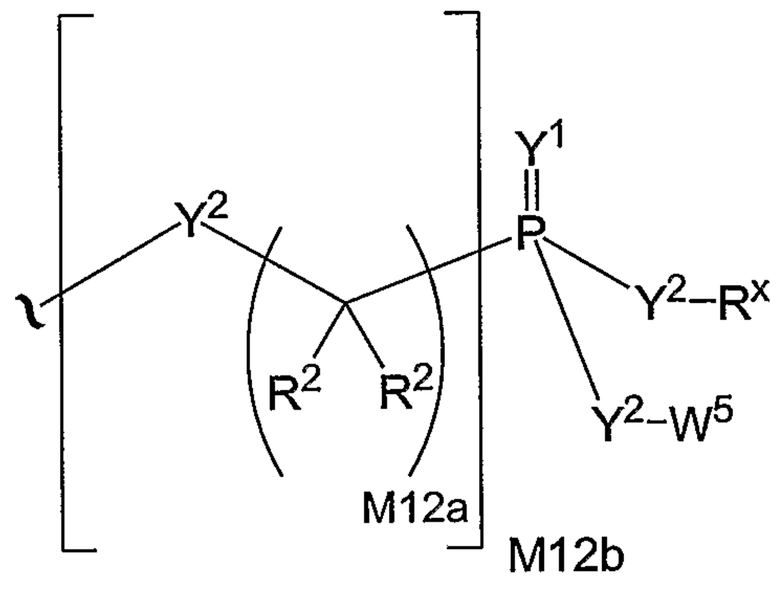


M12a ;

where W^5 is phenyl or substituted phenyl, and Y^{2c} is independently O, $N(R^y)$ or S.

18. An HIV integrase inhibitor compound of claim 17 where R^2 is H, M12a is 1, and Y^{2c} is independently O or $N(R^y)$.

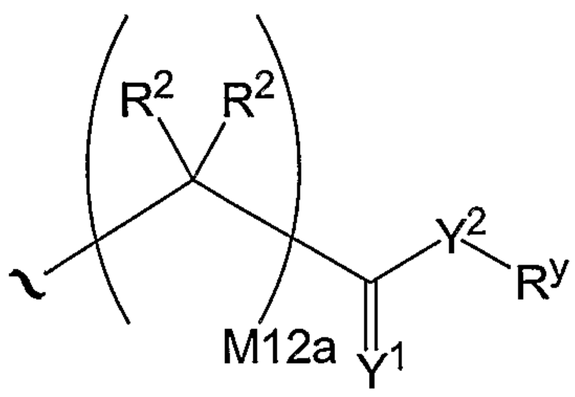
19. An HIV integrase inhibitor compound of claim 2 wherein A^3 is of the formula:



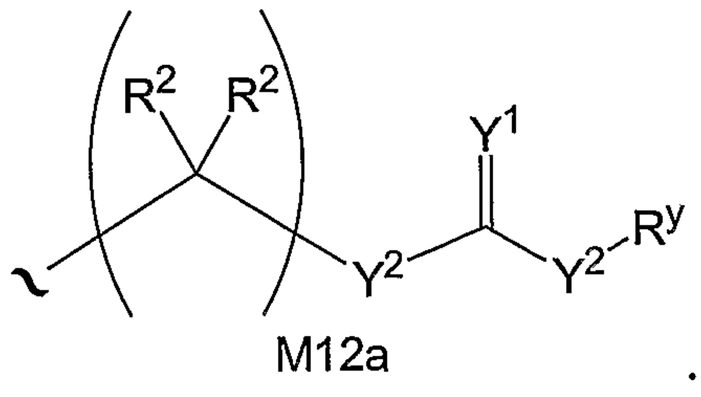
M12b

where W^5 is phenyl or substituted phenyl.

20. An HIV integrase inhibitor compound of claim 19 where R^x is selected from the groups:

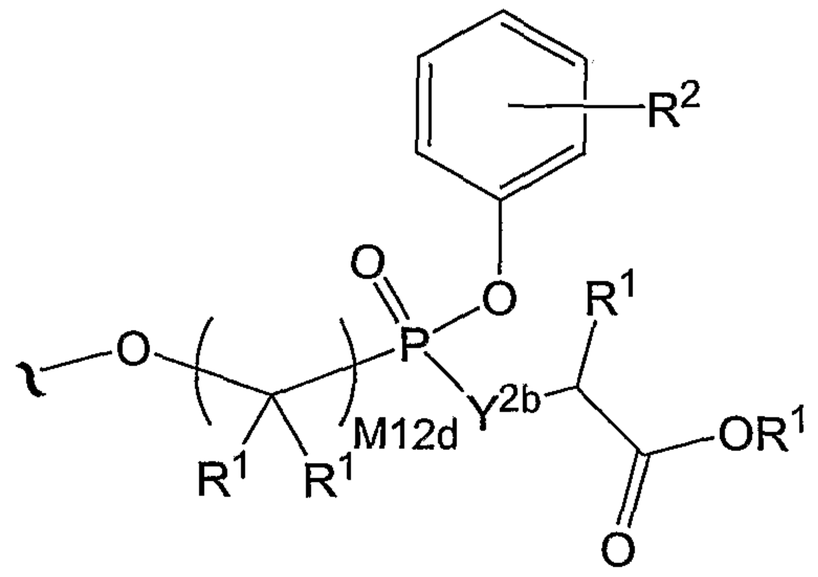


and



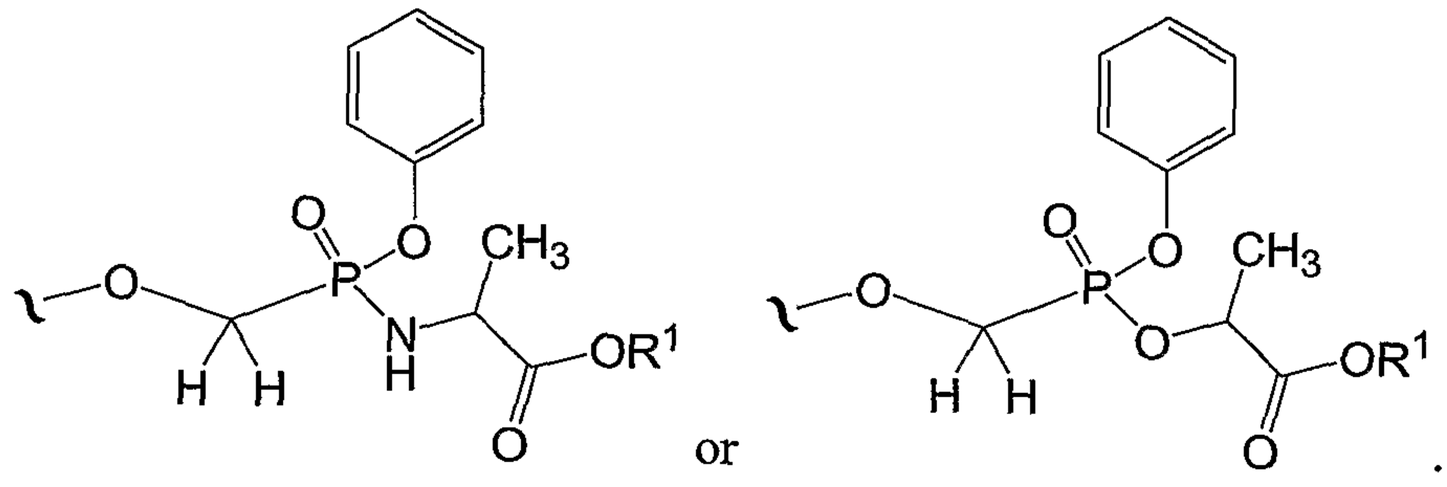
.

21. An HIV integrase inhibitor compound of claim 20 where A^3 is of the formula:



where Y^{2b} is O or $N(R^x)$; M12d is 1, 2, 3, 4, 5, 6, 7 or 8; and the phenyl carbocycle is substituted with 0 to 3 R^2 groups.

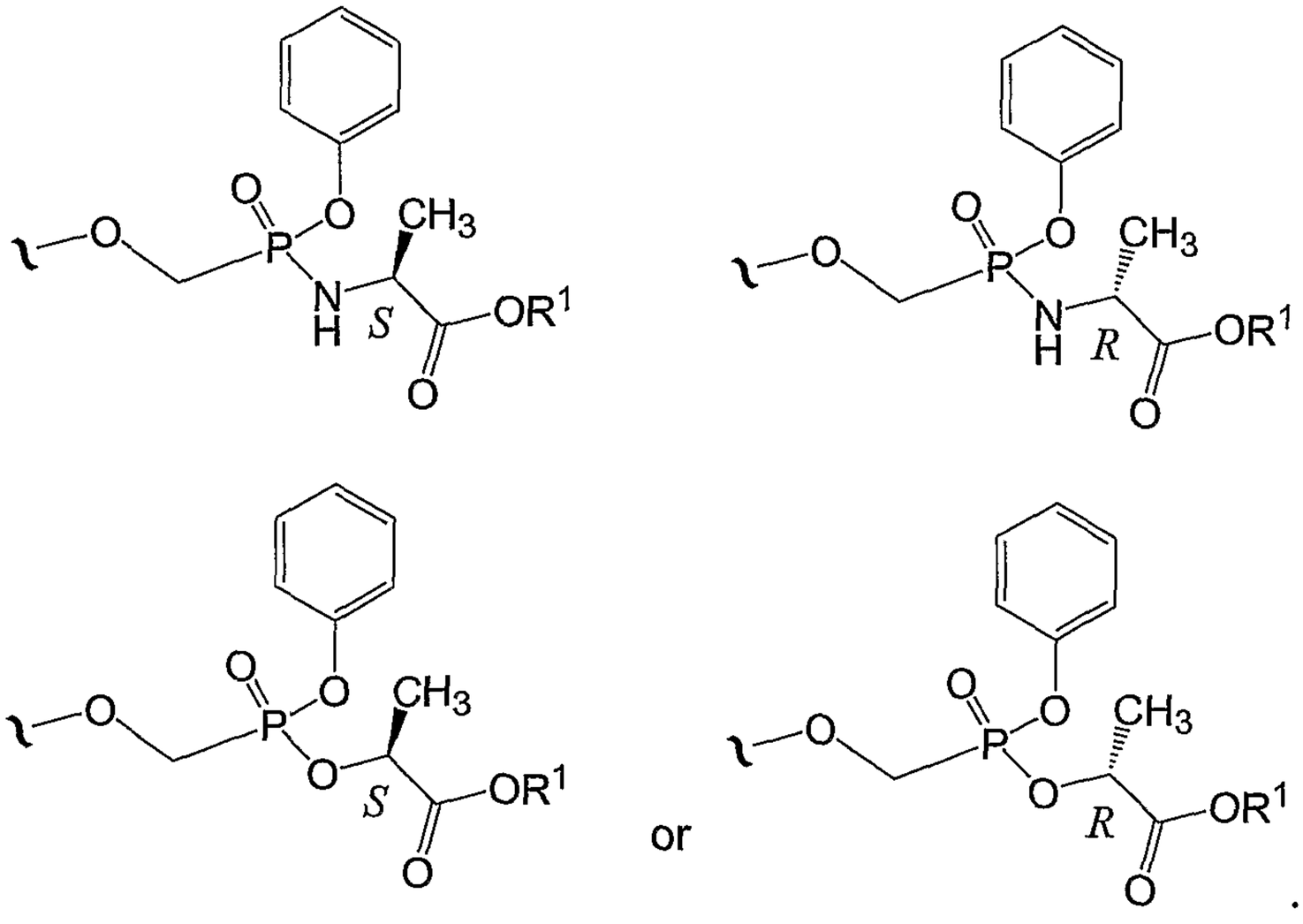
22. An HIV integrase inhibitor compound of claim 21 where A^3 is of the formula:



or

.

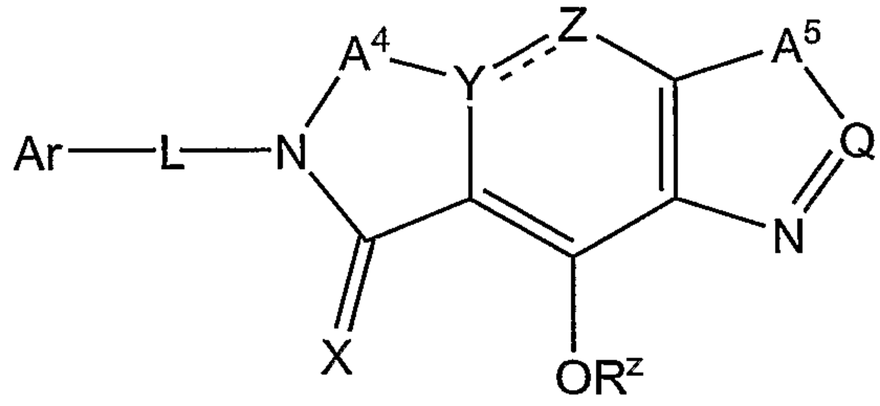
23. An HIV integrase inhibitor compound of claim 22 where A^3 is of the formula:



or

.

24. An HIV integrase inhibitor compound of **claim 2 or 3** selected from Formula I:

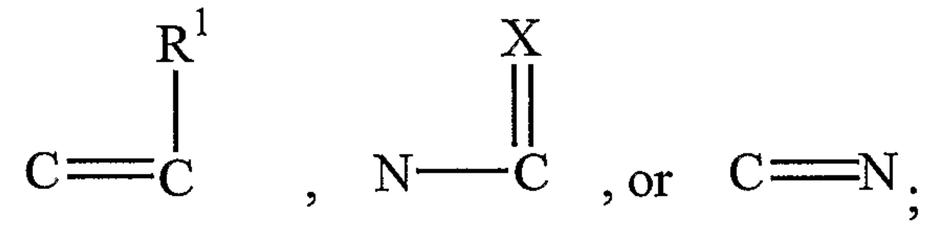


I

wherein:

A^4 and A^5 are each and independently a moiety forming a five, six, or seven membered ring; or A^4 and A^5 are independently selected from the group consisting of O, S, NR, $C(R^2)_2$, CR^2OR, $CR^2OC(=O)R$, C(=O), C(=S), CR^2SR, C(=NR), $C(R^2)_2$–$C(R^3)_2$, $C(R^2)$=$C(R^3)$, $C(R^2)_2$–O, NR–$C(R^3)_2$, N=$C(R^3)$, N=N, SO_2–NR, $C(=O)C(R^3)_2$, C(=O)NR, $C(R^2)_2$–$C(R^3)_2$–$C(R^3)_2$, $C(R^2)$=$C(R^3)$–$C(R^3)_2$, $C(R^2)C(=O)NR$, $C(R^2)C(=S)NR$, $C(R^2)$=N–$C(R^3)_2$, $C(R^2)$=N–NR, and N=$C(R^3)$–NR;

Q is N, $^+$NR, or CR^4;

Y=Z is 

X may be O, S, NH, NR, N–OR, N–NR_2, N–CR_2OR or N–CR_2NR_2;

R^z is H; a protecting group selected from benzyhydryl ($CHPh_2$), trialkylsilyl (R_3Si), 2-trimethylsiloxyethyl, alkoxymethyl (CH_2OR), and ester (C(=O)R); or a prodrug moiety;

R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of H, F, Cl, Br, I, OH, –NH_2, –NH_3^+, –NHR, –NR_2, –NR_3^+, C_1–C_8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, C_1–C_8 alkylsulfonate, C_1–C_8 alkylamino, 4-dialkylaminopyridinium, C_1–C_8 alkylhydroxyl, C_1–C_8 alkylthiol, –SO_2R, –SO_2Ar, –SOAr, –SR, –SAr, –SO_2NR_2 (sulfonamide), –SOR, –CO_2R, –$C(=O)NR_2$, 5-7 membered ring lactam, 5-7 membered ring lactone, –CN, –N_3, –NO_2, C_1–C_8 alkoxy, C_1–C_8 trifluoroalkyl, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_3–C_{12} carbocycle, C_3–C_{12}

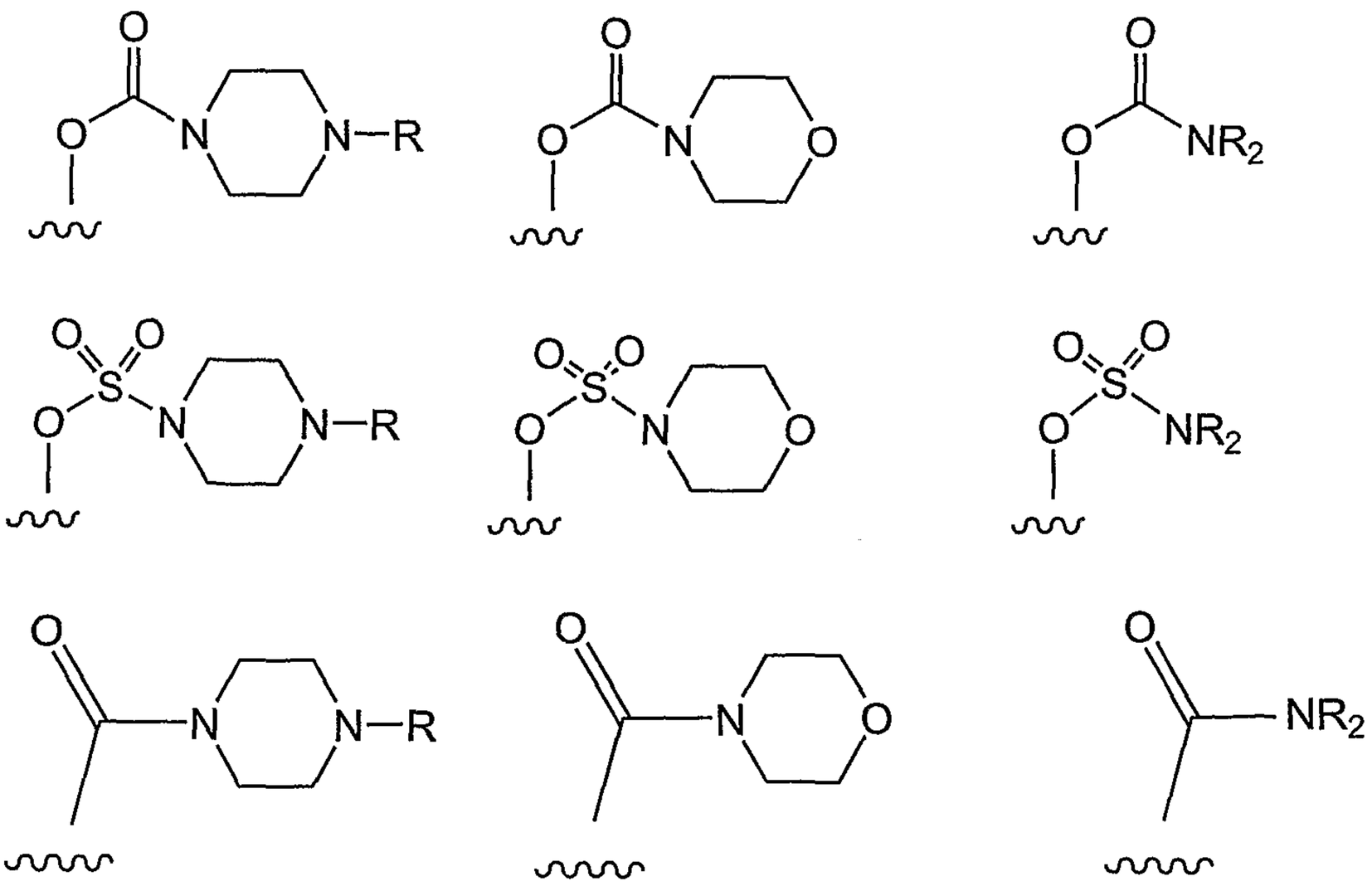
substituted carbocycle, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, C_2–C_{20} substituted heteroaryl, polyethyleneoxy, phosphonate, phosphate, a prodrug moiety, –OC(=O)OR, –OC(=O)NR_2, –OC(=S)NR_2, –OC(=O)NRNR_2, –OC(=O)R, –C(=O)NRNR_2, –C(=O)R, –OSO_2NR_2 (sulfamate), –$NRSO_2$R, –NRC(=S)NR_2, –OSO_2R (sulfonate), –P(=O)$(OR)_2$, –P(=O)(OR)(NR_2), –P(=O)$(NR_2)_2$, –P(=S)$(OR)_2$, –P(=S)(OR)(NR_2), –P(=S)$(NR_2)_2$, and including prodrug substituted forms thereof; and

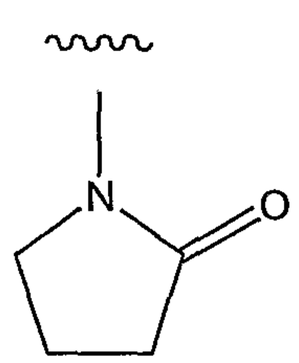
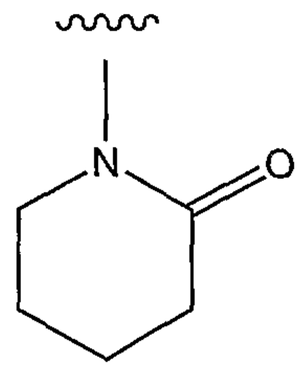
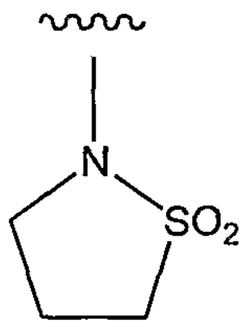
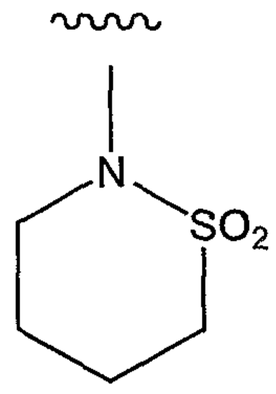
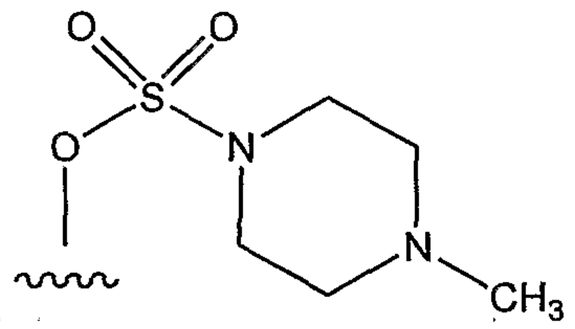
wherein when taken together on a single carbon, two R^2 or two R^3 may form a spiro ring; and

Ar is C_3–C_{12} carbocycle, C_3–C_{12} substituted carbocycle, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, or C_2–C_{20} substituted heteroaryl;

which is substituted with one or more covalently attached A^0 groups.

25. An HIV integrase inhibitor compound of claim 2 or 3 having Formula I as described in claim 24, wherein R^1, R^2, R^3, and R^4 include the structures:

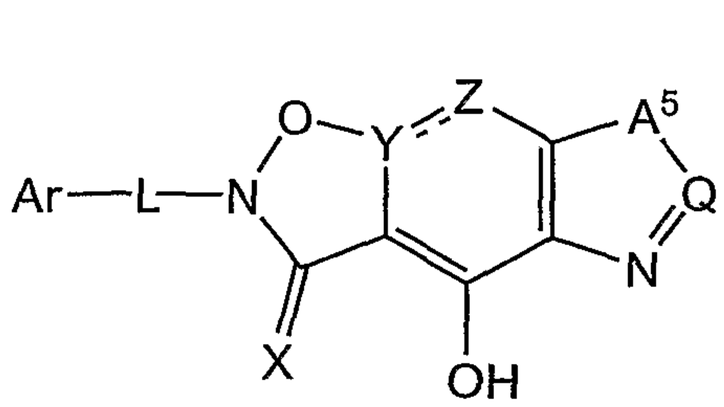


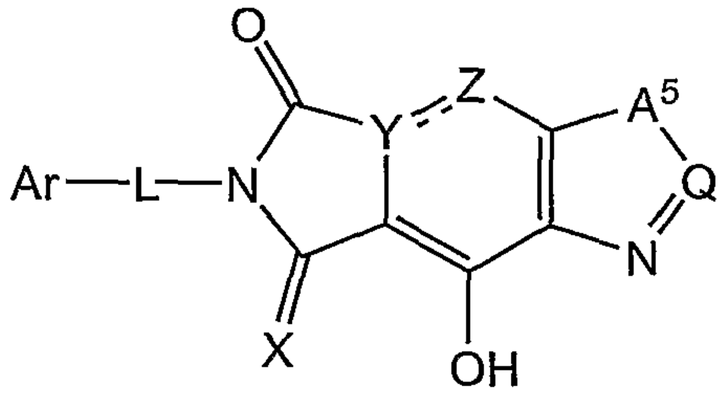






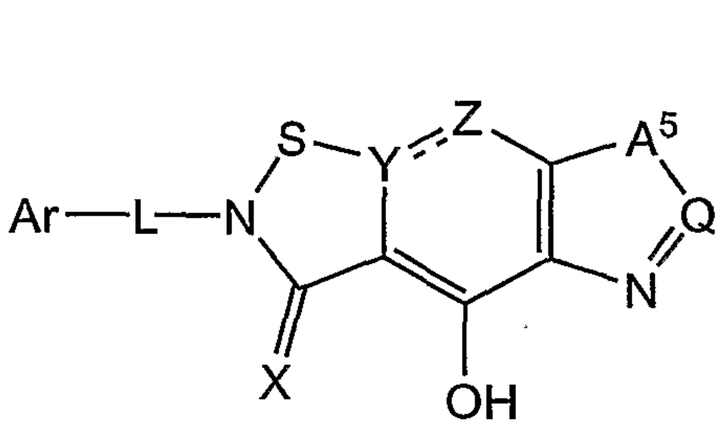
where the wavy line indicates the point of covalent attachment on the tricyclic structure; and

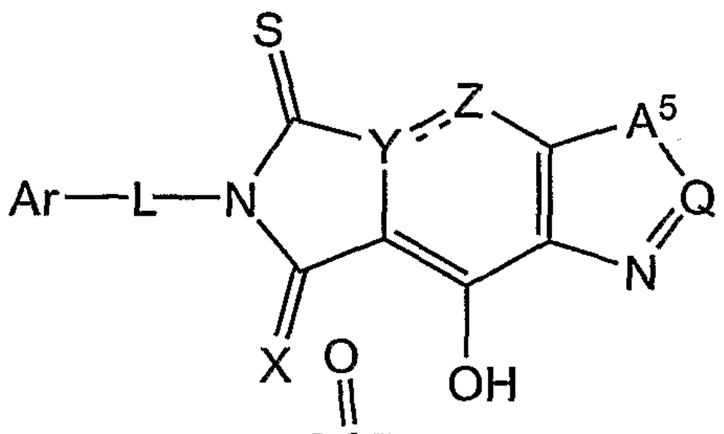
which is substituted with one or more covalently attached A^0 groups.

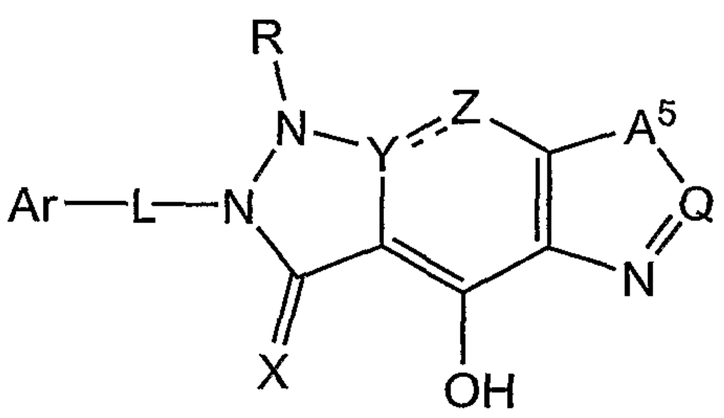
26. A Formula I HIV integrase inhibitor compound of claim 24 selected from the structures:

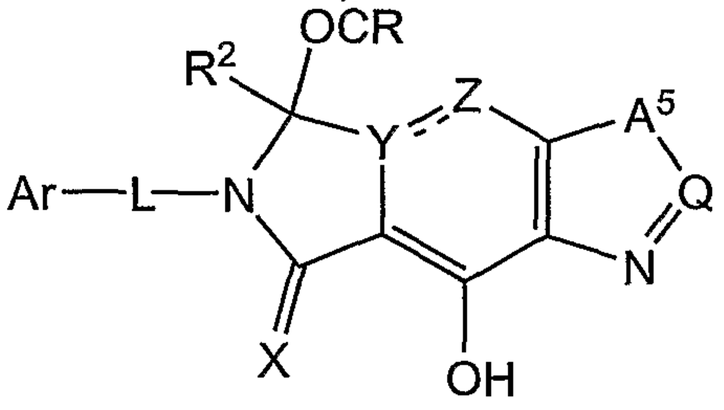


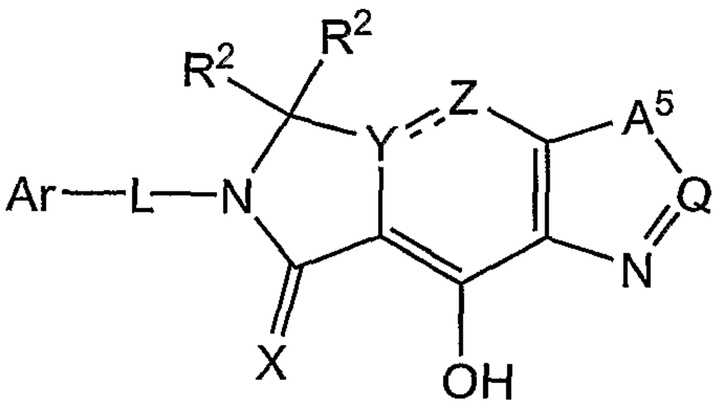


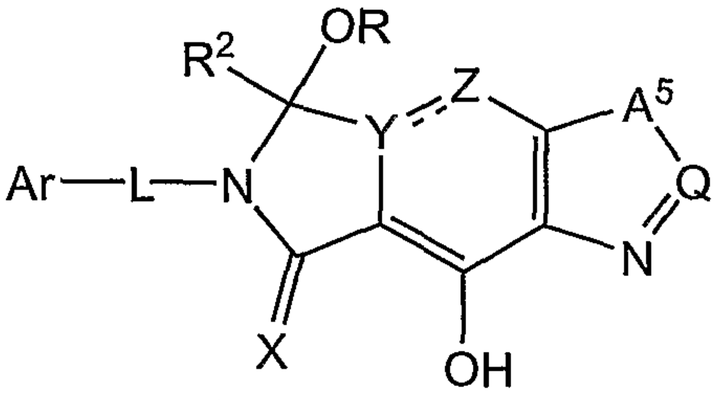


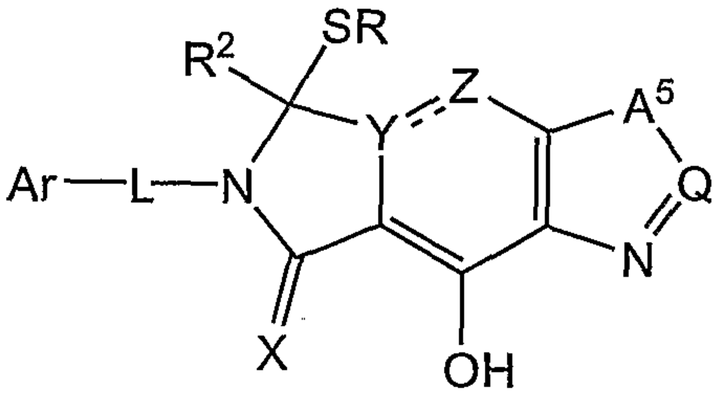


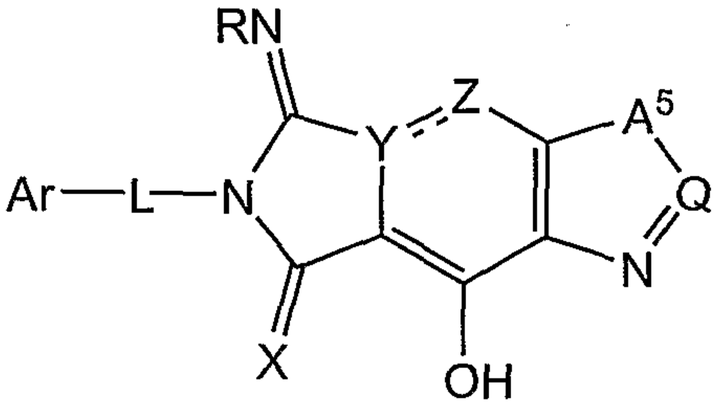




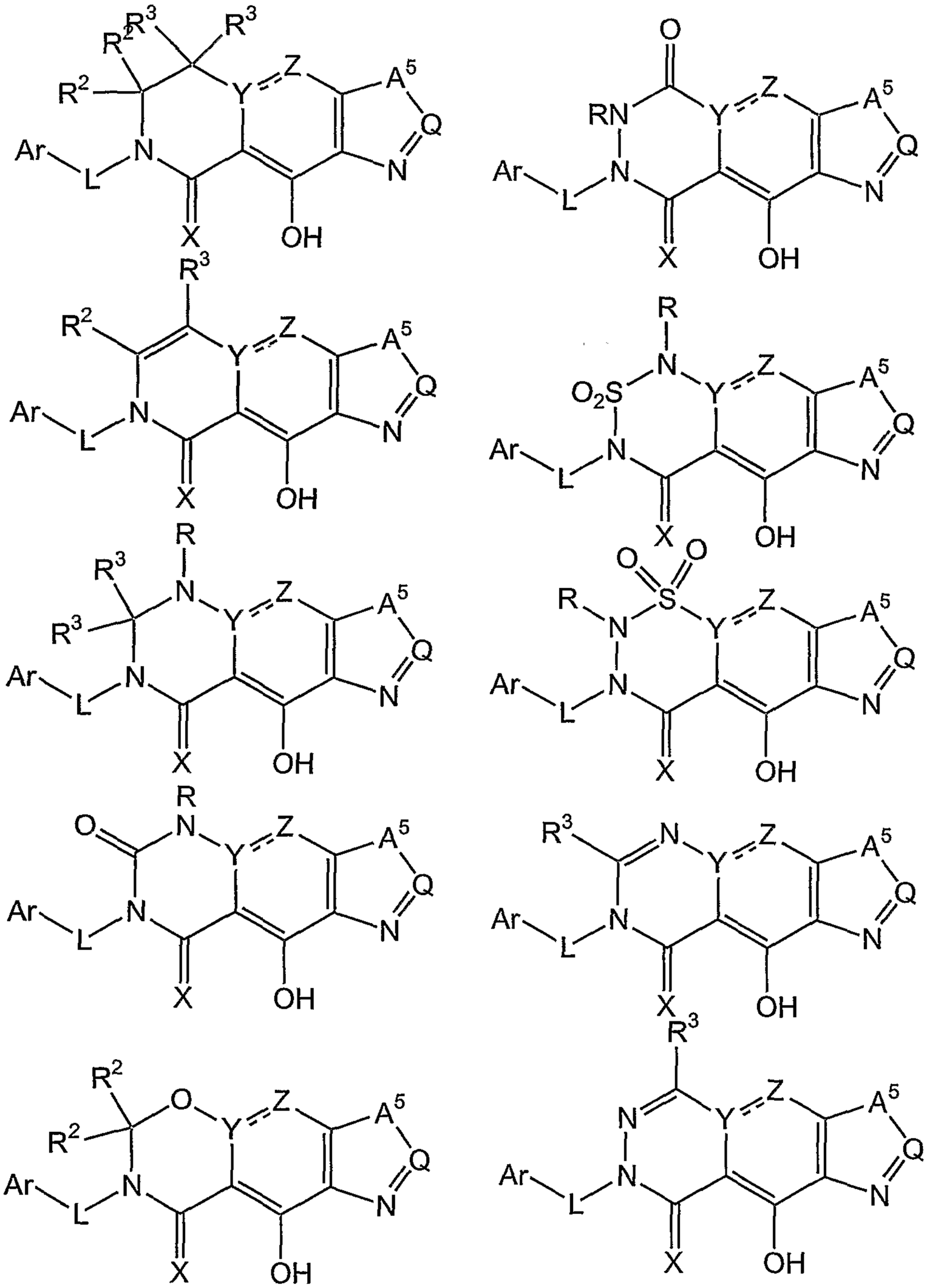




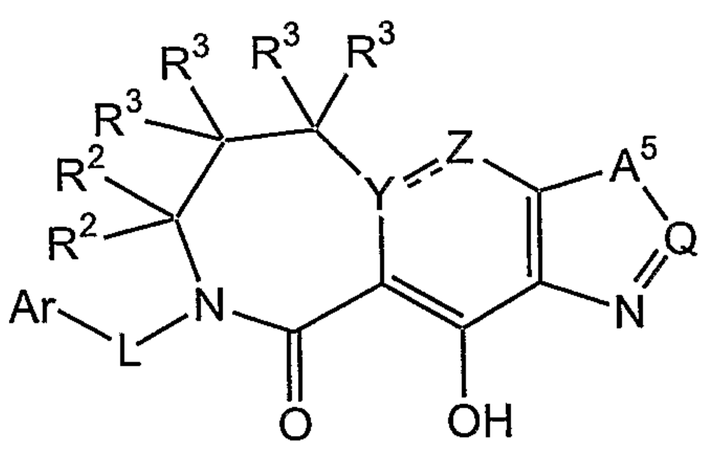
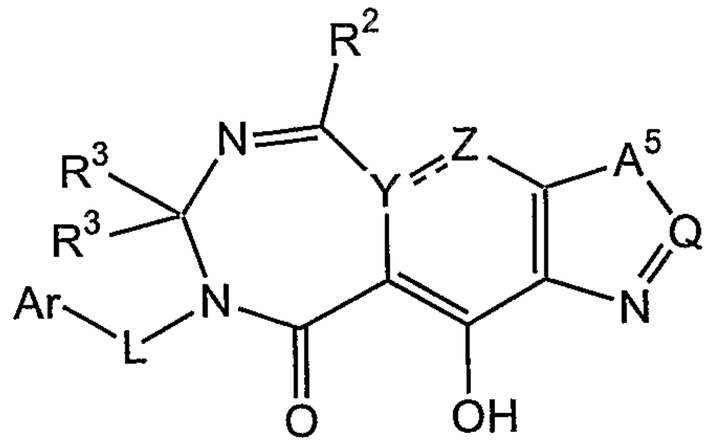
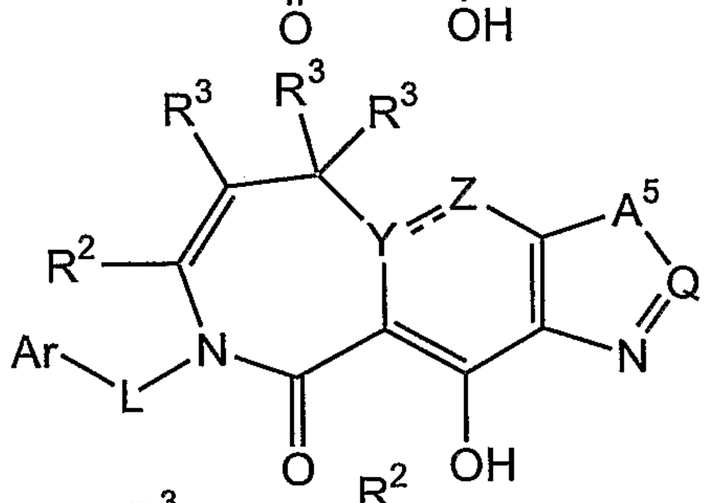
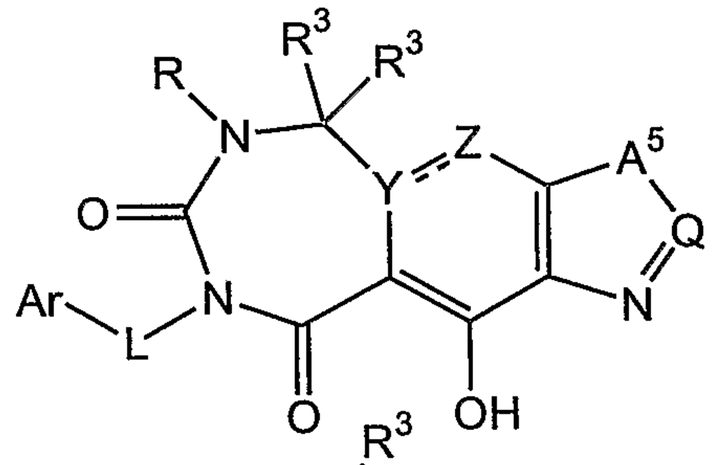
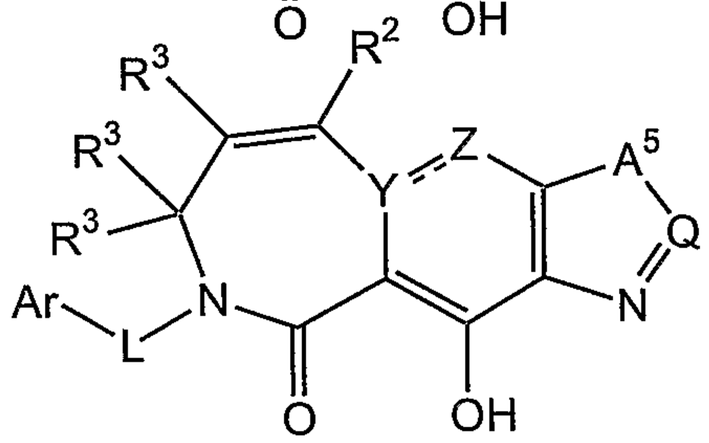
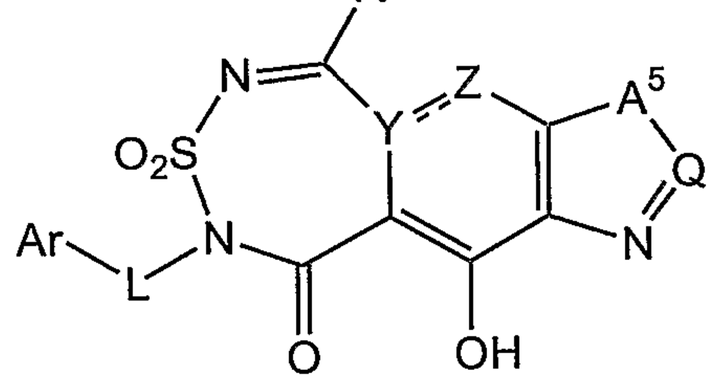
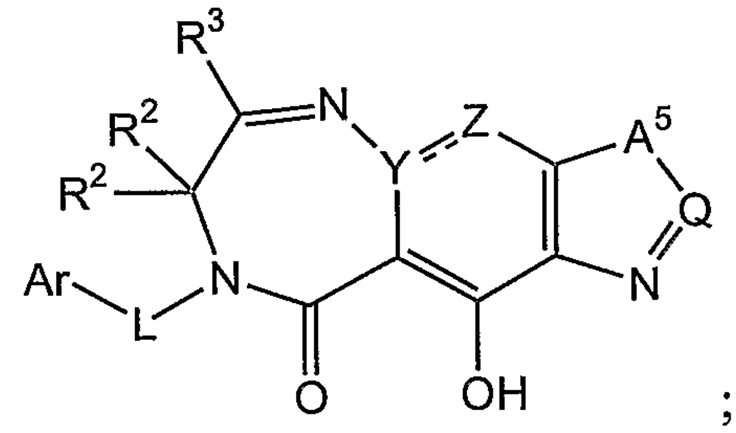




27. A Formula I HIV integrase inhibitor compound of claim 24 selected from the structures:

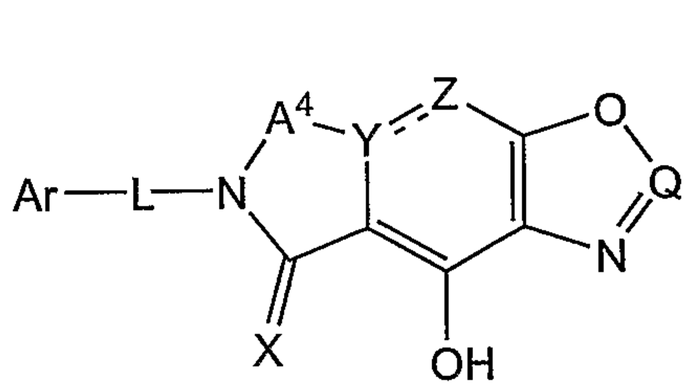


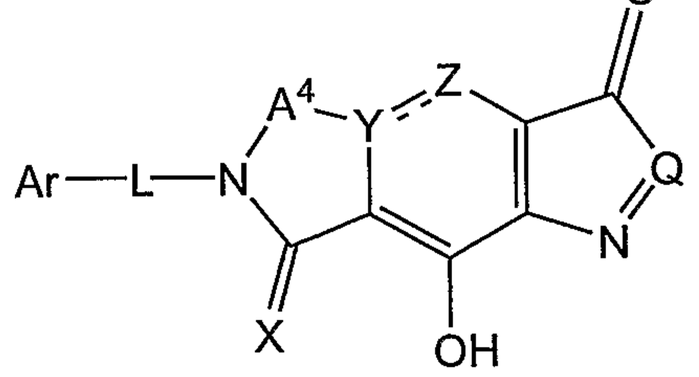
28. An HIV integrase inhibitor compound of claim 2 or 3 of Formula I as described in claim 24, wherein the compound has the formula:

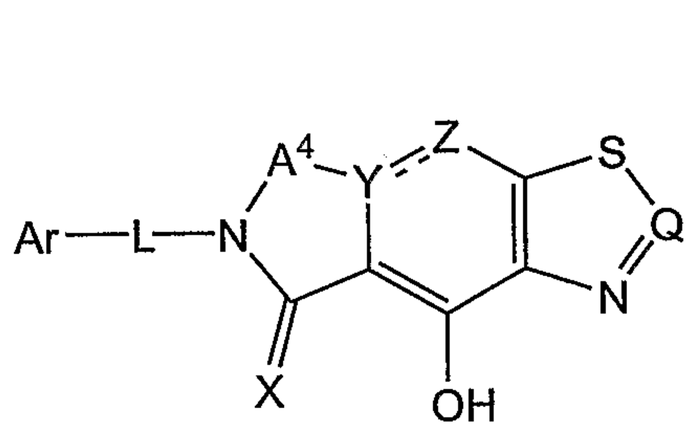







;

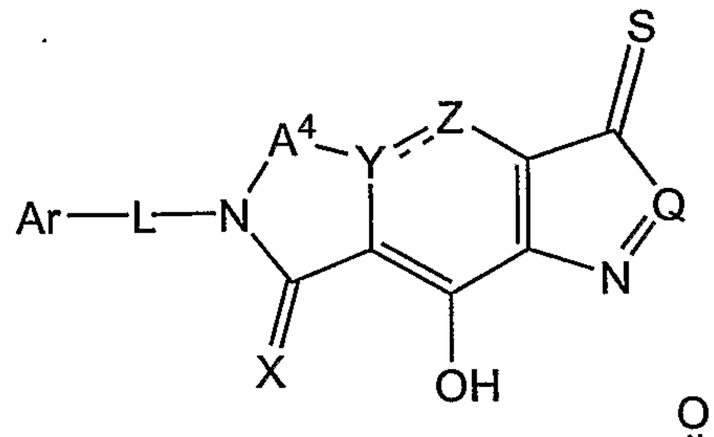
which is substituted with one or more covalently attached A^0 groups.

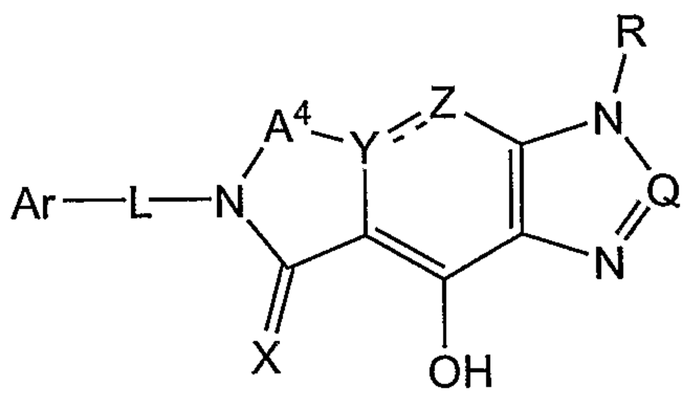
29. A Formula I HIV integrase inhibitor compound of claim 24 selected from the structures:

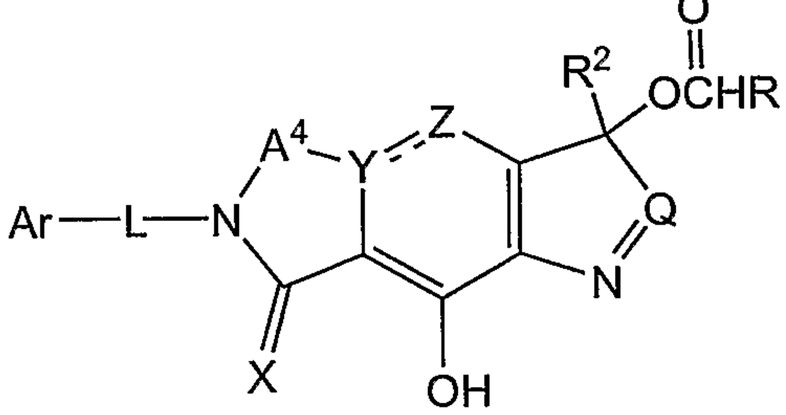


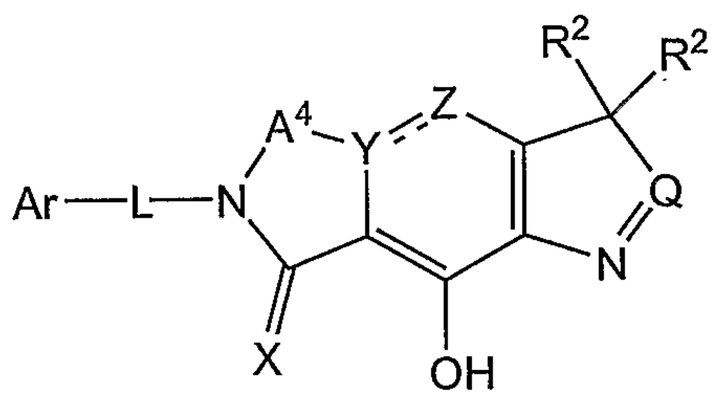


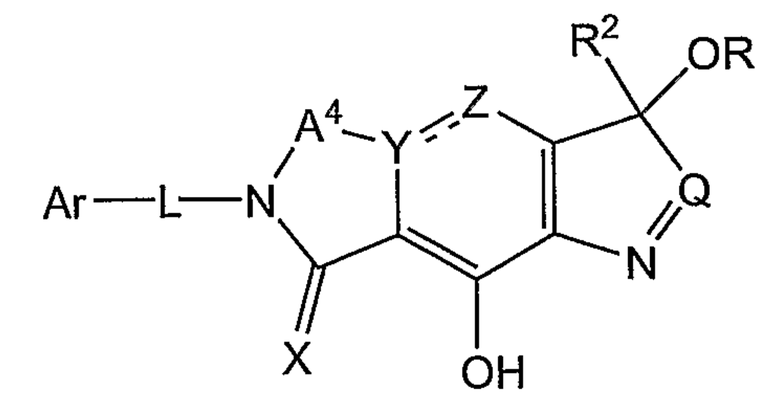


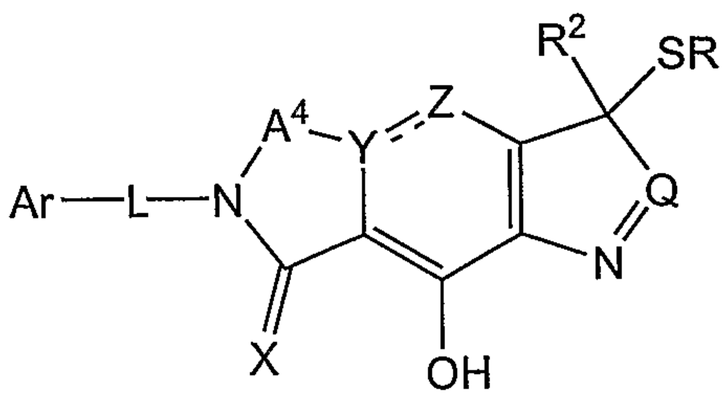












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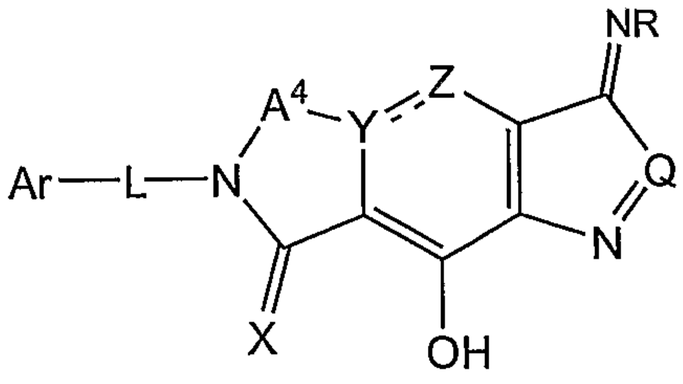

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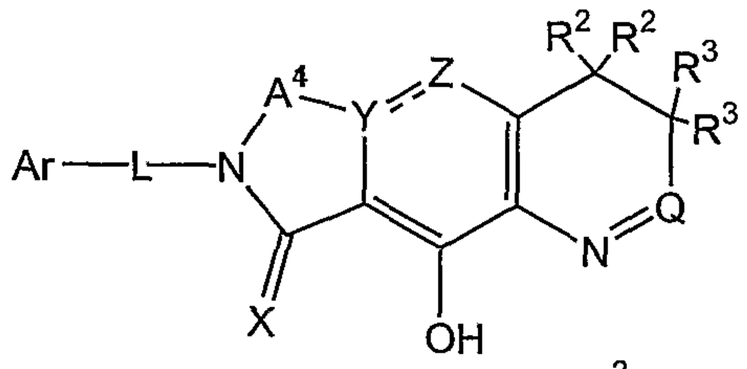
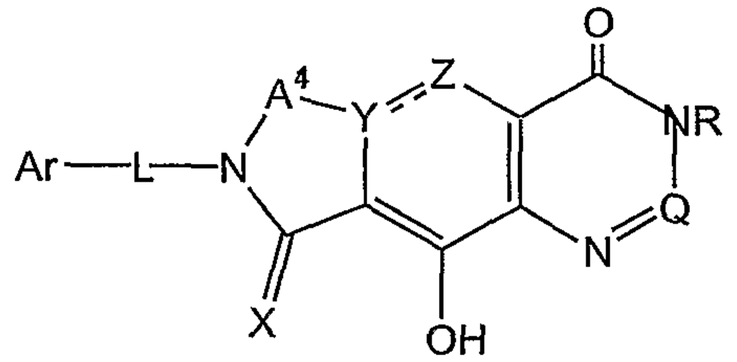
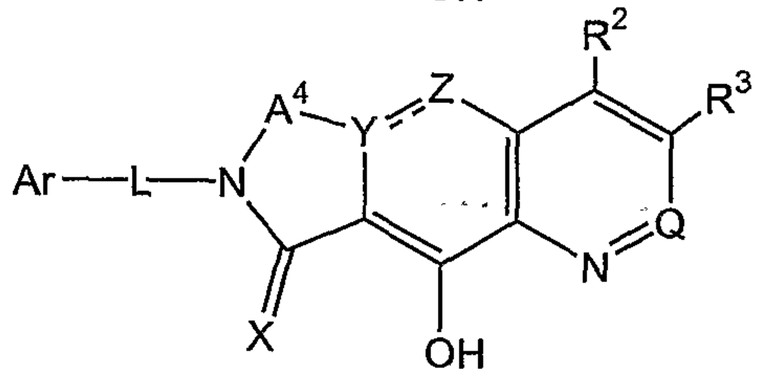
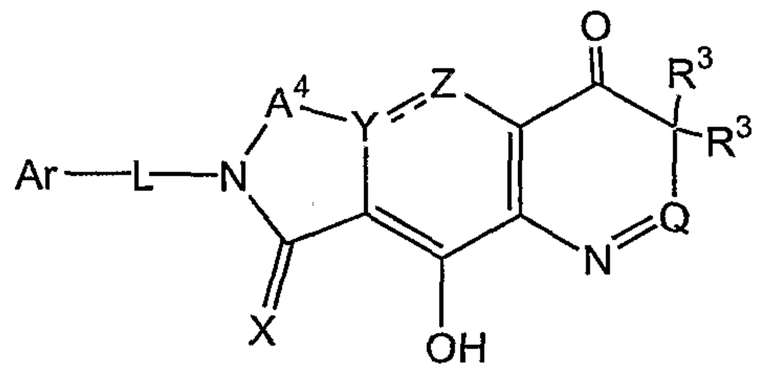
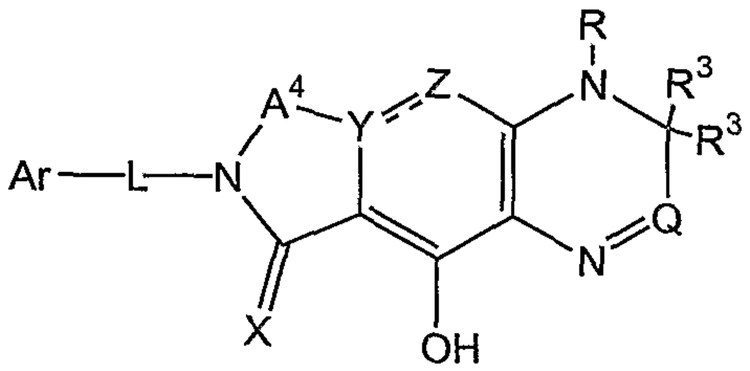
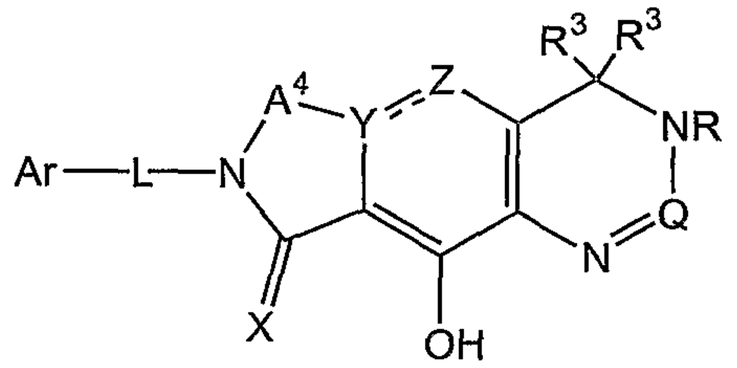
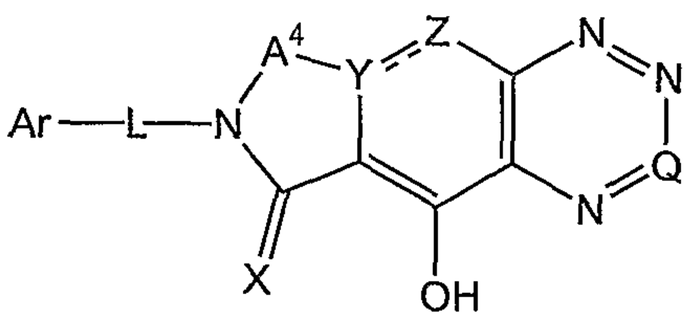
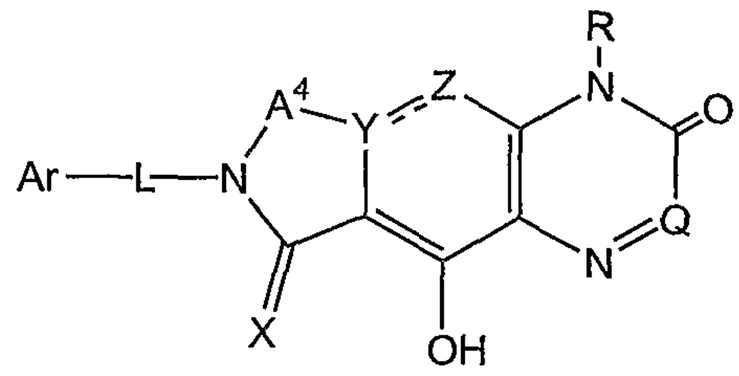
30. A Formula I HIV integrase inhibitor compound of claim 24 selected from the structures:

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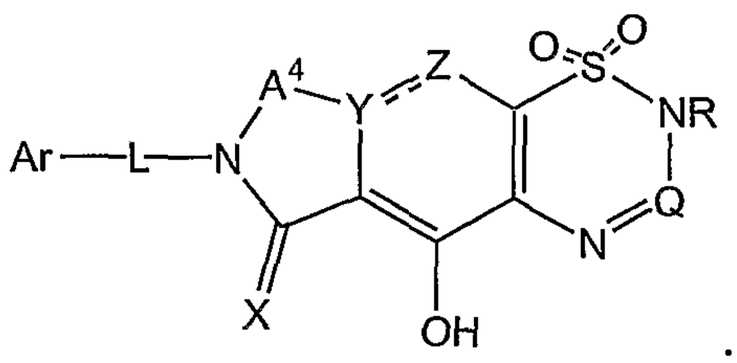

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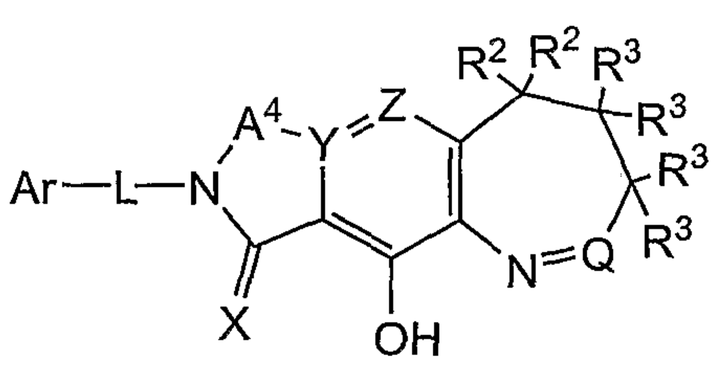
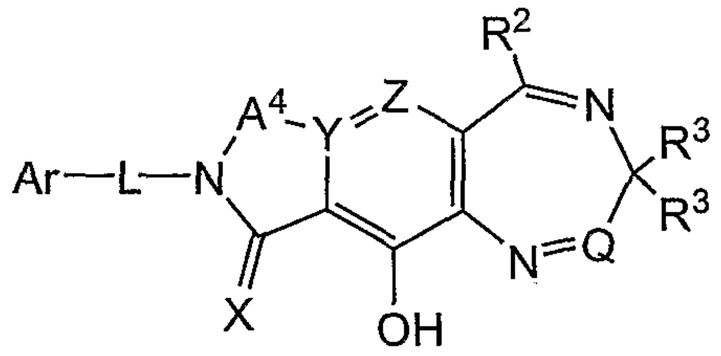
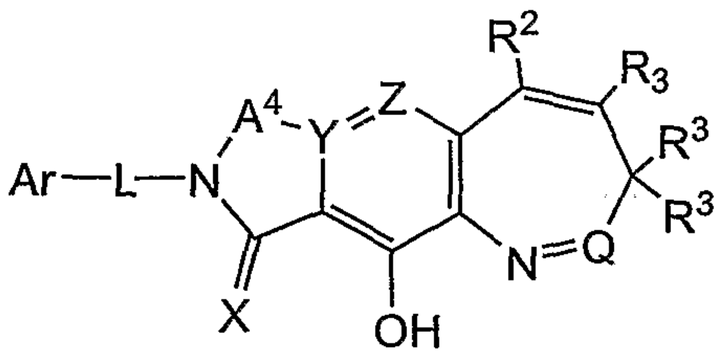
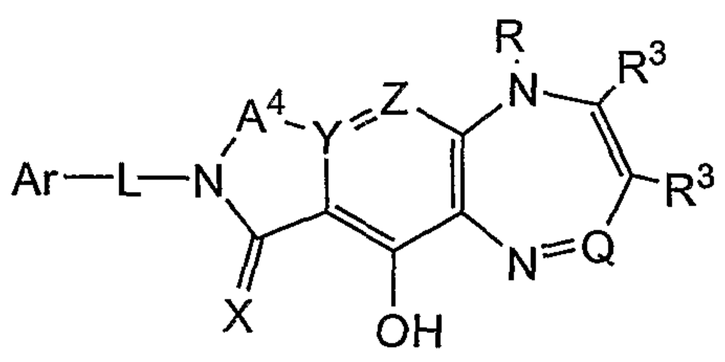
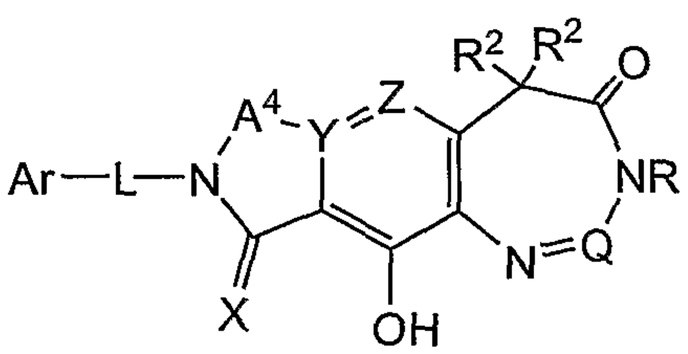
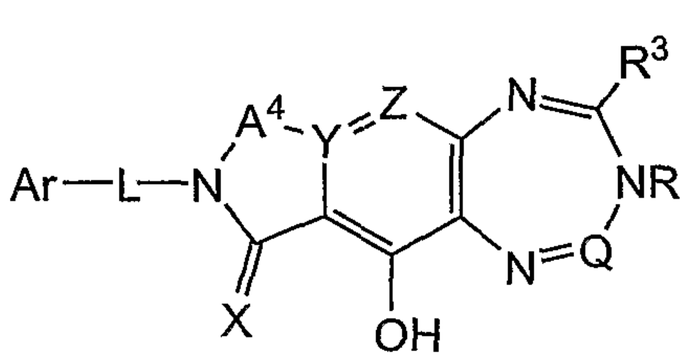
31. An HIV integrase inhibitor compound of claim 2 or 3 having Formula I as described in claim 24, wherein the compound has the formula:

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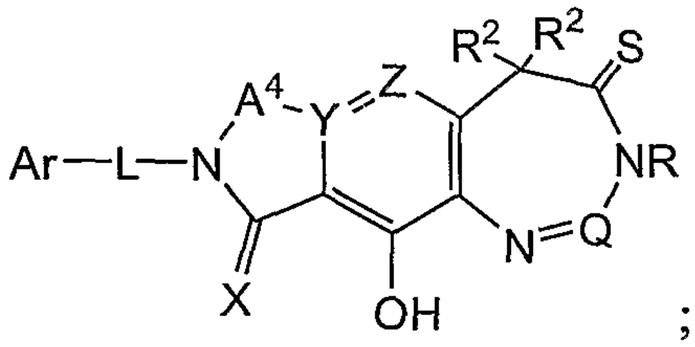
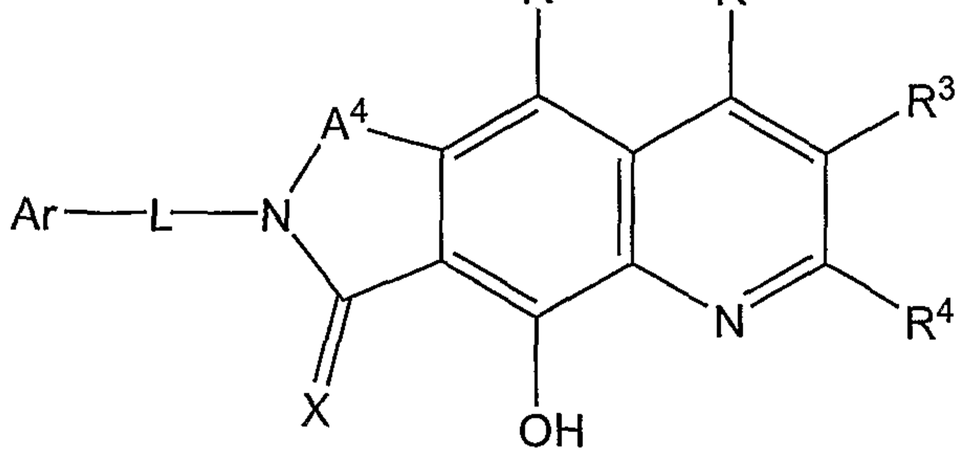
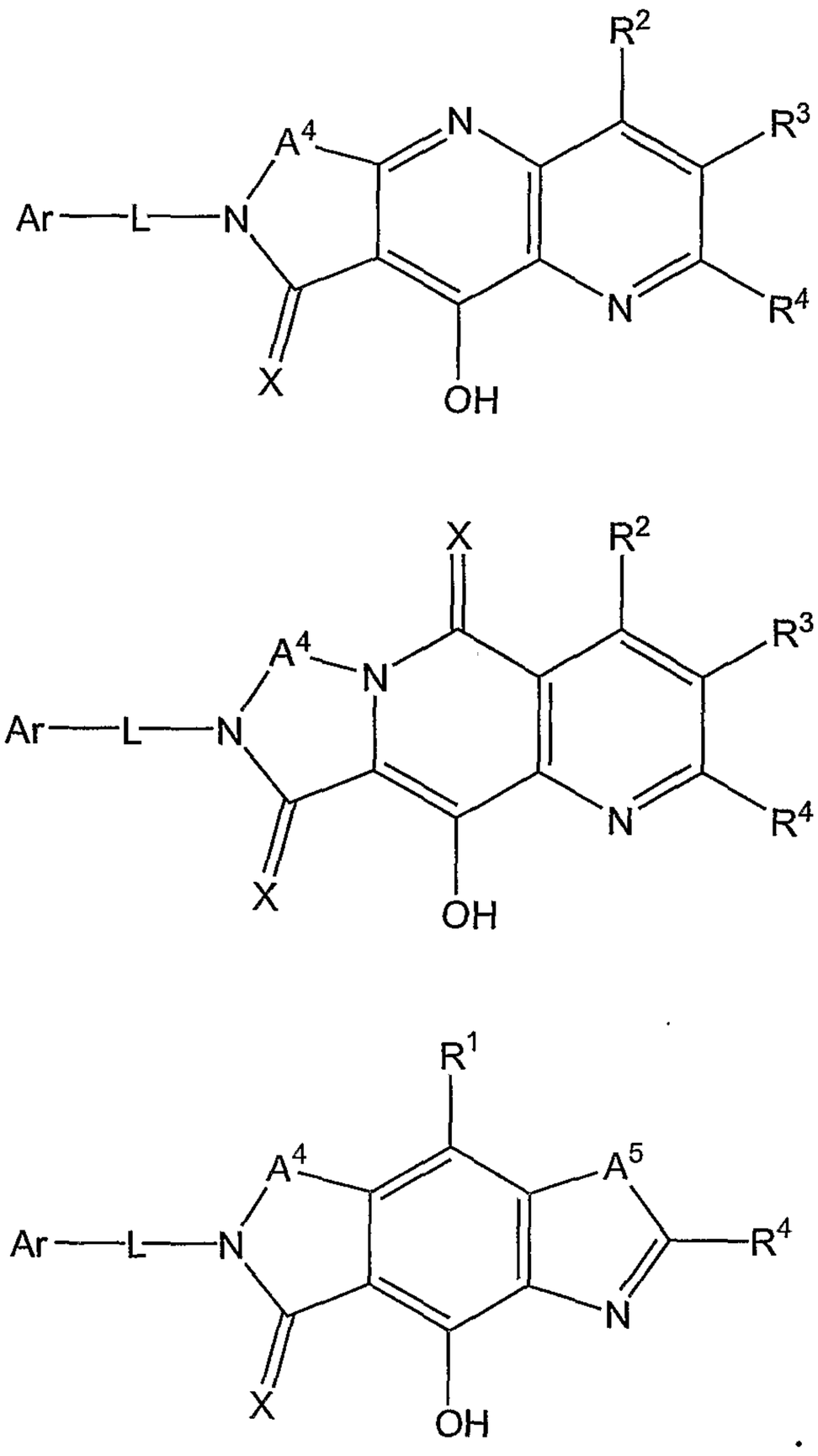

;

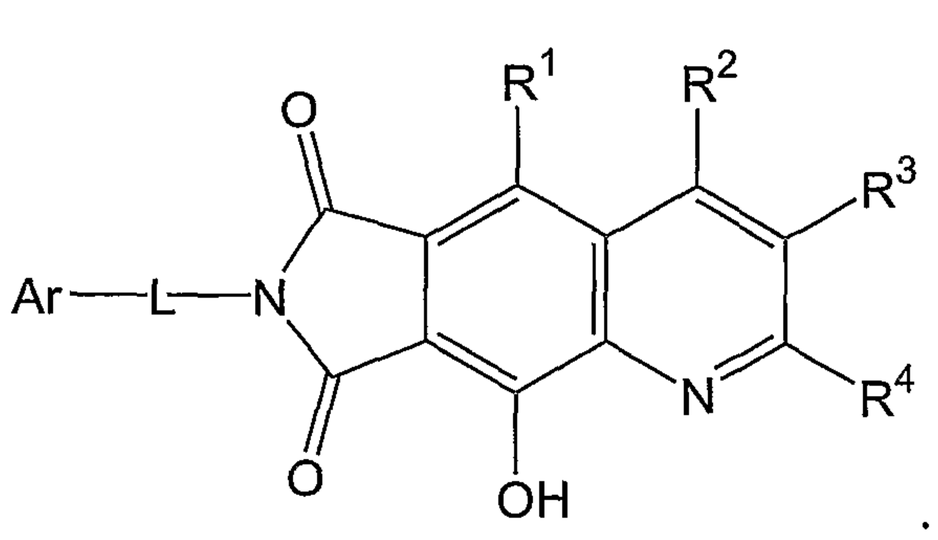
which is substituted with one or more covalently attached A^0 groups.

32. A Formula I HIV integrase inhibitor compound of claim 24 selected from the structures:

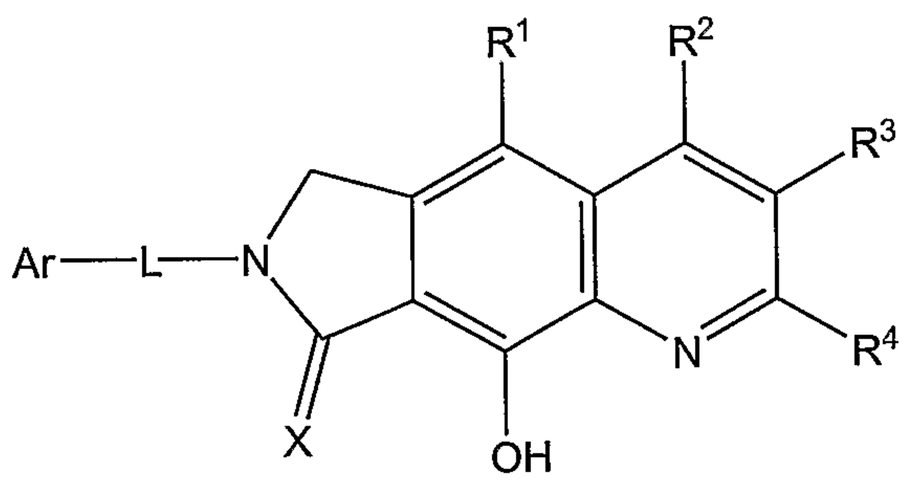




33. A Formula I HIV integrase inhibitor compound of claim 24 selected from the structures:



34. A Formula I HIV integrase inhibitor compound of claim 24 selected from the structures:



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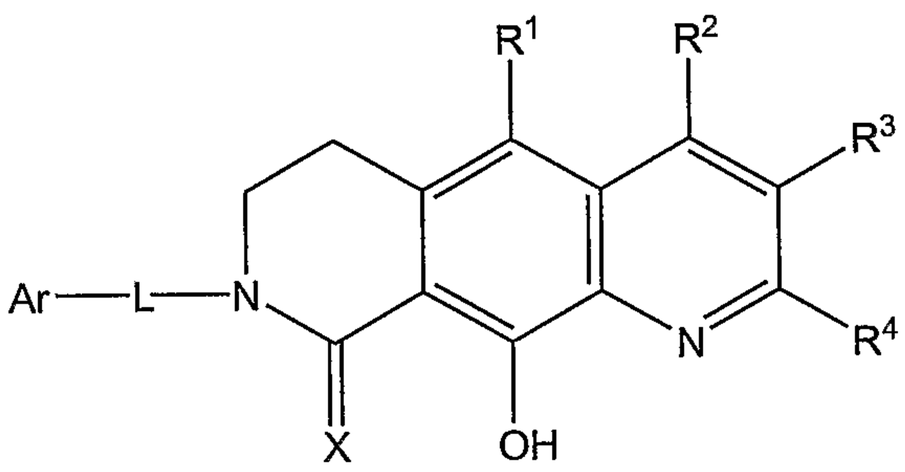
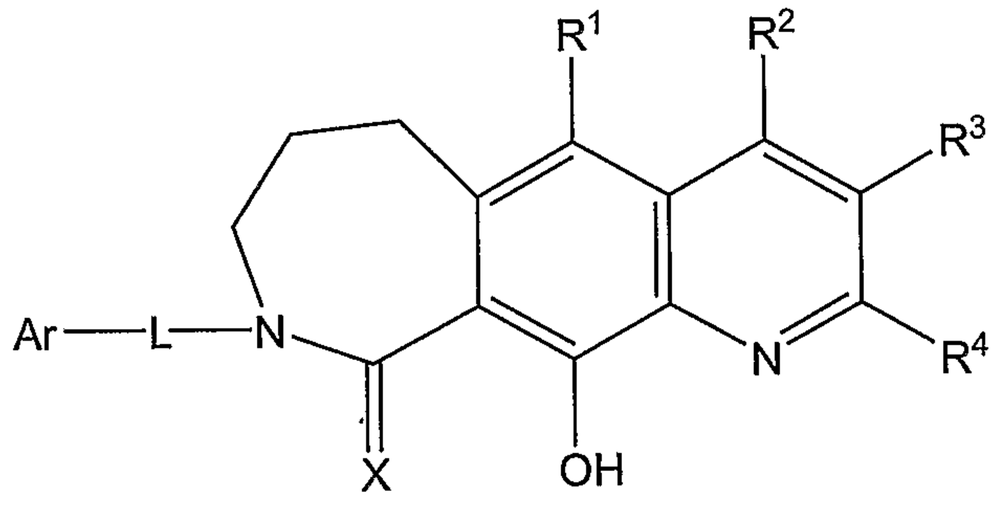
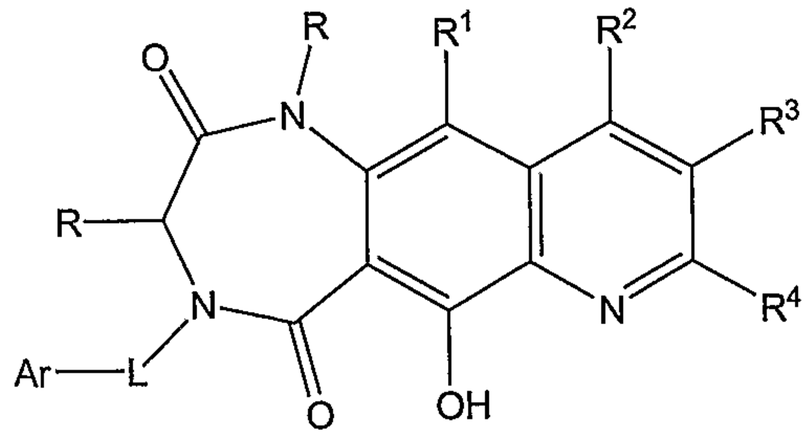


Ib



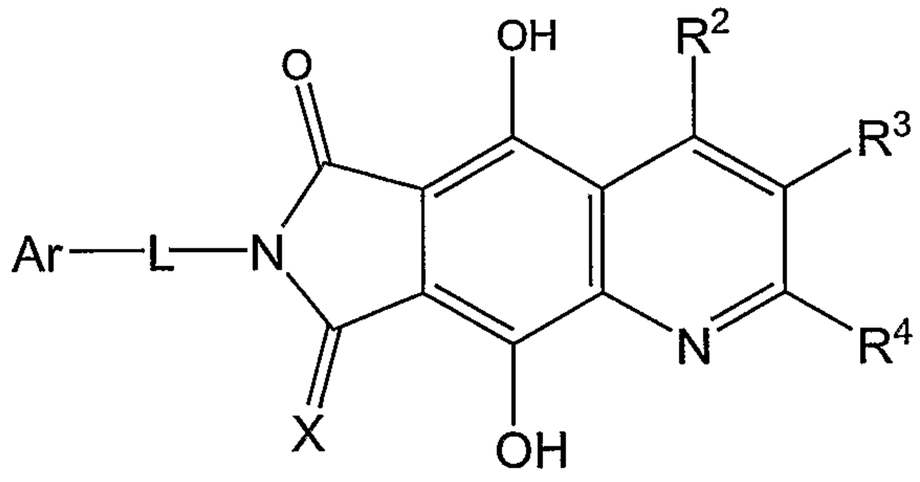
Ic.

35. A Formula I HIV integrase inhibitor compound of claim 24 selected from the structures:



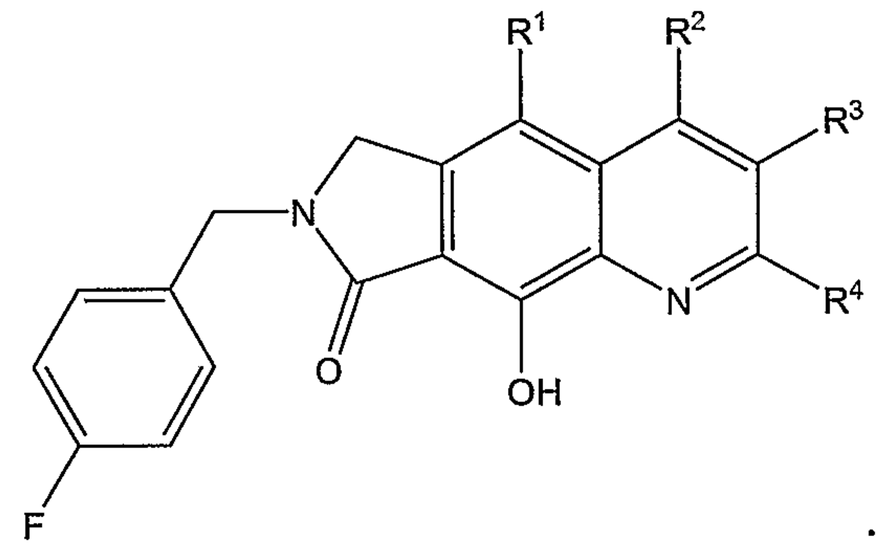
Id.

36. A Formula I HIV integrase inhibitor compound of claim 24 selected from the structures:



Ie.

37. A Formula I HIV integrase inhibitor compound of claim 24 selected from the structures:



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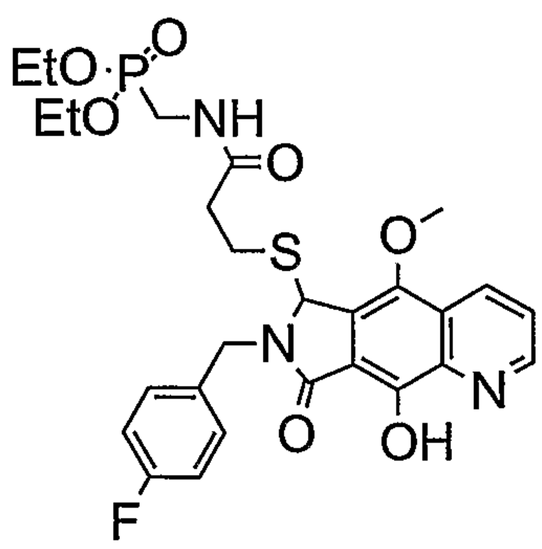
38. A Formula I HIV integrase inhibitor compound of claim 24 selected from the structures:



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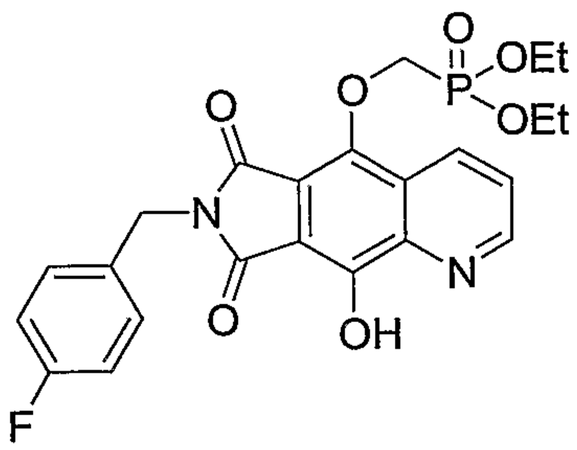

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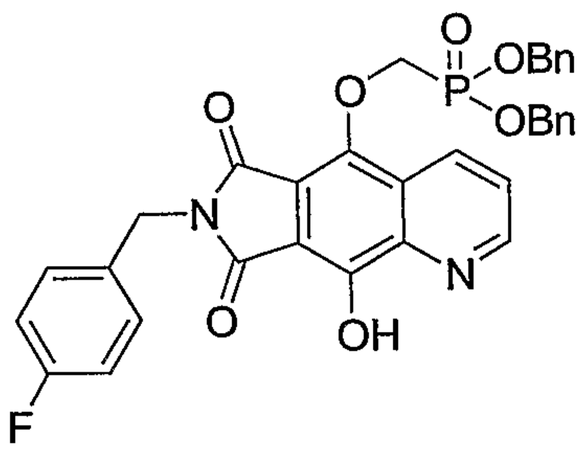

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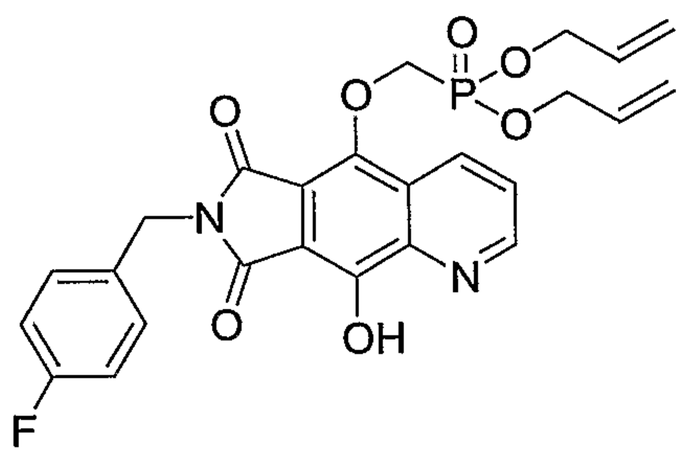

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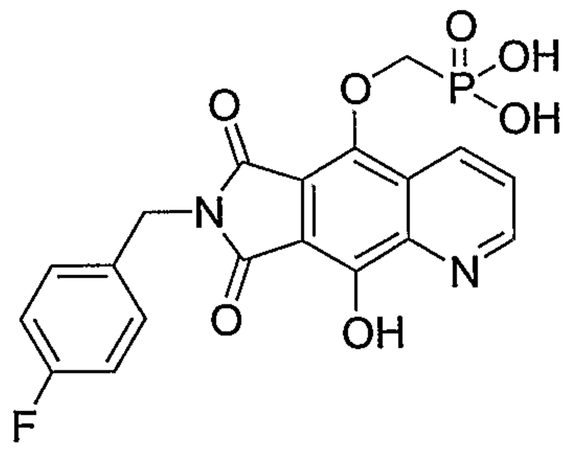

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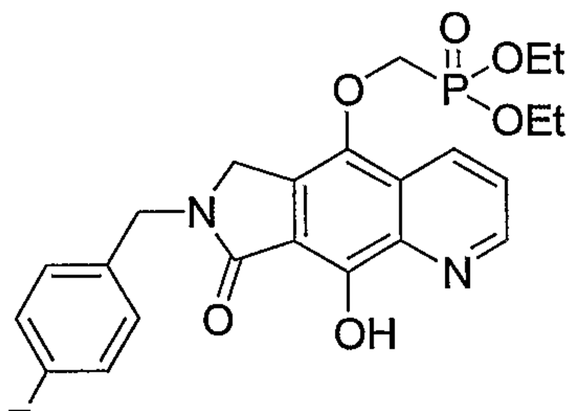
157



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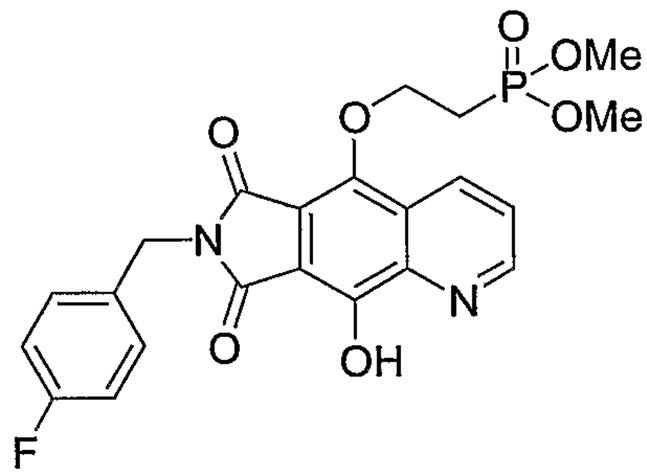

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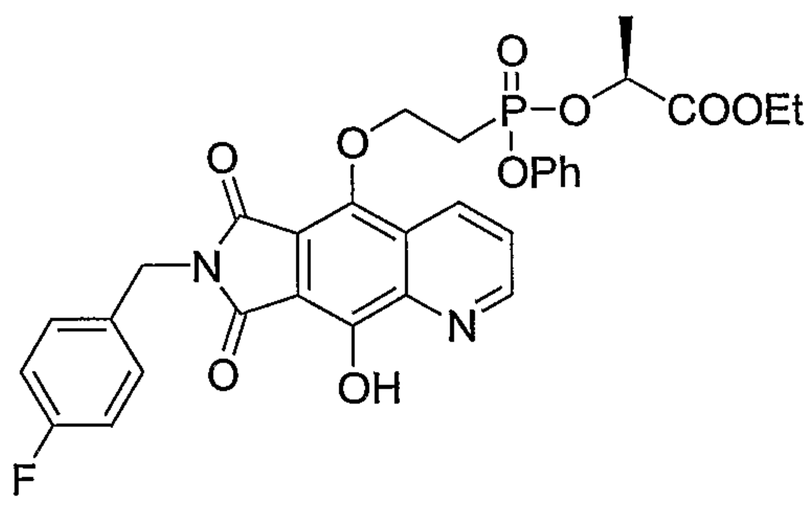
165



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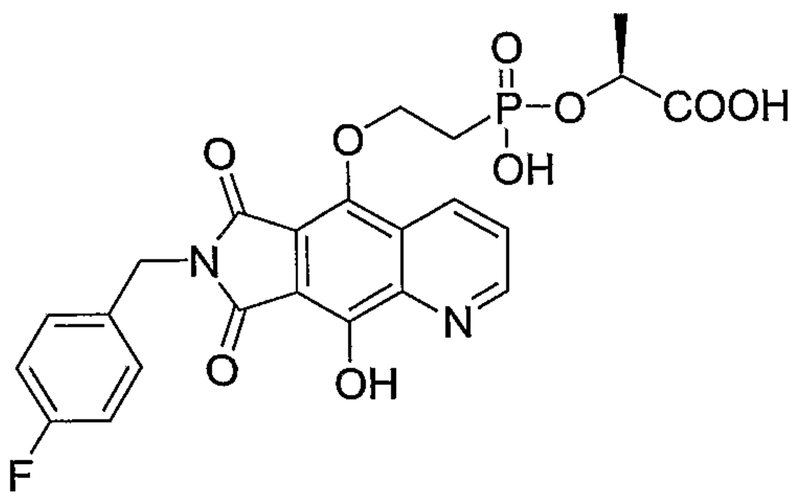

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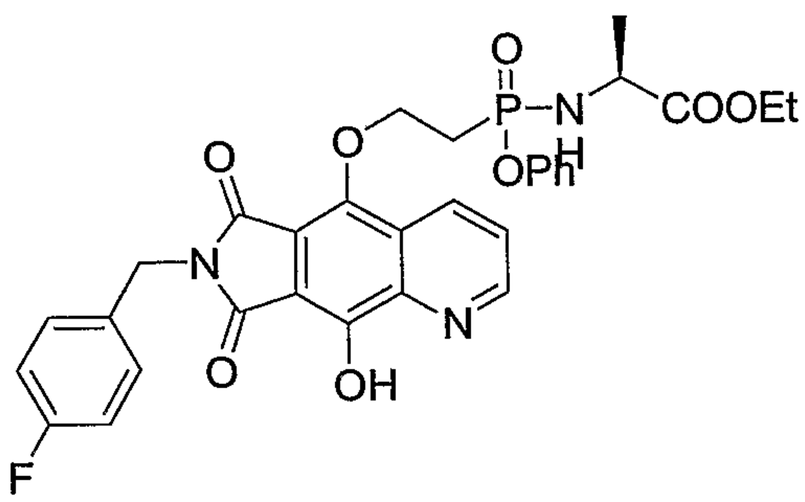

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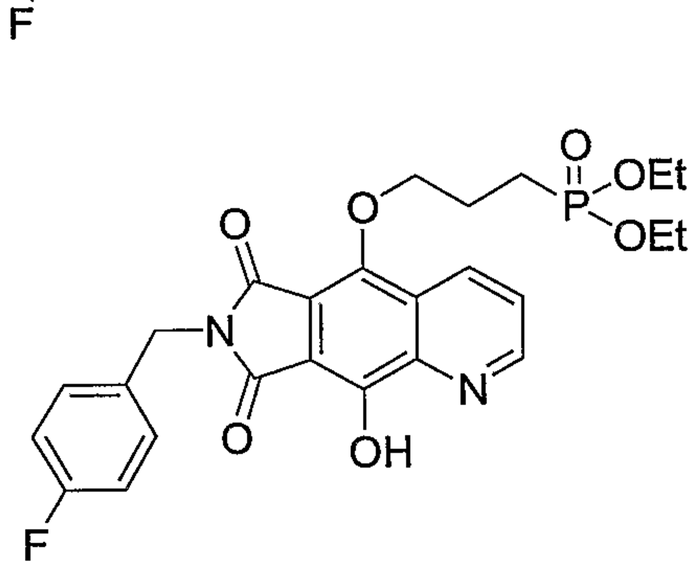

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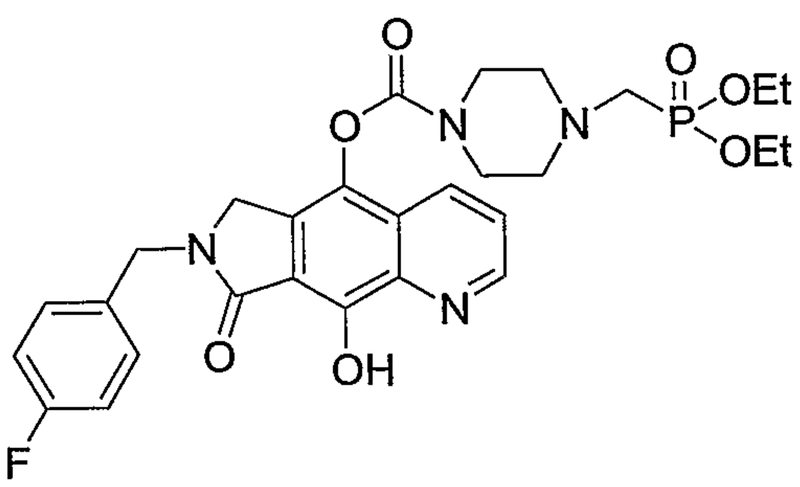

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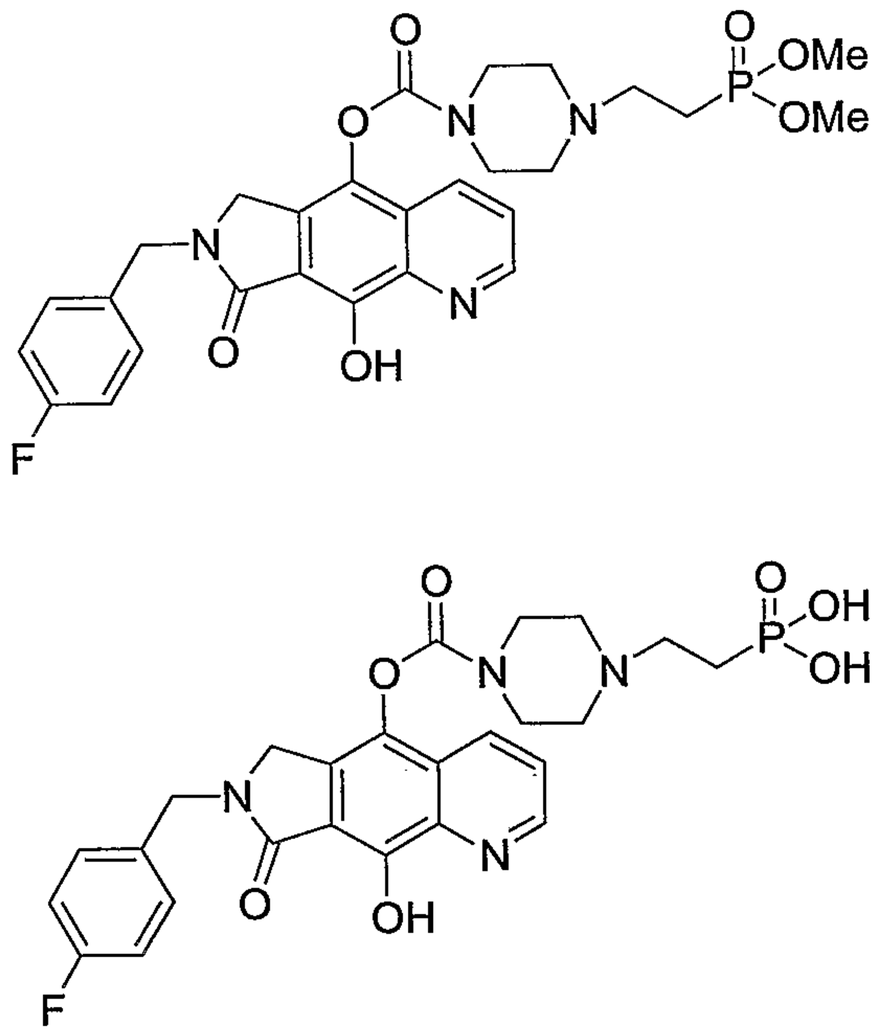

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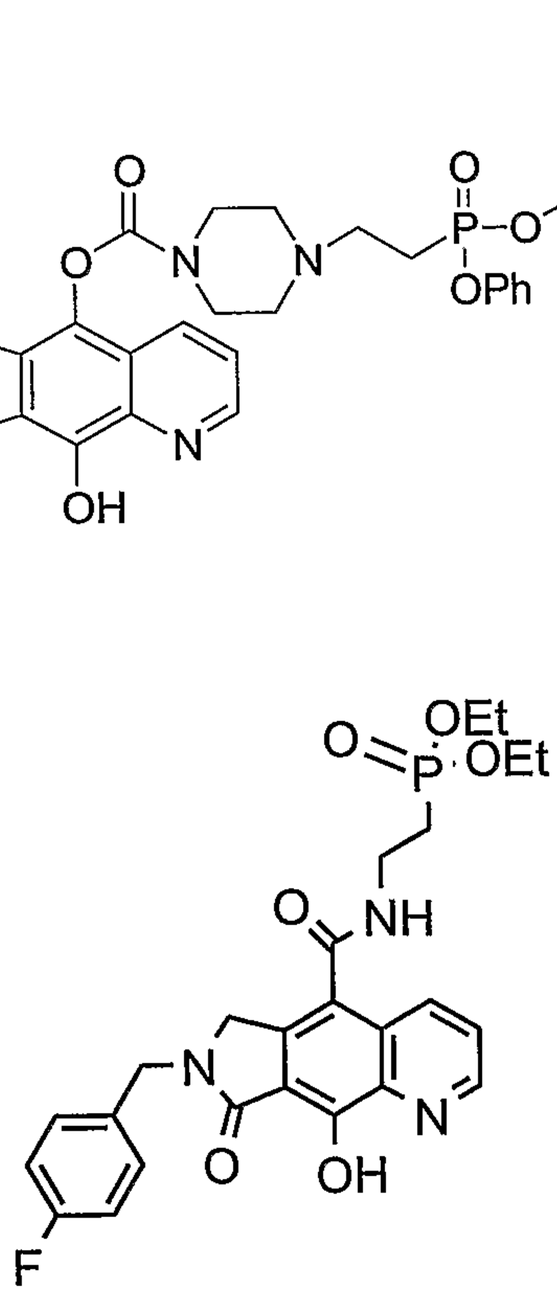

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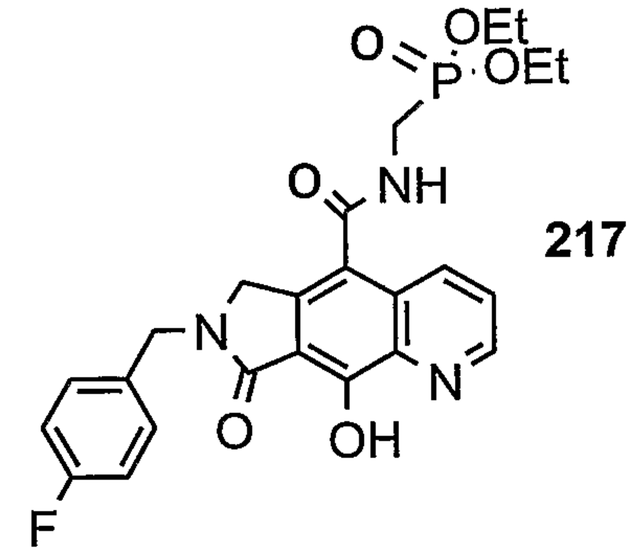

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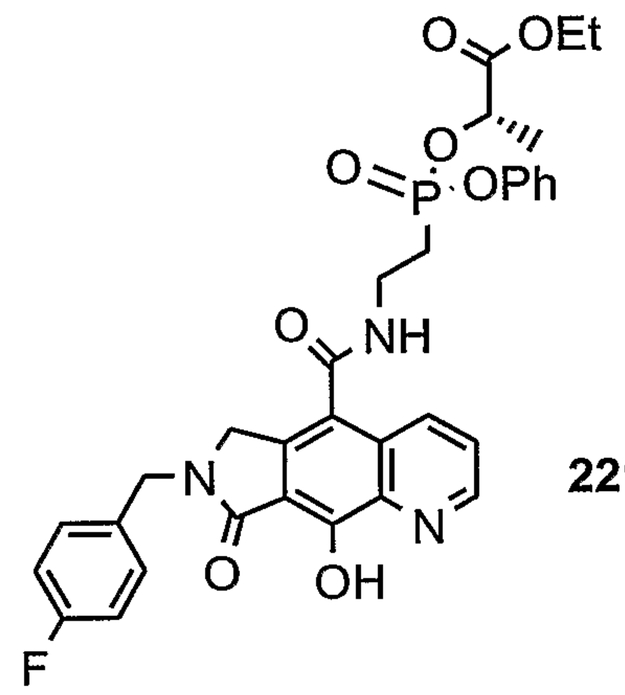

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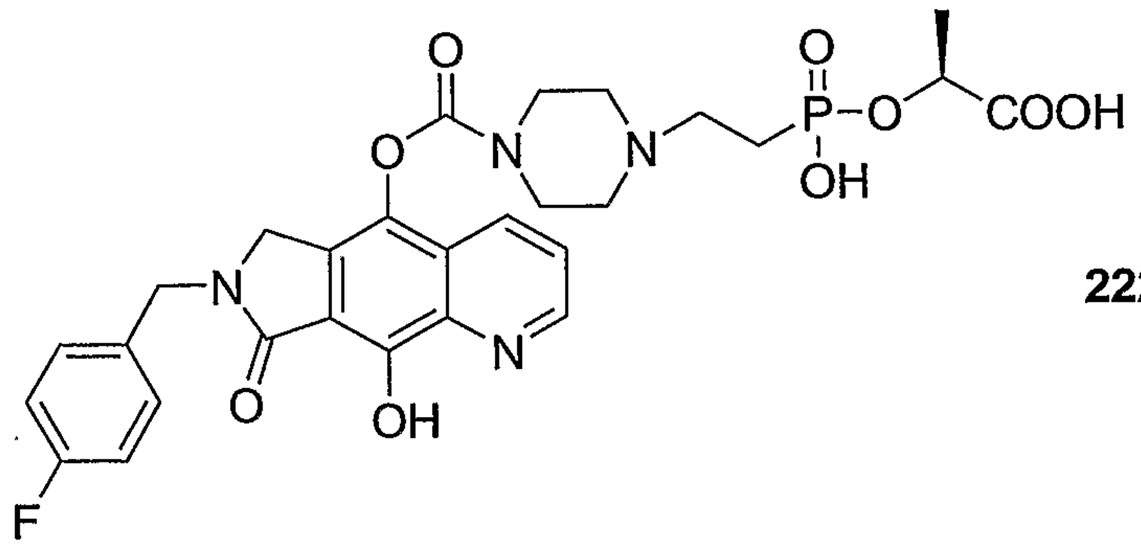

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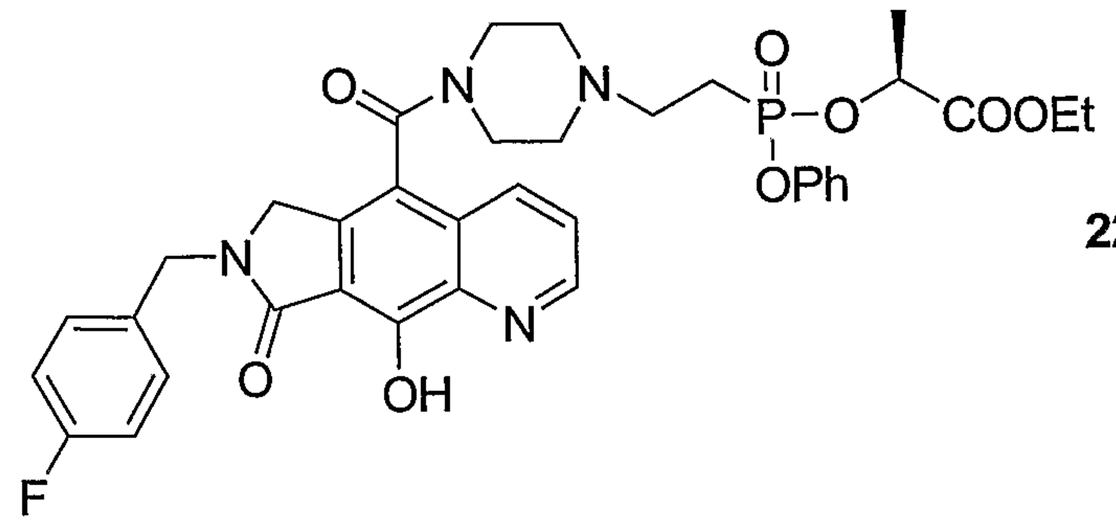

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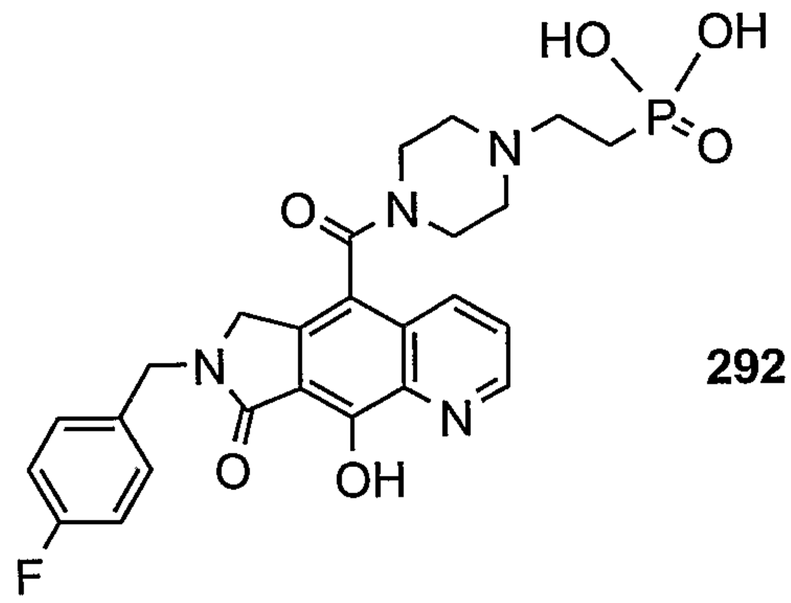

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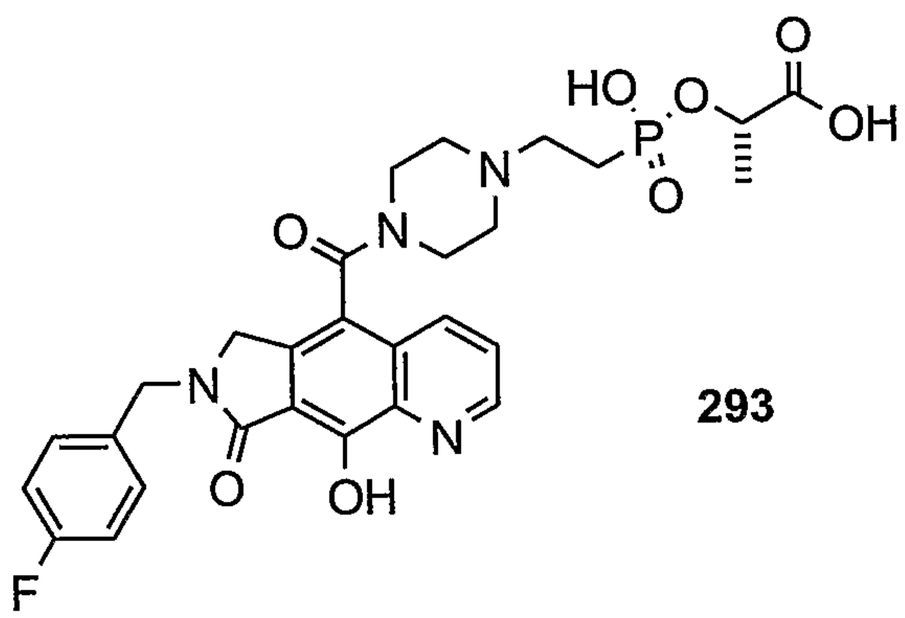

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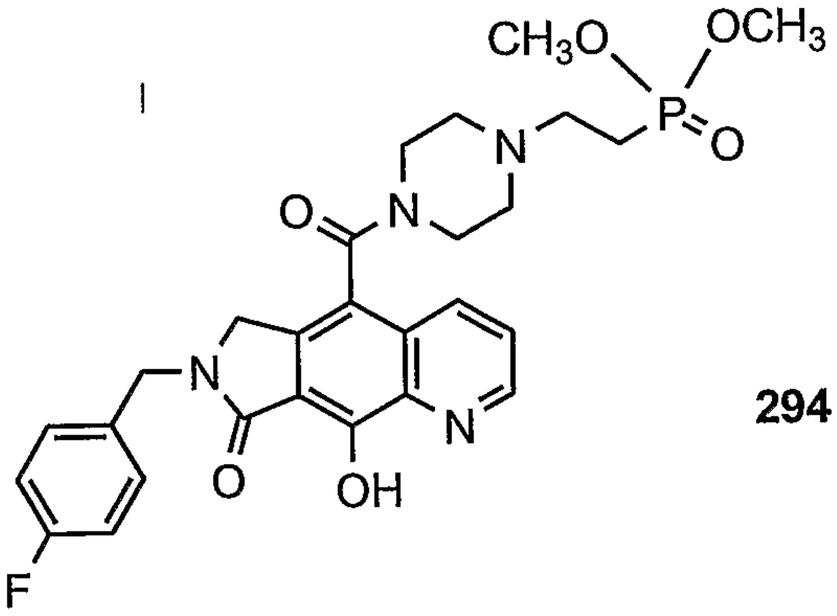

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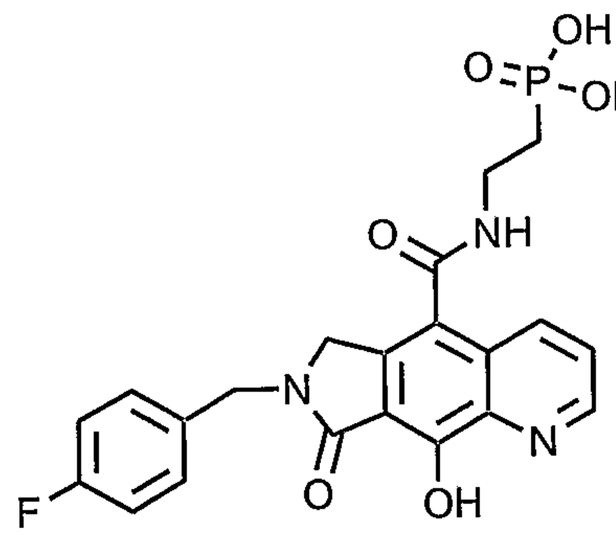

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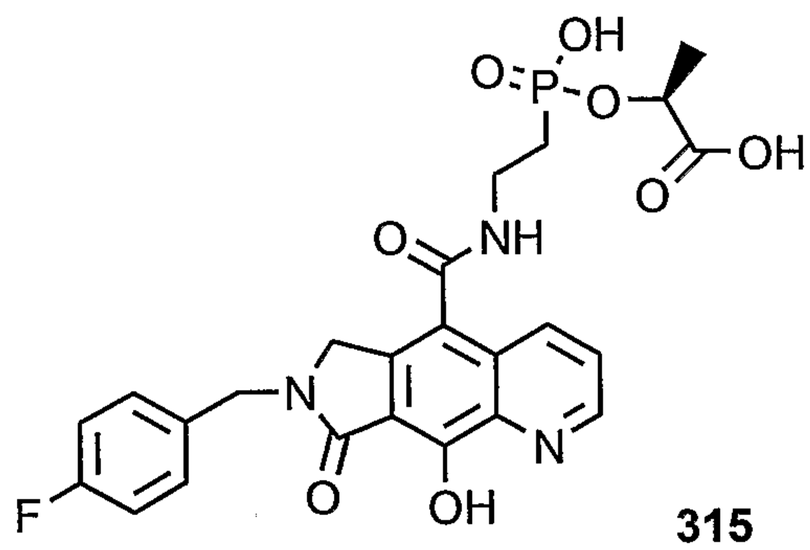
and



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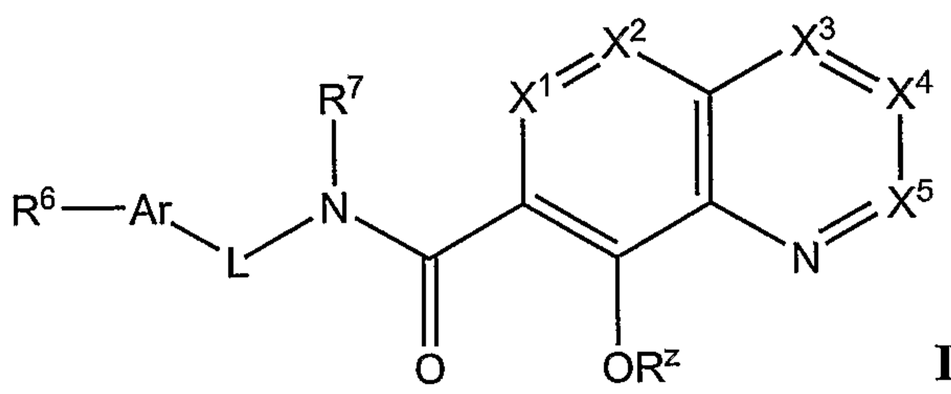
39. An HIV integrase inhibitor compound of claim 2 or 3 selected from Formula II:



II

wherein:

X^1 is CR^1, NR, or N;

X^2 is CR^2, NR, or N;

X^3 is CR^3, NR, or N;

X^4 is CR^4, NR, or N;

X^5 is CR^5, NR, or N;

at least one of X^1, X^2, X^3, X^4, and X^5 is NR or N;

R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are independently selected from the group consisting of H, F, Cl, Br, I, OH, $-NH_2$, $-NH_3^+$, -NHR, $-NR_2$, $-NR_3^+$, C_1-C_8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, C_1-C_8 alkylsulfonate, C_1-C_8 alkylamino, 4-dialkylaminopyridinium, C_1-C_8 alkylhydroxyl, C_1-C_8 alkylthiol, $-SO_2R$, $-SO_2Ar$, -SOAr, -SR, -SAr, $-SO_2NR_2$ (sulfonamide), -SOR, $-CO_2R$, $-C(=O)NR_2$, 5-7 membered ring lactam, 5-7 membered ring lactone, -CN, $-N_3$, $-NO_2$, C_1-C_8 alkoxy, C_1-C_8 trifluoroalkyl, C_1-C_8 alkyl, C_1-C_8 substituted alkyl, C_3-C_{12} carbocycle, C_3-C_{12} substituted carbocycle, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20}

heteroaryl, C_2–C_{20} substituted heteroaryl, polyethyleneoxy, phosphonate, phosphate, a prodrug moiety, –OC(=O)OR, –OC(=O)NR_2, –OC(=S)NR_2, –OC(=O)$NRNR_2$, –OC(=O)R, –C(=O)$NRNR_2$, –C(=O)R, –OSO_2NR_2 (sulfamate), –$NRSO_2R$, –NRC(=S)NR_2, –OSO_2R (sulfonate), –P(=O)$(OR)_2$, –P(=O)(OR)(NR_2), –P(=O)$(NR_2)_2$, –P(=S)$(OR)_2$, –P(=S)(OR)(NR_2), –P(=S)$(NR_2)_2$, and including prodrug substituted forms thereof;

at least one of R, R^1, R^2, R^3, R^4, R^5, R^6, and R^7 comprises a phosphonate group;wherein the phosphonate group may be a prodrug moiety; or the phosphonate group is directly attached to a ring carbon (CR^1, CR^2, CR^3, CR^4 or CR^5) of Formula II;

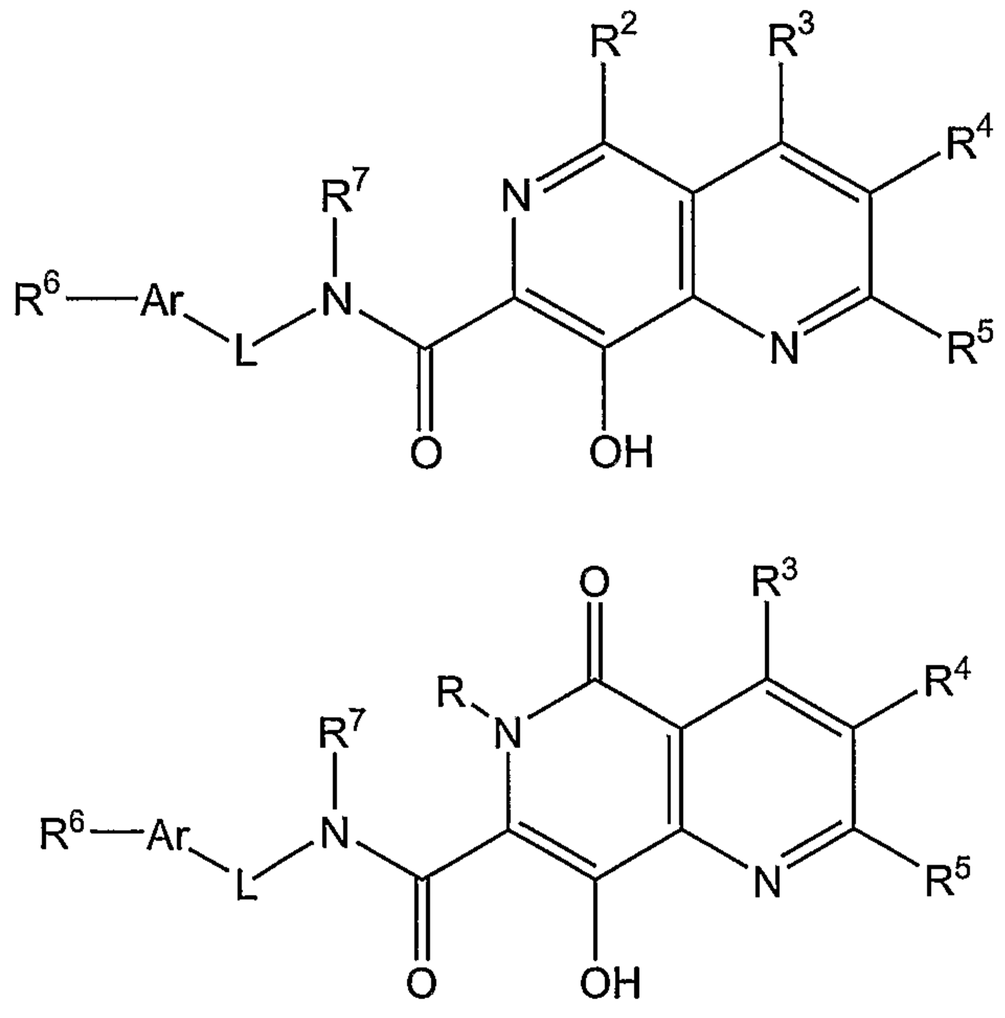
R^z is H, a protecting group, or a prodrug moiety;

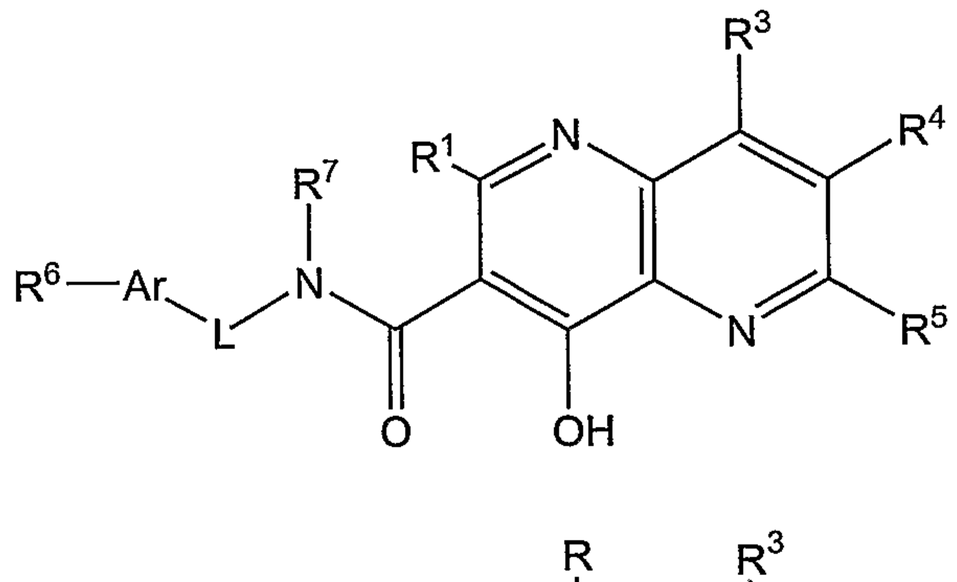
Ar is C_3–C_{12} carbocycle, C_3–C_{12} substituted carbocycle, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, or C_2–C_{20} substituted heteroaryl; and

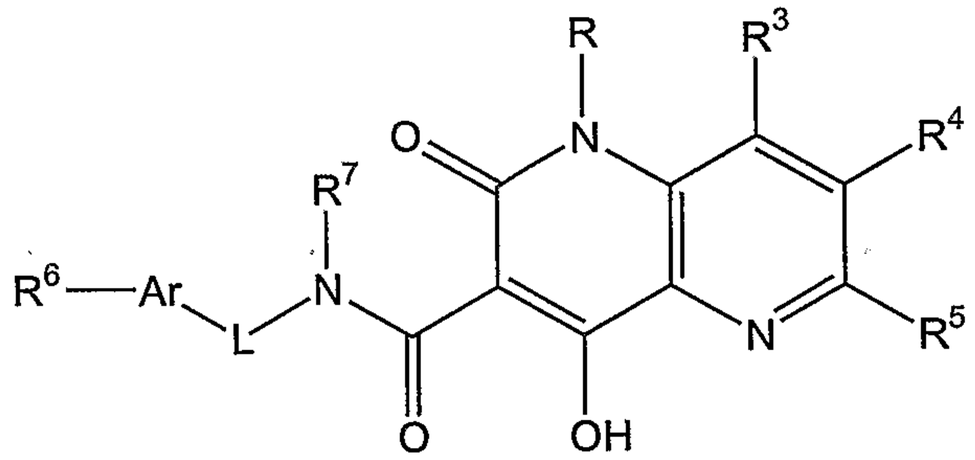
Ar is covalently attached to L and to one or more R^6; and

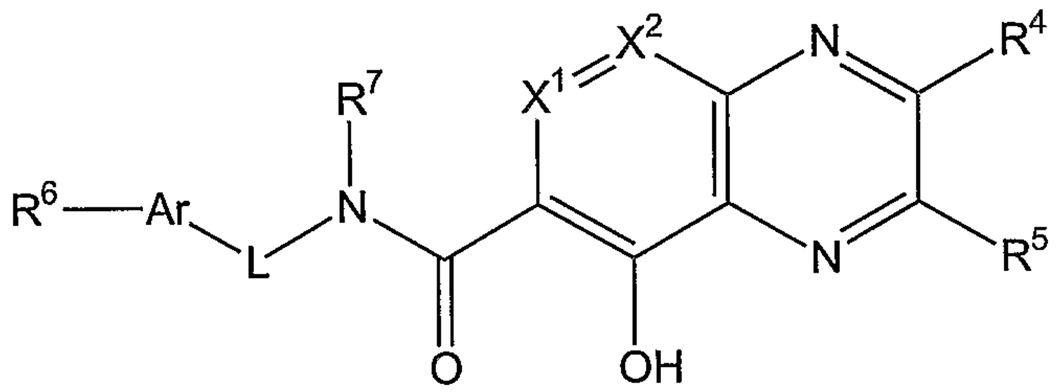
which is substituted with one or more covalently attached A^0 groups.

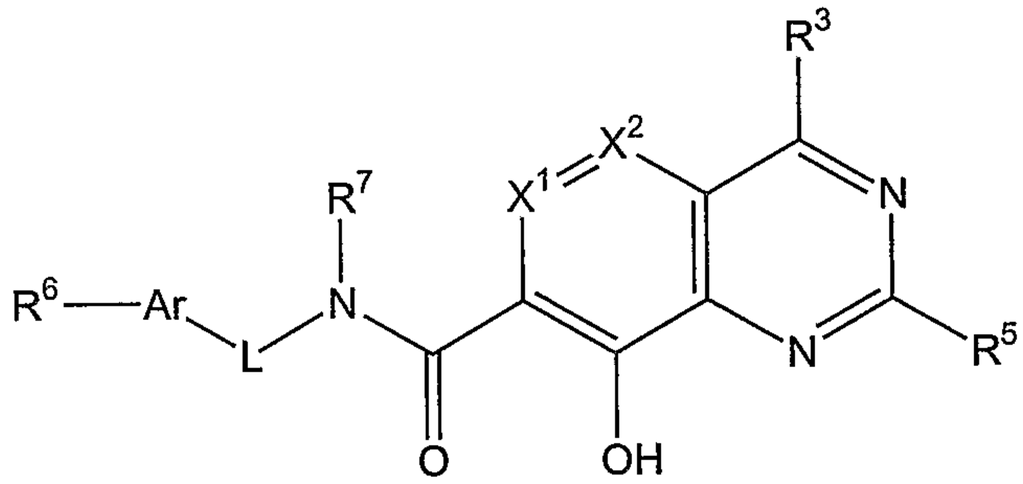
40. A Formula II HIV integrase inhibitor compound of claim 39 selected from the structures:

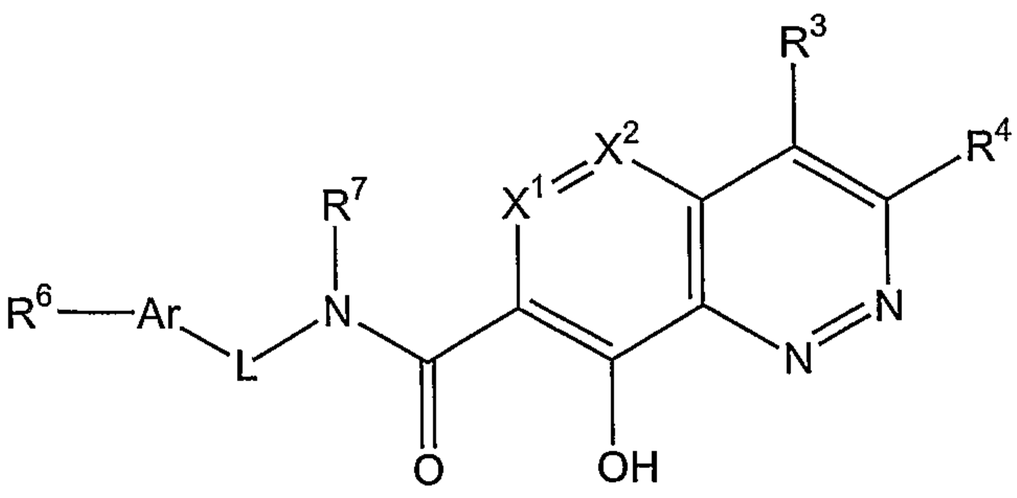


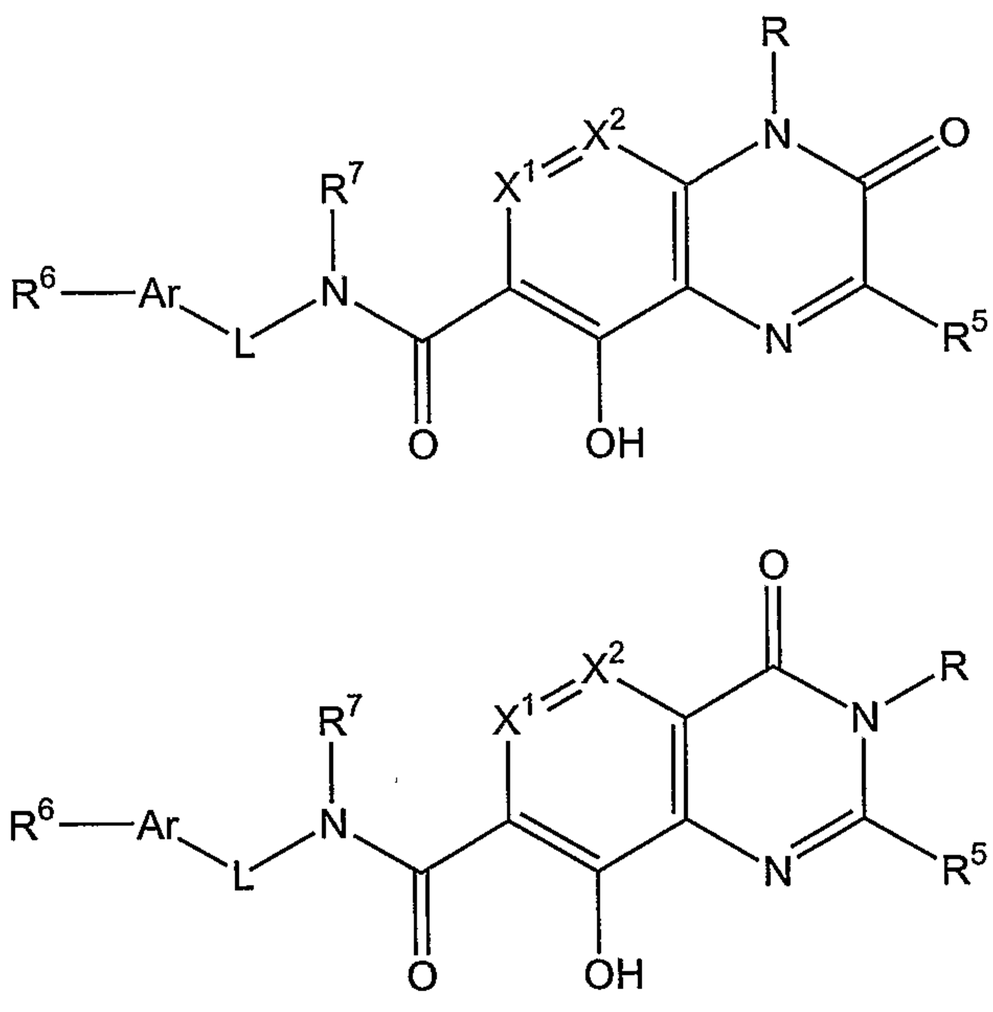




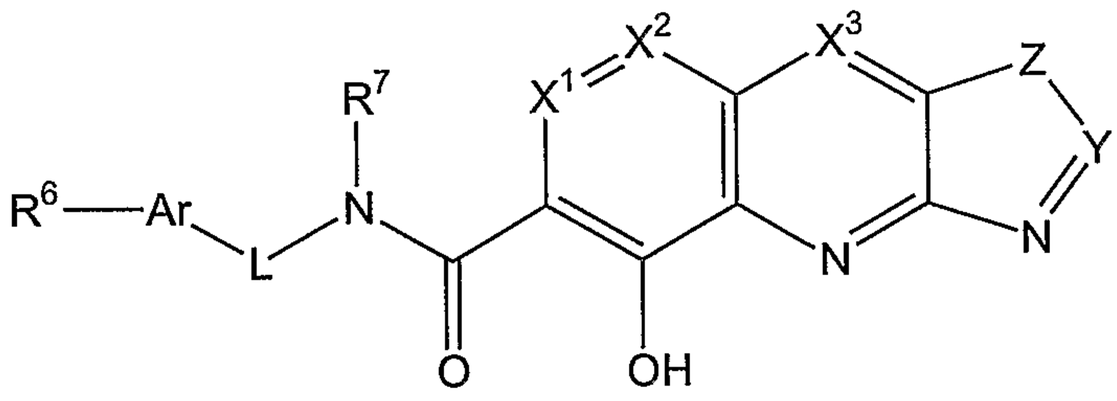


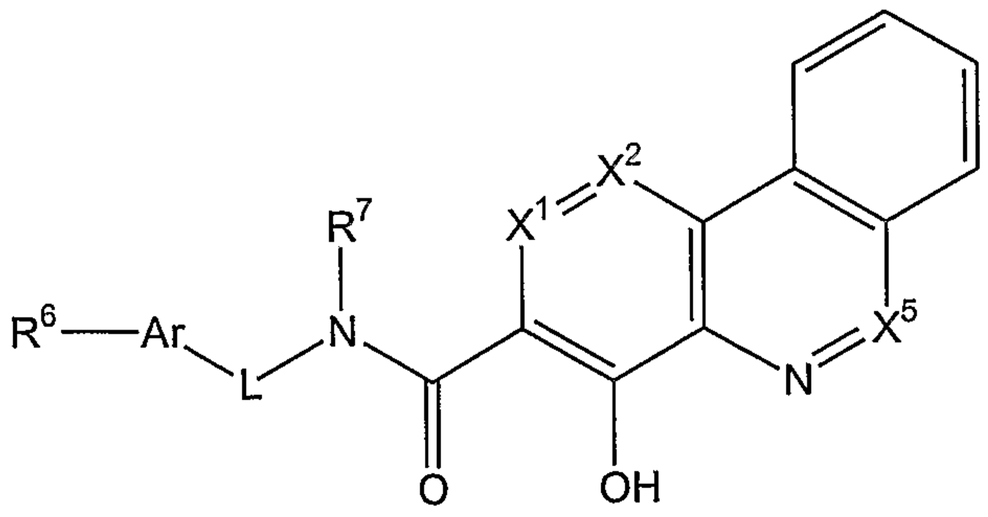


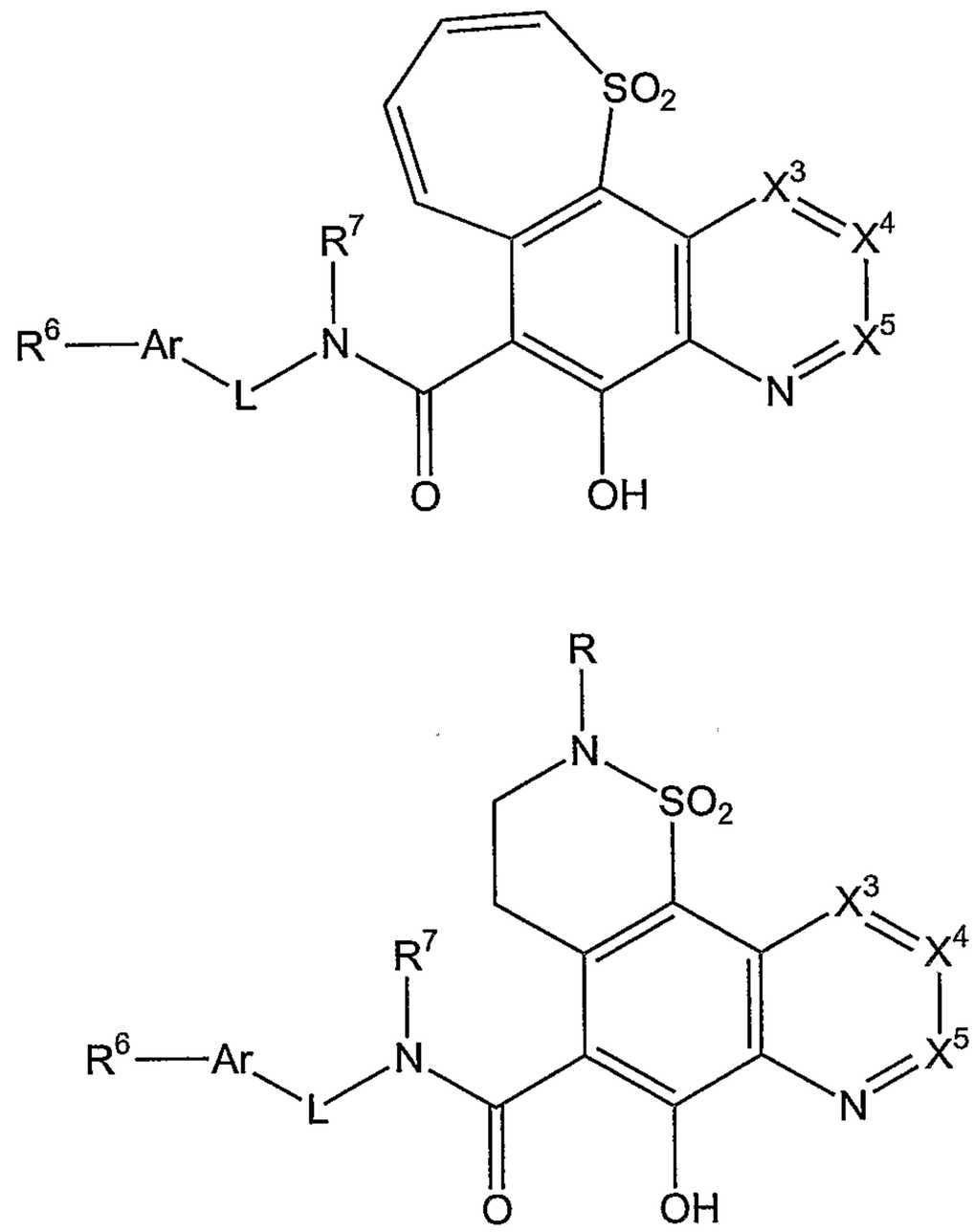




41. An HIV integrase inhibitor compound of claim 2 or 3 having Formula II as described in claim 39, wherein the compound has the formula:

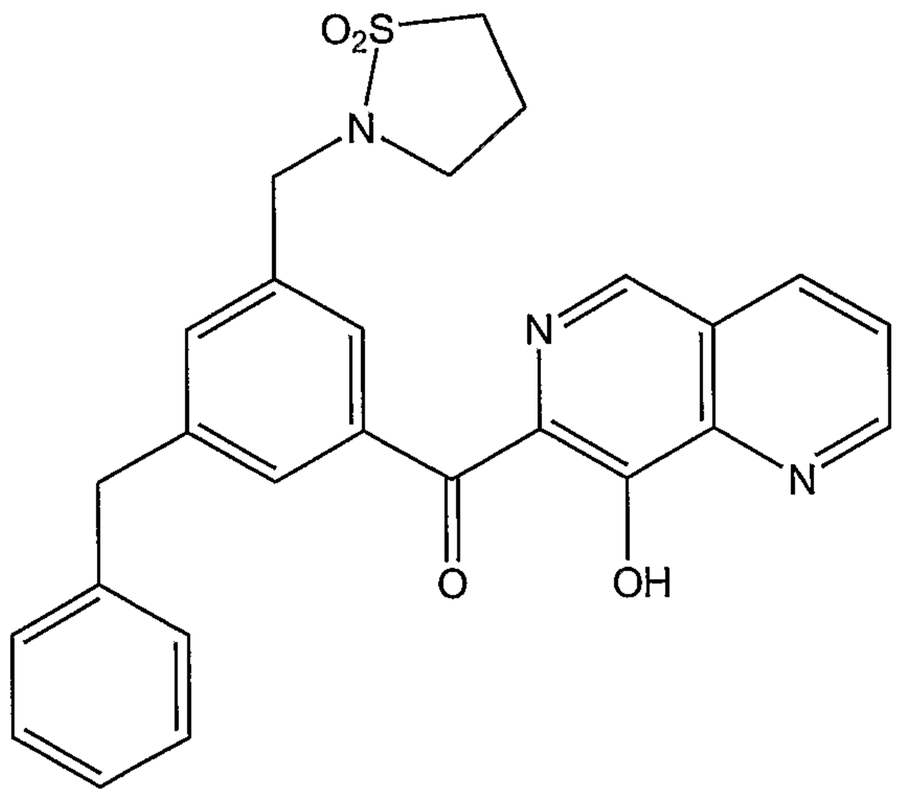






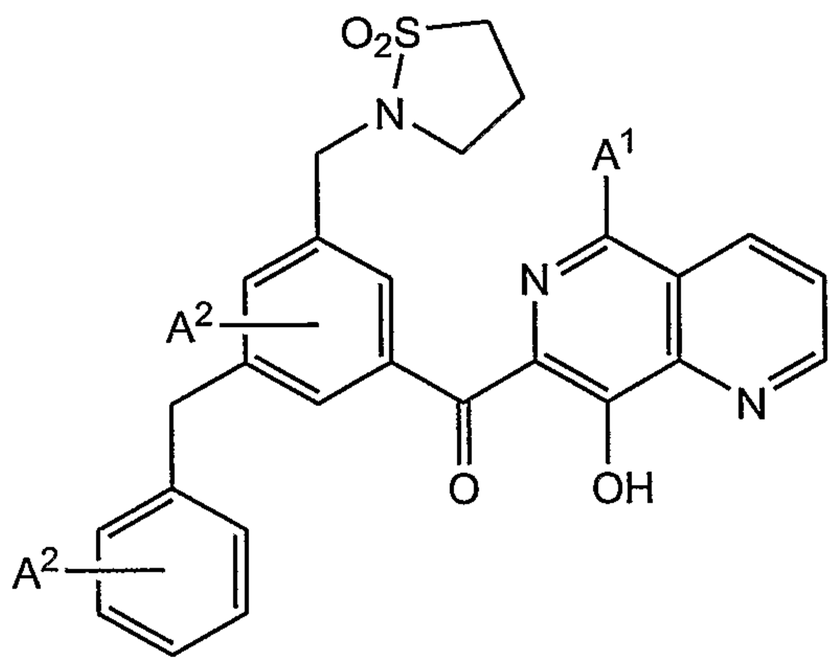
which is substituted with one or more covalently attached A^0 groups.

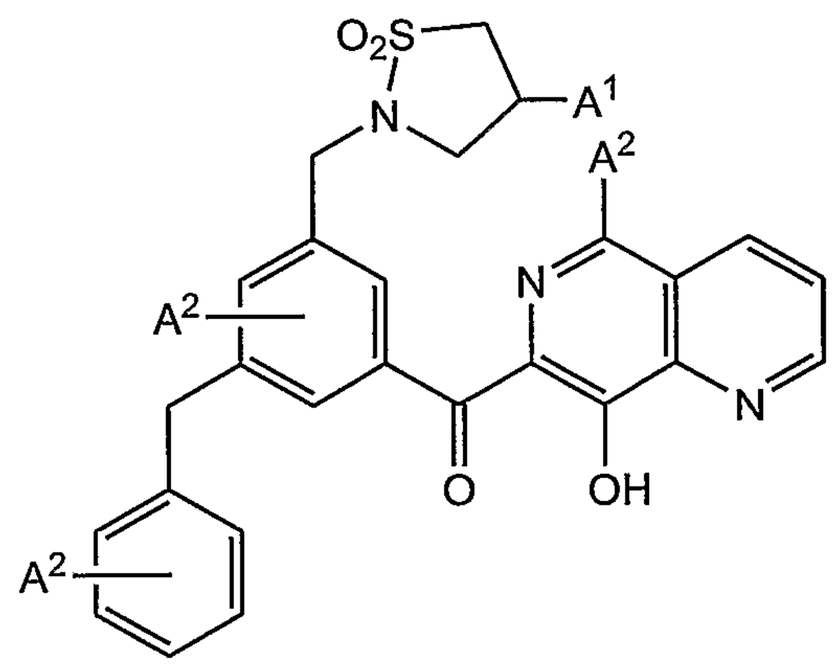
42. An HIV integrase inhibitor compound of claim 2 or 3 having Formula II as described in claim 39, wherein the compound has the formula:

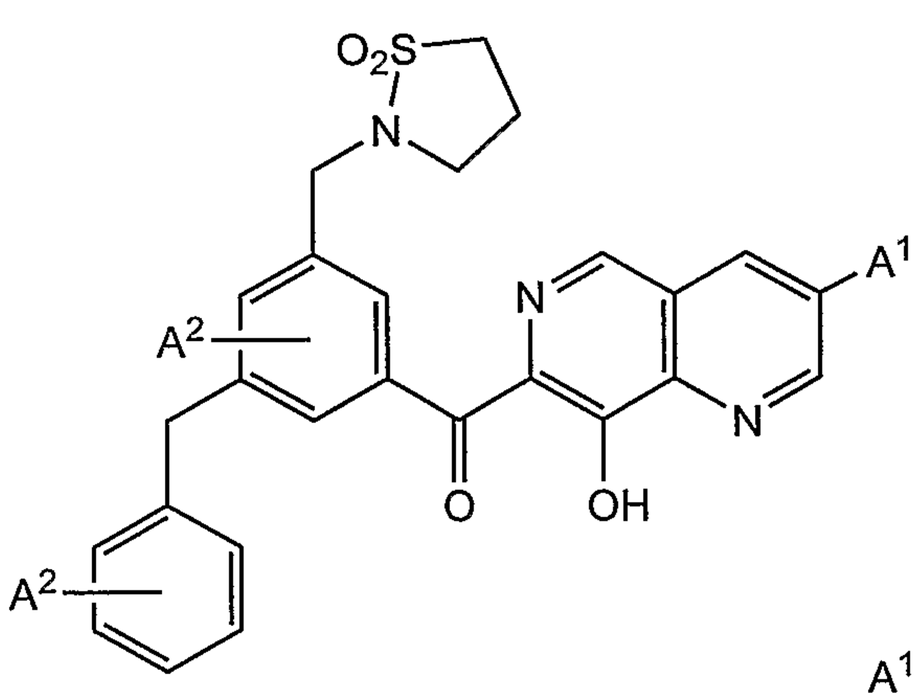


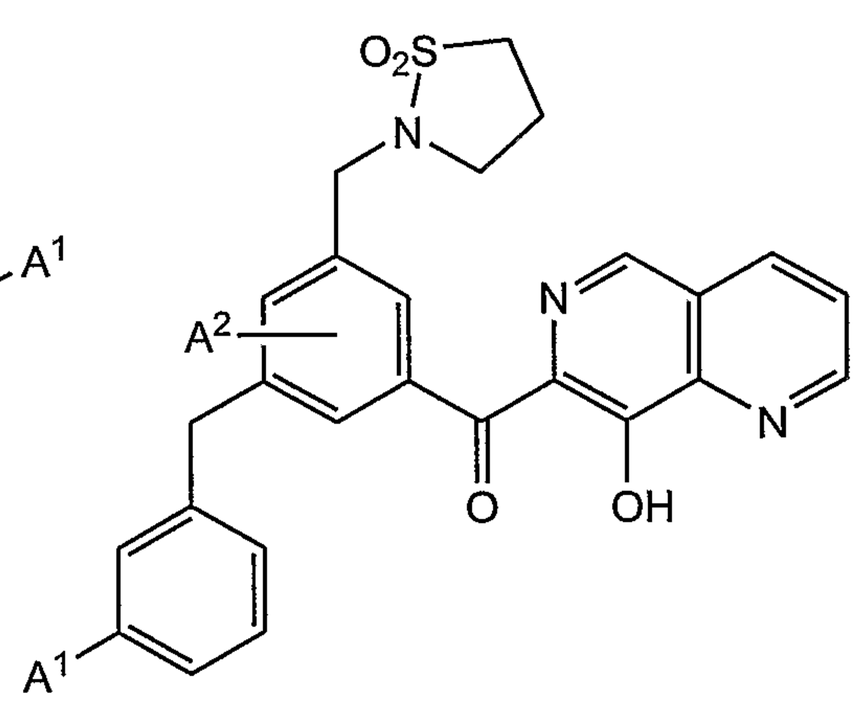
where at least one aryl or sultam ring carbon atom is substituted with an A^1 group, and any aryl or sultam ring carbon atom may be substituted with an A^2 group.

43. A Formula II HIV integrase inhibitor compound of claim 42 selected from the structures:

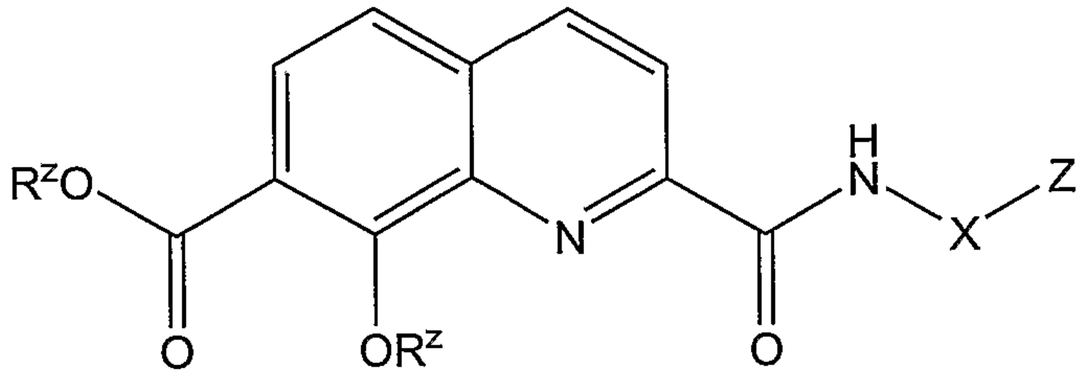








44. An HIV integrase inhibitor compound of claim 2 selected from Formula III:



III

wherein

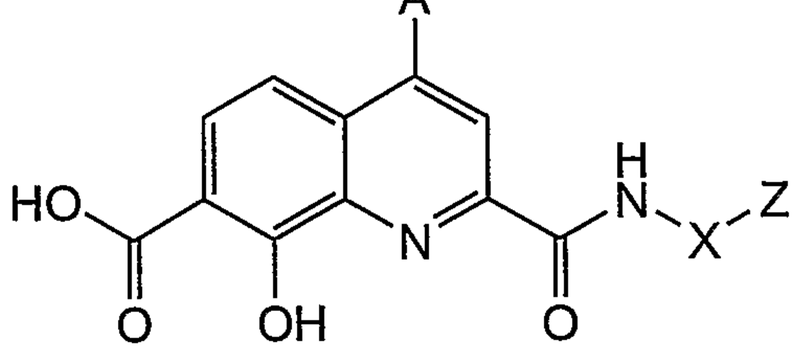
R^z is H, a protecting group, or a prodrug moiety;

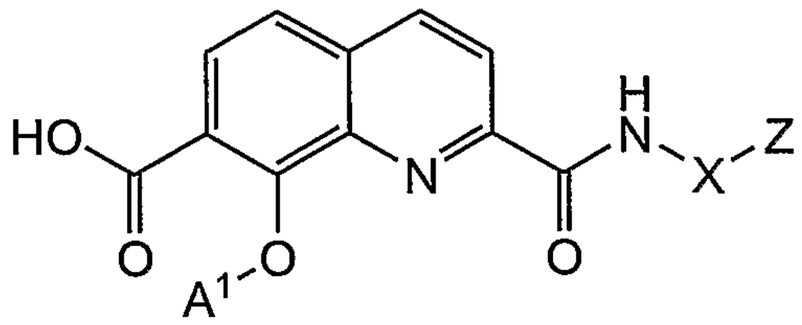
X is L; and

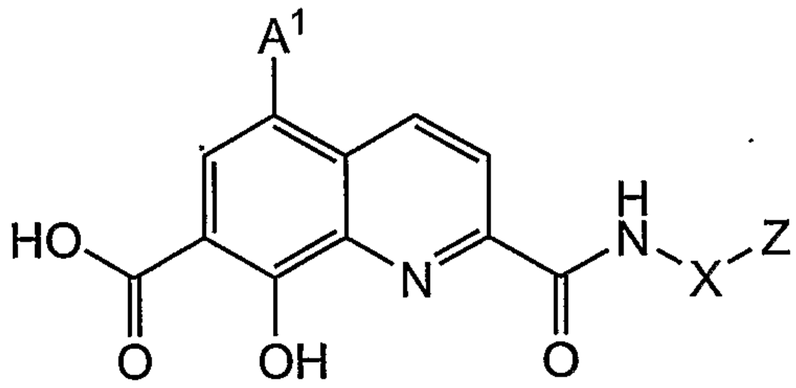
Z is C_3–C_{12} carbocycle, C_3–C_{12} substituted carbocycle, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, or C_2–C_{20} substituted heteroaryl;

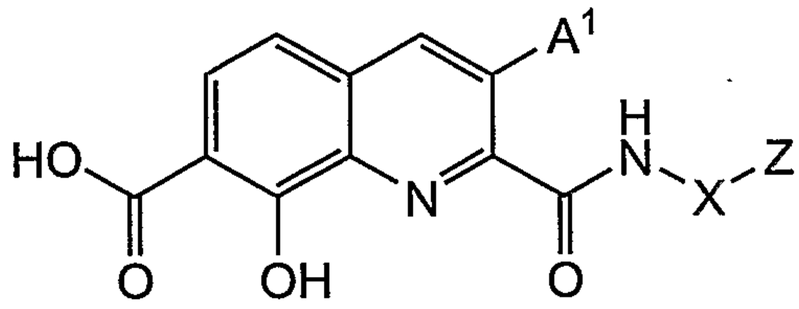
which is substituted with one or more covalently attached A^0 groups.

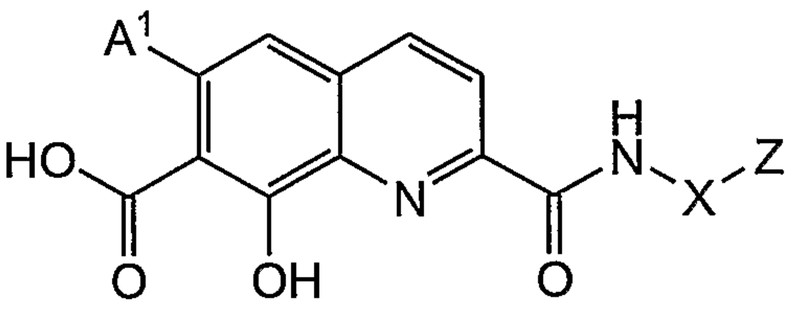
45. A Formula III HIV integrase inhibitor compound of claim 44 selected from the structures:

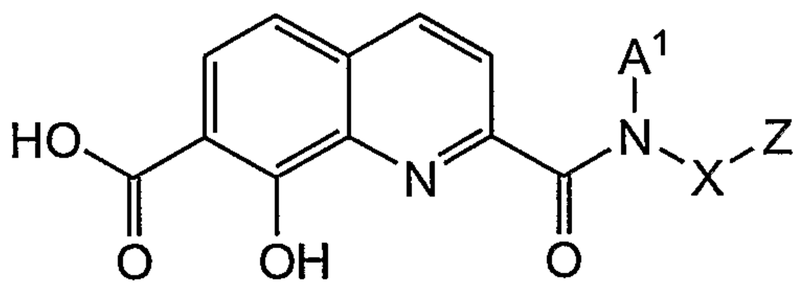


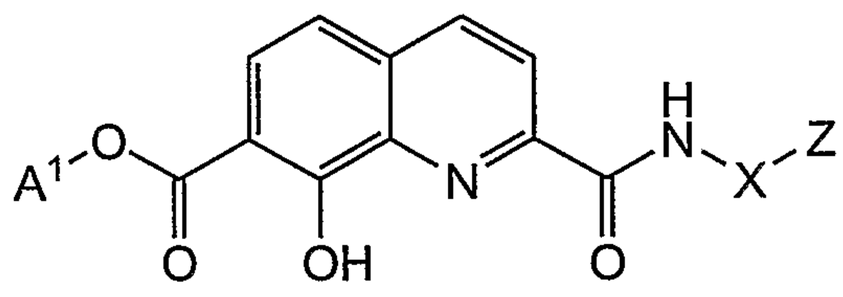












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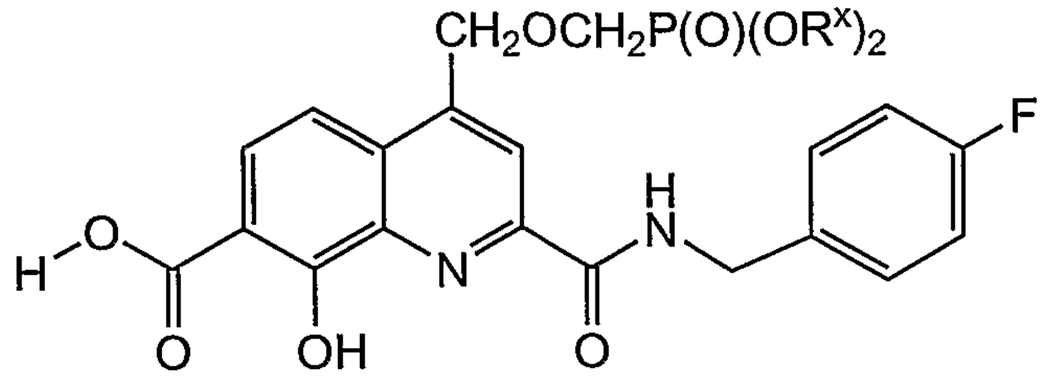
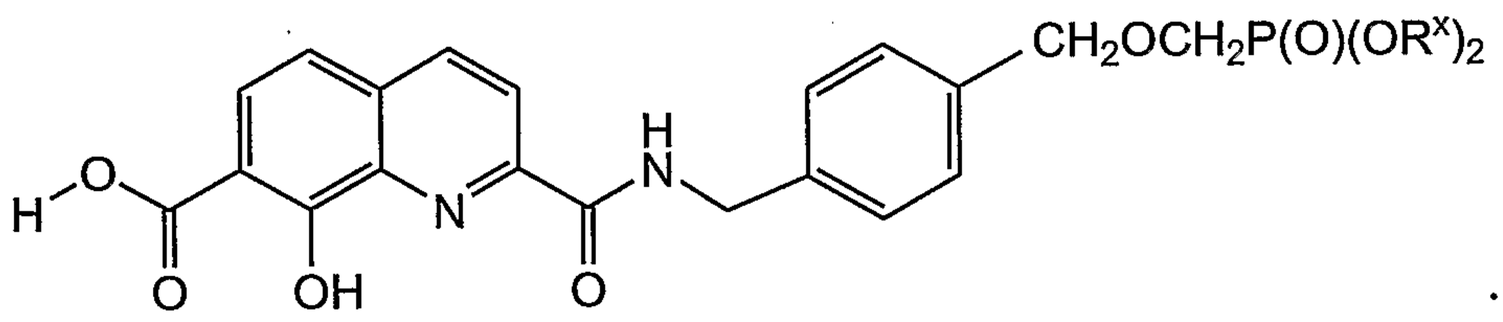
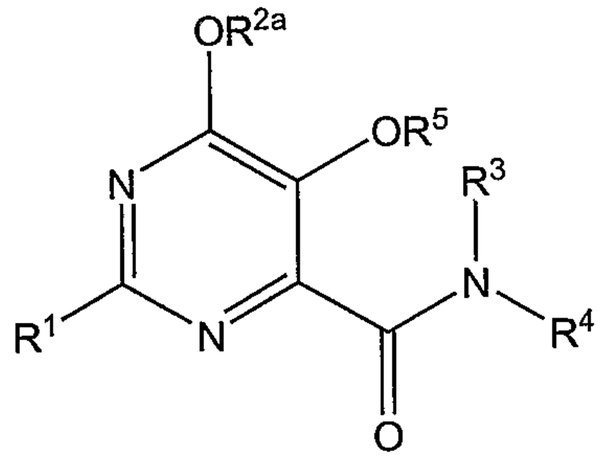
46. A Formula III HIV integrase inhibitor compound of claim 45 selected from the structures:





47. An HIV integrase inhibitor compound of claim 2 selected from Formula IV:



IV

wherein:

R^1 is selected from H, F, Cl, Br, I, OH, OR, amino ($-NH_2$), ammonium ($-NH_3^+$), alkylamino ($-NHR$), dialkylamino ($-NR_2$), trialkylammonium ($-NR_3^+$), carboxyl ($-CO_2H$), sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, 4-dialkylaminopyridinium, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide ($-SOAr$), arylthio ($-SAr$), sulfonamide ($-SO_2NR_2$), alkylsulfoxide ($-SOR$), formyl ($-CHO$), ester ($-CO_2R$), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile ($-CN$), azido ($-N_3$), nitro ($-NO_2$), C_1-C_{18} alkyl, C_1-C_{18} substituted alkyl, C_2-C_{18} alkenyl, C_2-C_{18} substituted alkenyl, C_2-C_{18} alkynyl, C_2-C_{18} substituted alkynyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heterocycle, and C_2-C_{20} substituted

heterocycle, phosphonate, phosphate, polyethyleneoxy, a protecting group, and a prodrug moiety;

R^{2a} and R^5 are each independently selected from the group consisting of H, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, 4-dialkylaminopyridinium, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide ($-SOAr$), arylthio ($-SAr$), sulfonamide ($-SO_2NR_2$), alkylsulfoxide ($-SOR$), formyl ($-CHO$), ester ($-CO_2R$), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile ($-CN$), azido ($-N_3$), nitro ($-NO_2$), C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocycle, C_2–C_{20} substituted heterocycle, phosphonate, phosphate, polyethyleneoxy, a protecting group, and a prodrug moiety;

R^3, and R^4 are each independently selected from the group consisting of H, OH, OR, amino ($-NH_2$), ammonium ($-NH_3^+$), alkylamino ($-NHR$), dialkylamino ($-NR_2$), trialkylammonium ($-NR_3^+$), carboxyl ($-CO_2H$), sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, 4-dialkylaminopyridinium, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide ($-SOAr$), arylthio ($-SAr$), sulfonamide ($-SO_2NR_2$), alkylsulfoxide ($-SOR$), formyl ($-CHO$), ester ($-CO_2R$), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile ($-CN$), azido ($-N_3$), nitro ($-NO_2$), C_1–C_{18} alkyl, C_1–C_{18} substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heterocycle, C_2–C_{20} substituted heterocycle, phosphonate, phosphate, polyethyleneoxy, a protecting group, and a prodrug moiety;

R is independently selected from the group consisting of H, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl;

R, R^1, R^{2a}, R^3, R^4, or R^5 may independently comprise A^1, A^3 or L–A^3; and

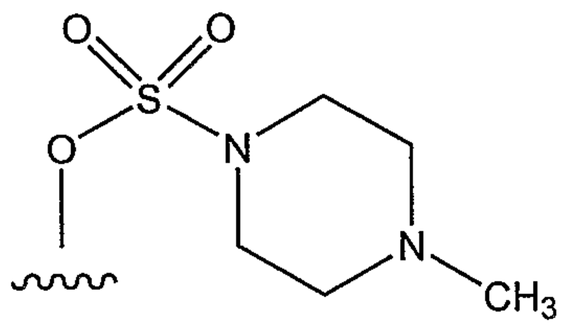
at least one of R, R^1, R^{2a}, R^3, R^4, and R^5 comprises a phosphonate group;

wherein the compound is substituted with one or more covalently attached A^0 groups.

.

48. An HIV integrase inhibitor compound of claim 2or 3 having Formula IV as described in claim 47 wherein R^1, R^{2a}, R^3, R^4, and R^5 are independently selected from the group consisting of $-C(=S)NR_2$, $-C(=O)OR$, $-C(=O)NR_2$, $-C(=O)NRNR_2$, $-C(=O)R$, $-SO_2NR_2$, $-NRSO_2R$, $-NRC(=S)NR_2$, $-SR$, $-S(O)R$, $-SO_2R$, $-SO_2R$, $-P(=O)(OR)_2$, $-P(=O)(OR)(NR_2)$, $-P(=O)(NR_2)_2$, $-P(=S)(OR)_2$, $-P(=S)(OR)(NR_2)$, and $-P(=S)(NR_2)_2$;
which is substituted with one or more covalently attached A^0 groups.;
including prodrug substituted forms thereof.

49. An HIV integrase inhibitor compound of claim 2 or) having Formula IV as described in claim 47 wherein R^1, R^{2a}, R^3, R^4, and R^5 individually or in combination form a 4-7 membered ring lactam, carbonate, or sultam, or piperazinyl sulfamate having the structure:

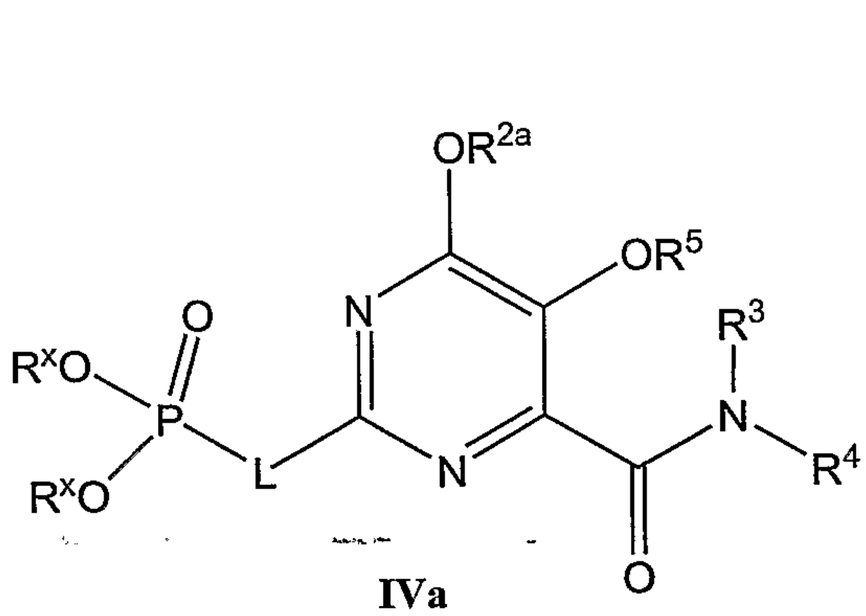


;

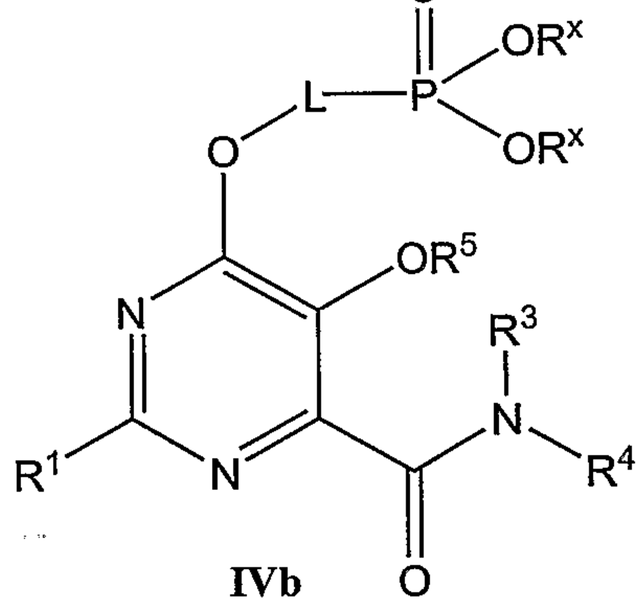
which is substituted with one or more covalently attached A^0 groups.

50. An HIV integrase inhibitor compound of claim 2 or 3 having Formula IV as described in claim 47 wherein R^1, R^{2a}, R^3, R^4, and R^5 are independently selected from the group consisting of $-OC(=S)NR_2$, $-OC(=O)OR$, $-OC(=O)NR_2$, $-OC(=O)NRNR_2$, $-OC(=O)R$, $-OP(=O)(OR)_2$, $-OP(=O)(OR)(NR_2)$, $-OP(=O)(NR_2)_2$, $-OP(=S)(OR)_2$, $-OP(=S)(OR)(NR_2)$, and $-OP(=S)(NR_2)_2$,
which is substituted with one or more covalently attached A^0 groups;
including prodrug substituted forms thereof.

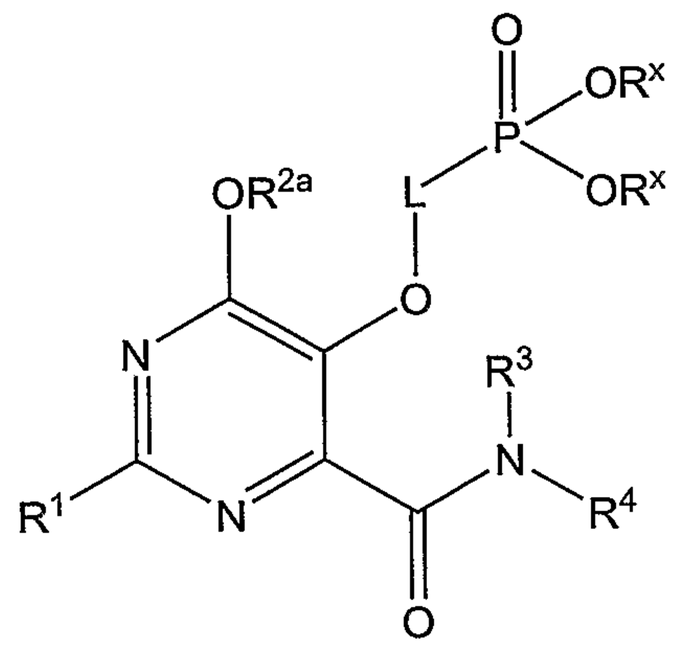
51. A Formula IV HIV integrase inhibitor compound of claim 47 selected from the structures:



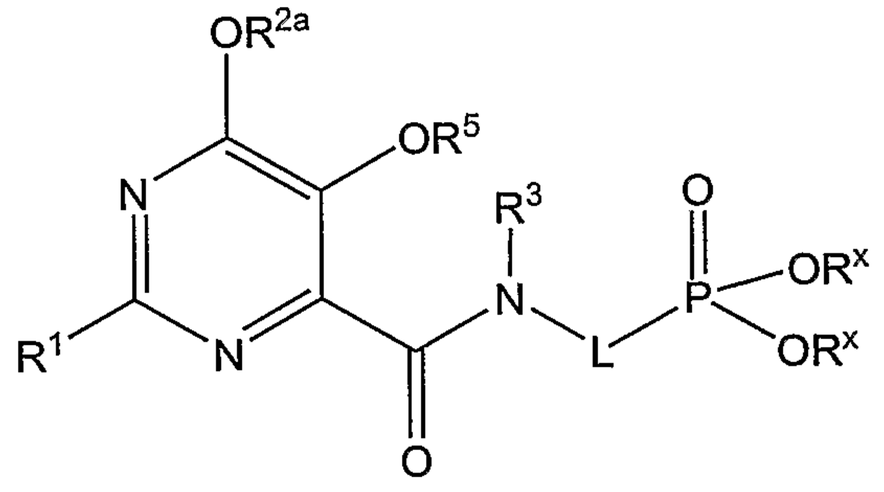
IVa



IVb

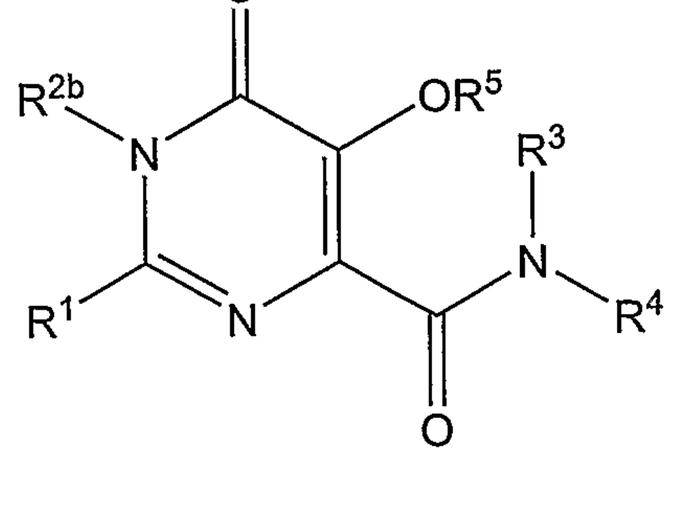


IVc



IVd

52. An HIV integrase inhibitor compound of claim 2 selected from Formula V:



V

wherein:

R^1 is selected from the group consisting of H, F, Cl, Br, I, OH, OR, amino ($-NH_2$), ammonium ($-NH_3^+$), alkylamino (–NHR), dialkylamino ($-NR_2$), trialkylammonium ($-NR_3^+$), carboxyl ($-CO_2H$), sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, 4-dialkylaminopyridinium, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide (–SOAr), arylthio (–SAr), sulfonamide ($-SO_2NR_2$), alkylsulfoxide (–SOR), formyl (–CHO), ester ($-CO_2R$), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile (–CN), azido ($-N_3$), nitro ($-NO_2$), C_1-C_{18} alkyl, C_1-C_{18} substituted alkyl, C_2-C_{18} alkenyl, C_2-C_{18} substituted alkenyl, C_2-C_{18} alkynyl, C_2-C_{18} substituted alkynyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heterocycle, C_2-C_{20} substituted heterocycle, phosphonate, phosphate, polyethyleneoxy, a protecting group, and a prodrug moiety;

R^5 is selected from the group consisting of H, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, 4-dialkylaminopyridinium, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide (–SOAr), arylthio (–SAr), sulfonamide ($-SO_2NR_2$), alkylsulfoxide (–SOR), formyl (–CHO), ester ($-CO_2R$), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile (–CN), azido ($-N_3$), nitro ($-NO_2$), C_1-C_{18} alkyl, C_1-C_{18} substituted alkyl, C_2-C_{18} alkenyl, C_2-C_{18} substituted alkenyl, C_2-C_{18} alkynyl, C_2-C_{18} substituted alkynyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heterocycle, C_2-C_{20} substituted heterocycle, phosphonate, phosphate, polyethyleneoxy, a protecting group, and a prodrug moiety;

R^{2b}, R^3, and R^4 are each independently selected from the group consisting of H, OH, OR, amino ($-NH_2$), ammonium ($-NH_3^+$), alkylamino (–NHR), dialkylamino ($-NR_2$), trialkylammonium ($-NR_3^+$), carboxyl ($-CO_2H$), sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, 4-dialkylaminopyridinium, alkylsulfone ($-SO_2R$), arylsulfone ($-SO_2Ar$), arylsulfoxide (–SOAr), arylthio (–SAr), sulfonamide ($-SO_2NR_2$), alkylsulfoxide (–SOR), formyl (–CHO), ester ($-CO_2R$), amido ($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile (–CN), azido ($-N_3$), nitro ($-NO_2$), C_1-C_{18} alkyl, C_1-C_{18} substituted alkyl, C_2-C_{18} alkenyl, C_2-C_{18} substituted alkenyl, C_2-C_{18} alkynyl, C_2-C_{18} substituted alkynyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heterocycle, C_2-C_{20}

substituted heterocycle, phosphonate, phosphate, polyethyleneoxy, a protecting group, and a prodrug moiety;

R is independently selected from the group consisting of H, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl;

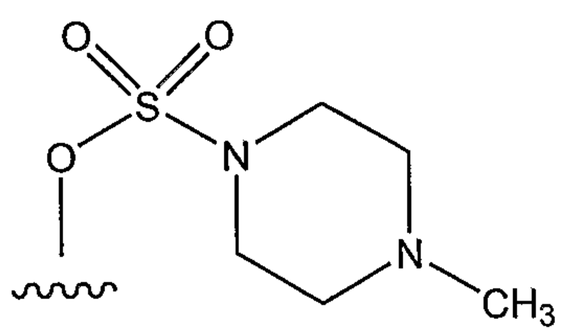
R, R^1, R^{2b}, R^3, R^4, or R^5 may independently comprise A^1, A^3 or L–A^3; and at least one of R, R^1, R^{2b}, R^3, R^4, and R^5 comprises an A^0 group.

53. An HIV integrase inhibitor compound of claim 2 or 3having Formula V as described in claim 52 wherein R^1, R^{2b}, R^3, R^4, and R^5 are independently selected from the group consisting of –C(=S)NR_2, –C(=O)OR, –C(=O)NR_2, –C(=O)$NRNR_2$, –C(=O)R, –SO_2NR_2, –$NRSO_2R$, –NRC(=S)NR_2, –SR, –S(O)R, –SO_2R, –SO_2R, –P(=O)$(OR)_2$, –P(=O)(OR)(NR_2), –P(=O)$(NR_2)_2$, –P(=S)$(OR)_2$, –P(=S)(OR)(NR_2), and –P(=S)$(NR_2)_2$;

which is substituted with one or more covalently attached A^0 groups.;

including prodrug substituted forms thereof.

54. An HIV integrase inhibitor compound of claim 2 or 3 having Formula V as described in claim 52 wherein R^1, R^{2b}, R^{2b}, R^3, R^4, and R^5 individually or in combination form a 4-7 membered ring lactam, carbonate, or sultam, or piperazinyl sulfamate having the structure:



which is substituted with one or more covalently attached A^0 groups;

including prodrug substituted forms thereof.

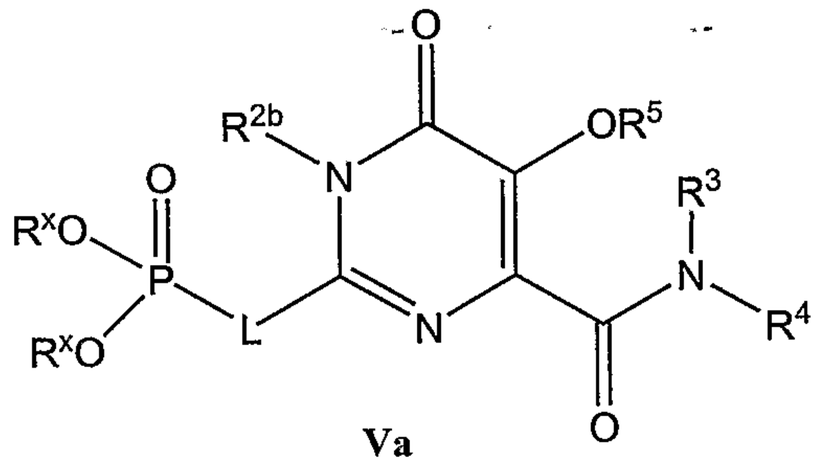
55. An HIV integrase inhibitor compound of claim 2or having Formula V as described in claim 52 wherein R^1 is selected from the group consisting of

$-OC(=S)NR_2$, $-OC(=O)OR$, $-OC(=O)NR_2$, $-OC(=O)NRNR_2$, $-OC(=O)R$, $-OP(=O)(OR)_2$, $-OP(=O)(OR)(NR_2)$, $-OP(=O)(NR_2)_2$, $-OP(=S)(OR)_2$, $-OP(=S)(OR)(NR_2)$, and $-OP(=S)(NR_2)_2$,

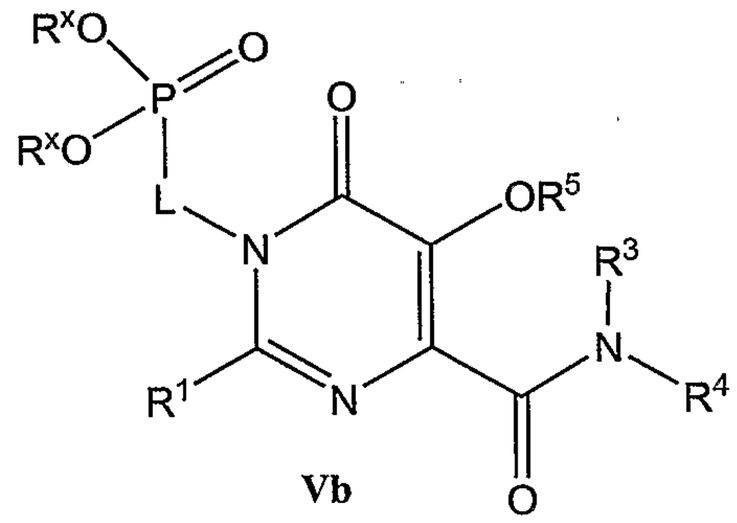
which is substituted with one or more covalently attached A^0 groups;

including prodrug substituted forms thereof.

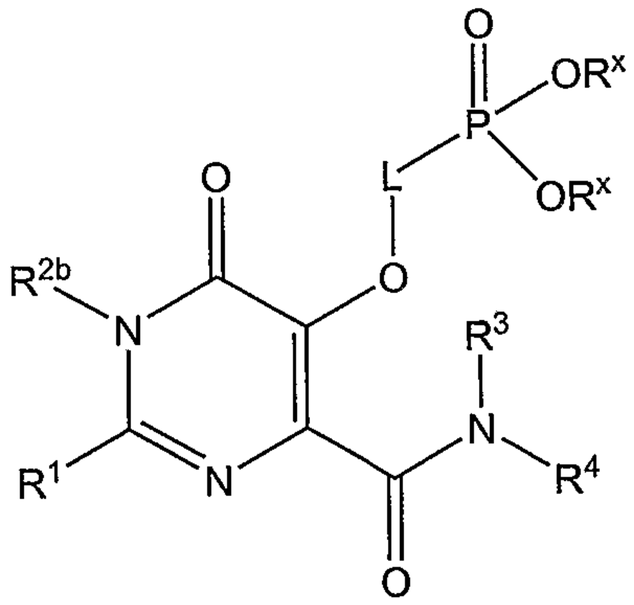
56. A Formula V HIV integrase inhibitor compound of claim 52 selected from the structures:



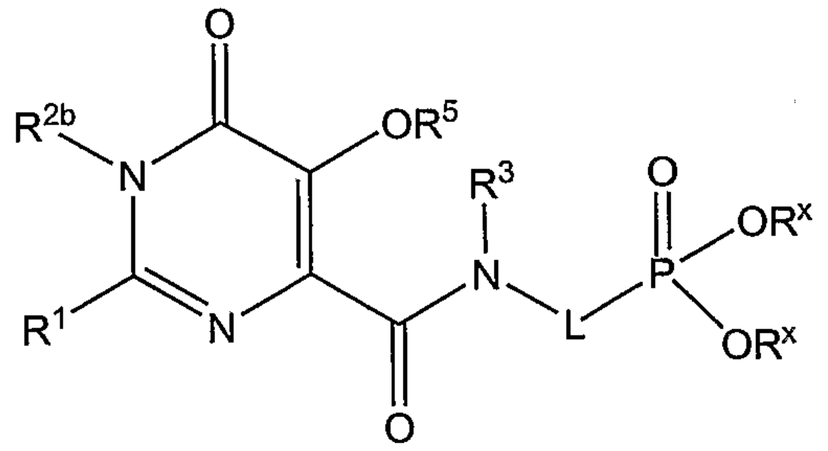
Va



Vb

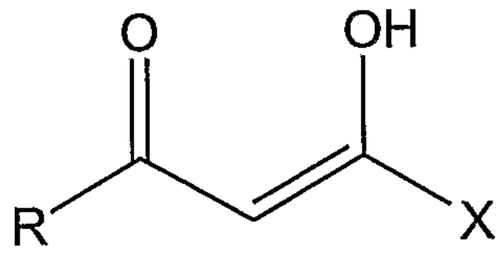


Vc



Vd

57. An HIV integrase inhibitor compound of claim 2 selected from Formula VI:



VI

wherein

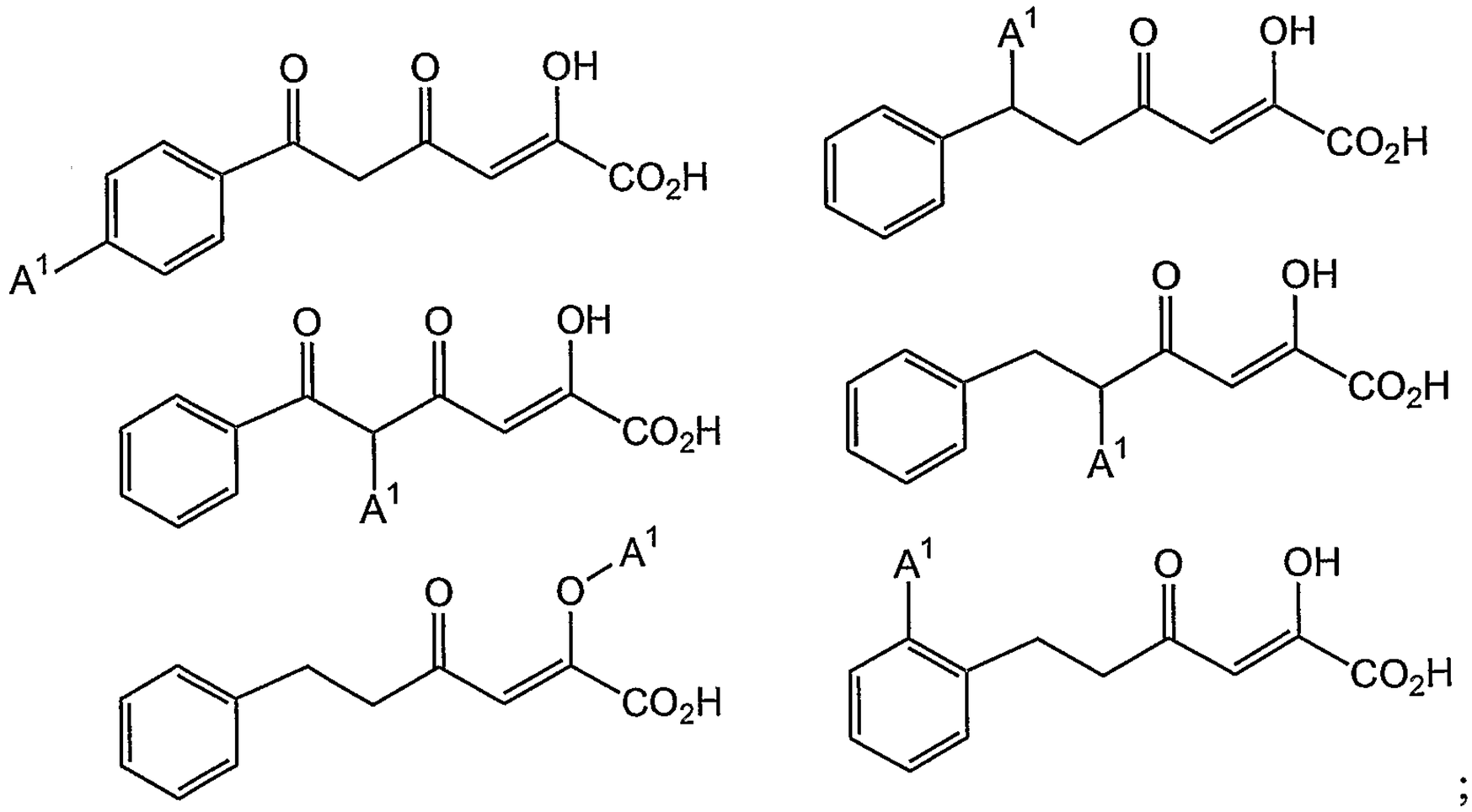
R is C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, or C_2–C_{20} substituted heteroaryl, C_1–C_8 alkylamino, C_1–C_8 substituted alkylamino, C_2–C_{18} alkenylamino, C_2–C_{18} substituted alkenylamino, C_2–C_{18} alkynylamino, C_2–C_{18} substituted alkynylamino, C_6–C_{20} arylamino, C_6–C_{20} substituted arylamino, C_2–C_{20} heteroarylamino, or C_2–C_{20} substituted heteroarylamino;

X is a carboxylic acid or ester group, a moiety with an acidic proton such as tetrazole or triazole, a substituted amide, aryl, substituted aryl, heteroaryl or heteroaryl; and

the Formula VI compound comprises at least one A^0 group.

58. A Formula VI HIV integrase inhibitor compound of claim 57 wherein R is thiophenyl, thioimidazolyl, benzothiophenyl, napthothiophenyl, pyrrolidinyl, pyrazolyl, indanyl, indolyl, sesamyl, and benzoxazolyl.

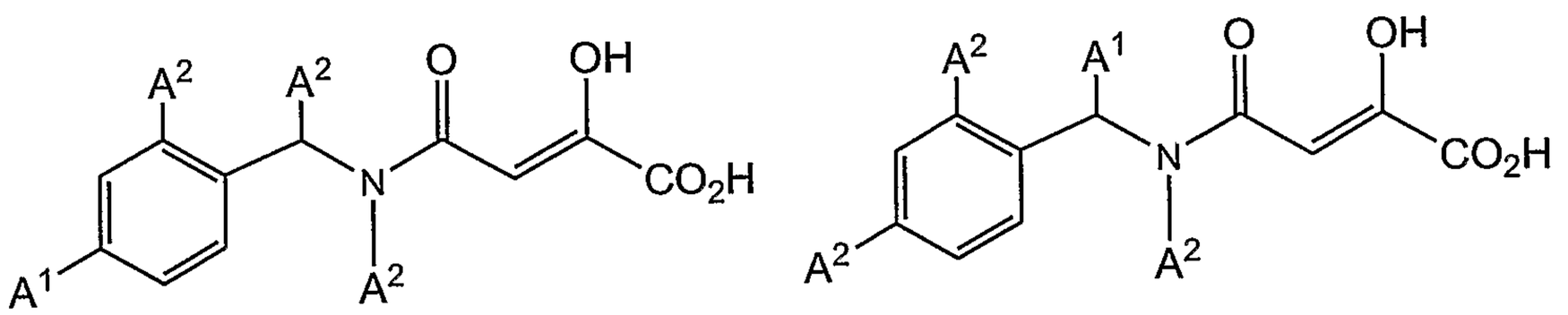
59. An HIV integrase inhibitor compound of claim 2or 3 having Formula VI as described in claim 57 selected from the structures:



;

which is substituted with one or more covalently attached A^0 groups.

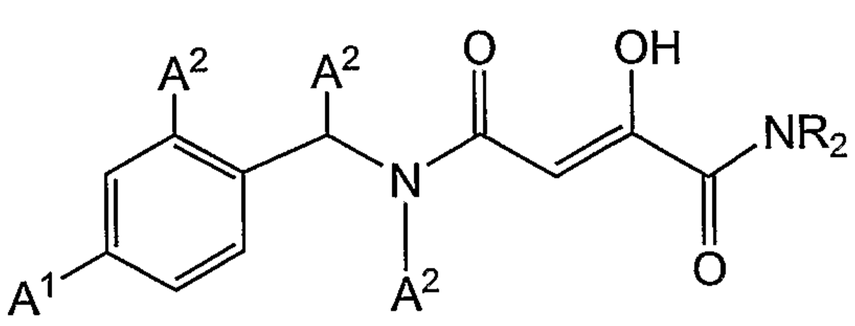
60. An HIV integrase inhibitor compound of claim 2or having Formula VI as described in claim 57 selected from the structures:

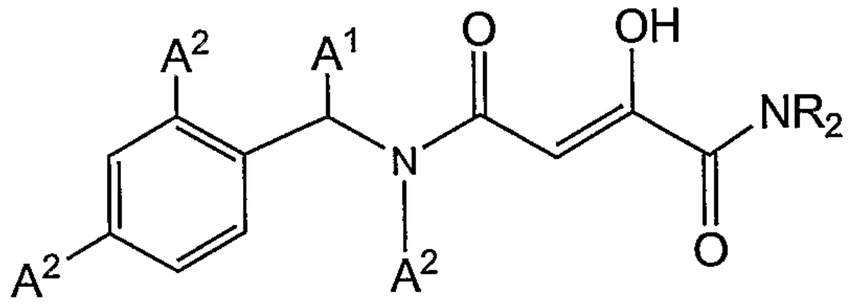


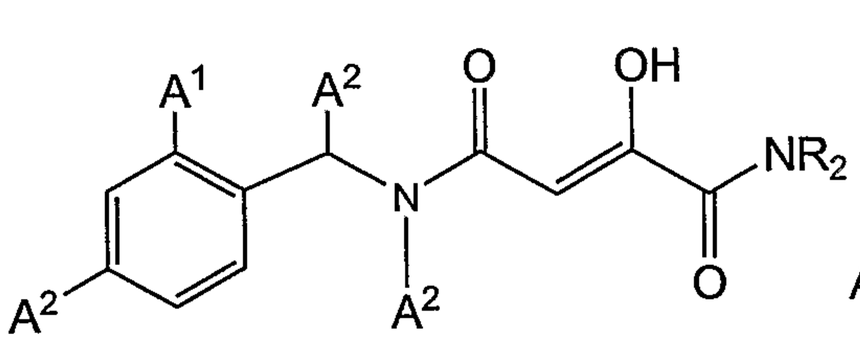
;

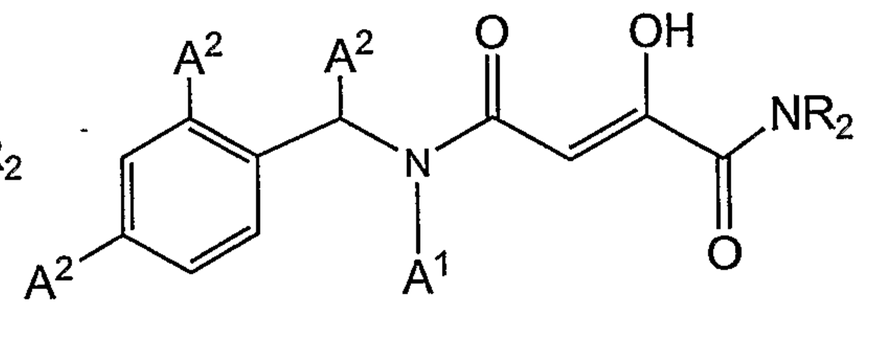
which is substituted with one or more covalently attached A^0 groups.

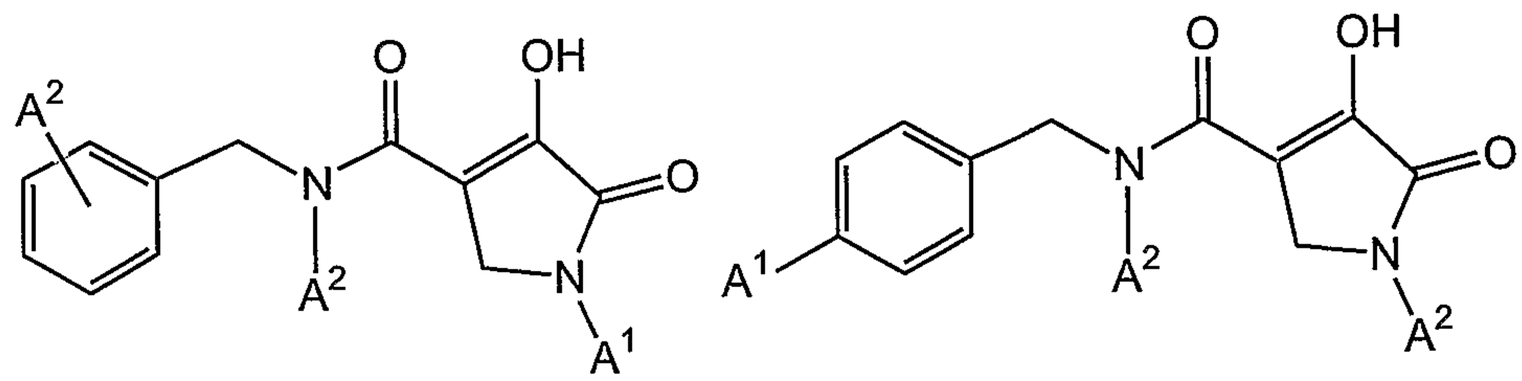
61. An HIV integrase inhibitor compound of claim 2 or 3 having Formula VI as described in claim 57 selected from the structures:

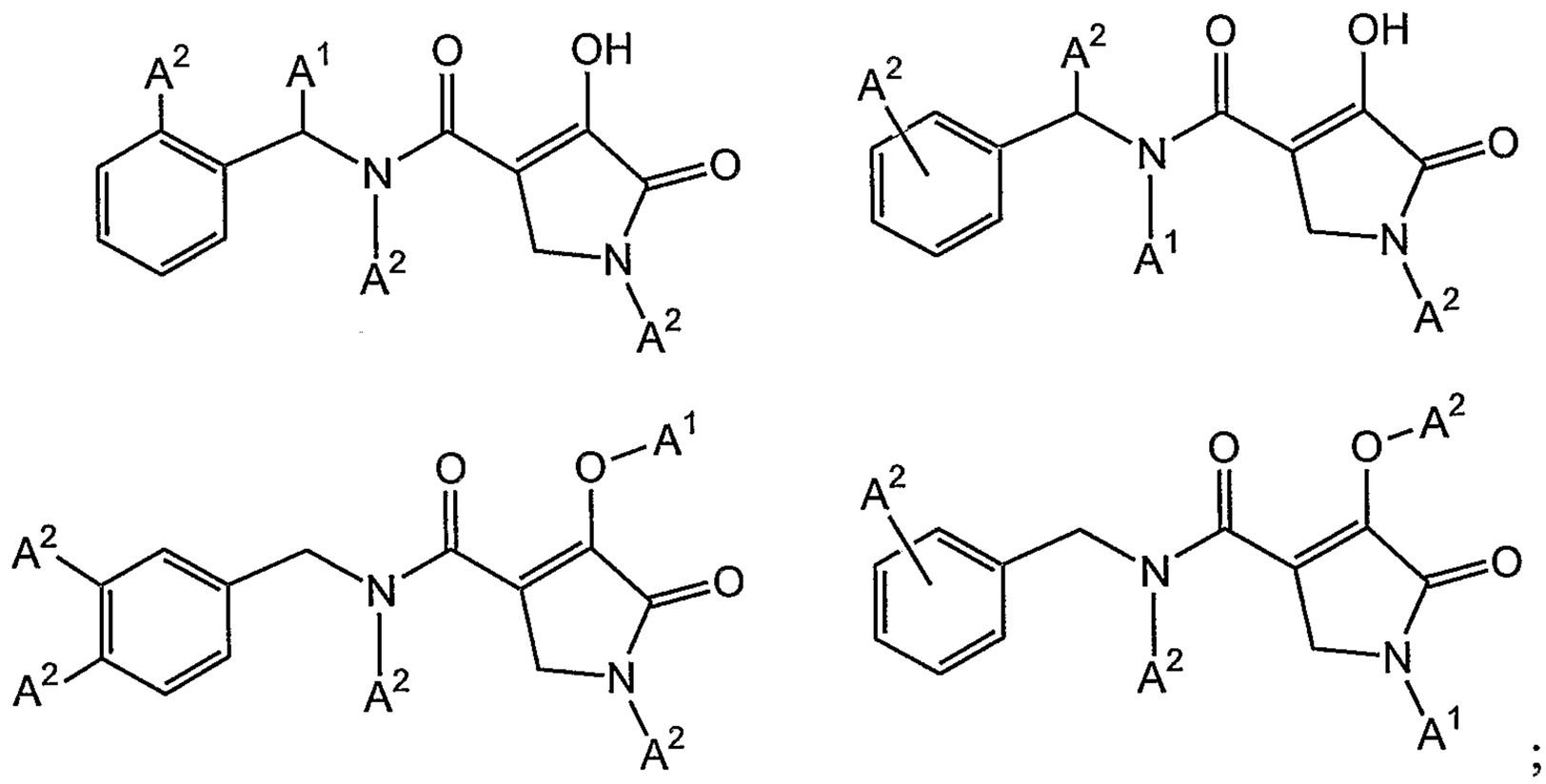








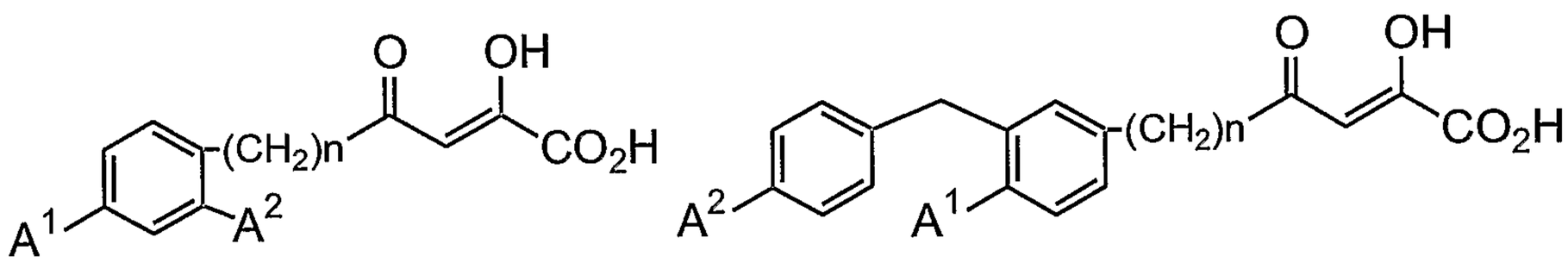


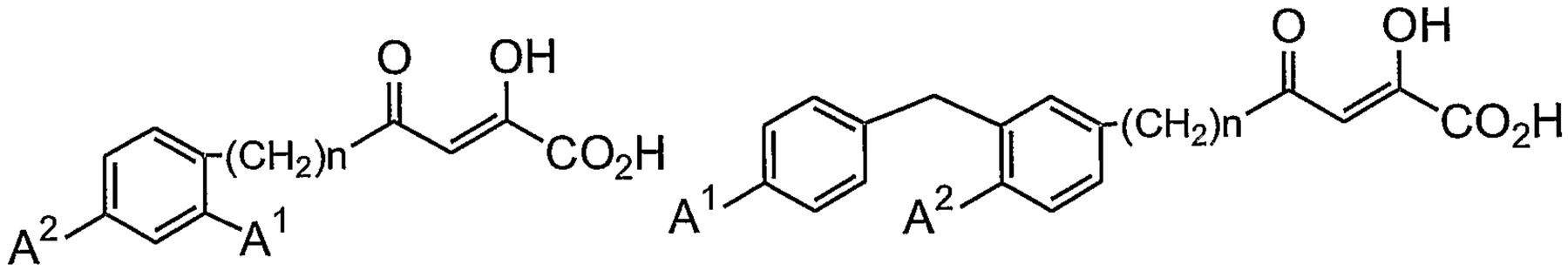


;

which is substituted with one or more covalently attached A^0 groups.

62. An HIV integrase inhibitor compound of claim 2 or 3 having Formula VI as described in claim 57 selected from the structures:



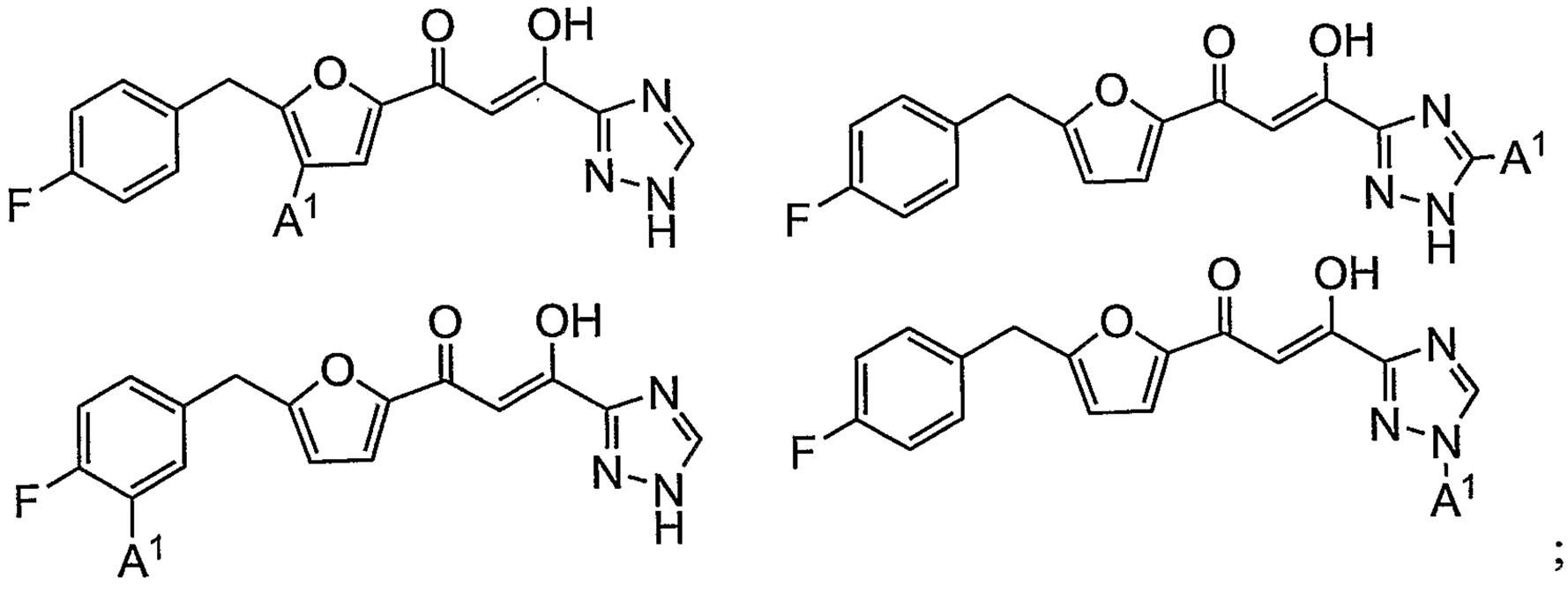


;

where n may be 1, 2, 3, 4, 5, or 6;

which is substituted with one or more covalently attached A^0 groups.

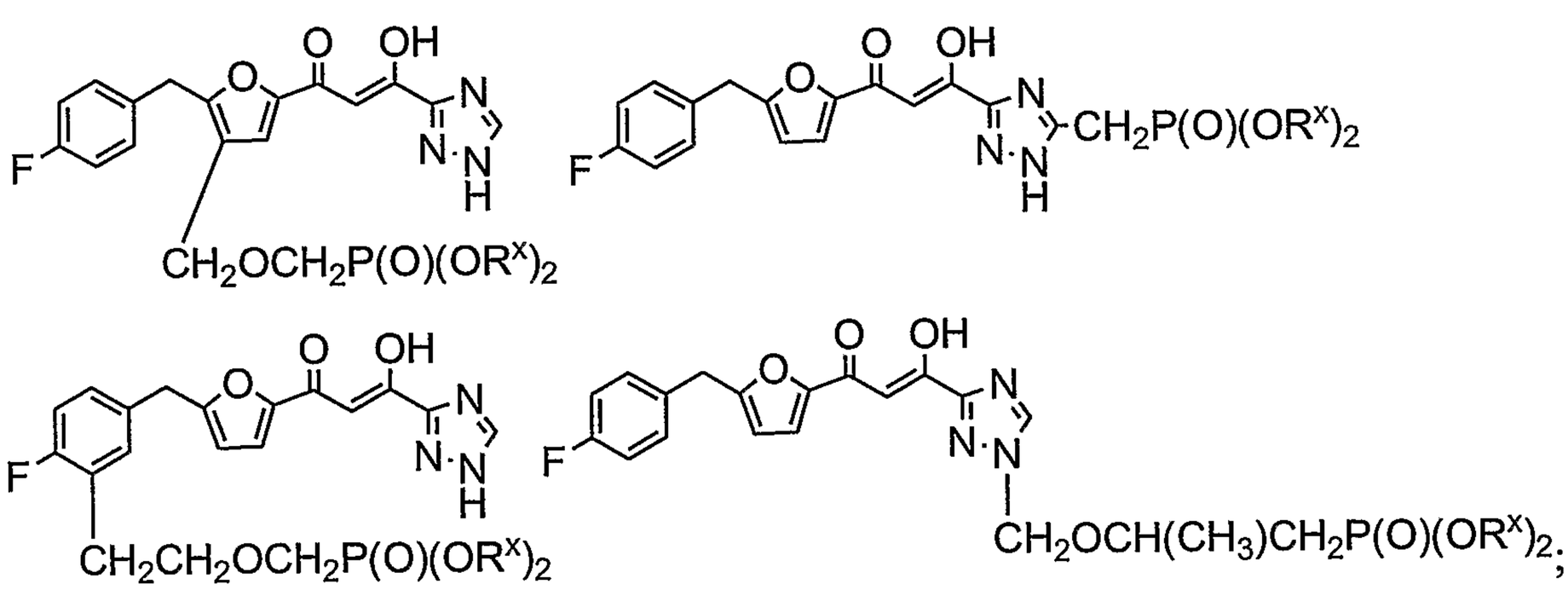
63. An HIV integrase inhibitor compound of claim 2 or 3 having Formula VI as described in claim 57 selected from the structures:



;

which is substituted with one or more covalently attached A^0 groups.

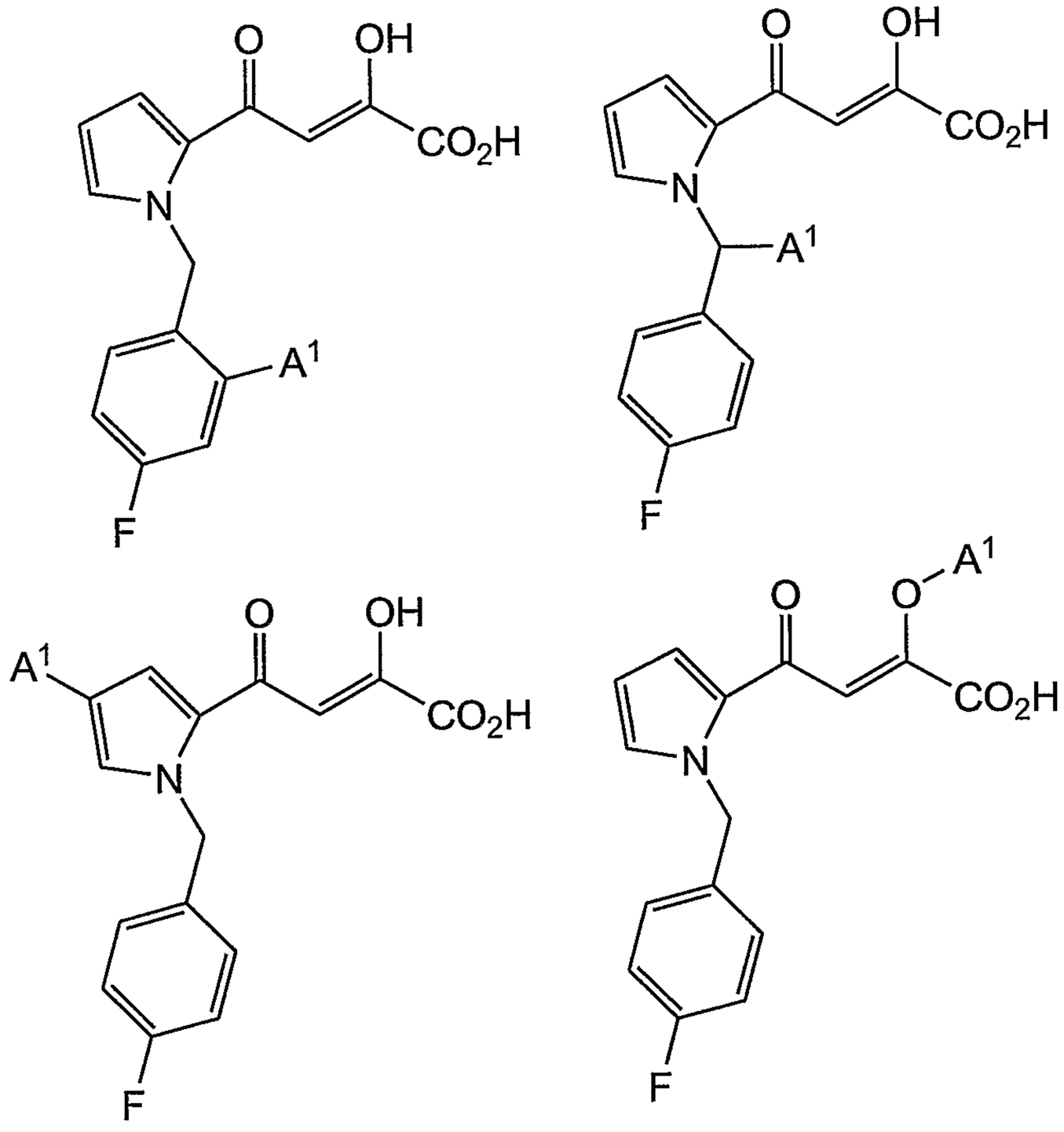
64. An HIV integrase inhibitor compound of claim 2 or 3 having Formula VI as described in claim 57 selected from the structures:



;

which is substituted with one or more covalently attached A^0 groups.

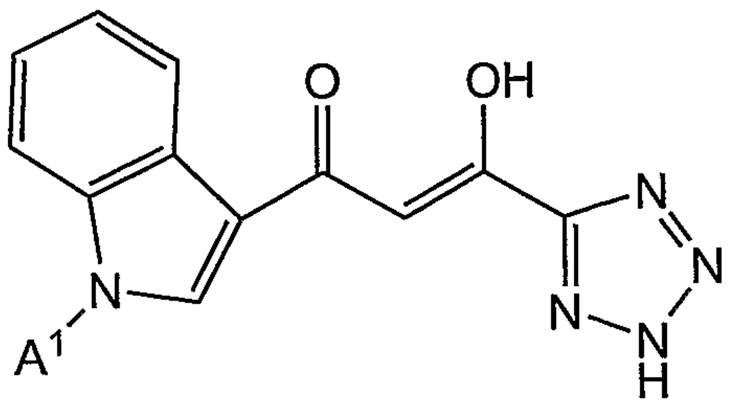
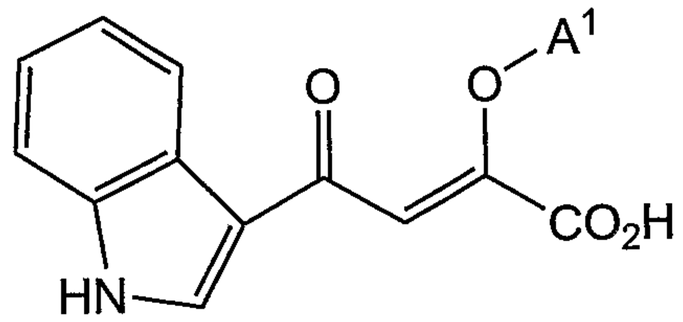
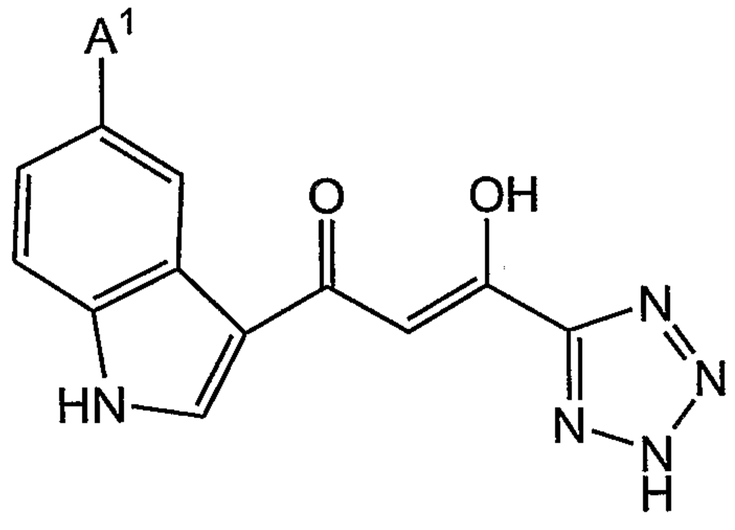
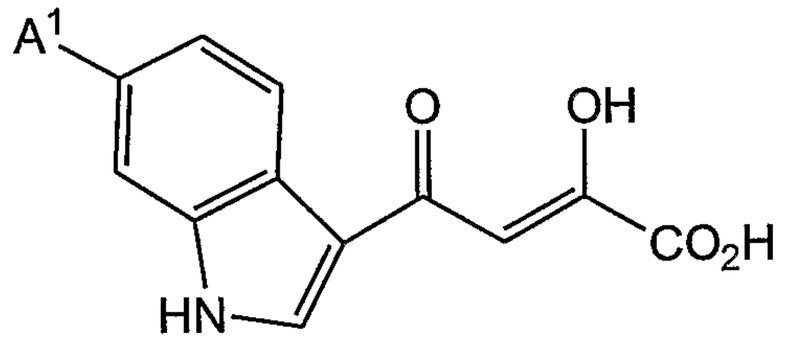
65. An HIV integrase inhibitor compound of claim 2 or 3 having Formula VI as described in claim 57 selected from the structures:



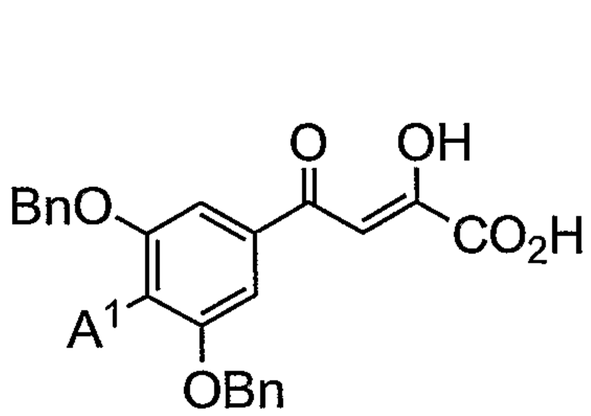
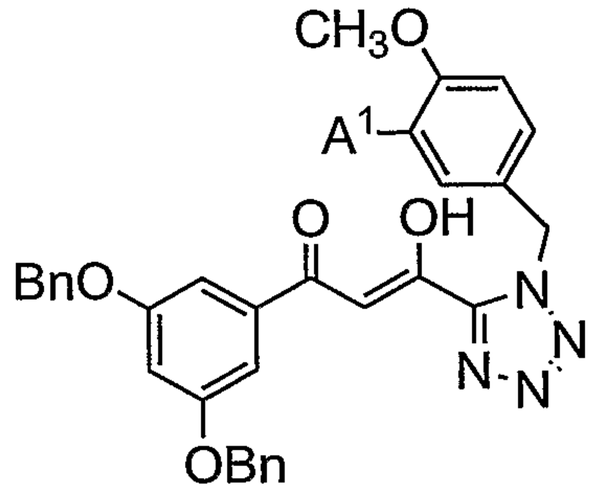
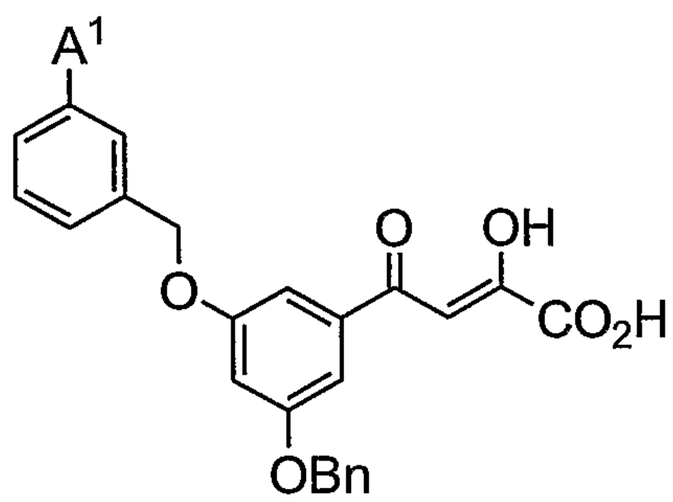
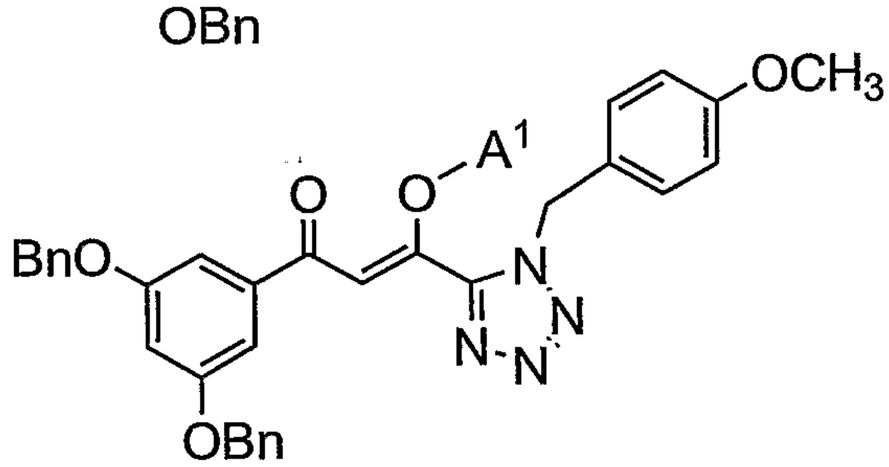
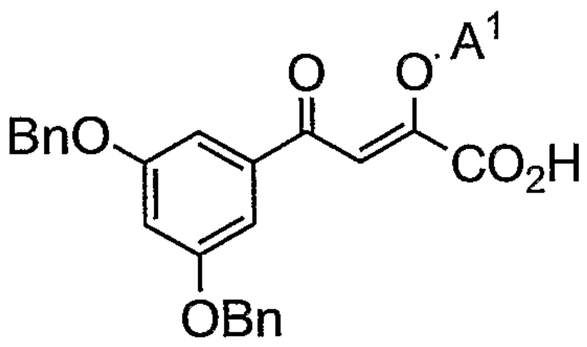
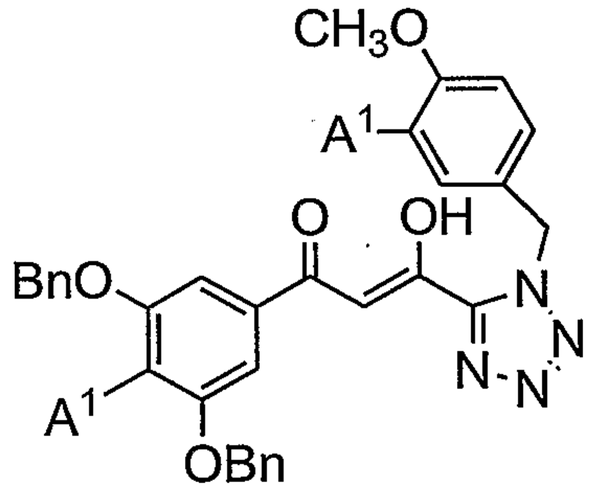
;

which is substituted with one or more covalently attached A^0 groups.

66. A Formula VI HIV integrase inhibitor compound of claim 57 selected from the structures:

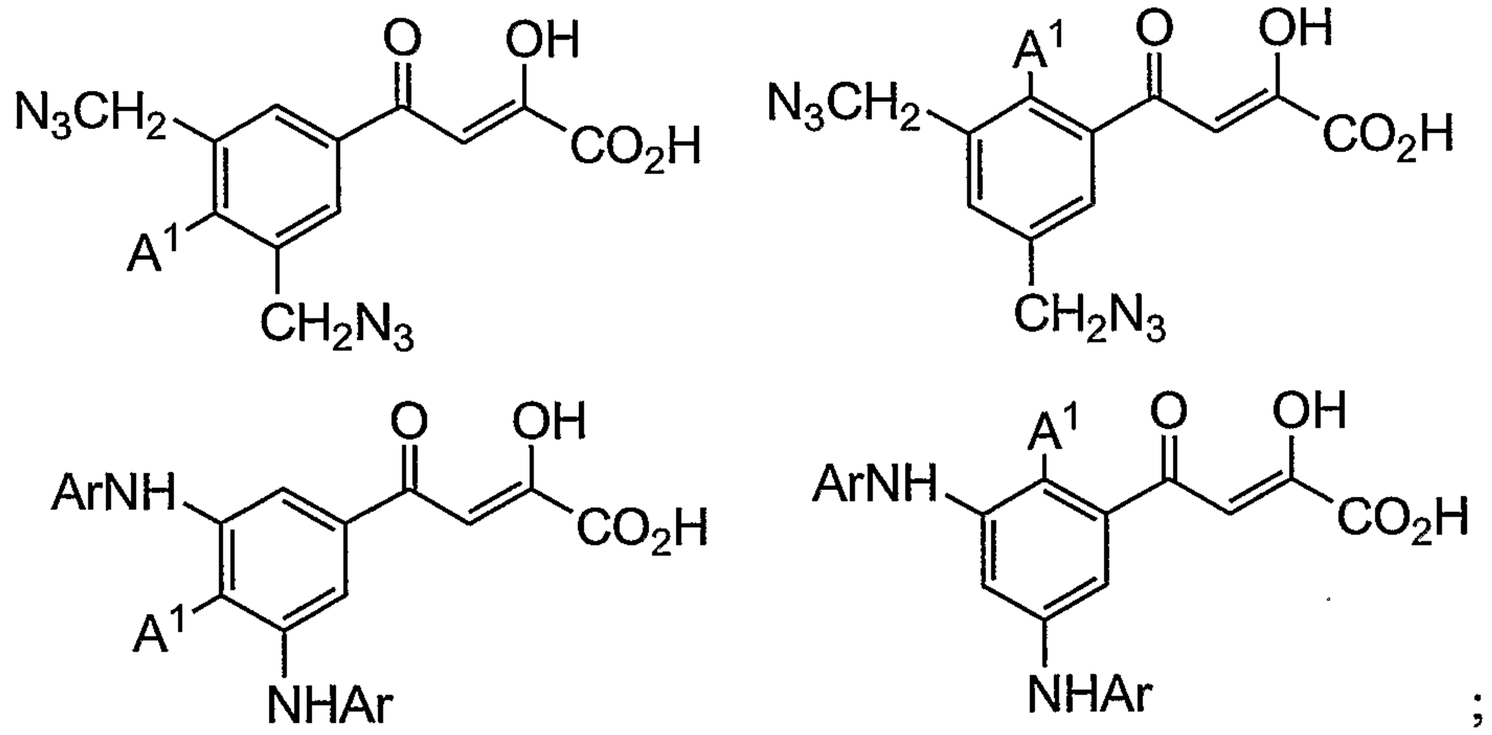





67. An HIV integrase inhibitor compound of claim 2 or 3 having Formula VI as described in claim 57 selected from the structures:







;

which is substituted with one or more covalently attached A^0 groups.

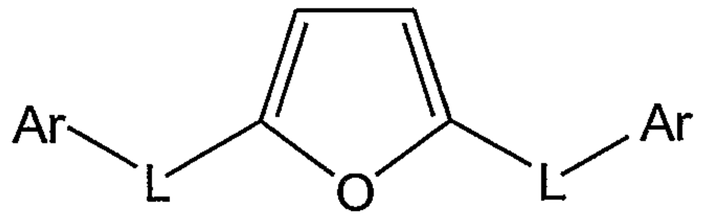
68. An HIV integrase inhibitor compound of claim 2 or 3 having Formula VI as described in claim 57 selected from the structures:



;

which is substituted with one or more covalently attached A^0 groups.

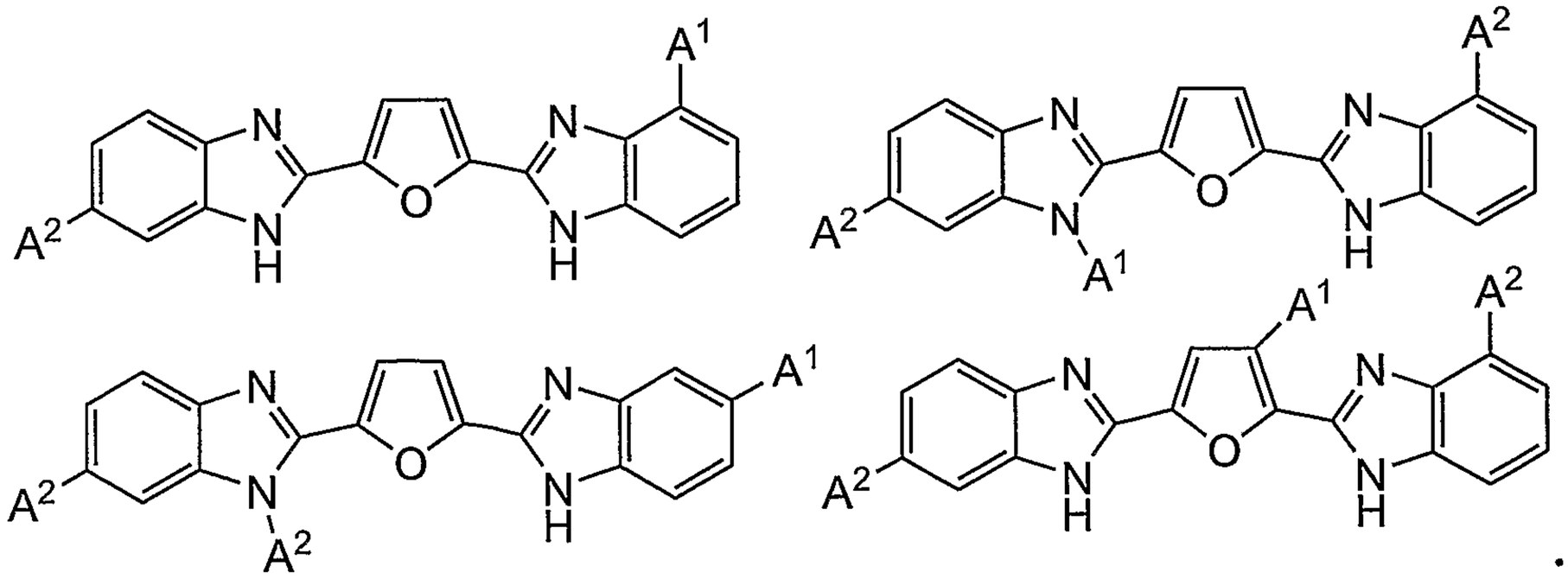
69. An HIV integrase inhibitor compound of claim 2 selected from Formula VII:



VII

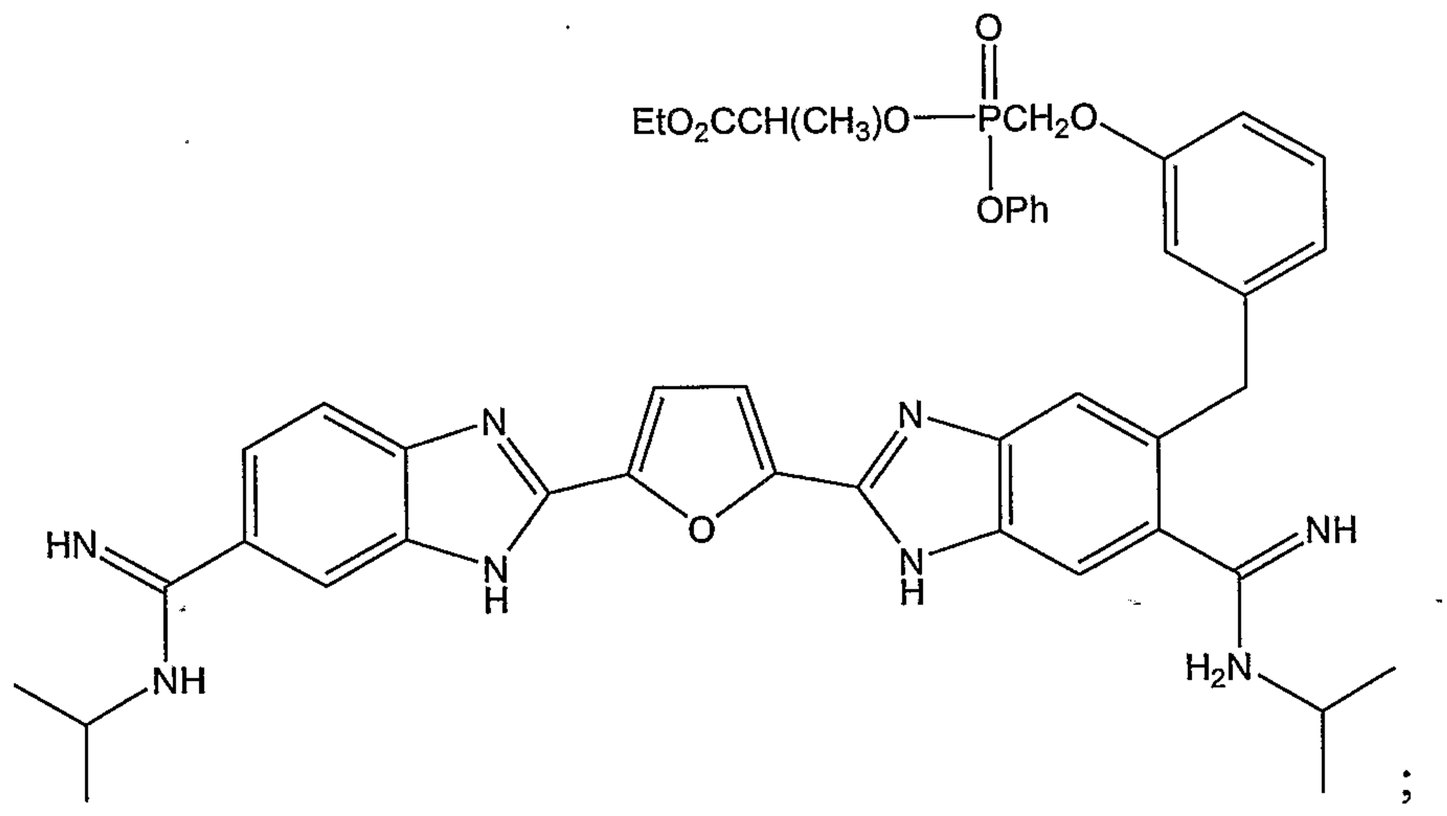
wherein Ar is C_3–C_{12} carbocycle, C_3–C_{12} substituted carbocycle, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, or C_2–C_{20} substituted heteroaryl; and the Formula VII compound comprises at least one A^0 group.

70. A Formula VII HIV integrase inhibitor compound of claim 69 selected from the structures:



.

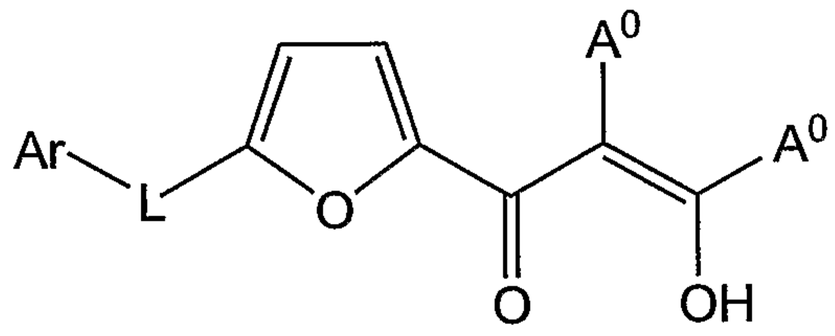
72. An HIV integrase inhibitor compound of claim 2 or 3 having Formula VII as described in claim 69 having the structure:



;

which is substituted with one or more covalently attached A^0 groups.

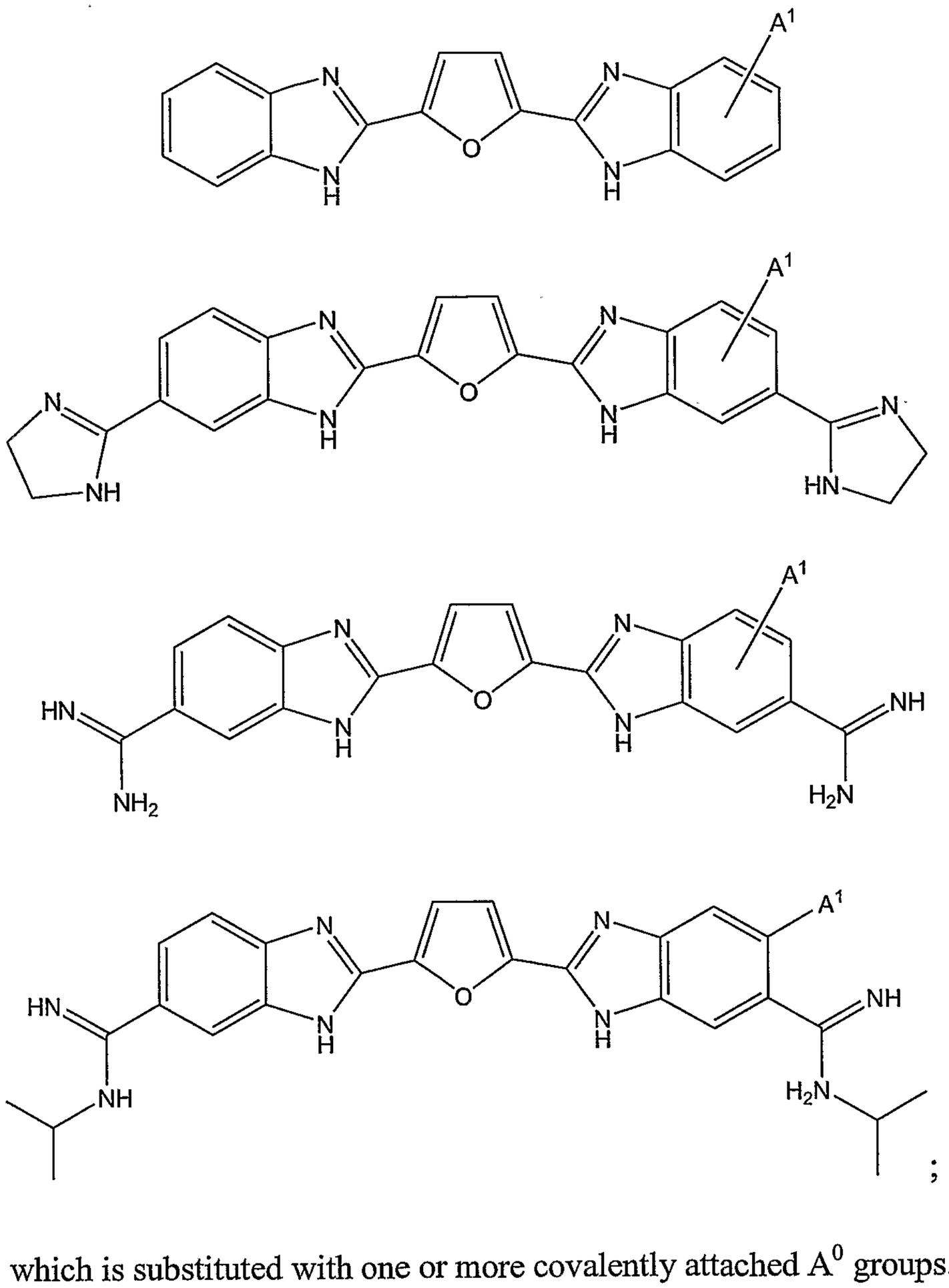
73. An HIV integrase inhibitor compound of claim 2 selected from Formula VIII:



VIII

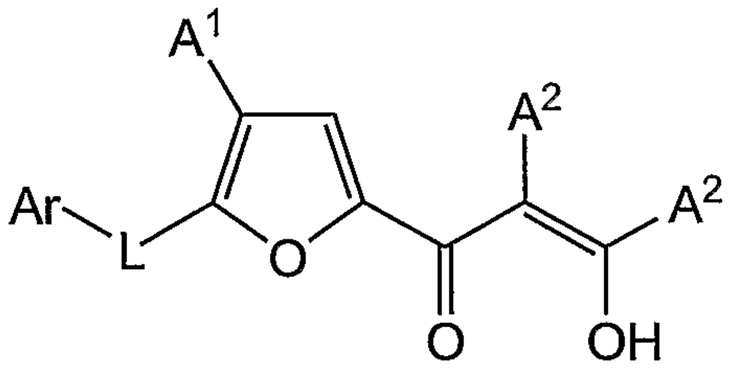
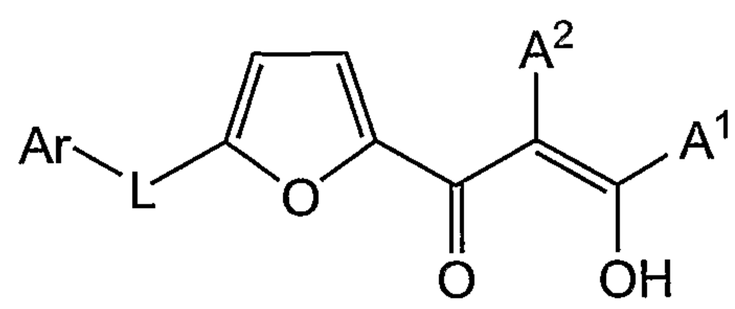
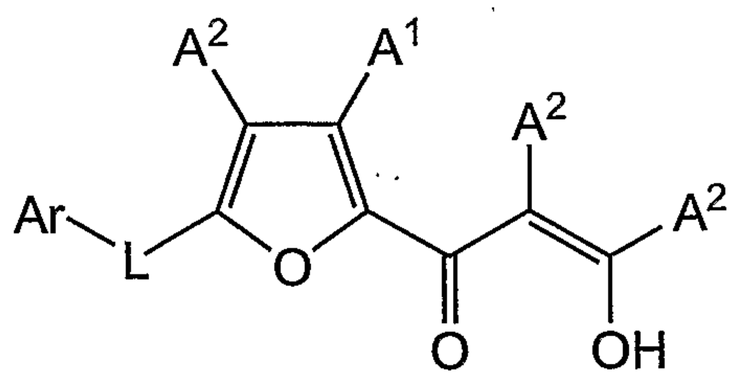
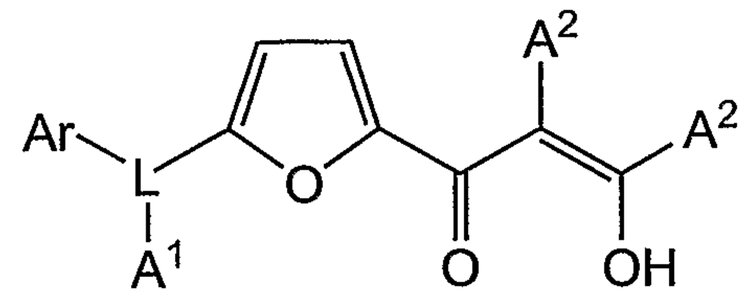
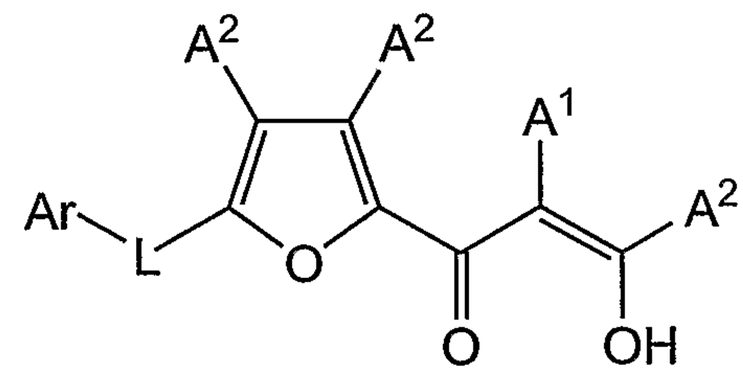
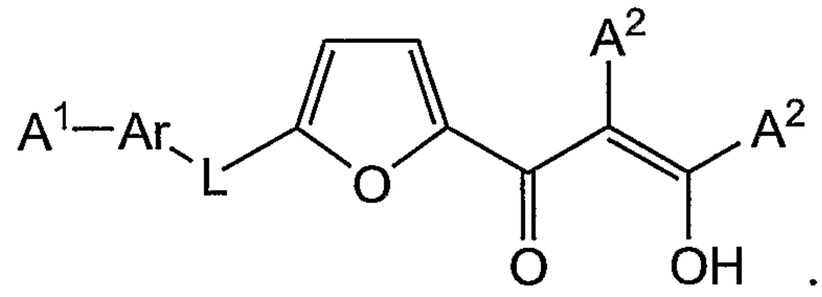
wherein Ar is C_3–C_{12} carbocycle, C_3–C_{12} substituted carbocycle, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, or C_2–C_{20} substituted heteroaryl; and the Formula VII compound comprises at least one A^0 group.

71. An HIV integrase inhibitor compound of claim 2 or 3 having Formula VII as described in claim 69 selected from the structures:



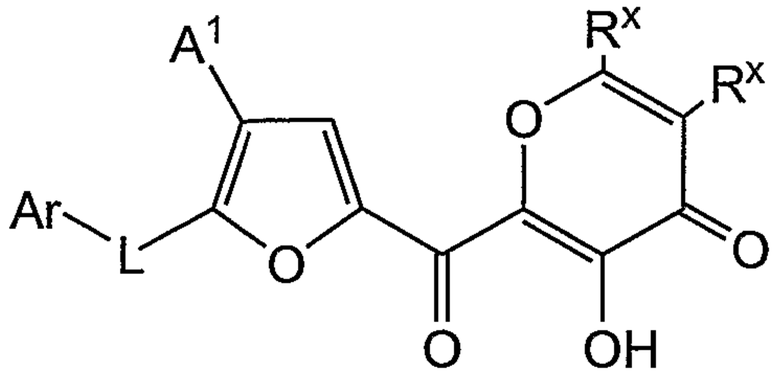
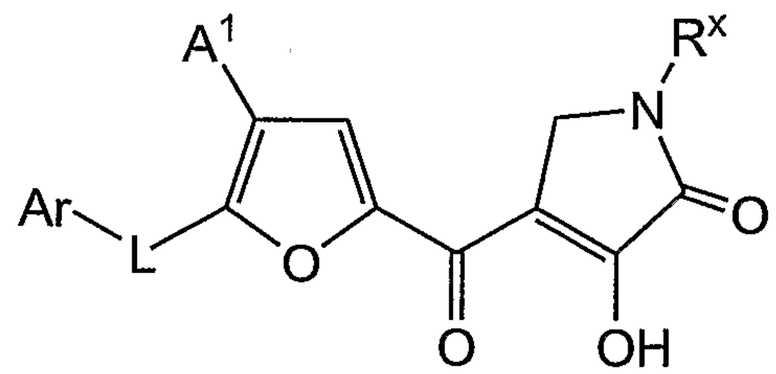
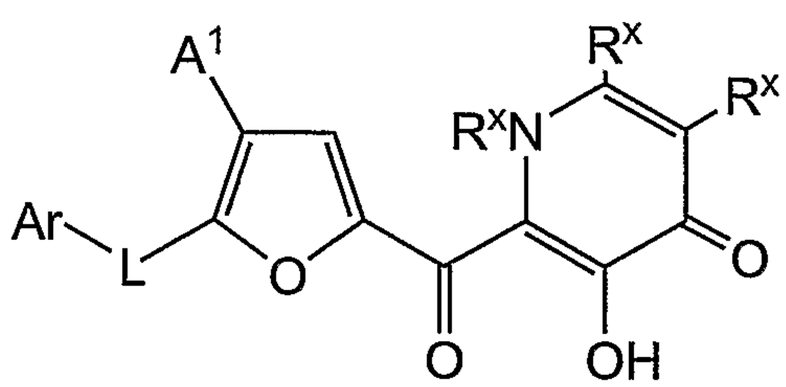
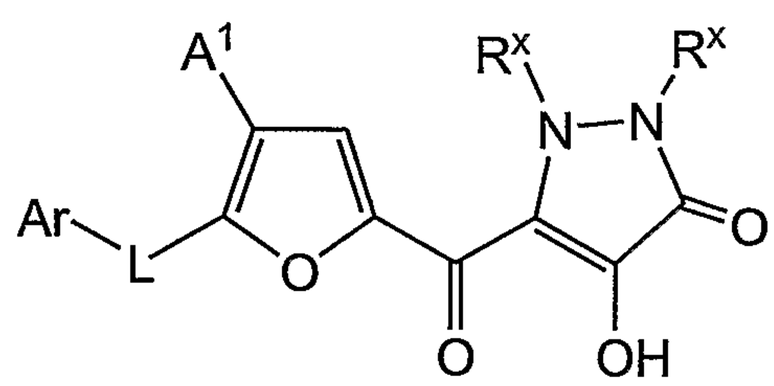
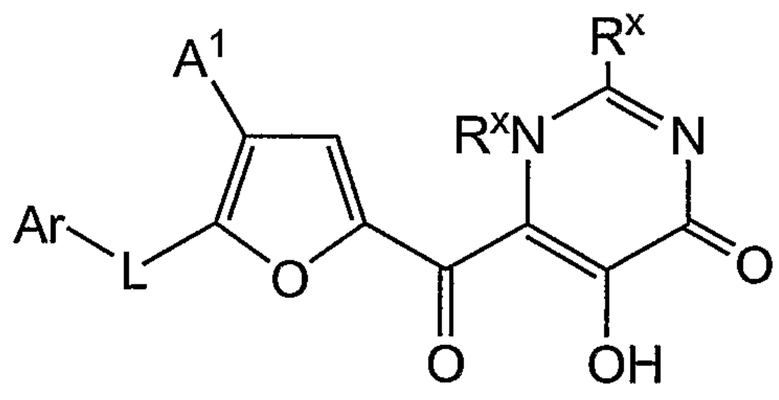
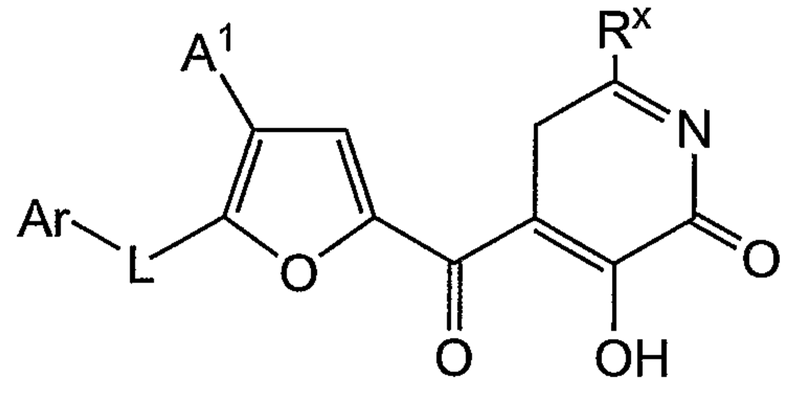
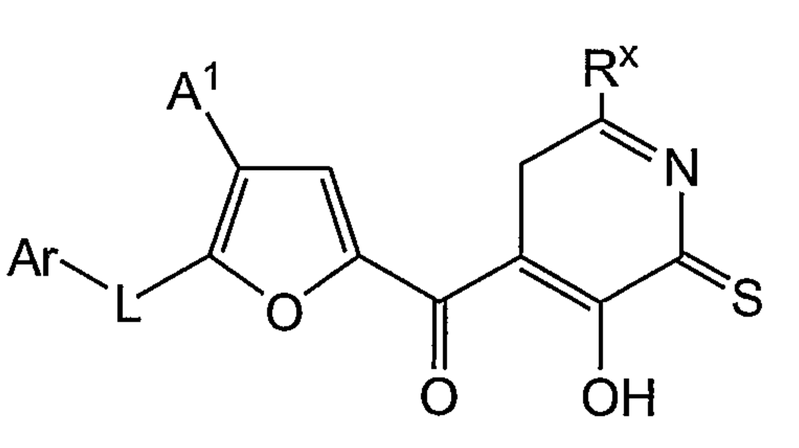
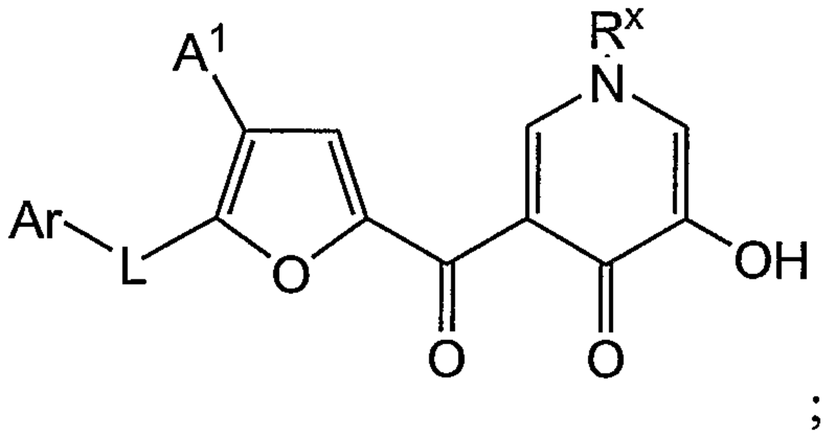
which is substituted with one or more covalently attached A^0 groups.

74. A Formula VIII HIV integrase inhibitor compound of claim 73 selected from the structures:

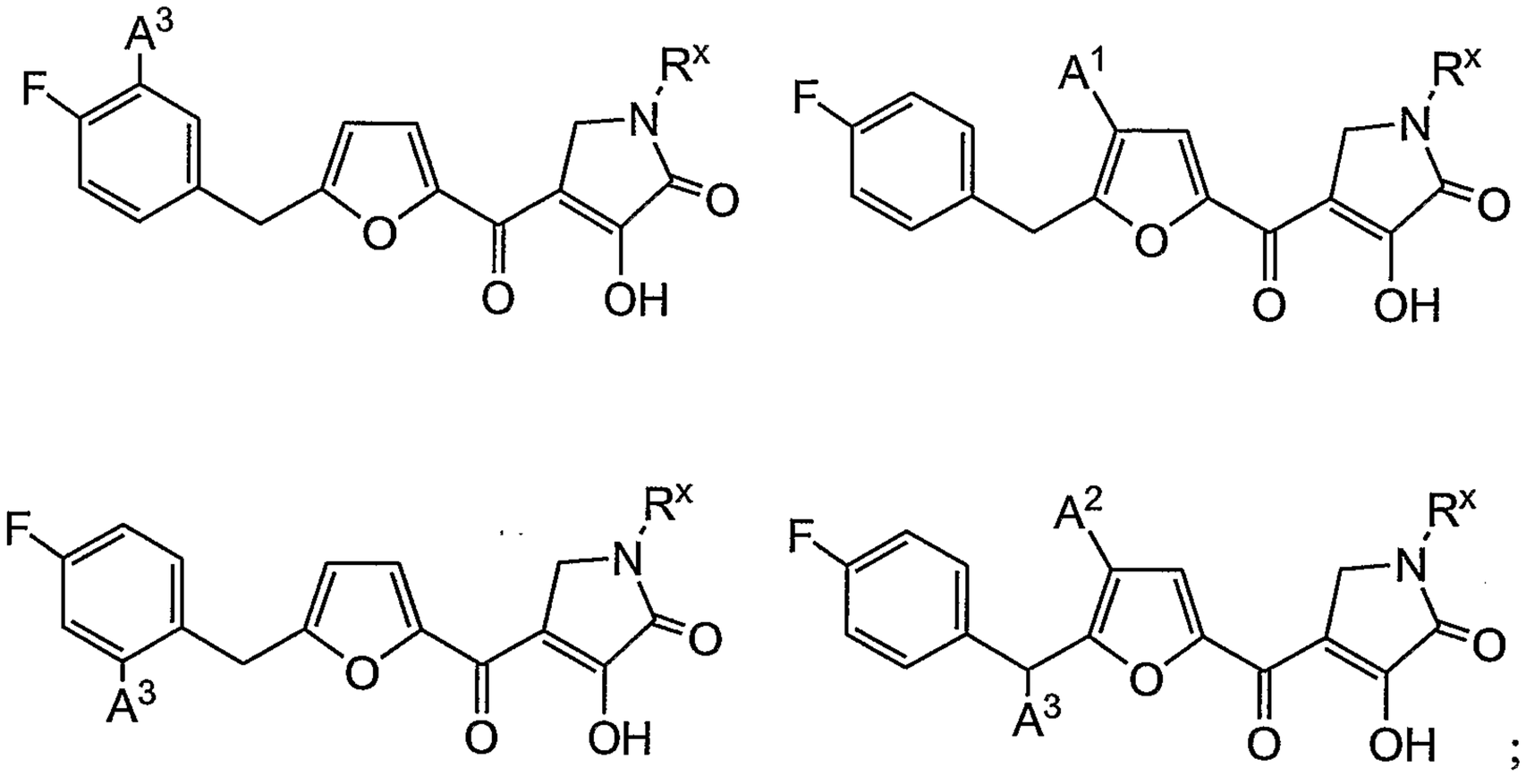
719

75. An HIV integrase inhibitor compound of claim 2 or 3 having Formula VIII as described in claim 73 selected from the structures:









;

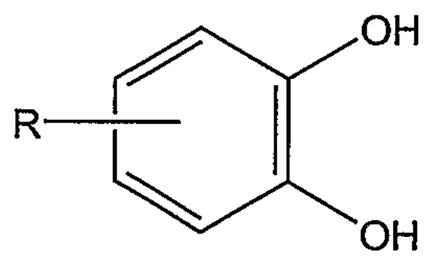
which is substituted with one or more covalently attached A^0 groups.

76. An HIV integrase inhibitor compound of claim 2 or 3 having Formula VIII as described in claim 73 selected from the structures:



which is substituted with one or more covalently attached A^0 groups.

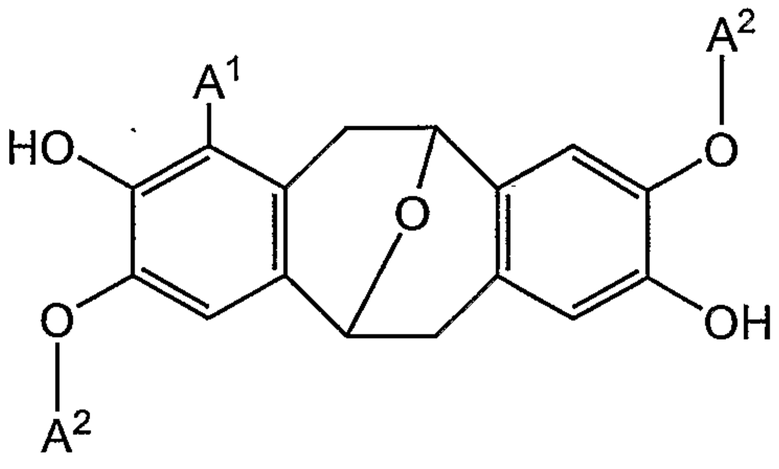
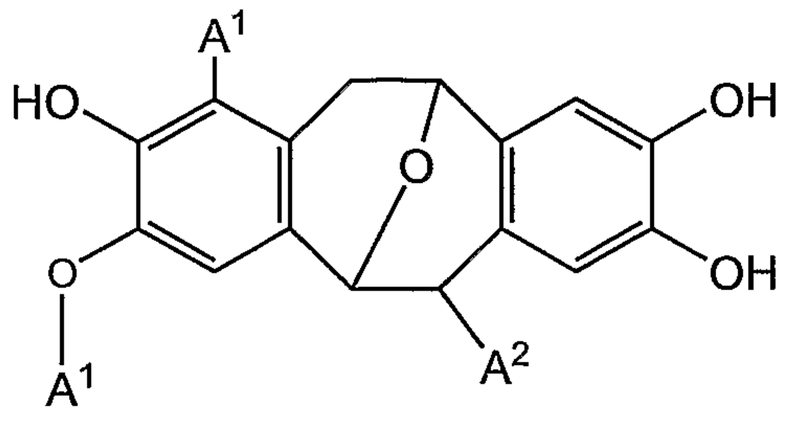
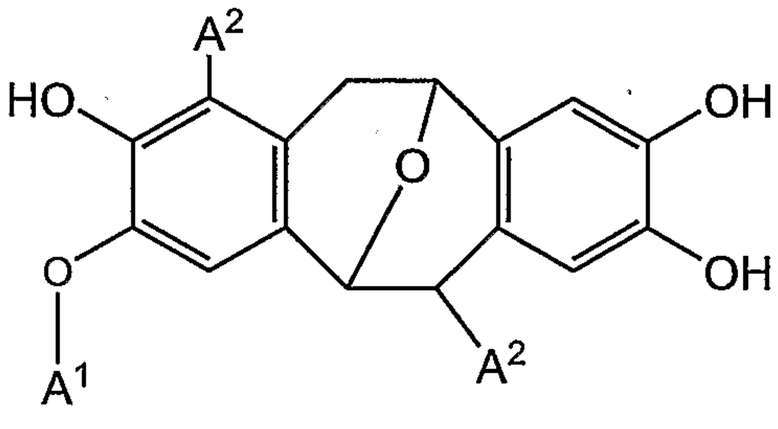
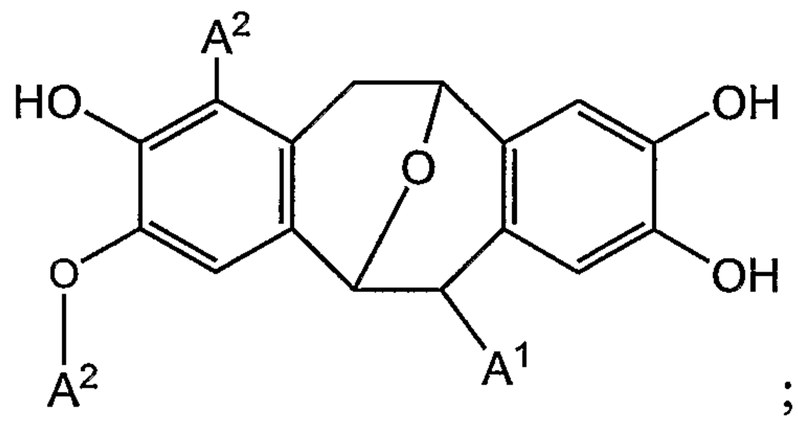
77. An HIV integrase inhibitor compound of claim 2 selected from Formula IX:



IX

wherein R is a HIV integrase inhibitor scaffold that is covalently attached to the catechol moiety through a single bond or a fused ring system, and the Formula IX compound comprises at least one A^0 group.

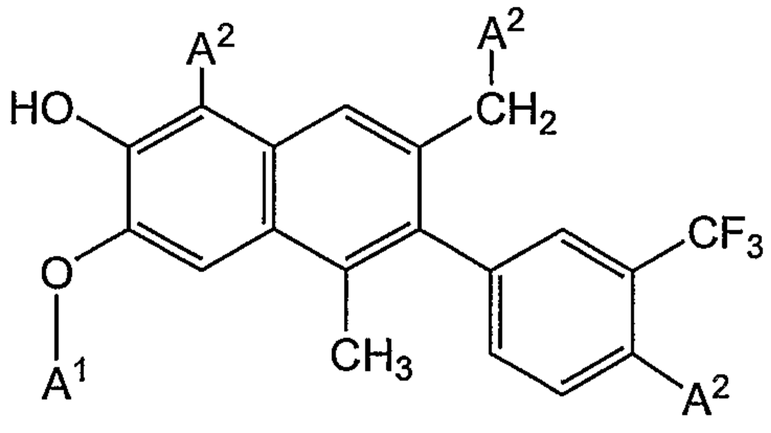
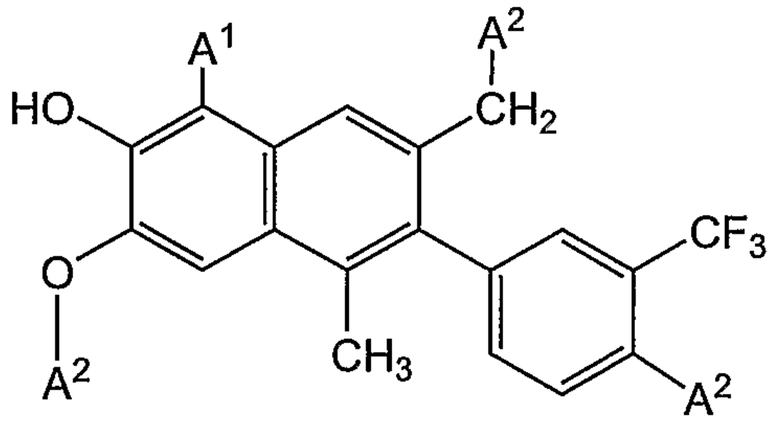
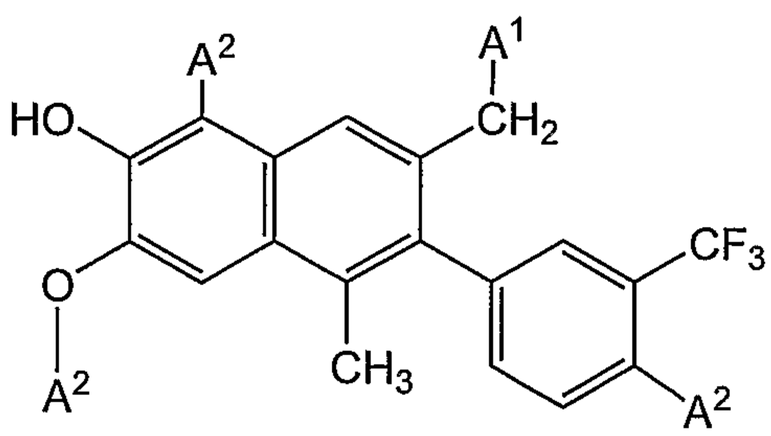
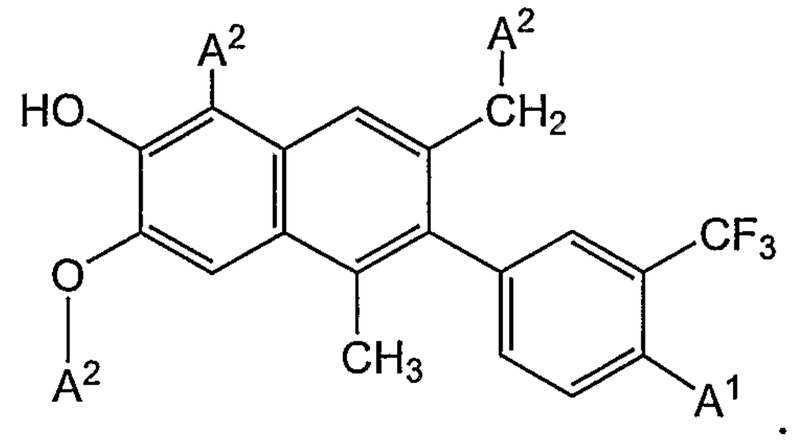
78. An HIV integrase inhibitor compound of claim 2 or 3 having Formula IX as described in claim 77 selected from the structures:

;

which is substituted with one or more covalently attached A^0 groups.

79. A Formula IX HIV integrase inhibitor compound of claim 77 selected from the structures:

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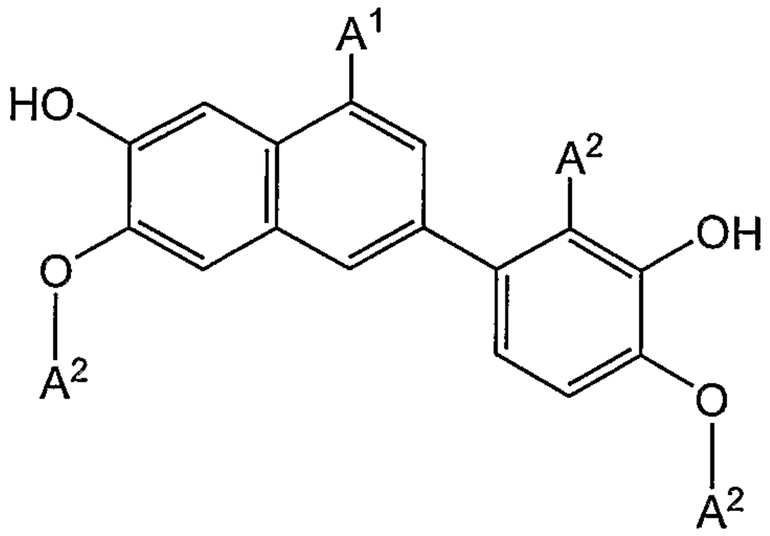
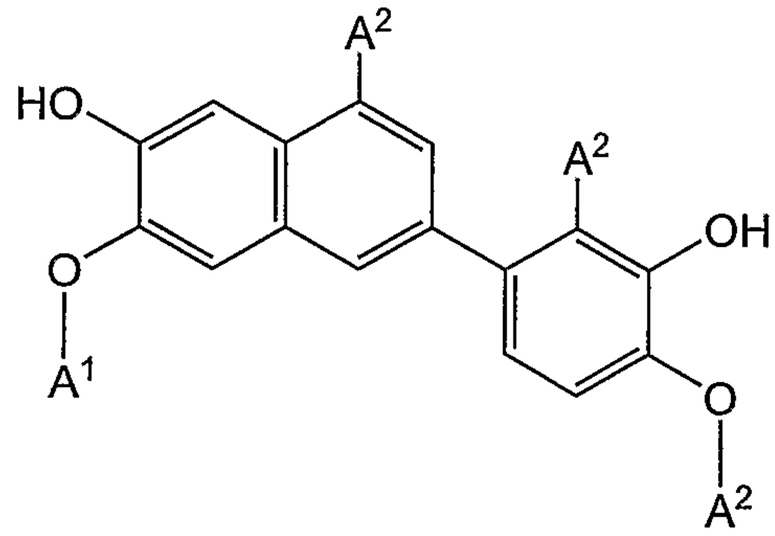
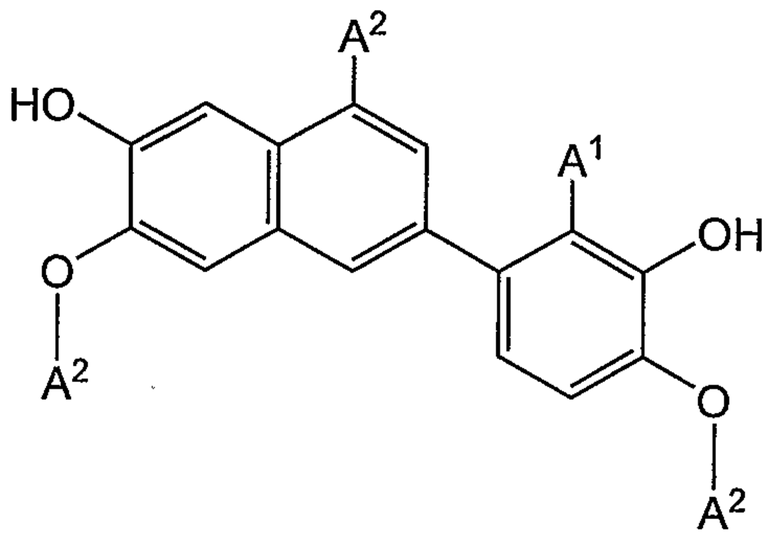
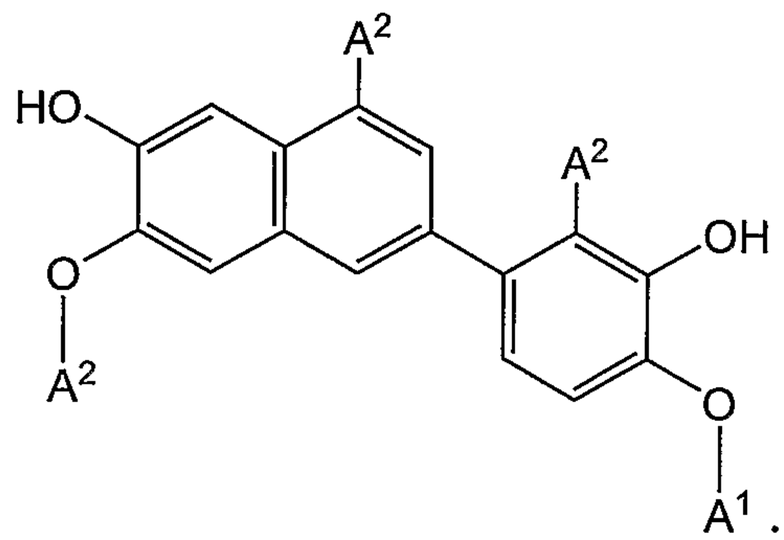
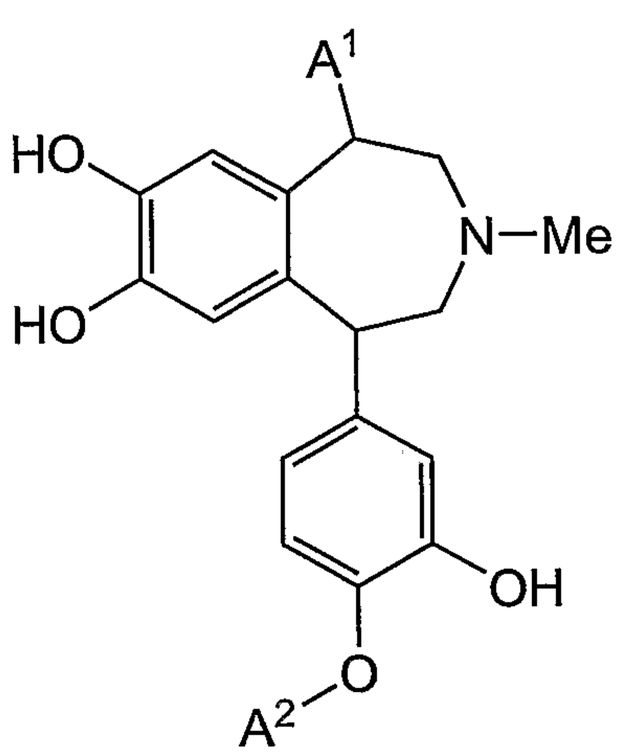
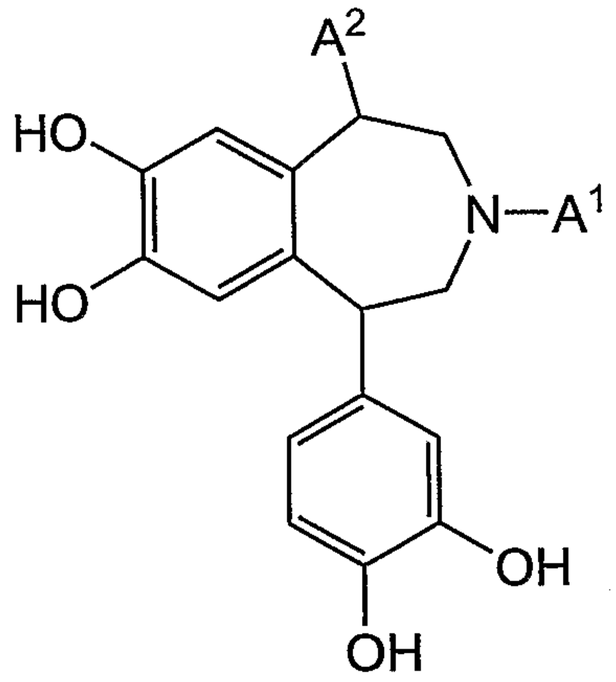
80. A Formula IX HIV integrase inhibitor compound of claim 77 selected from the structures:

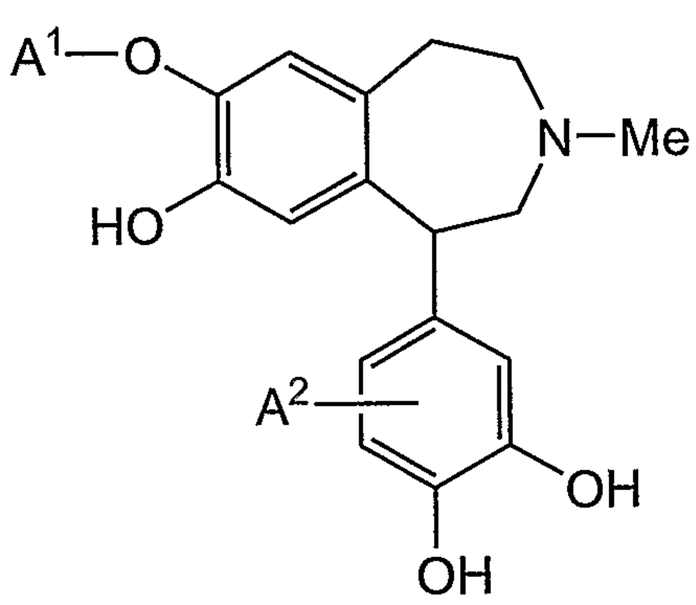





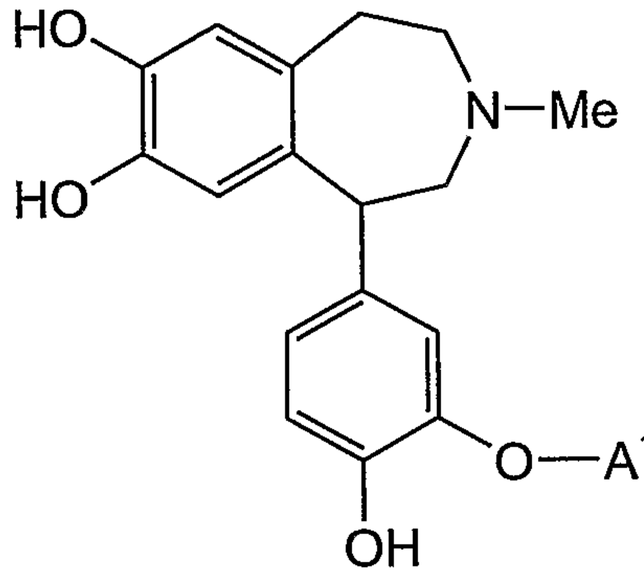
.

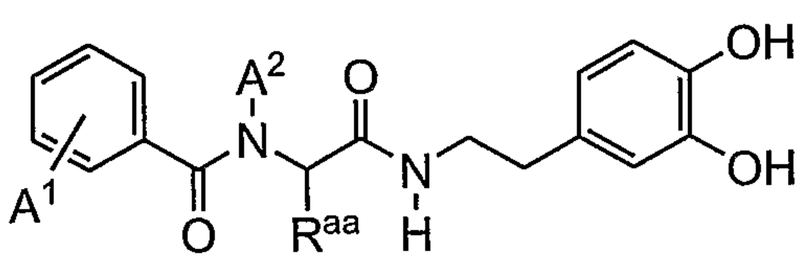
81. A Formula IX HIV integrase inhibitor compound of claim 77 selected from the structures:

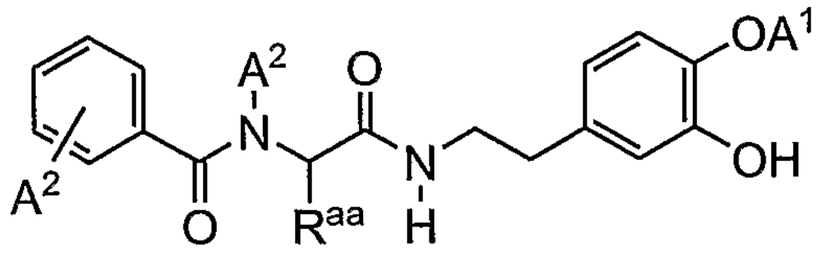


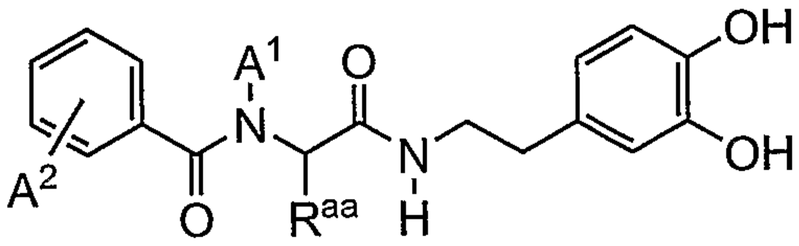


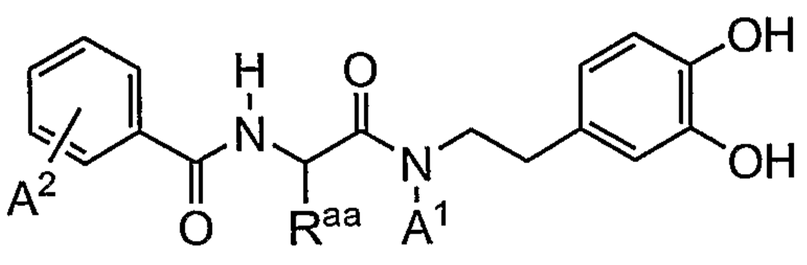


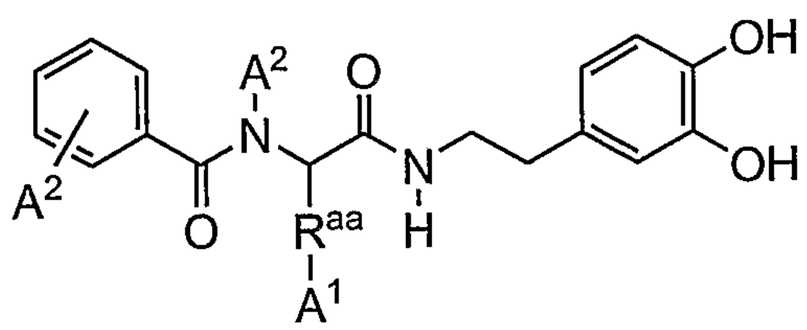


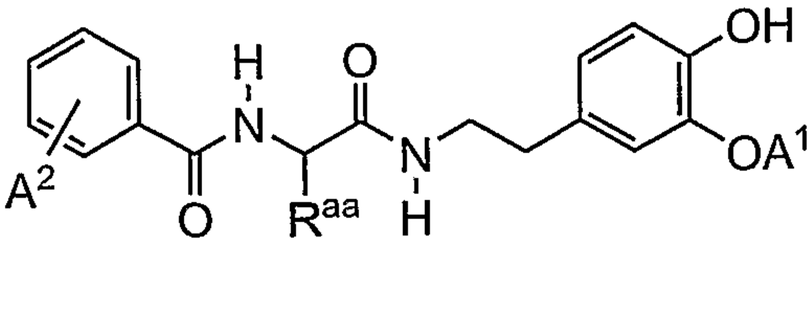






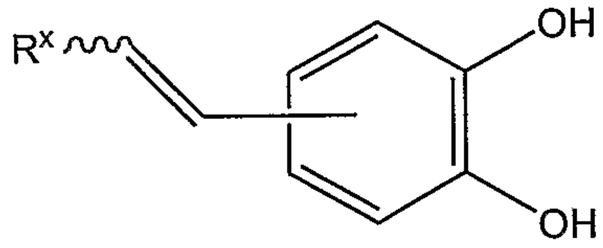






where R^{aa} is an amino acid side chain, including proline.

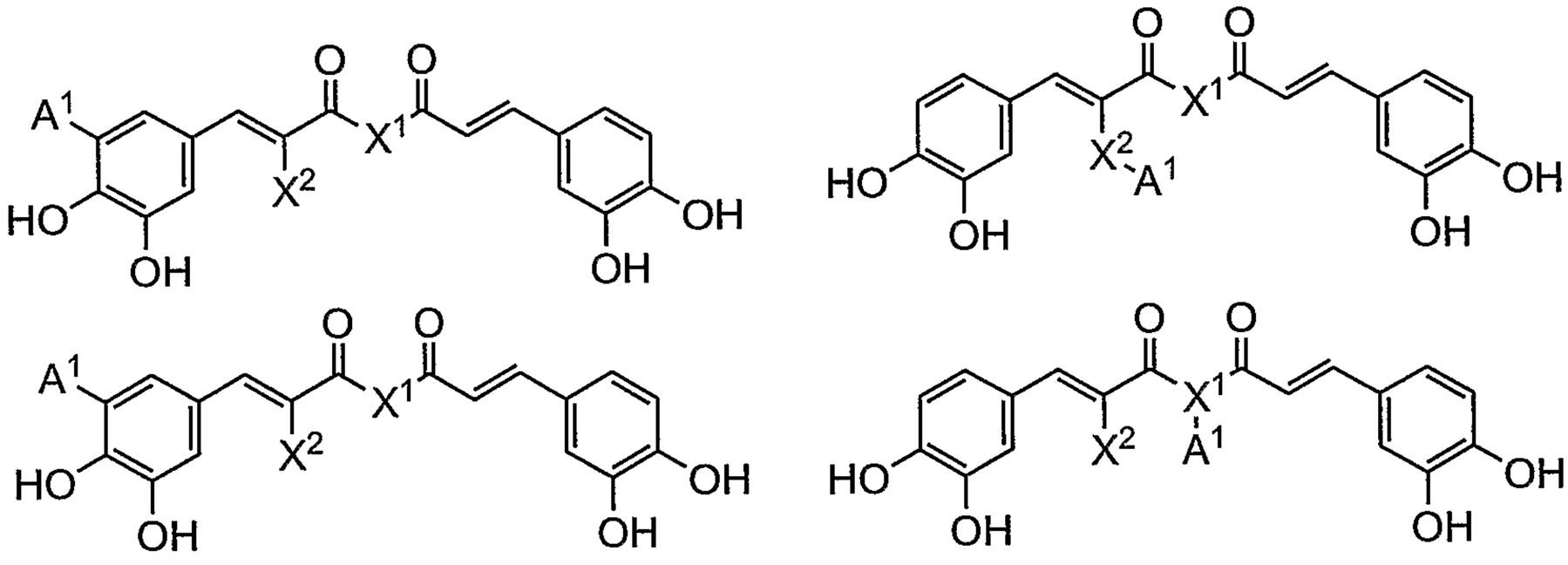
82. An HIV integrase inhibitor compound of claim 2 selected from Formula X:



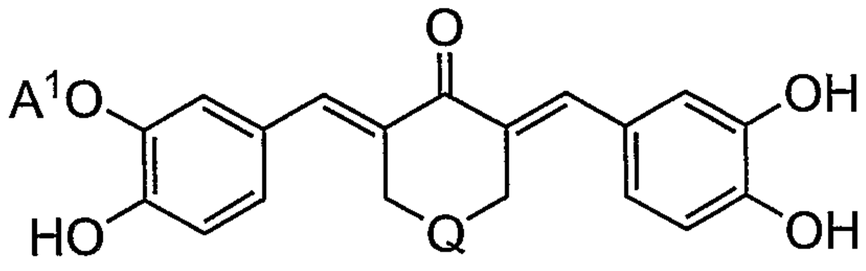
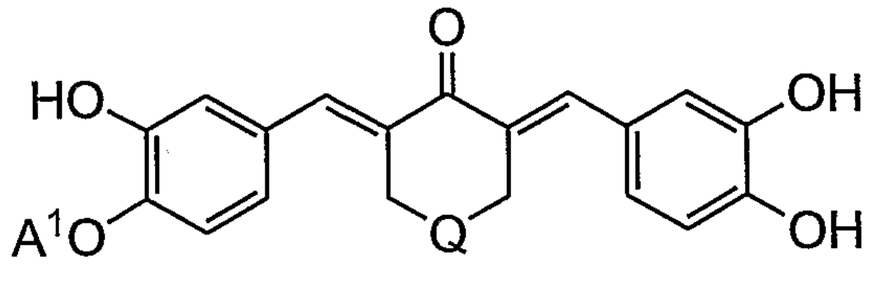
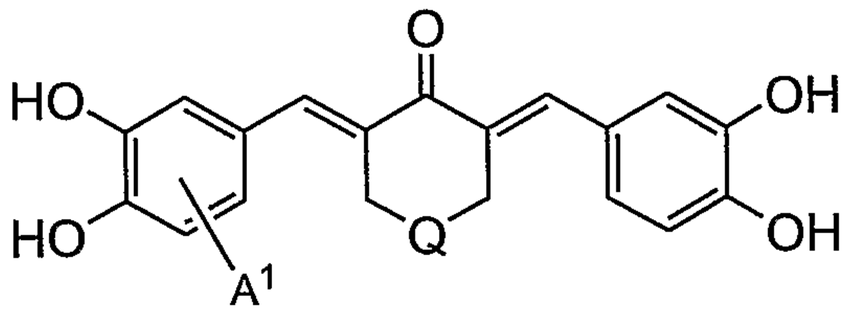
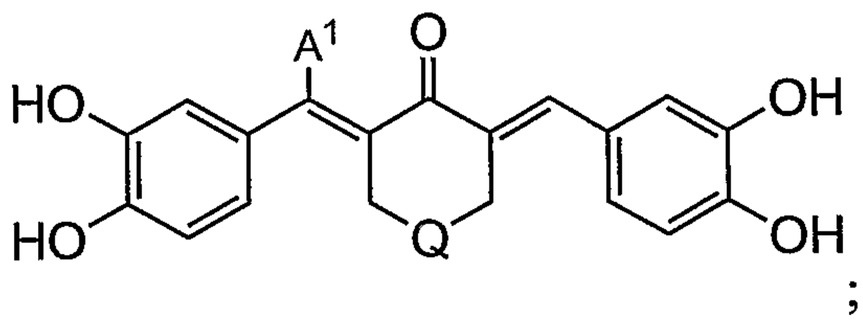
X

wherein R^x is a HIV integrase inhibitor scaffold that is covalently attached to the styryl catechol moiety through a single bond or a fused ring system, and the Formula X compound comprises at least one phosphonate group.

83. A Formula X HIV integrase inhibitor compound of claim 82 selected from the structures:

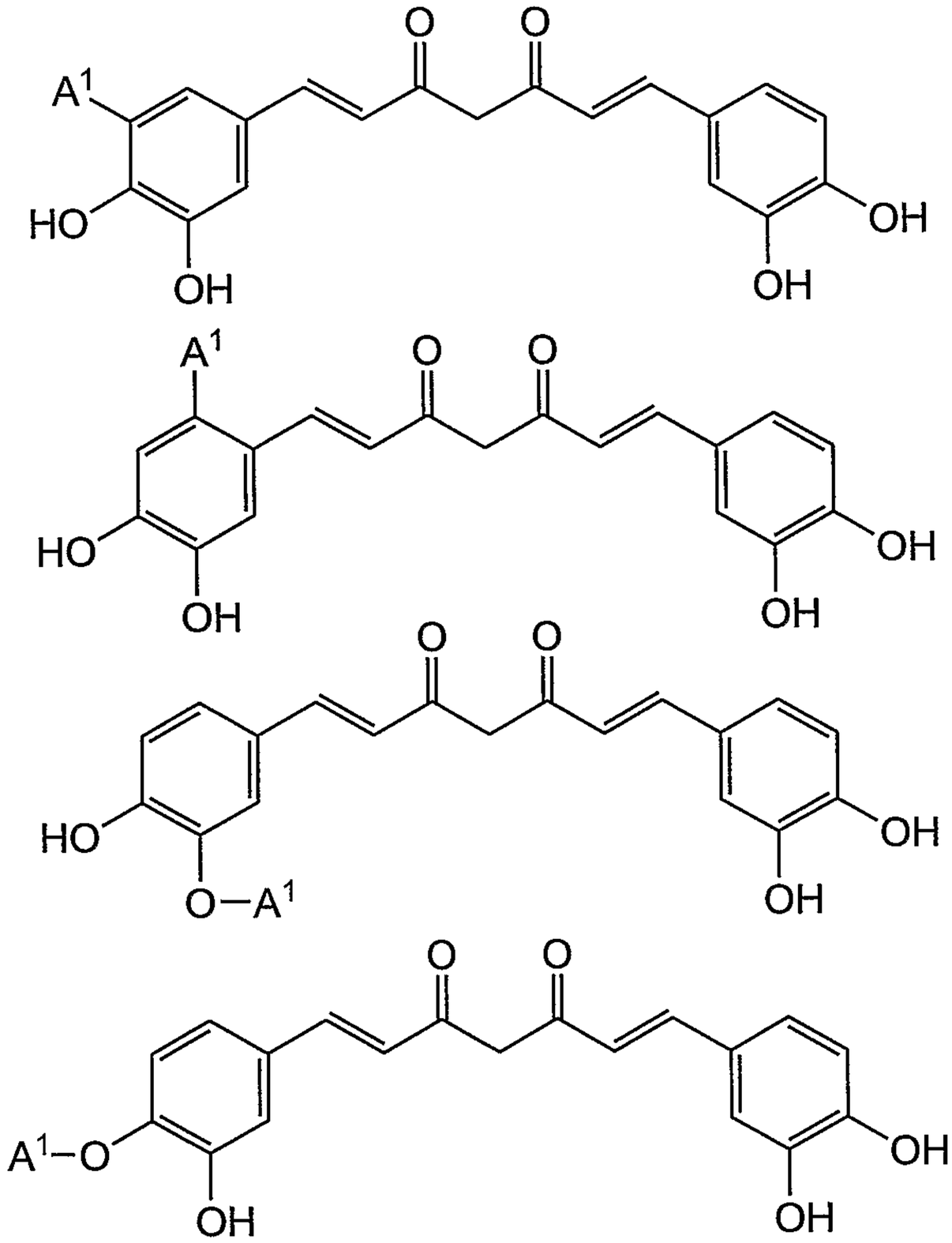


where X^1 is $-NH(CH_2)_nNH-$ where n is 1, 2, 3, 4, 5, or 6, alkylarylene, or arylene; and X^2 is CN, Br, or OH, and any carbon or hydroxyl oxygen atom may be independently substituted with A^2; and

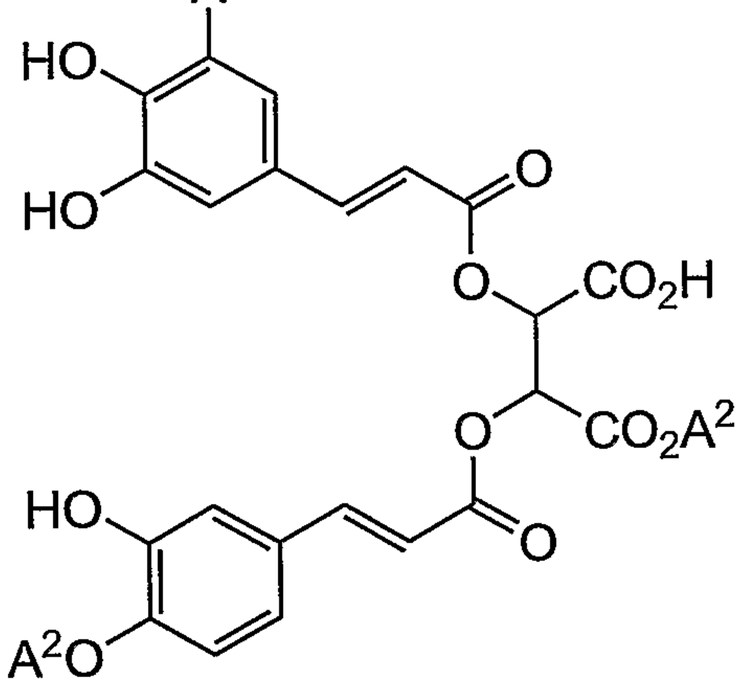




;

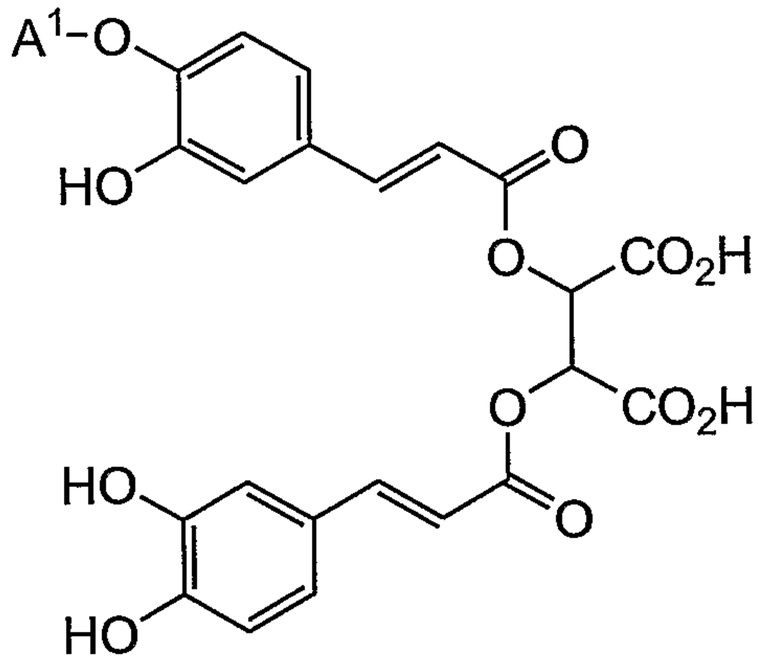
where Q is CH_2, O, S, NH, or NR.

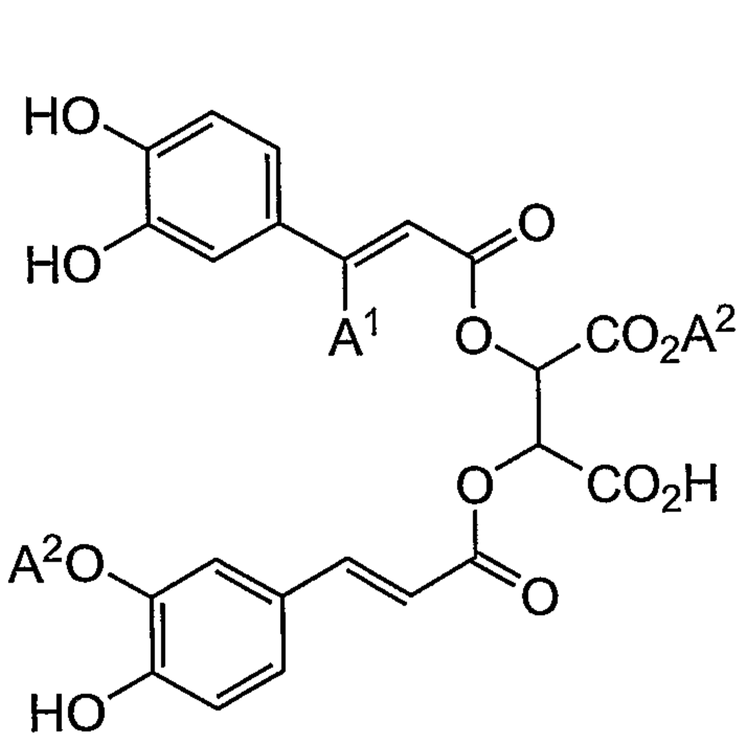
84. A Formula X HIV integrase inhibitor compound of claim 82 selected from the structures:

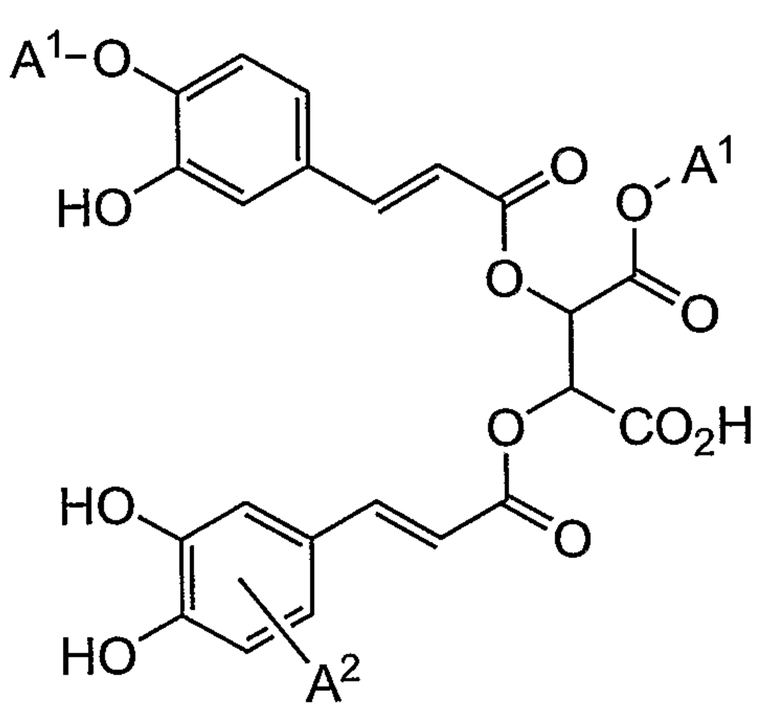


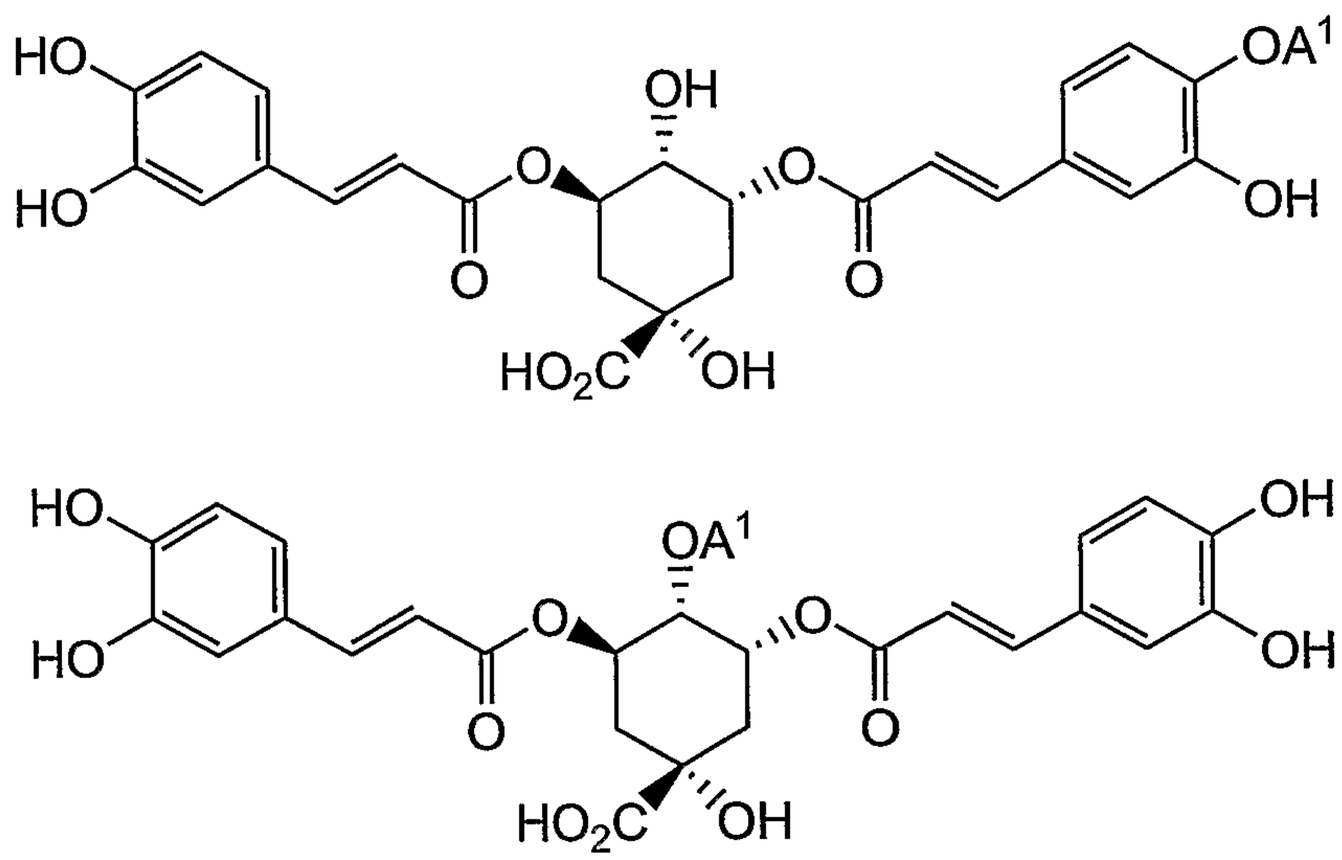
85. A Formula X HIV integrase inhibitor compound of claim 82 selected from the structures:

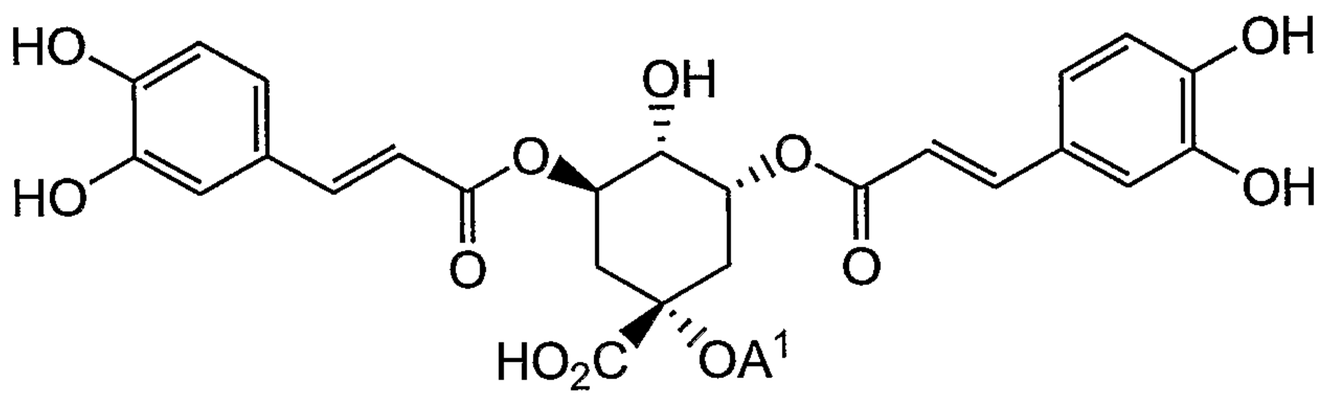




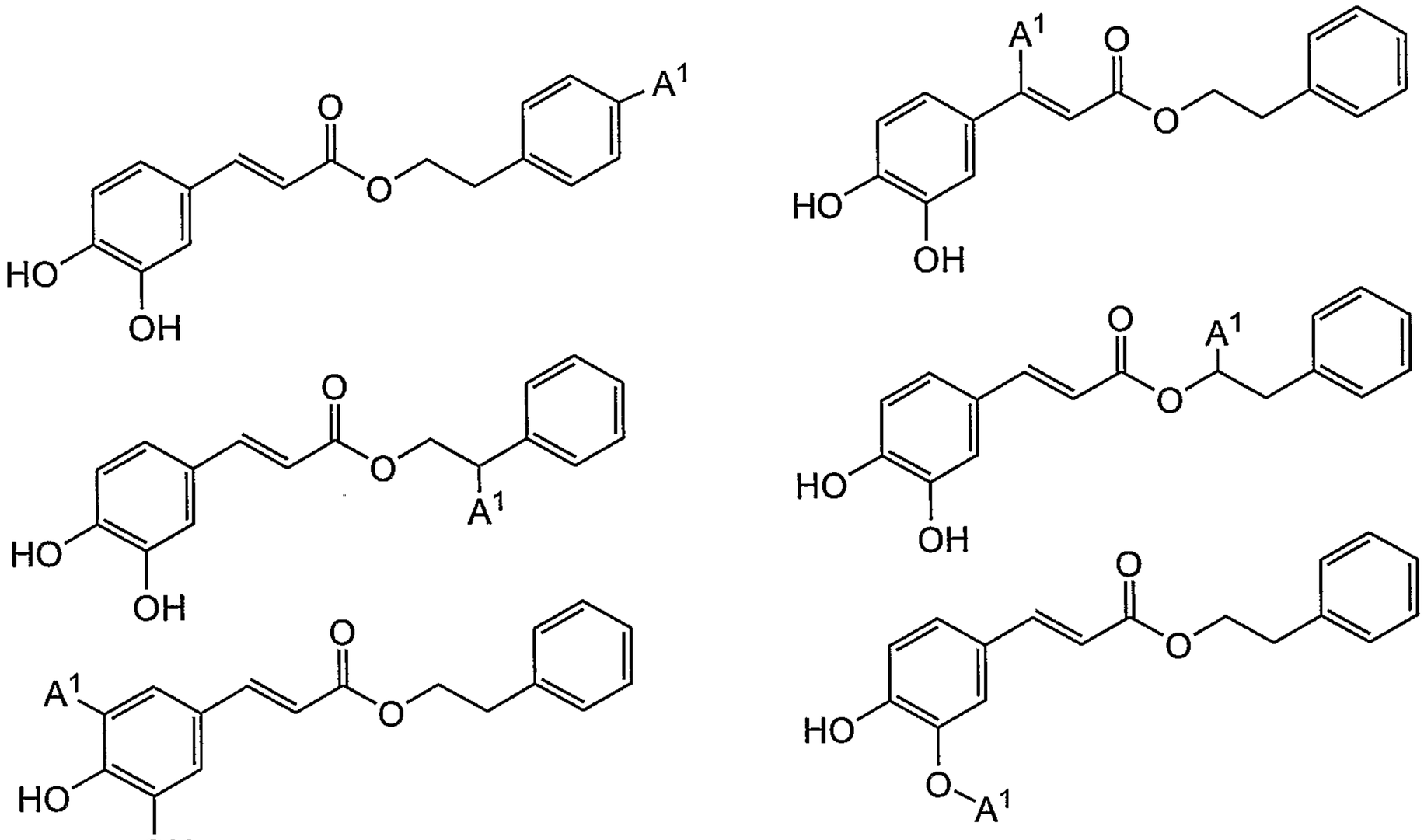




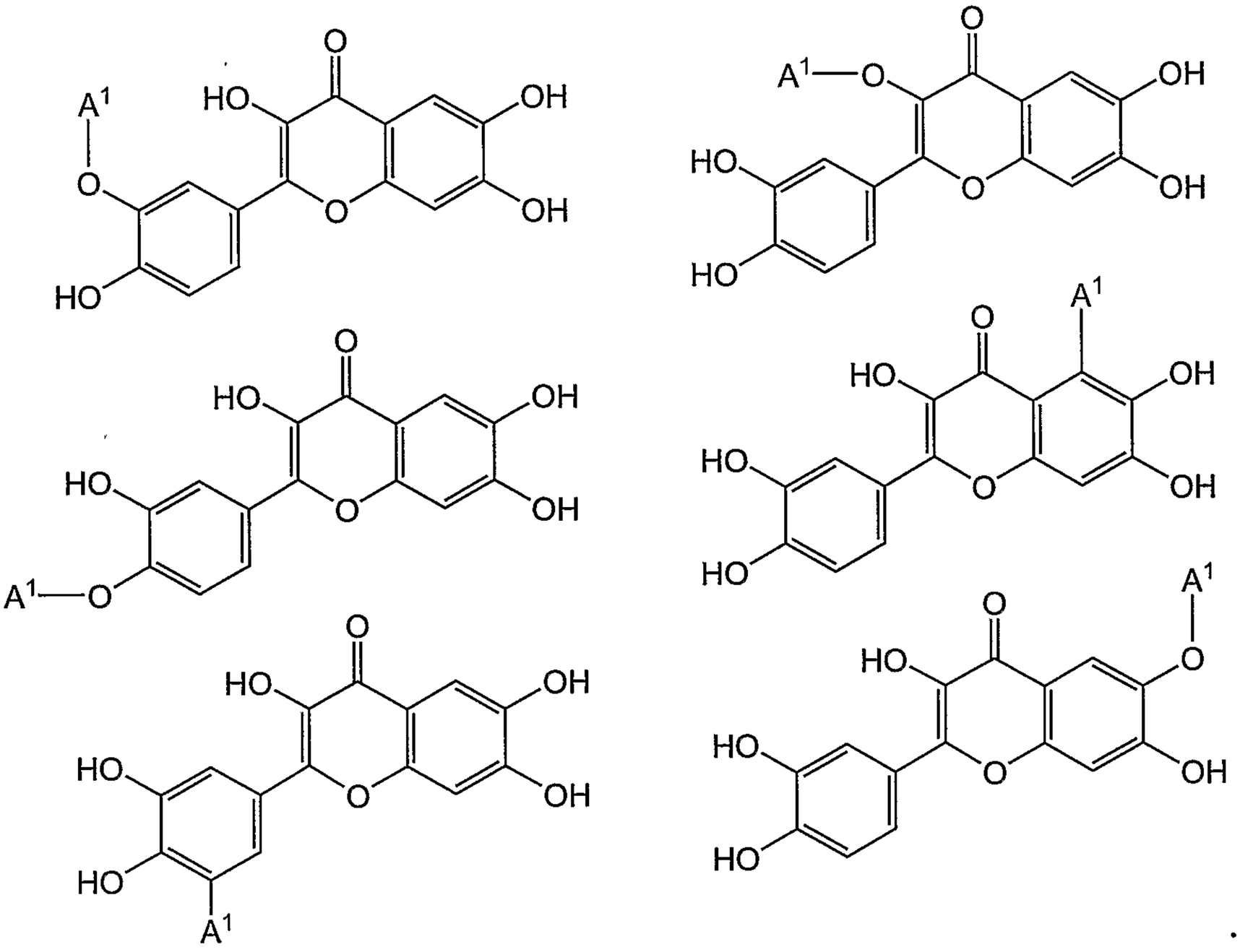




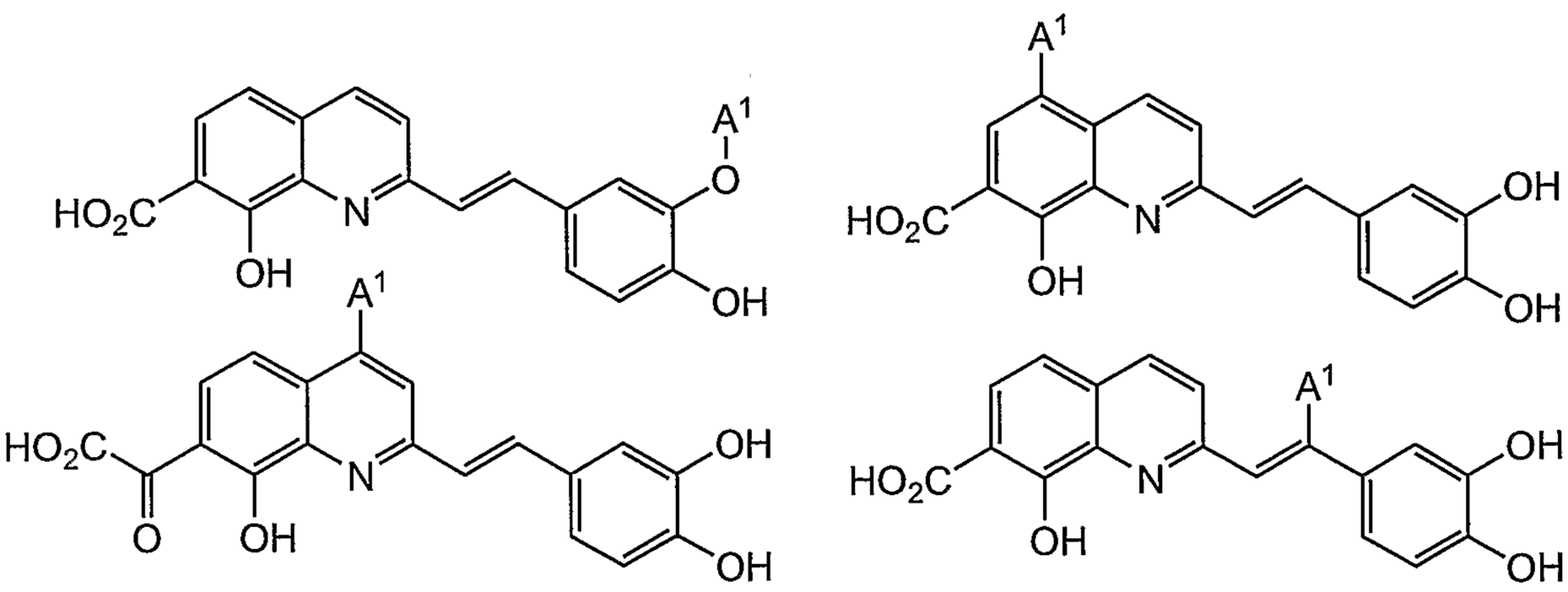
86. A Formula X HIV integrase inhibitor compound of claim 82 selected from the structures:



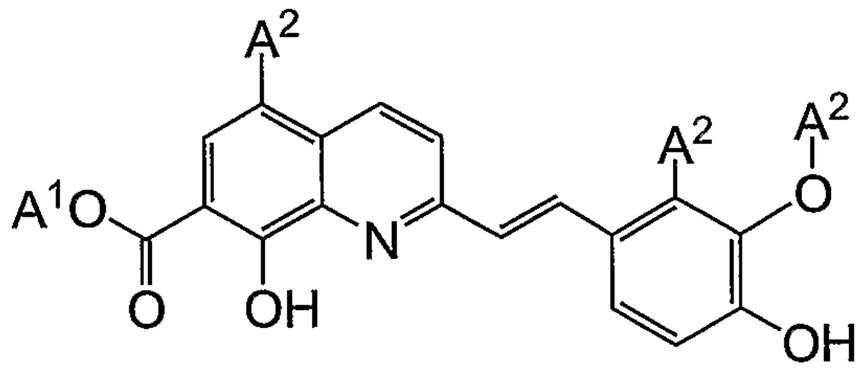
87. A Formula X HIV integrase inhibitor compound of claim 82 selected from the structures:

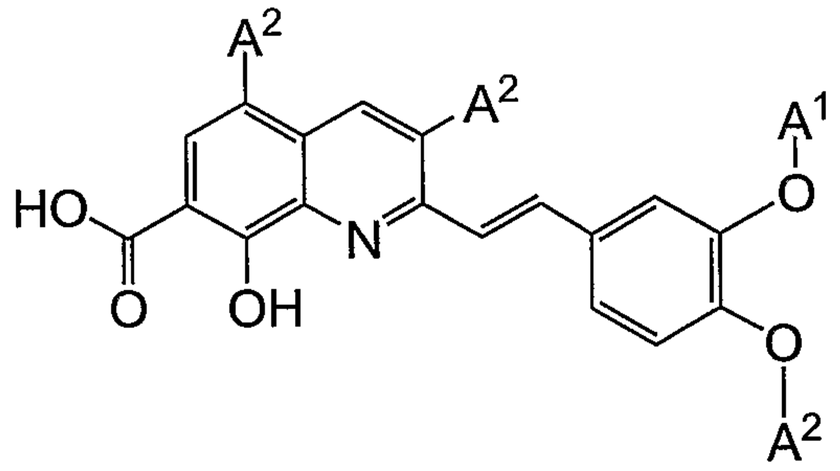


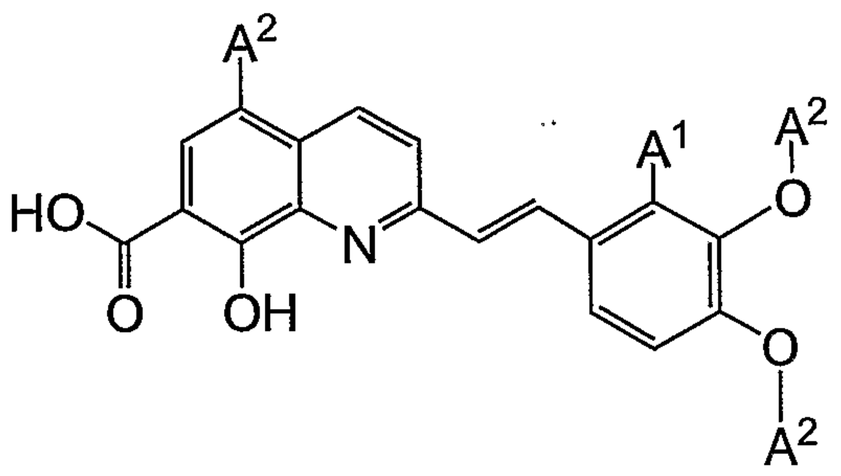
88. A Formula X HIV integrase inhibitor compound of claim 82 selected from the structures:

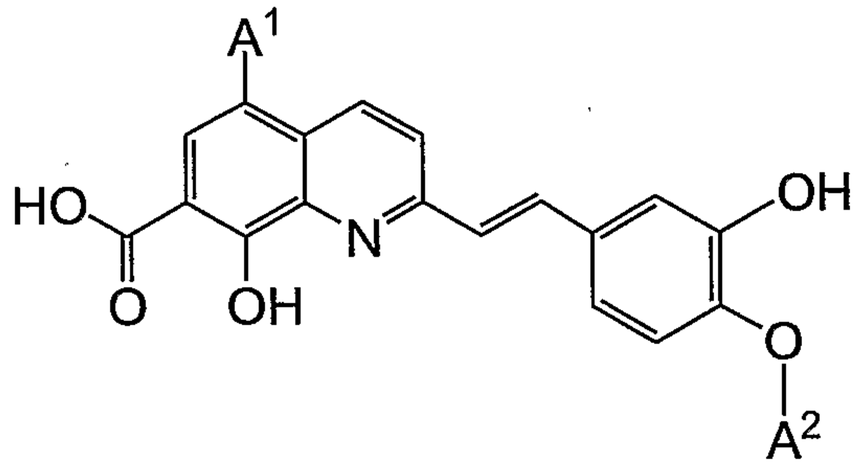


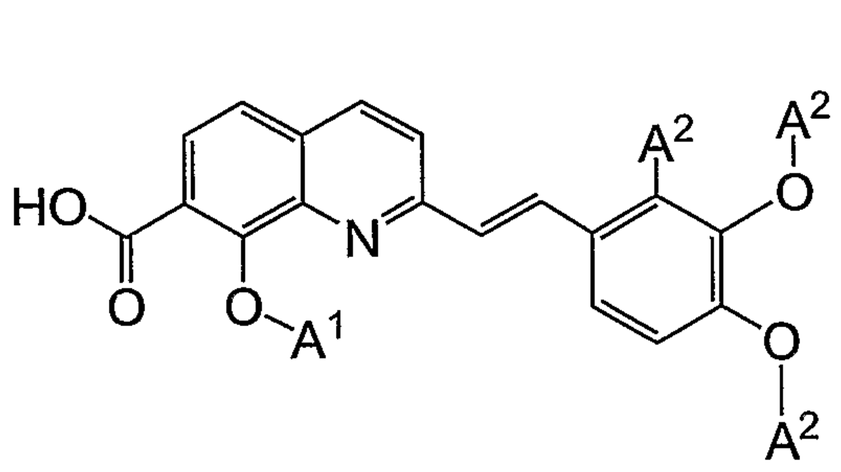
89. A Formula X HIV integrase inhibitor compound of claim 82 selected from the structures:

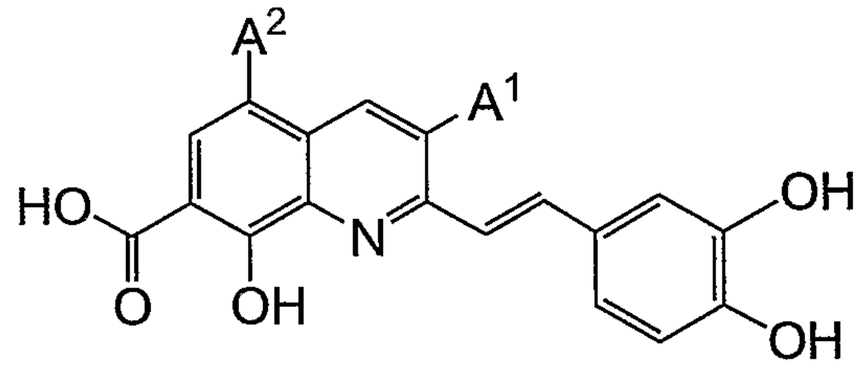


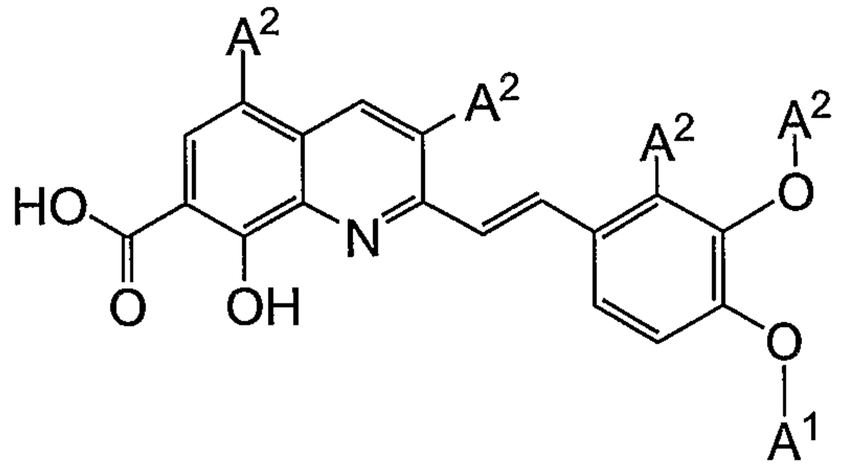






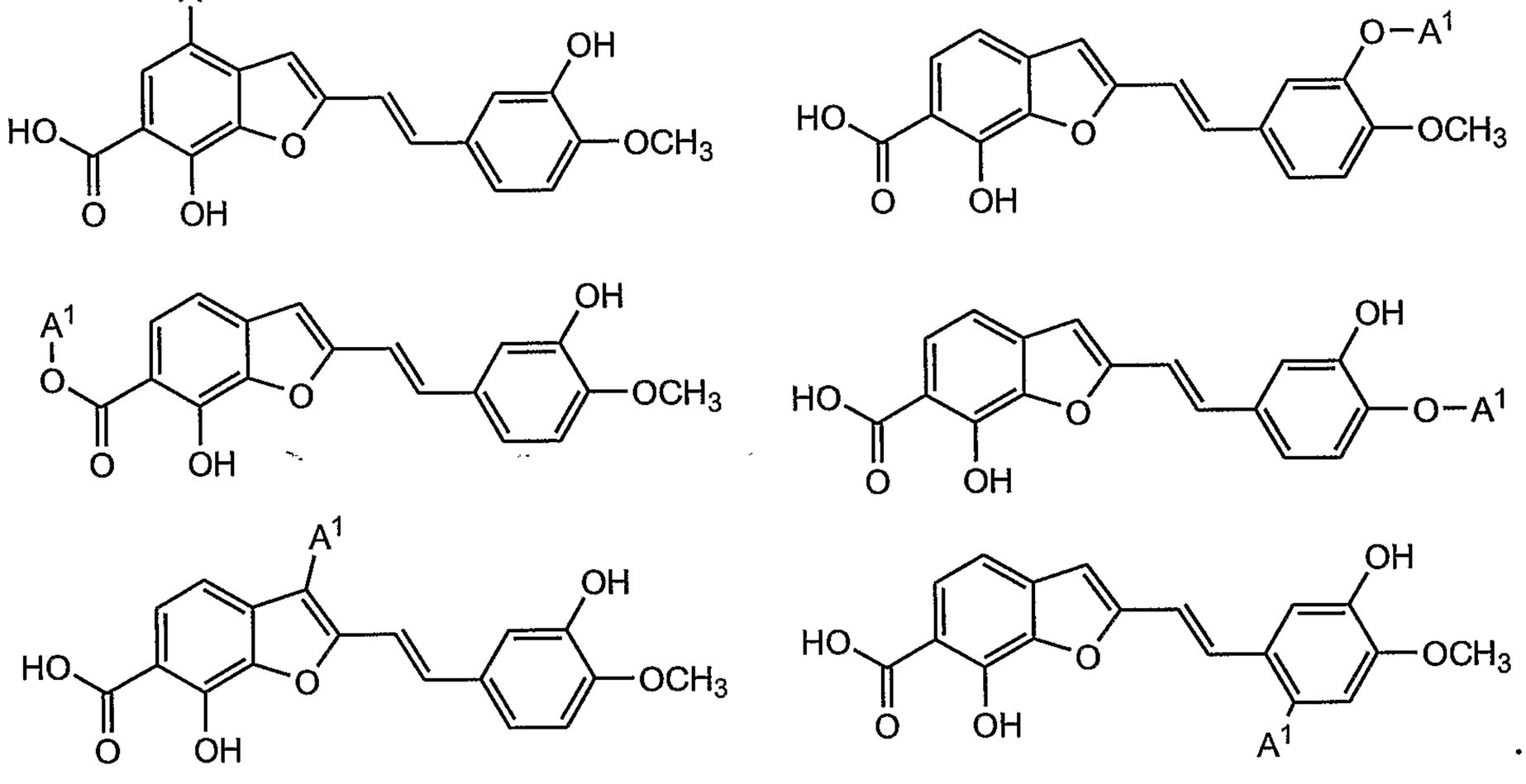




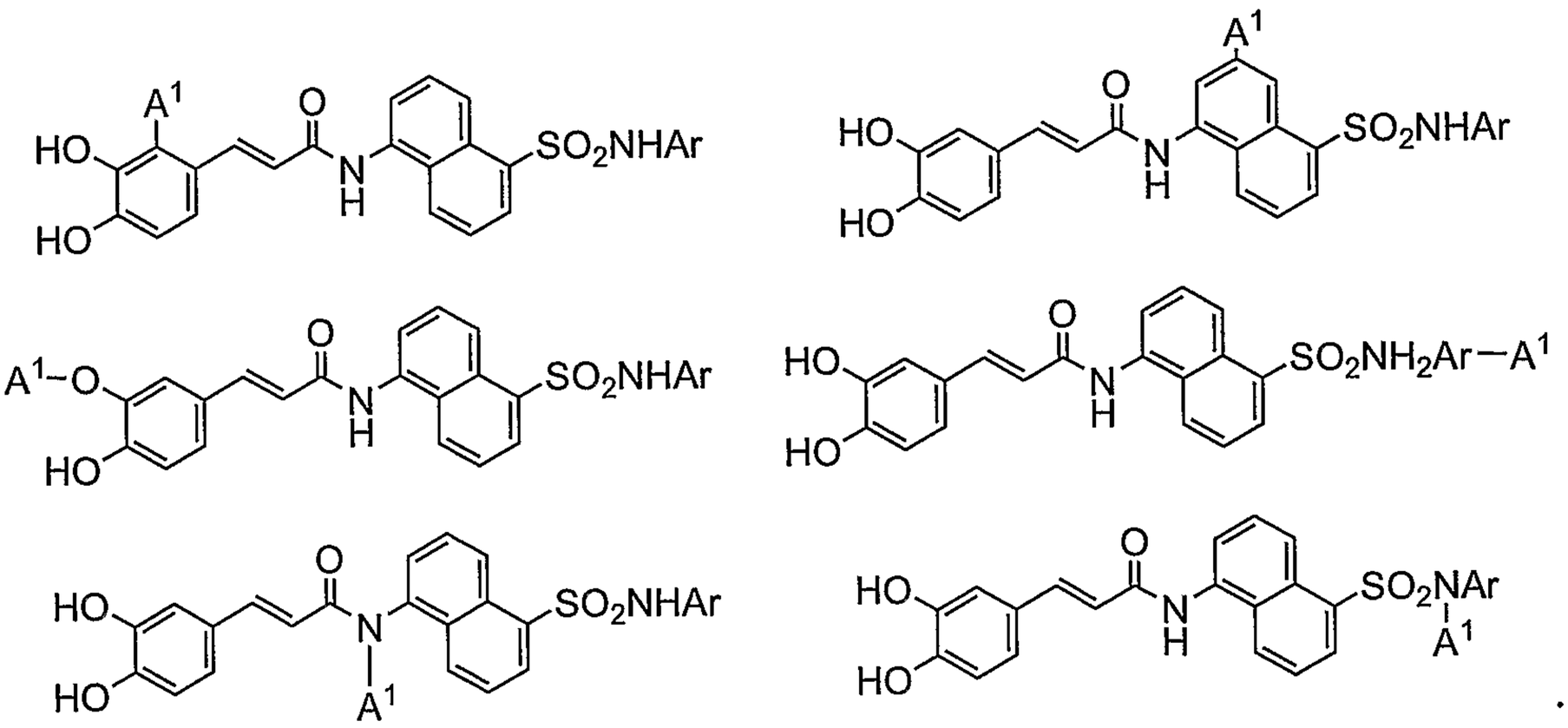


732

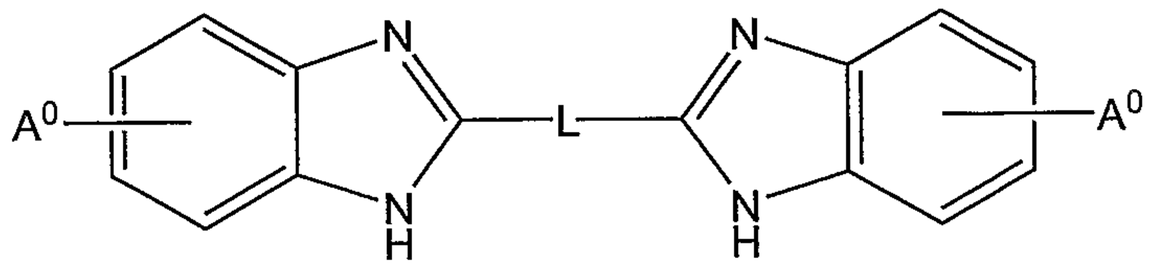
90. A Formula X HIV integrase inhibitor compound of claim 82 selected from the structures:



91. A Formula X HIV integrase inhibitor compound of claim 82 selected from the structures:



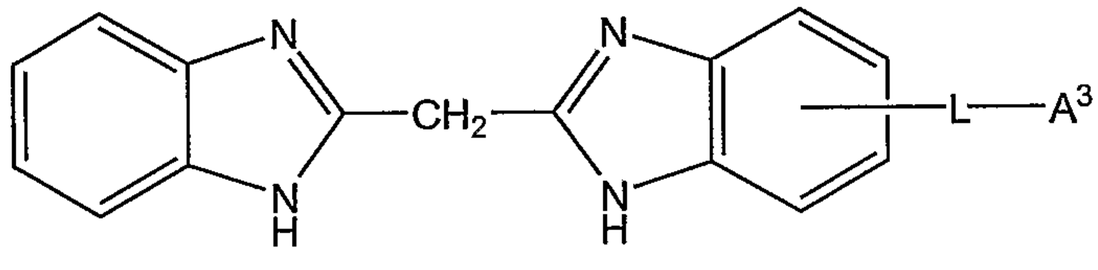
92. An HIV integrase inhibitor compound of claim 2 selected from Formula XI:

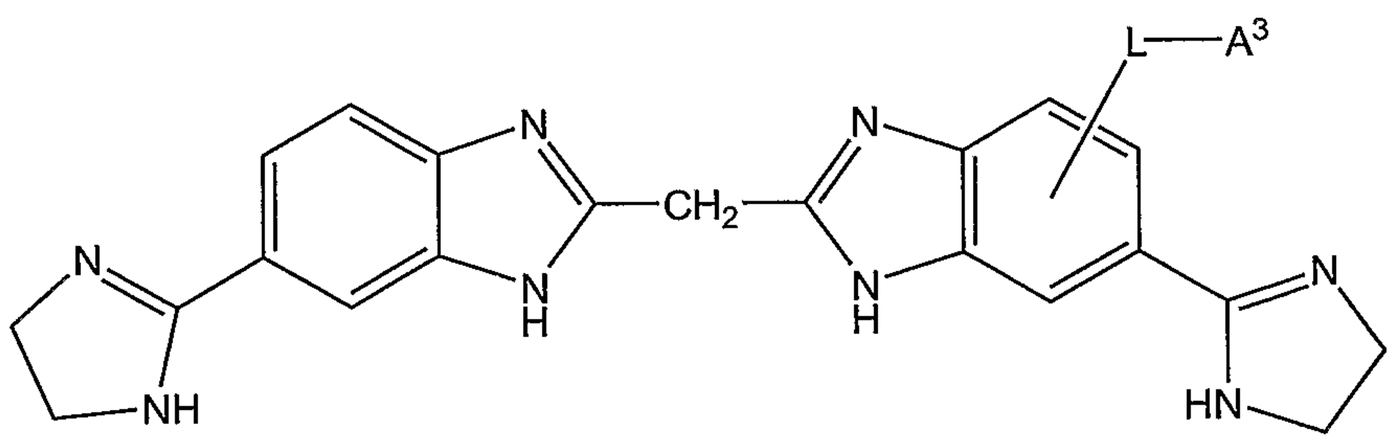


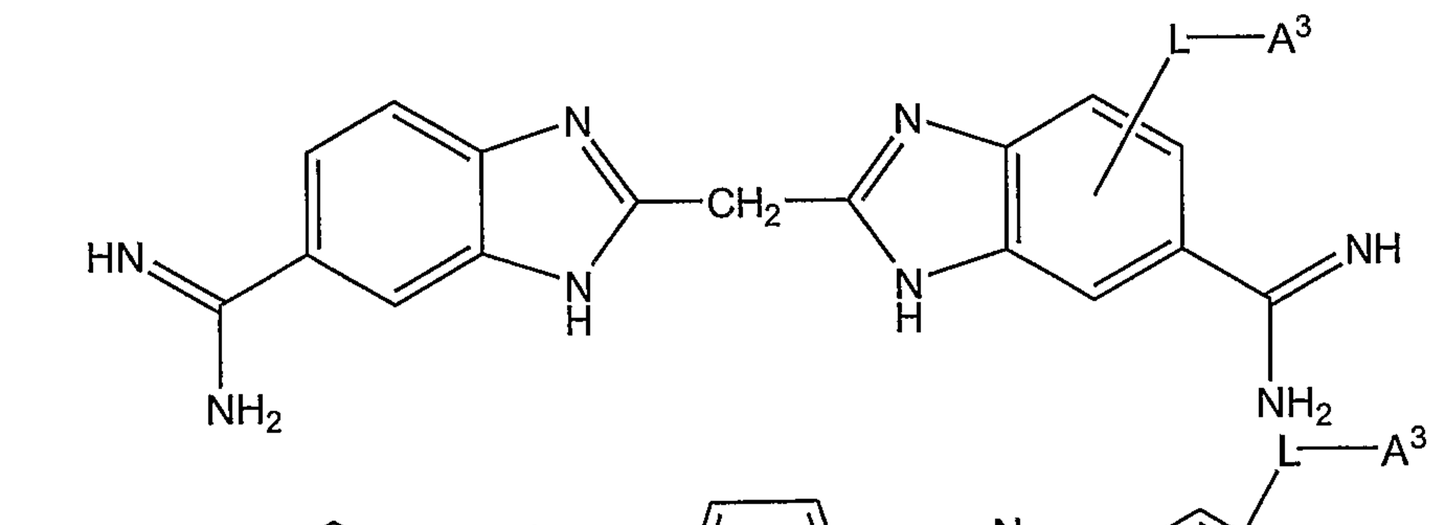
XI

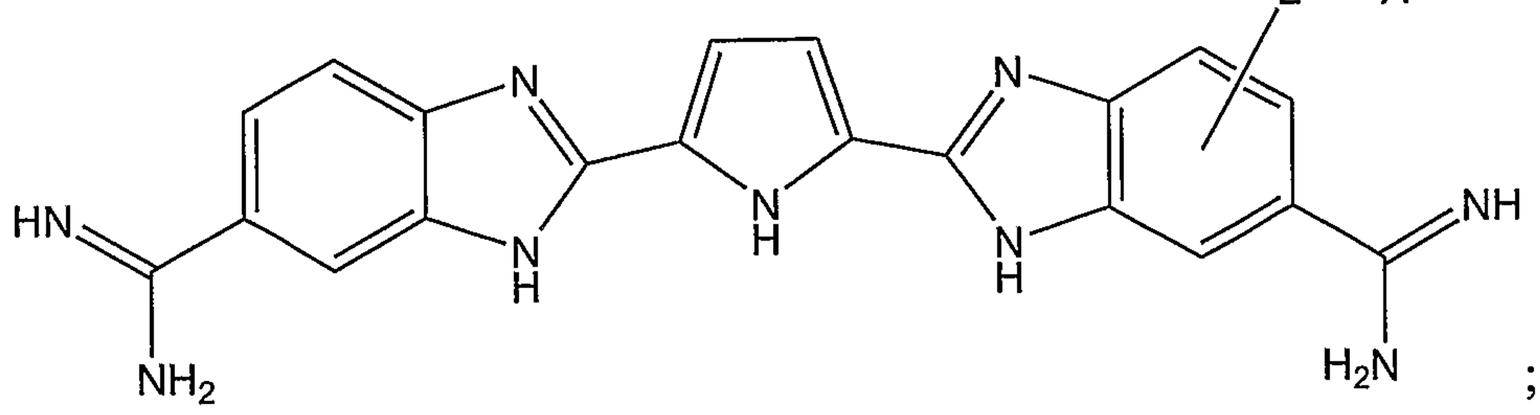
where Formula XI compound may be further substituted with fused ring systems, L is a linker, and the Formula XI compound comprises at least one A^0 group.

93. An HIV integrase inhibitor compound of claim 2 or 3 having Formula XI as described in claim 92 selected from the structures:





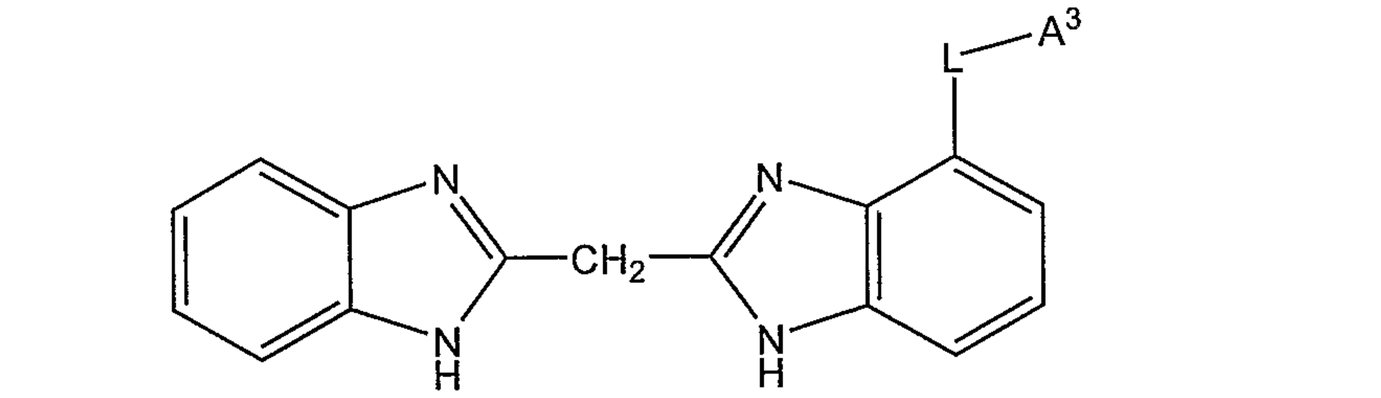


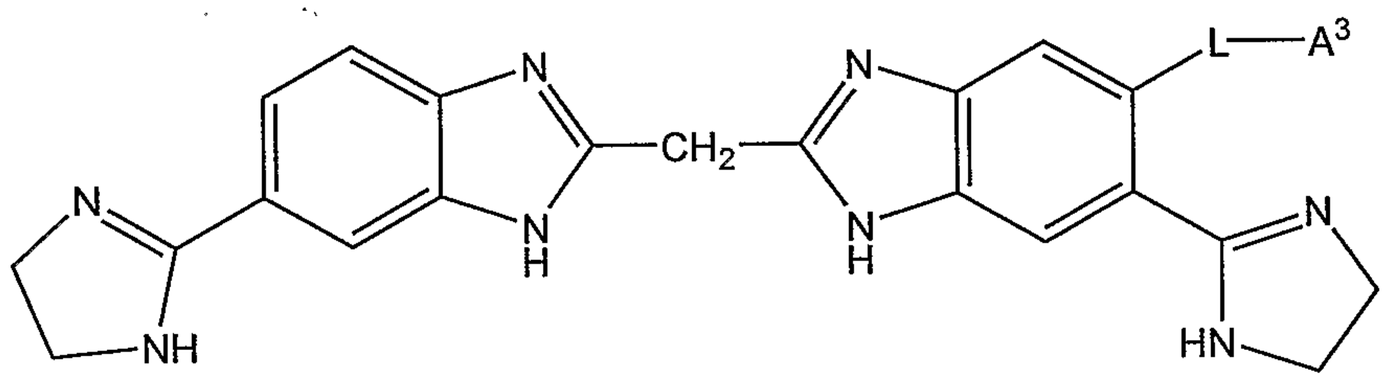


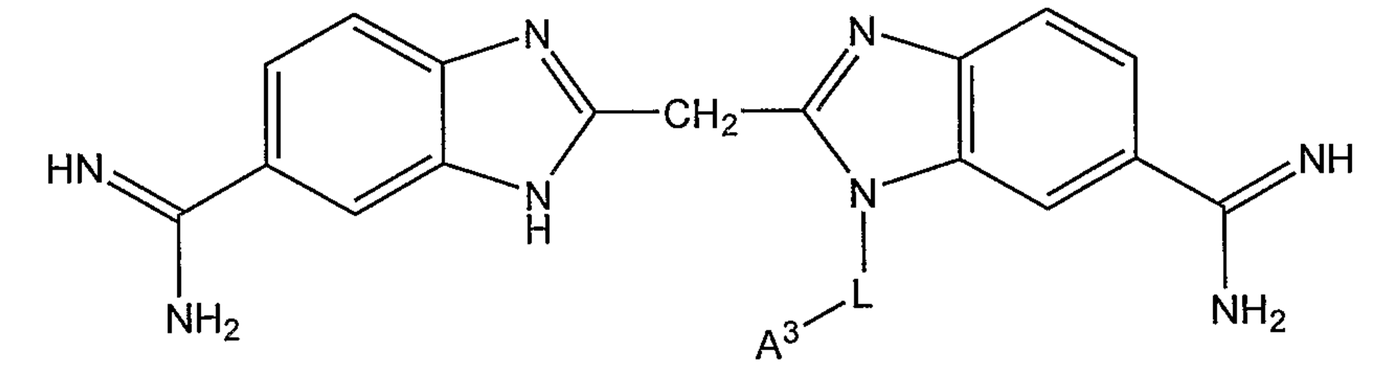
;

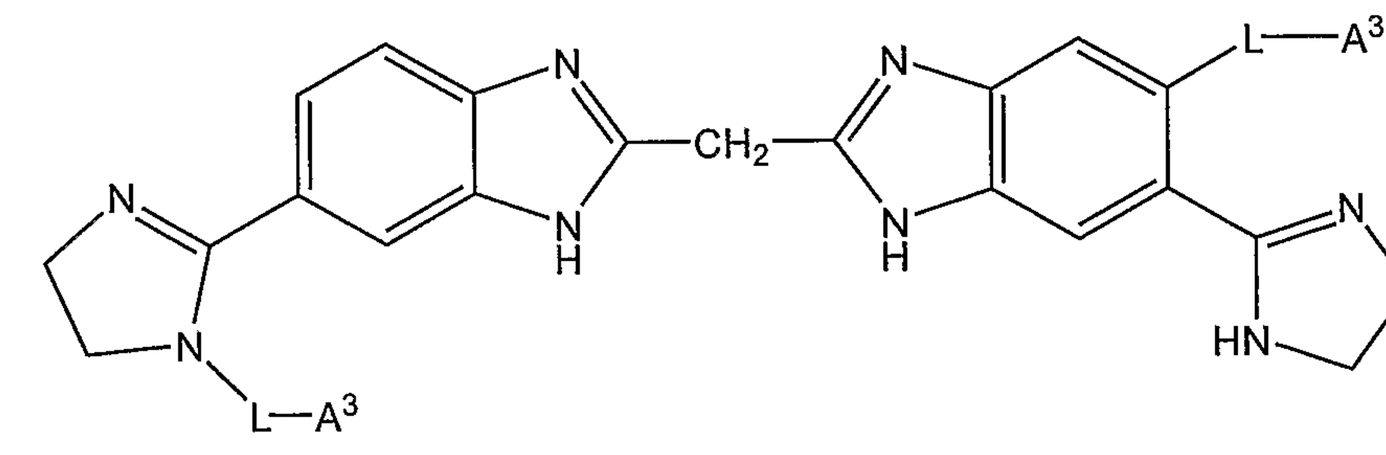
which is substituted with one or more covalently attached A^0 groups.

94. A Formula XI HIV integrase inhibitor compound of claim 93 selected from the structures:









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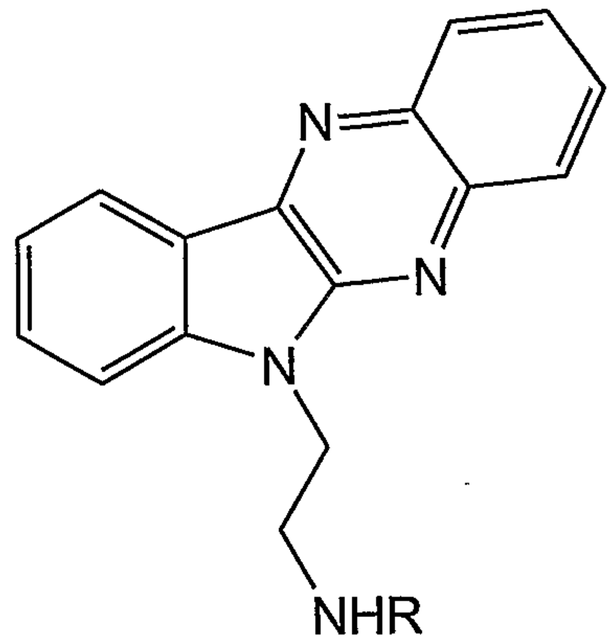
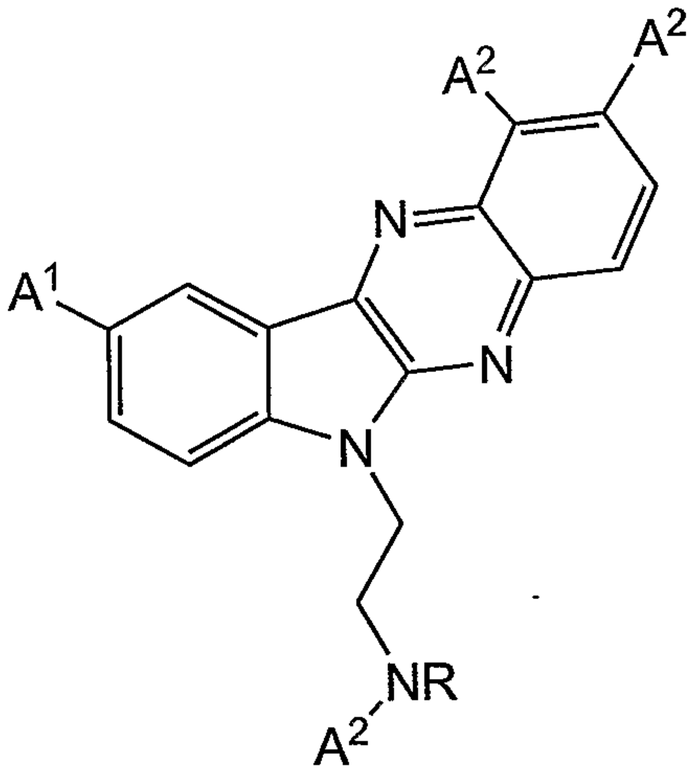
95. An HIV integrase inhibitor compound of claim 2 selected from Formula XII:

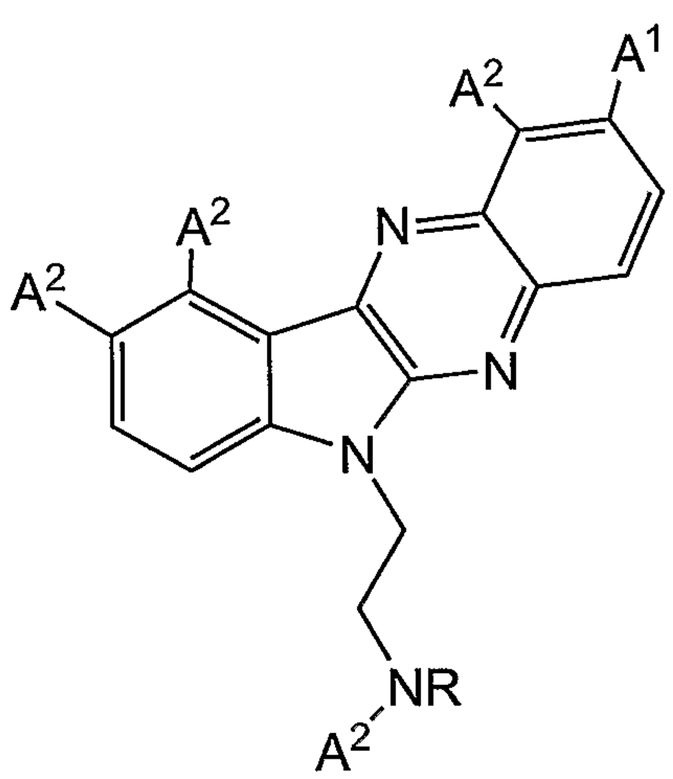


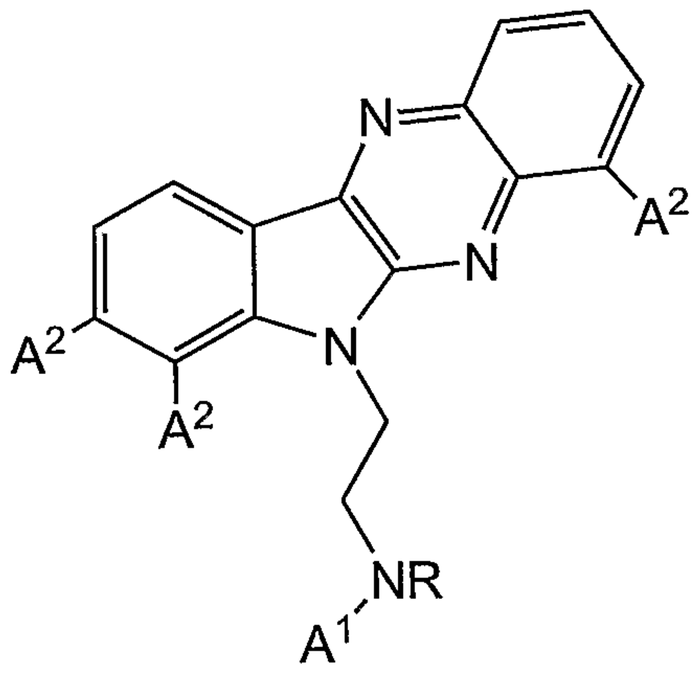
XII

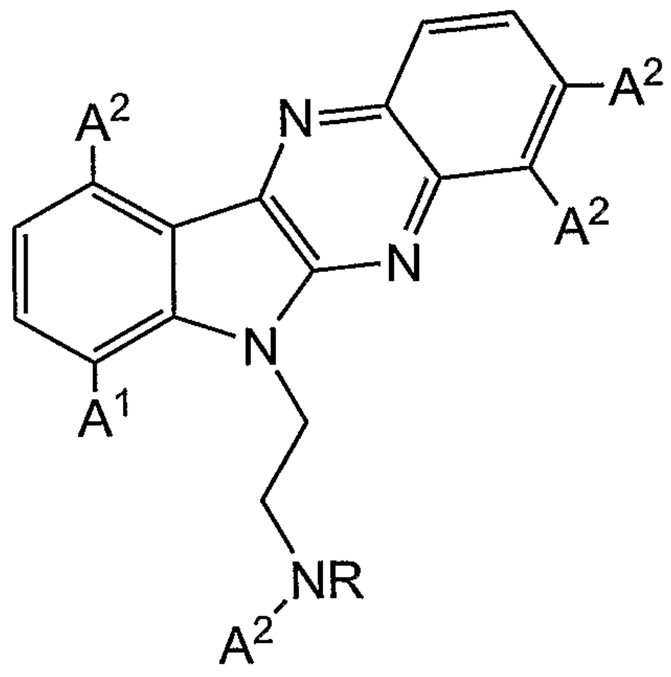
where a Formula XII compound comprises at least one phosphonate group.

96. A Formula XII HIV integrase inhibitor compound of claim 95 selected from the structures:

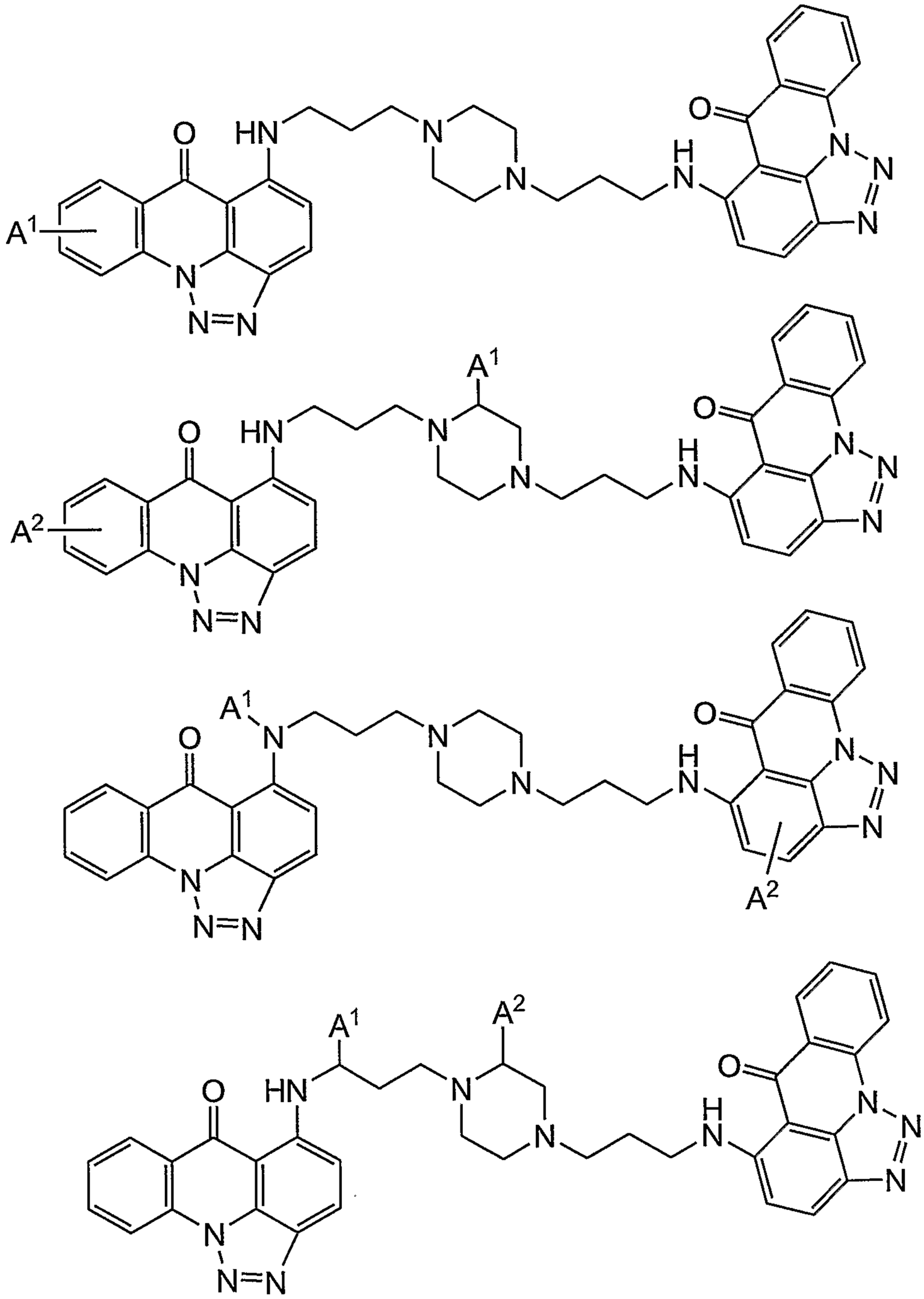




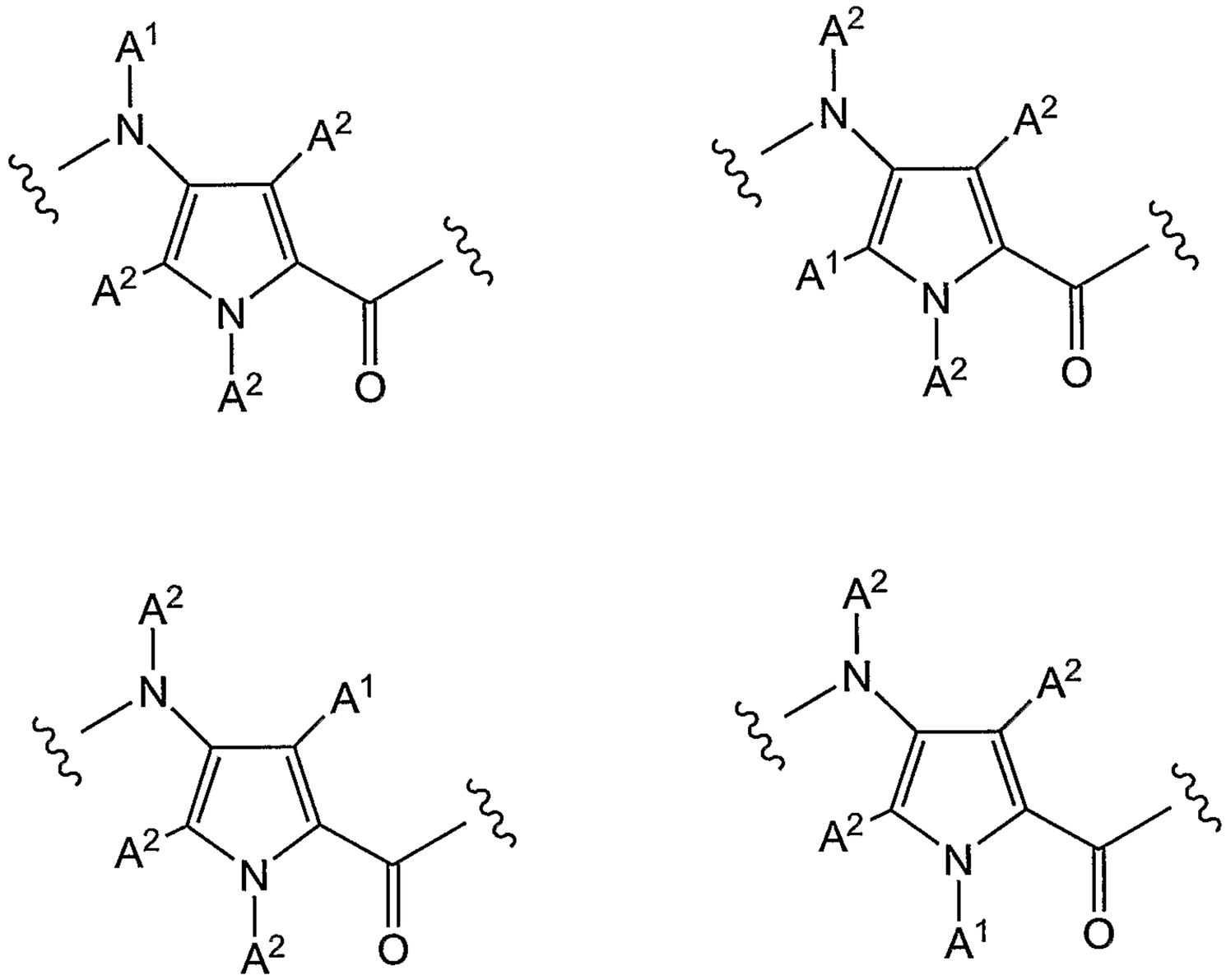




97. An HIV integrase inhibitor compound of claim 2 selected from the Formula XIII structures:

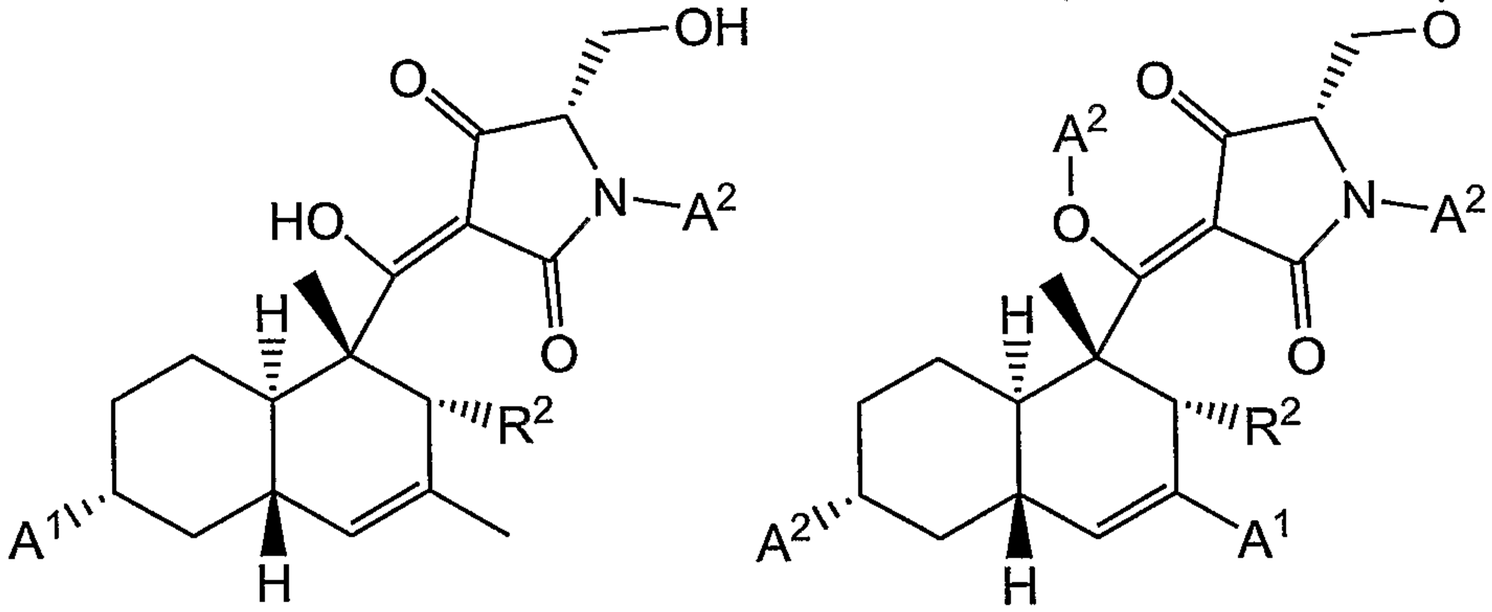


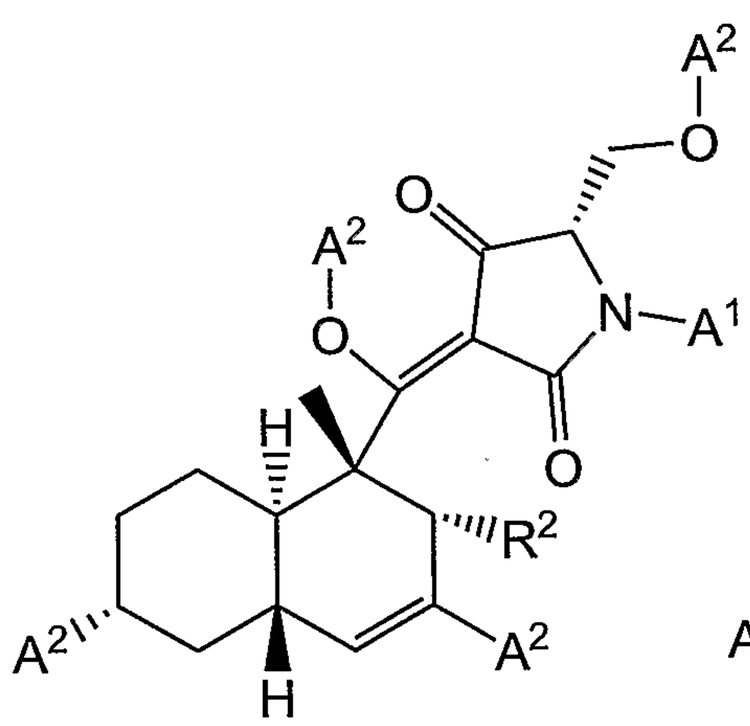
98. An HIV integrase inhibitor compound of claim 2 selected from the Formula XIV structures:

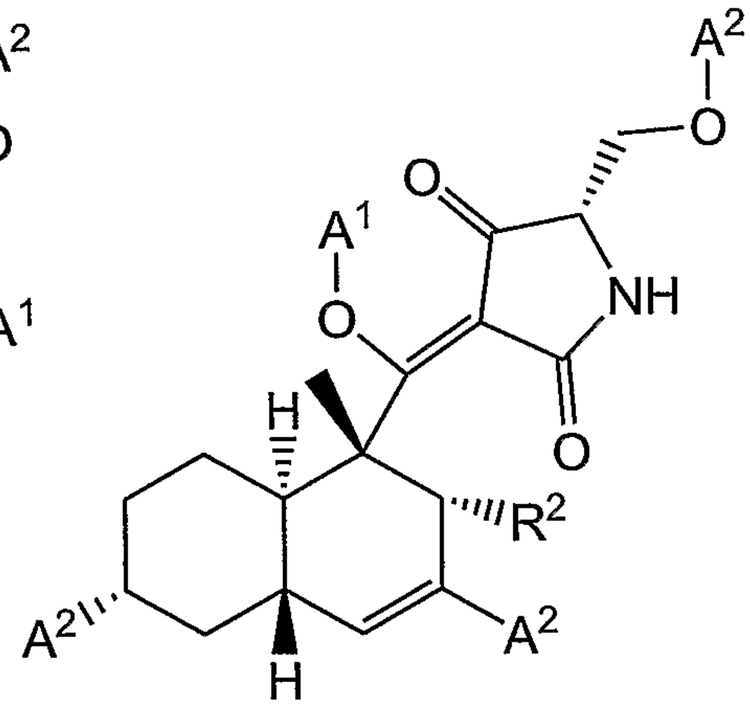


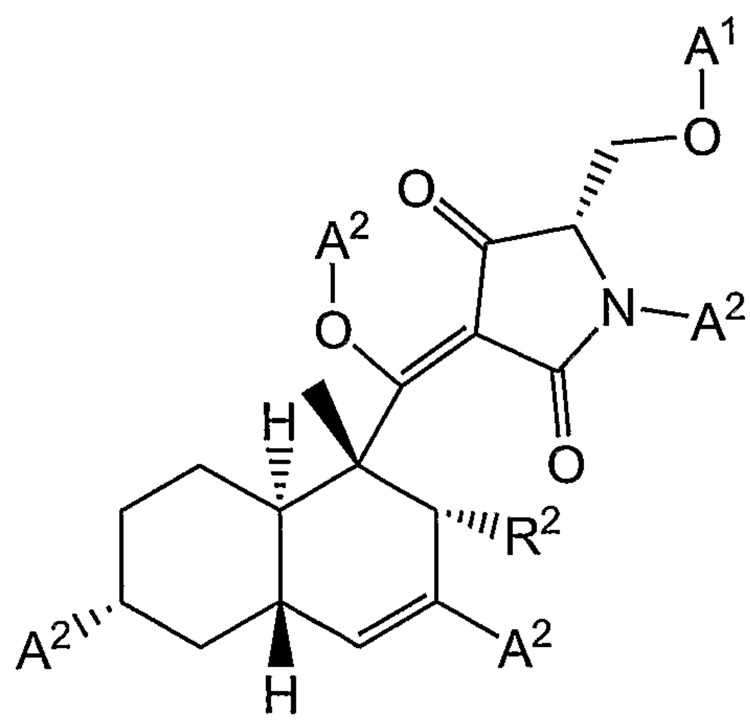
where the wavy lines indicate the depicted structure is a substructure of a repeating polymer molecule; and where a Formula XIV compound comprises at least one phosphonate group; and where one or more of the pyrrole amide monomer units in the polypyrrole amide molecule are substituted at one or more locations with a phosphonate group.

99. An HIV integrase inhibitor compound of claim 2 selected from the Formula XV structures:

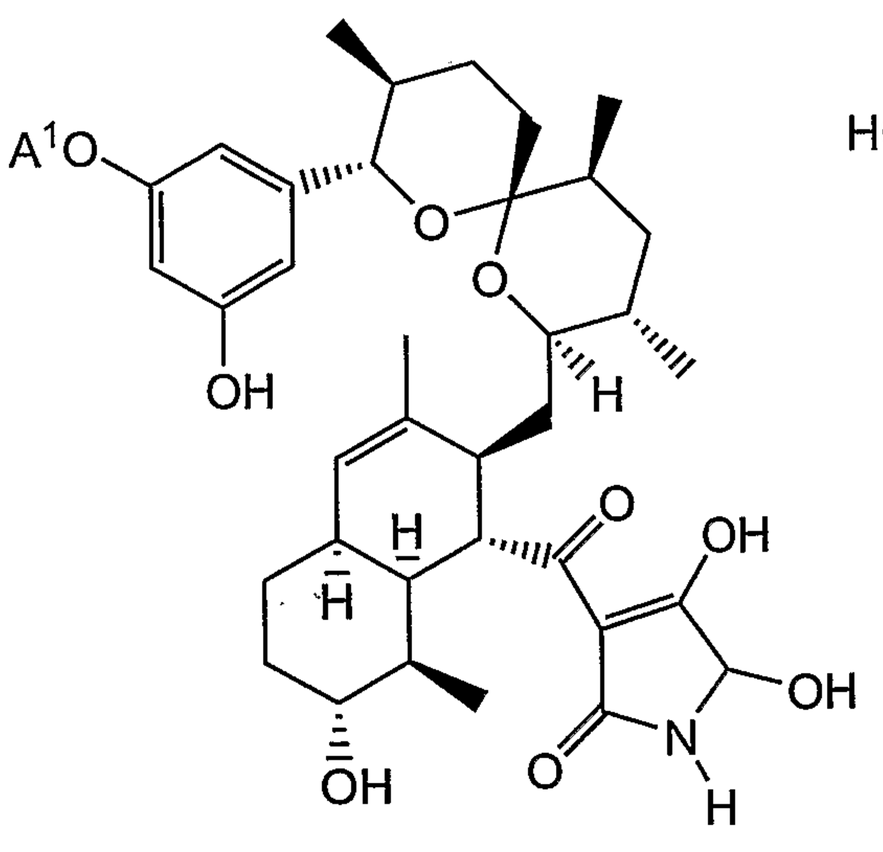


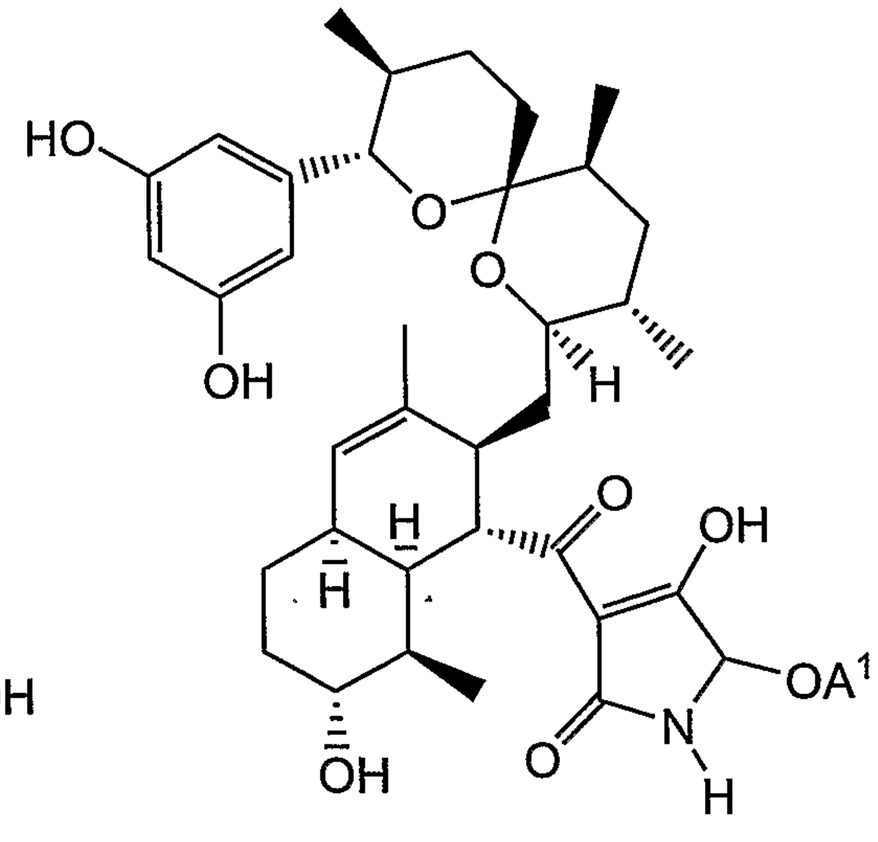


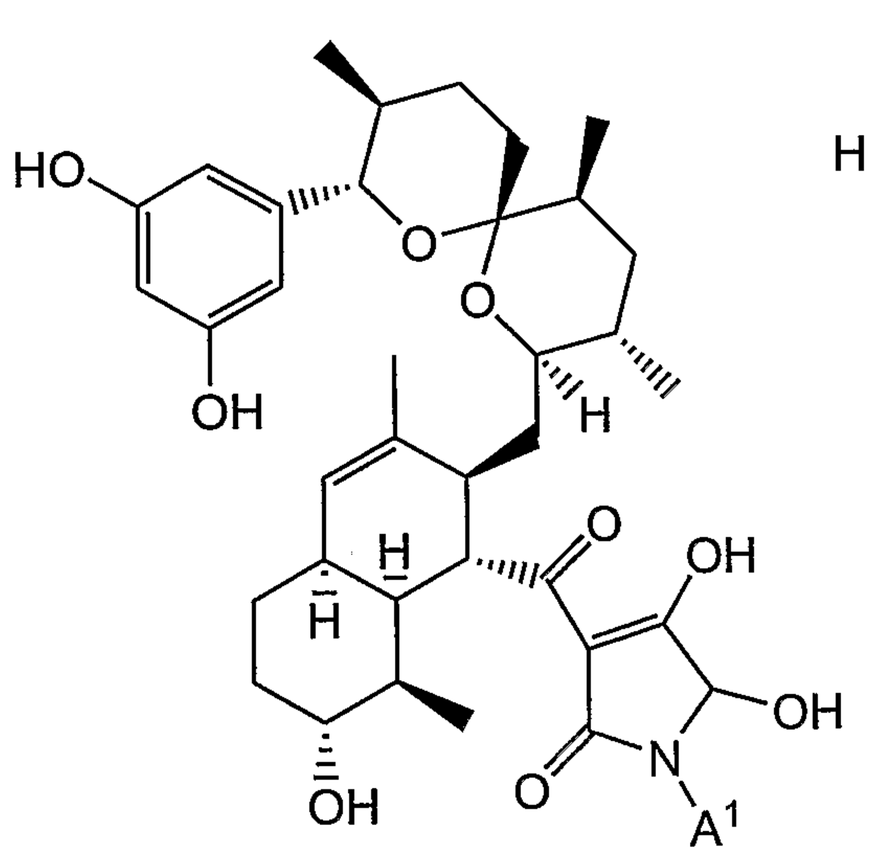


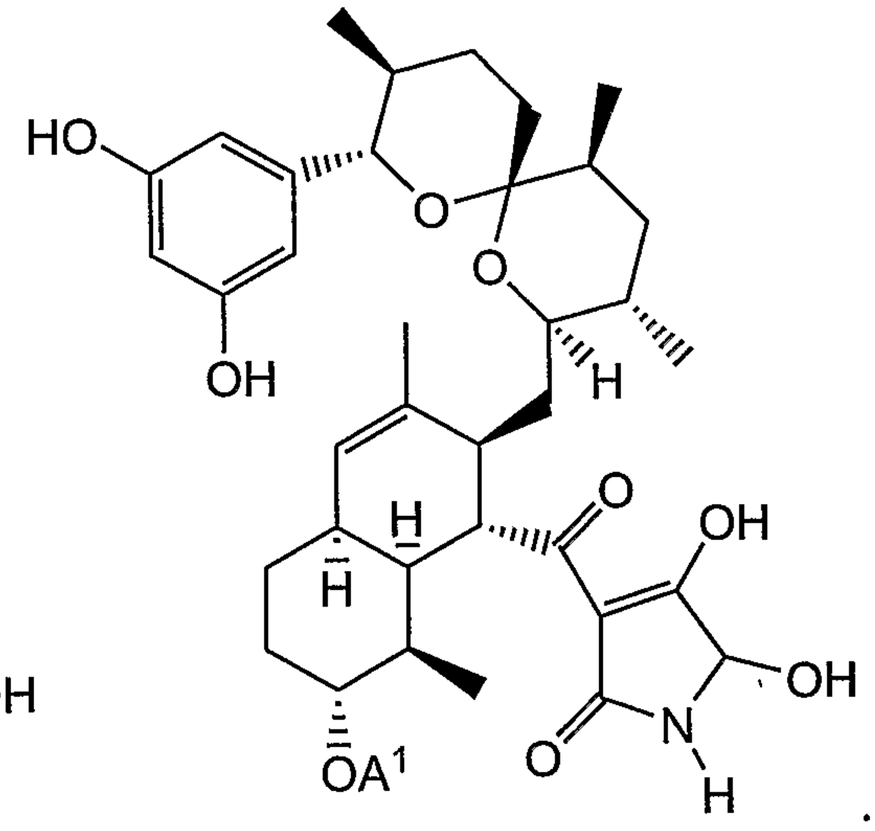


100. An HIV integrase inhibitor compound of claim 99 selected from the Formula XV structures:

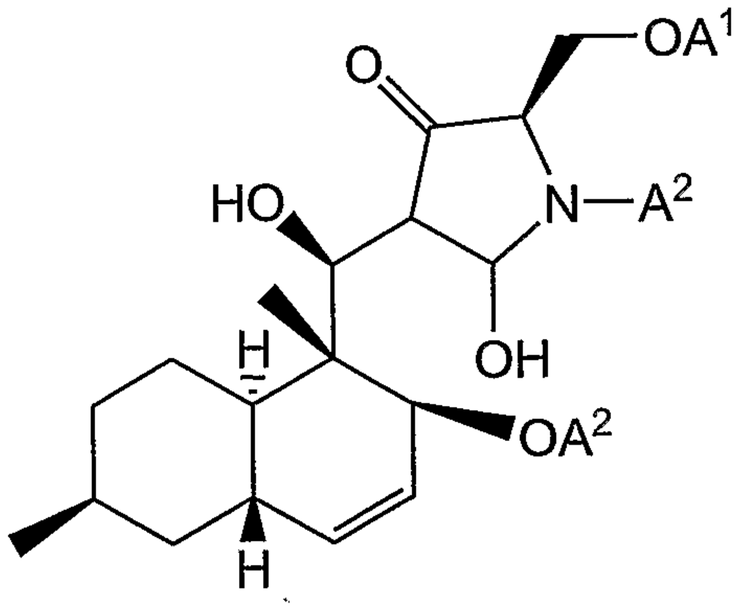


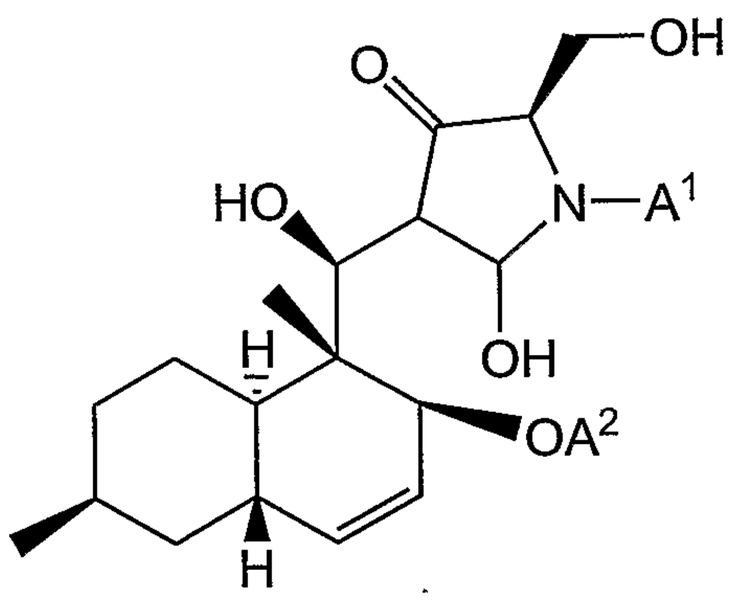


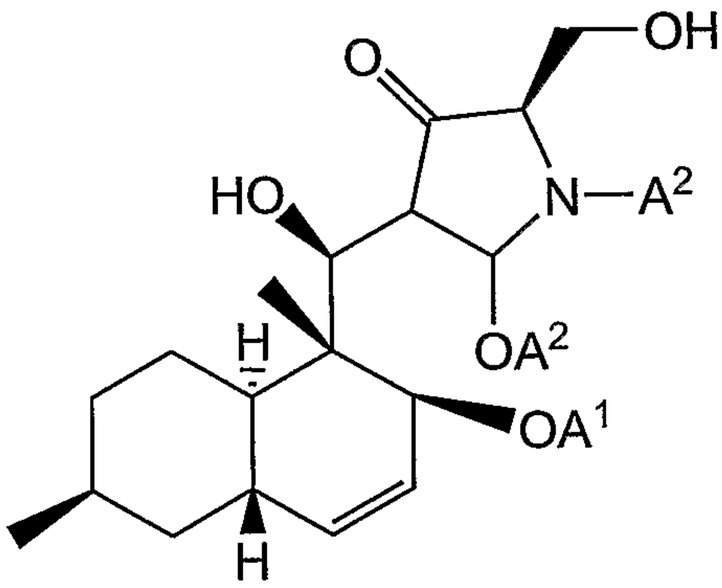


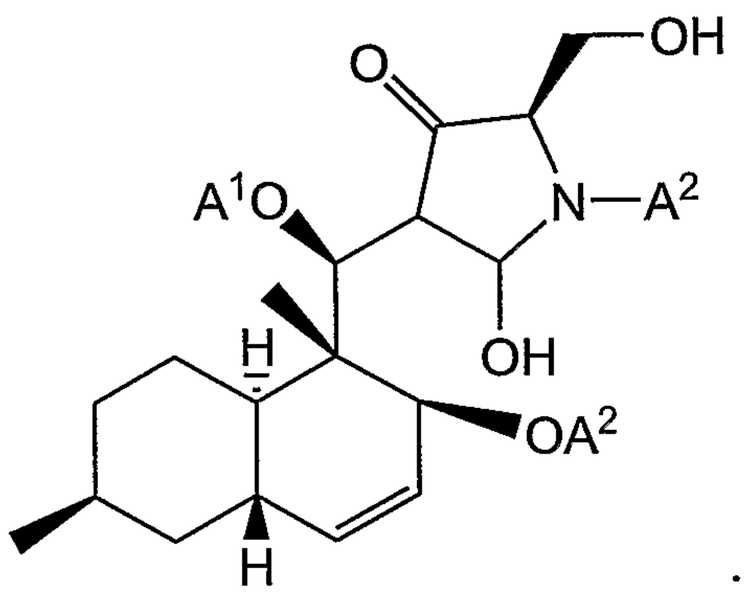


101. An HIV integrase inhibitor compound of claim 99 selected from the Formula XV structures:

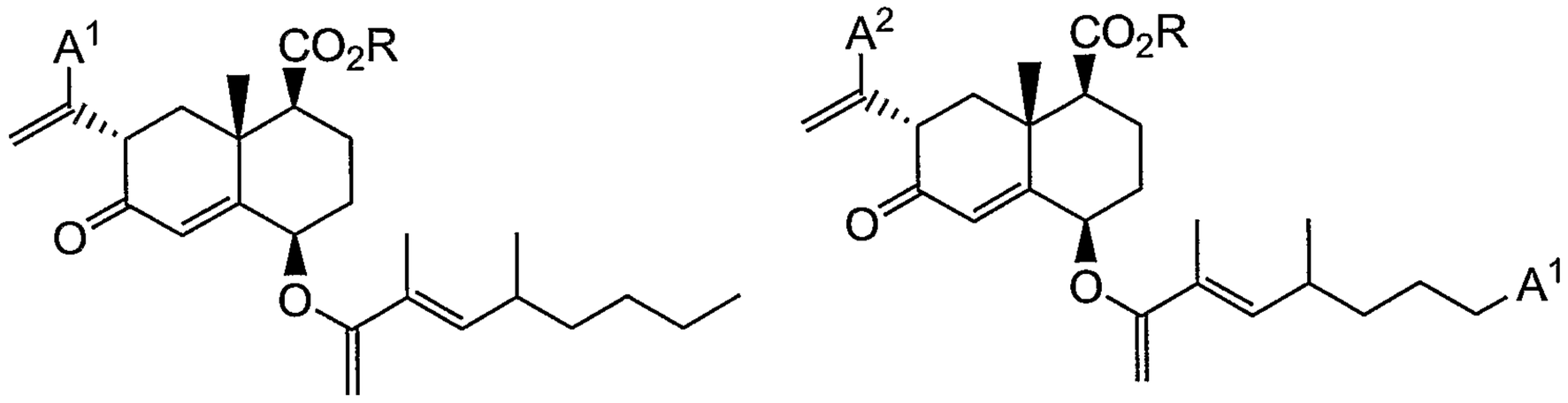


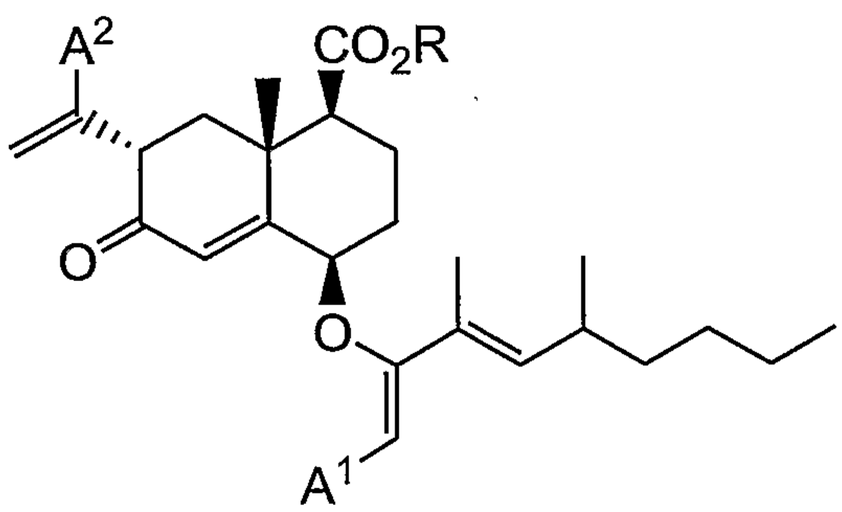


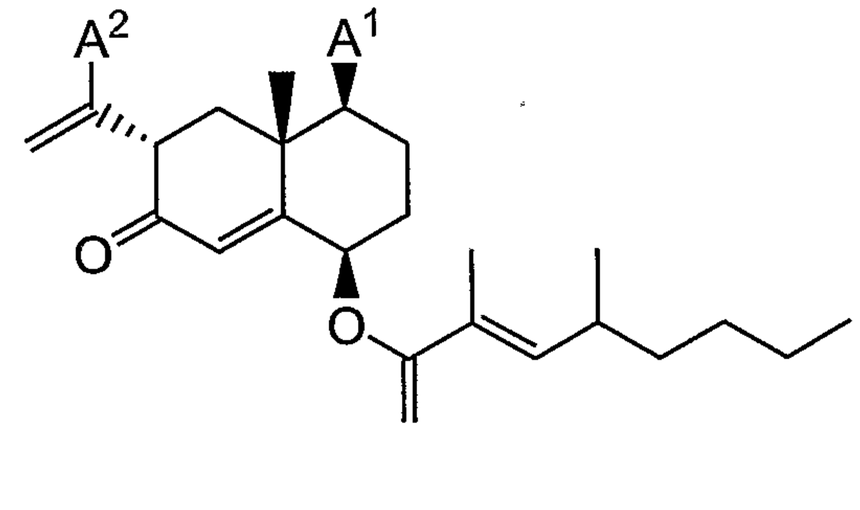




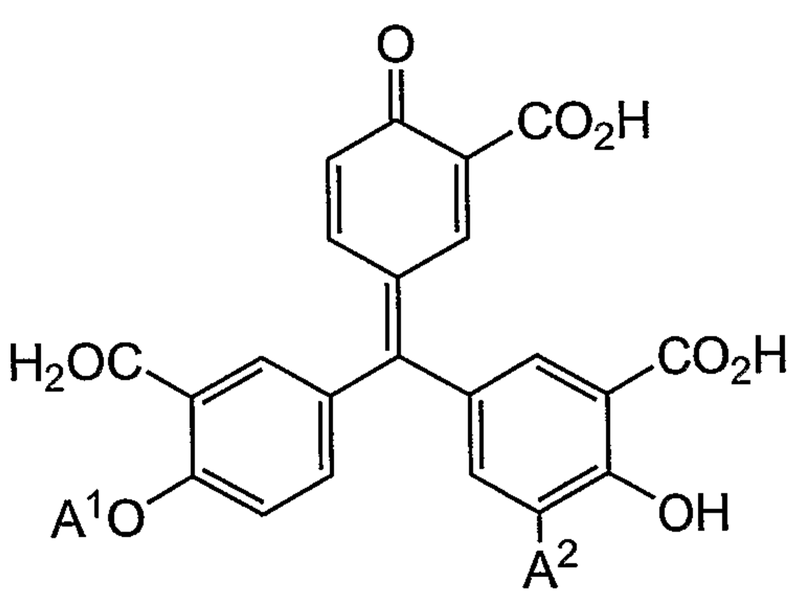
102. An HIV integrase inhibitor compound of claim 2 selected from the Formula XVI structures:

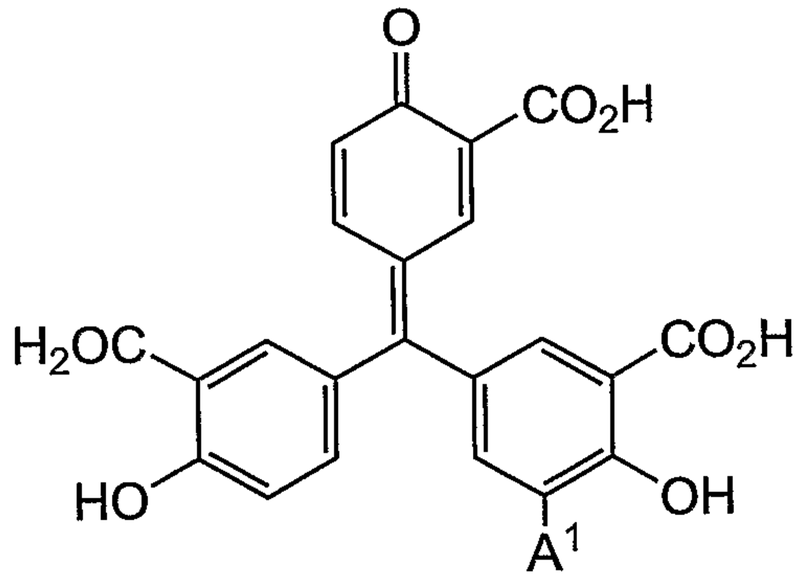


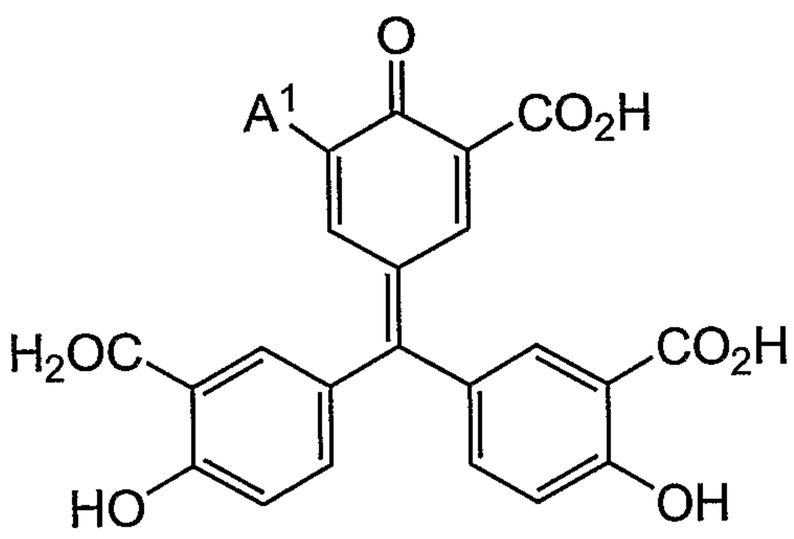


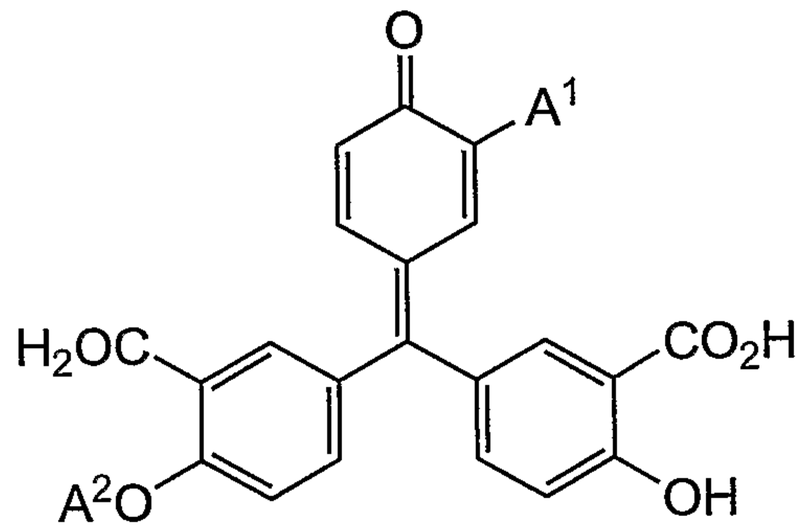


103. An HIV integrase inhibitor compound of claim 2 selected from the Formula XVII structures:

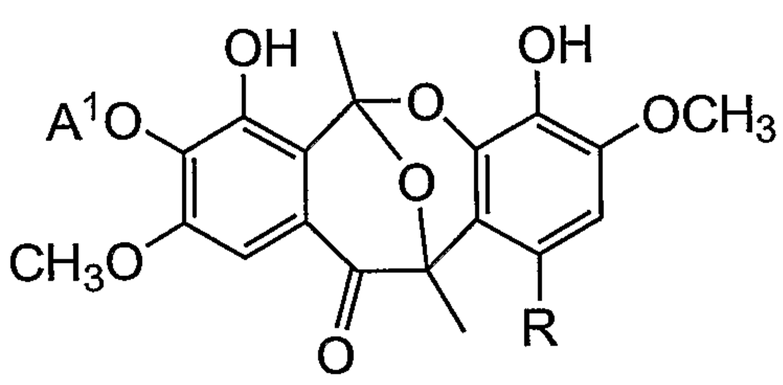


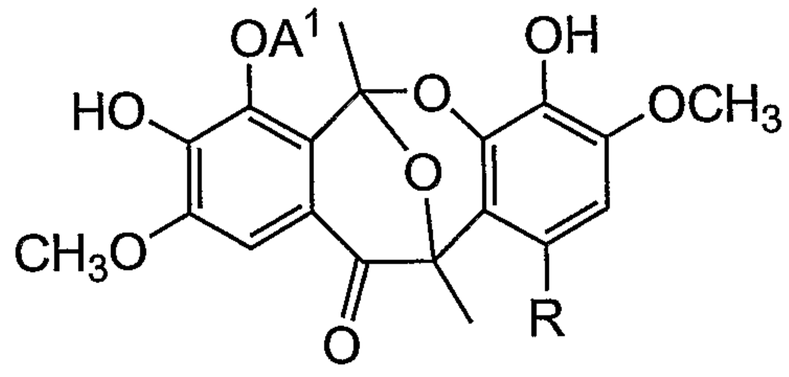


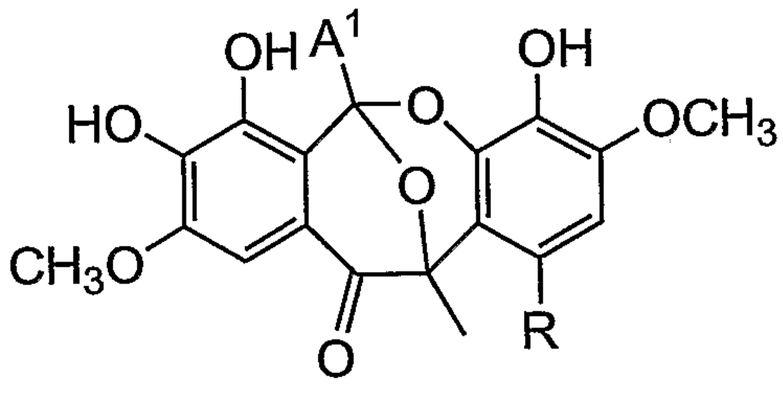


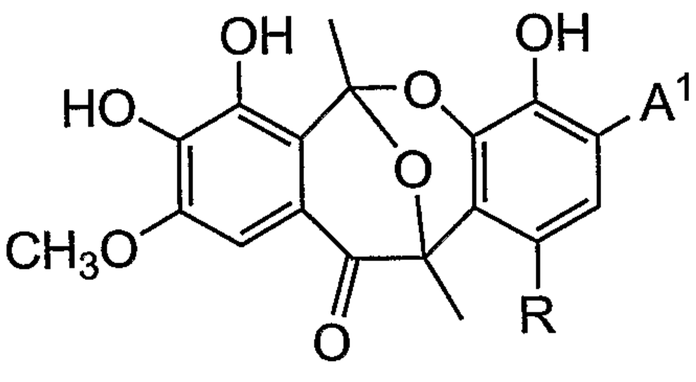


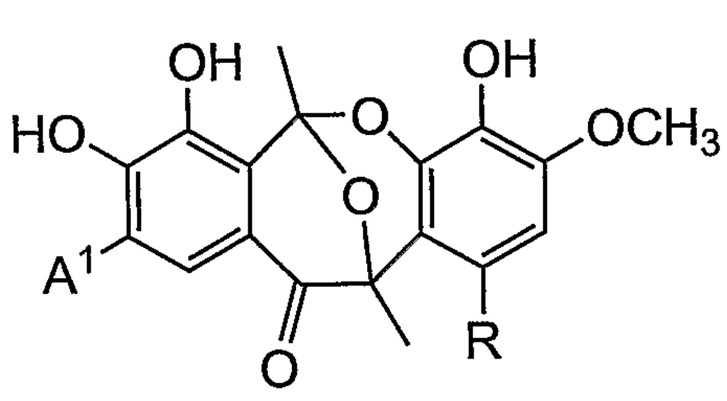
104. An HIV integrase inhibitor compound of claim 2 selected from the Formula XVIII structures:

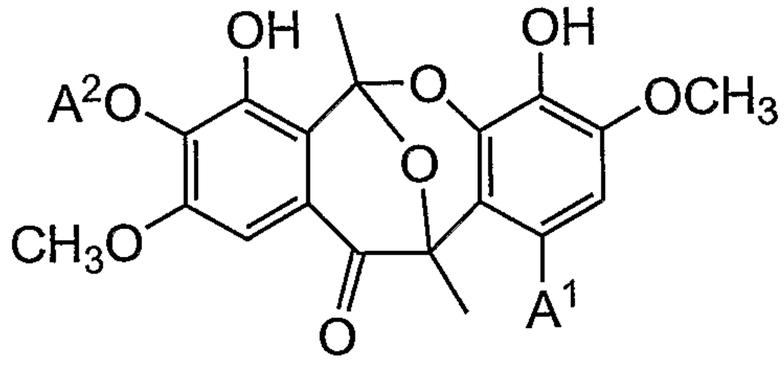




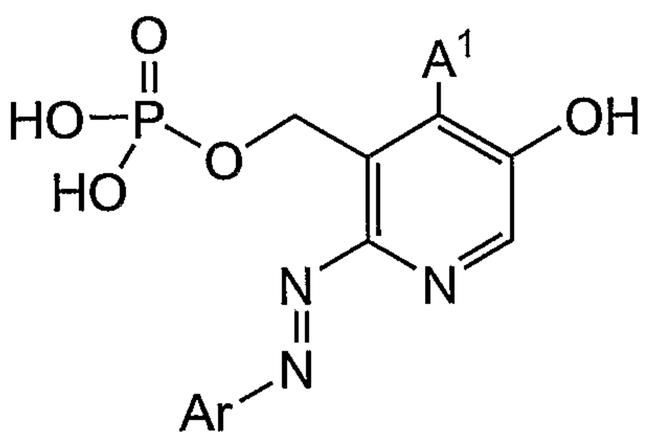


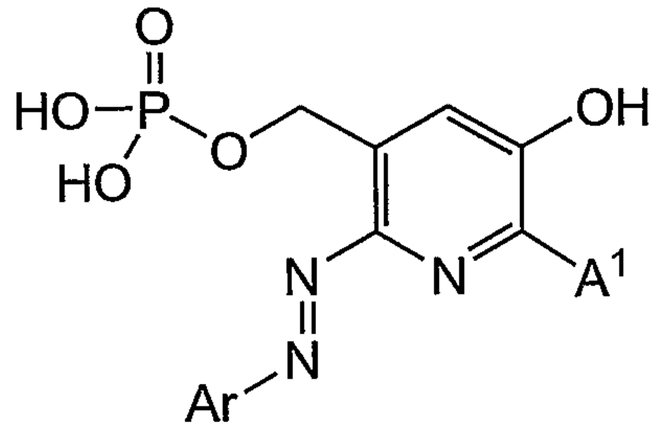


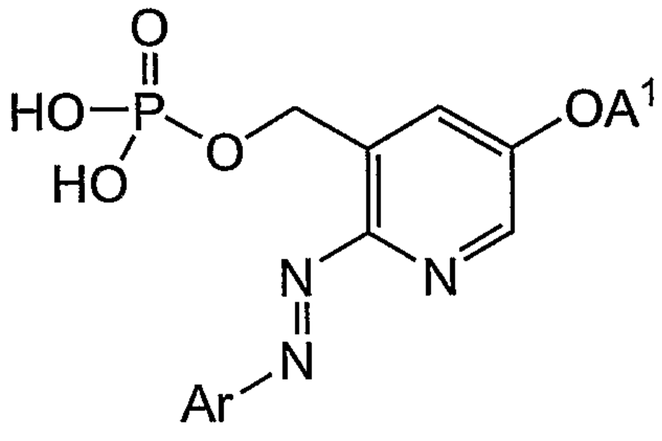


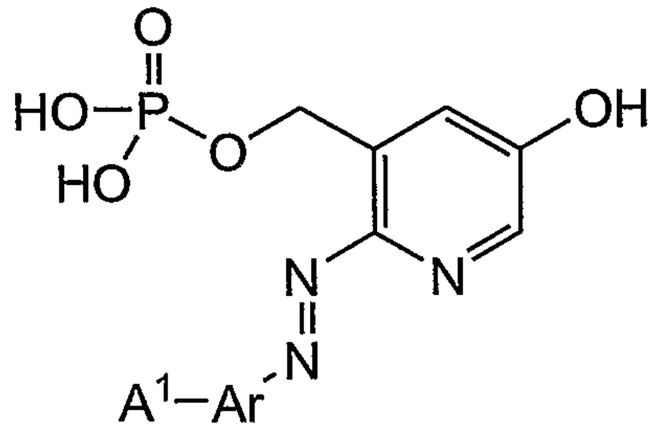


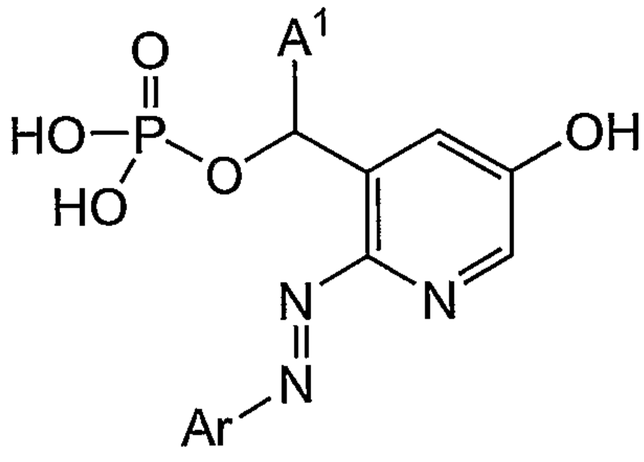
105. An HIV integrase inhibitor compound of claim 2 selected from the Formula XIX structures:

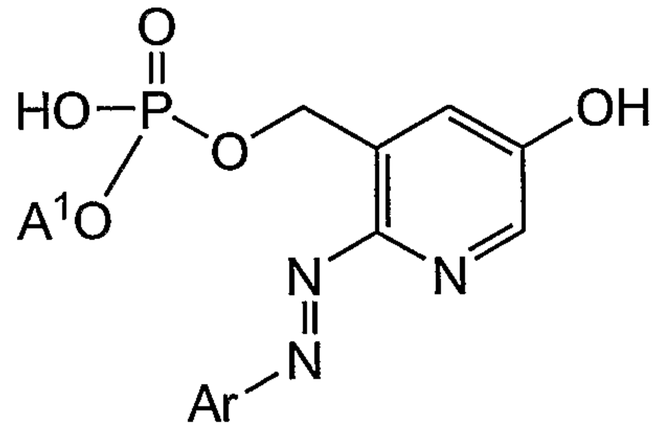




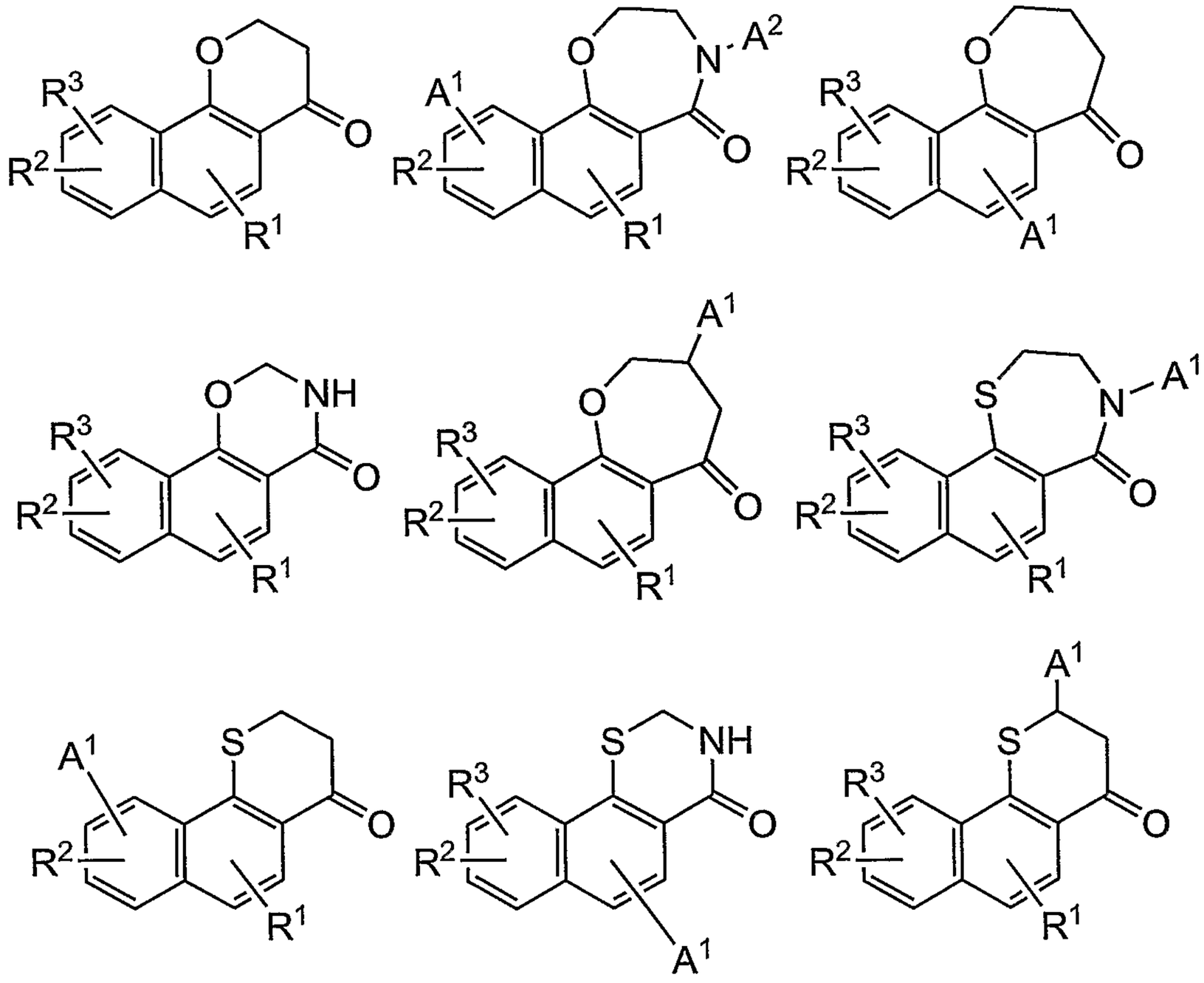








106. An HIV integrase inhibitor compound of claim 2 selected from the Formula XX structures:

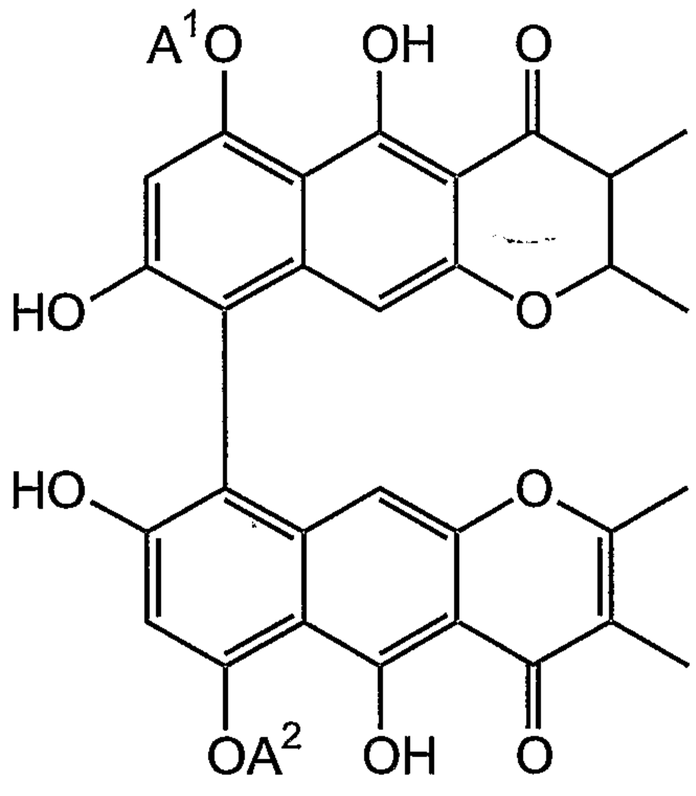


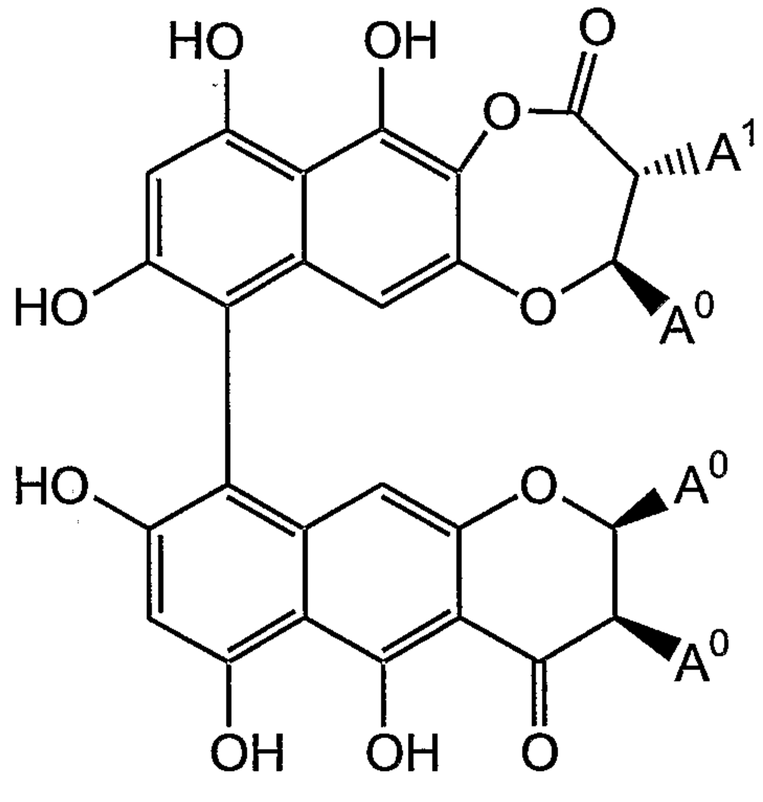
where

R^1 is H, substituted or unsubstituted C1-6 alkyl, halo, NO_2, NH_2, CO_2H, substituted or unsubstituted aryl, optionally benzene-fused 5- or 6-membered aromatic or saturated. heterocyclyl containing 1-3 heteroatoms selected from N, S, and O, substituted or unsubstituted aryl-carbonylamino; and

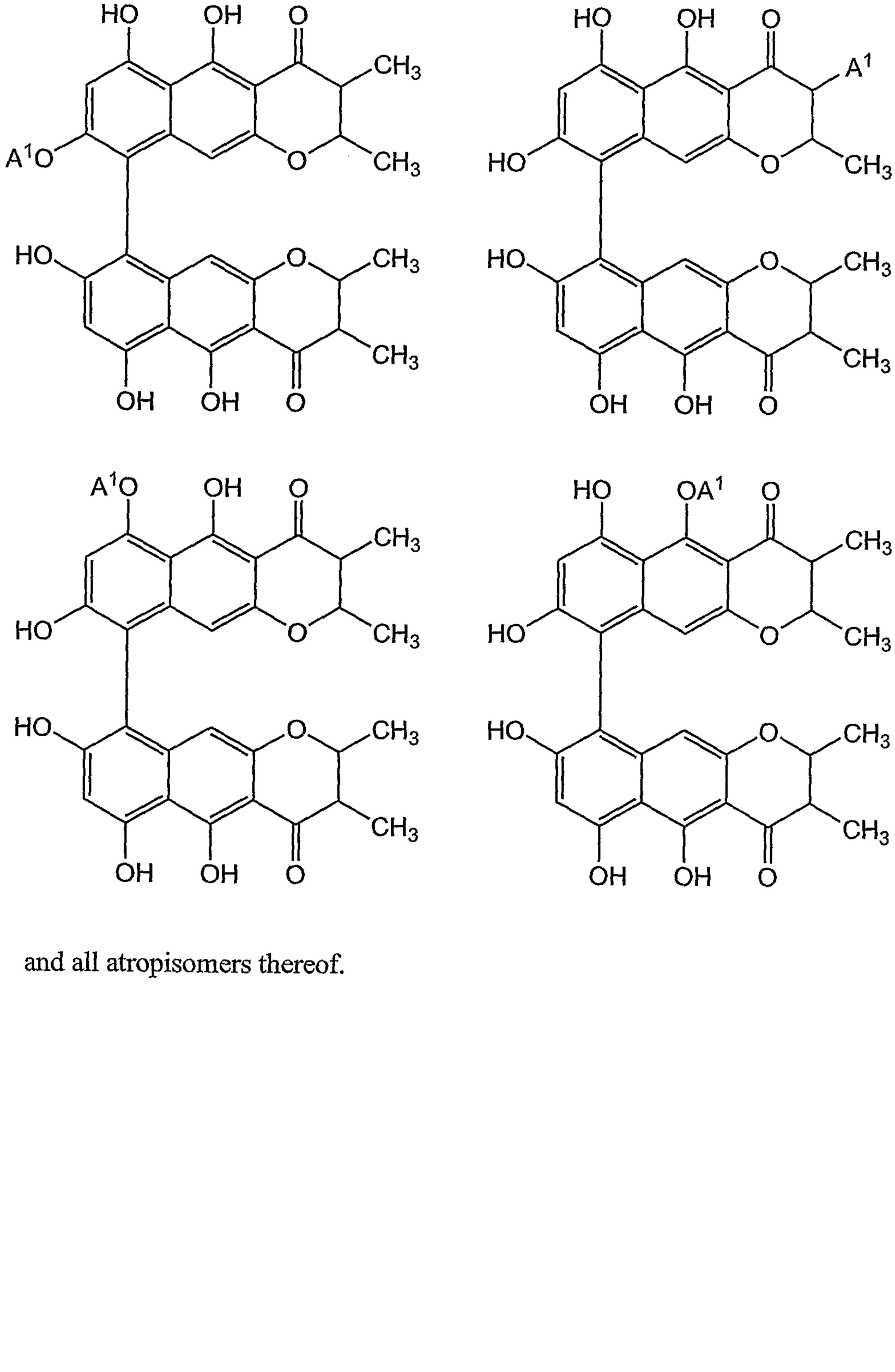
R^2 and R^3 are independently H, C_{1-6} alkyl or alkoxy, halo, NH_2, C_{1-6} alkylamino, di(C1-6 alkyl)amino, NO_2, CN, $CONH_2$, CO_2H, C_{2-7} alkylcarbonylamino, C_{3-13} alkoxycarbonylaminoalkoxy, C_{1-6} aminoalkoxy, C_{3-13} alkylcarbonylaminoalkoxy.

107. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXI structures:



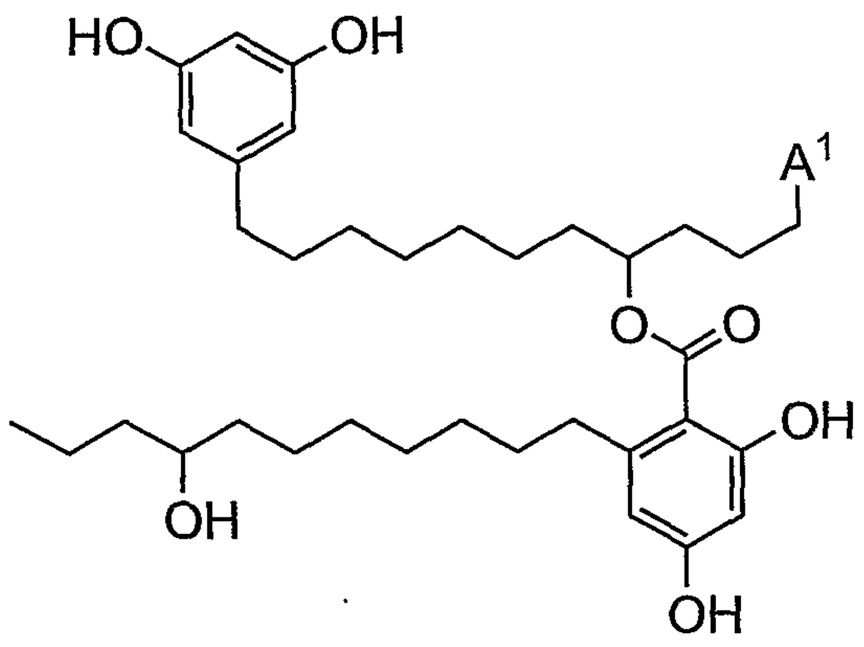
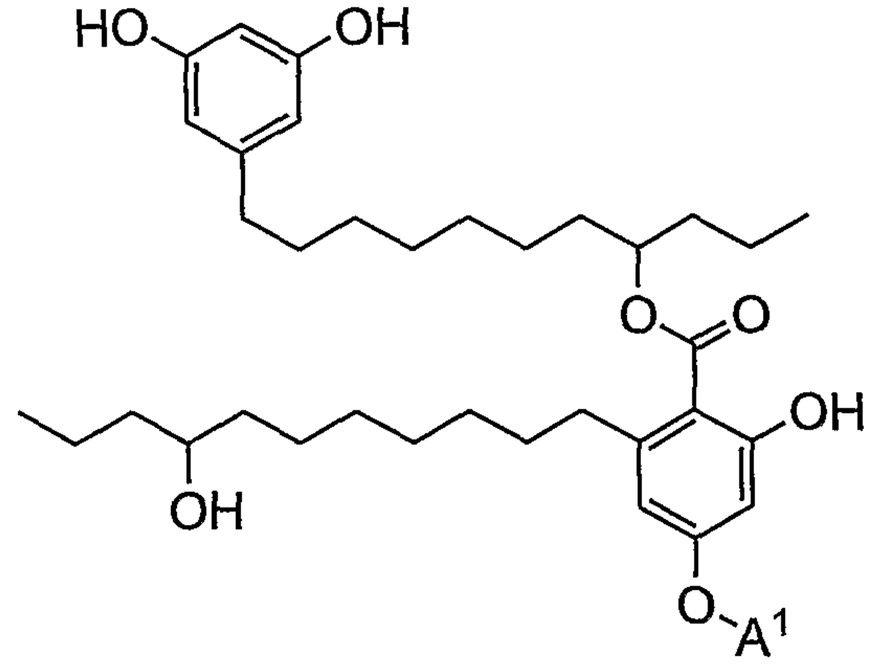
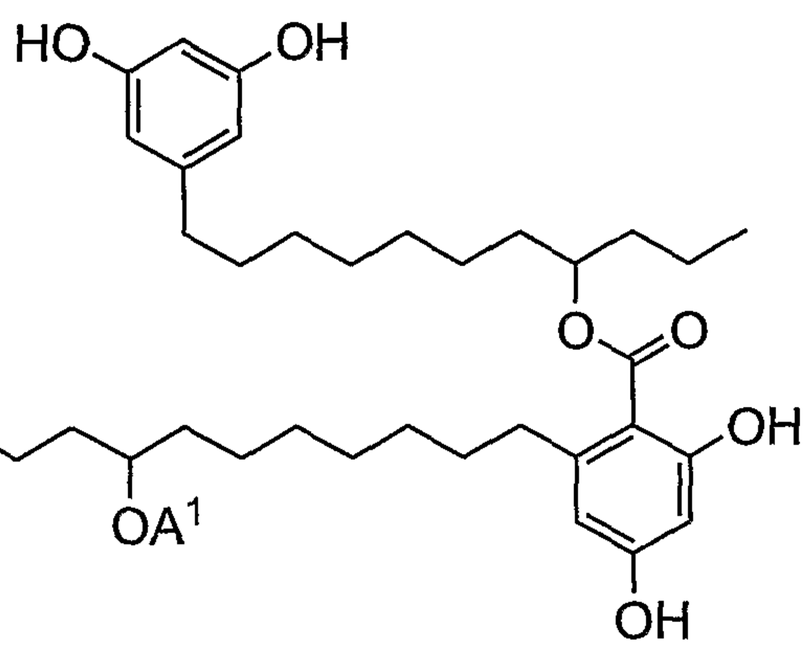
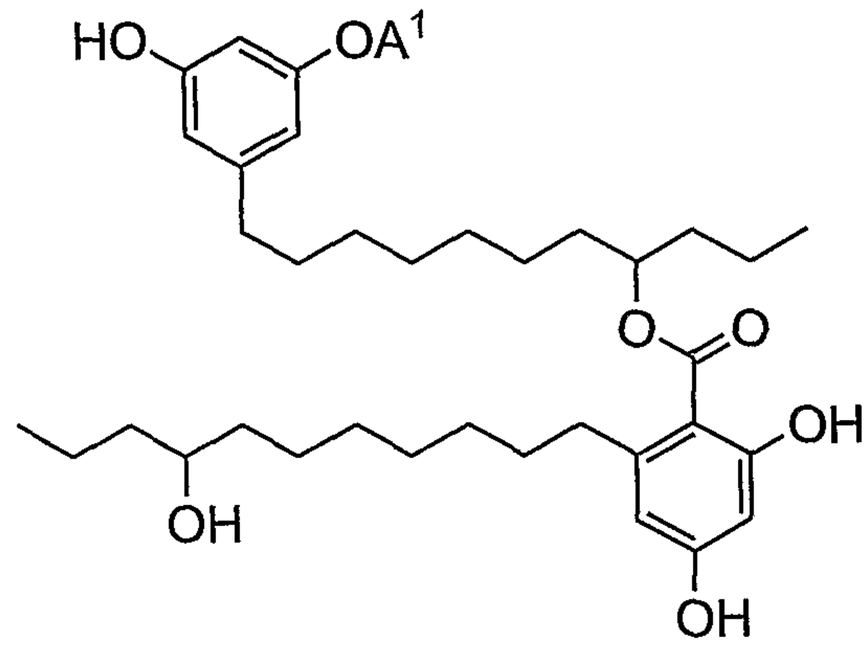


108. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXI structures:



and all atropisomers thereof.

109. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXII structures:

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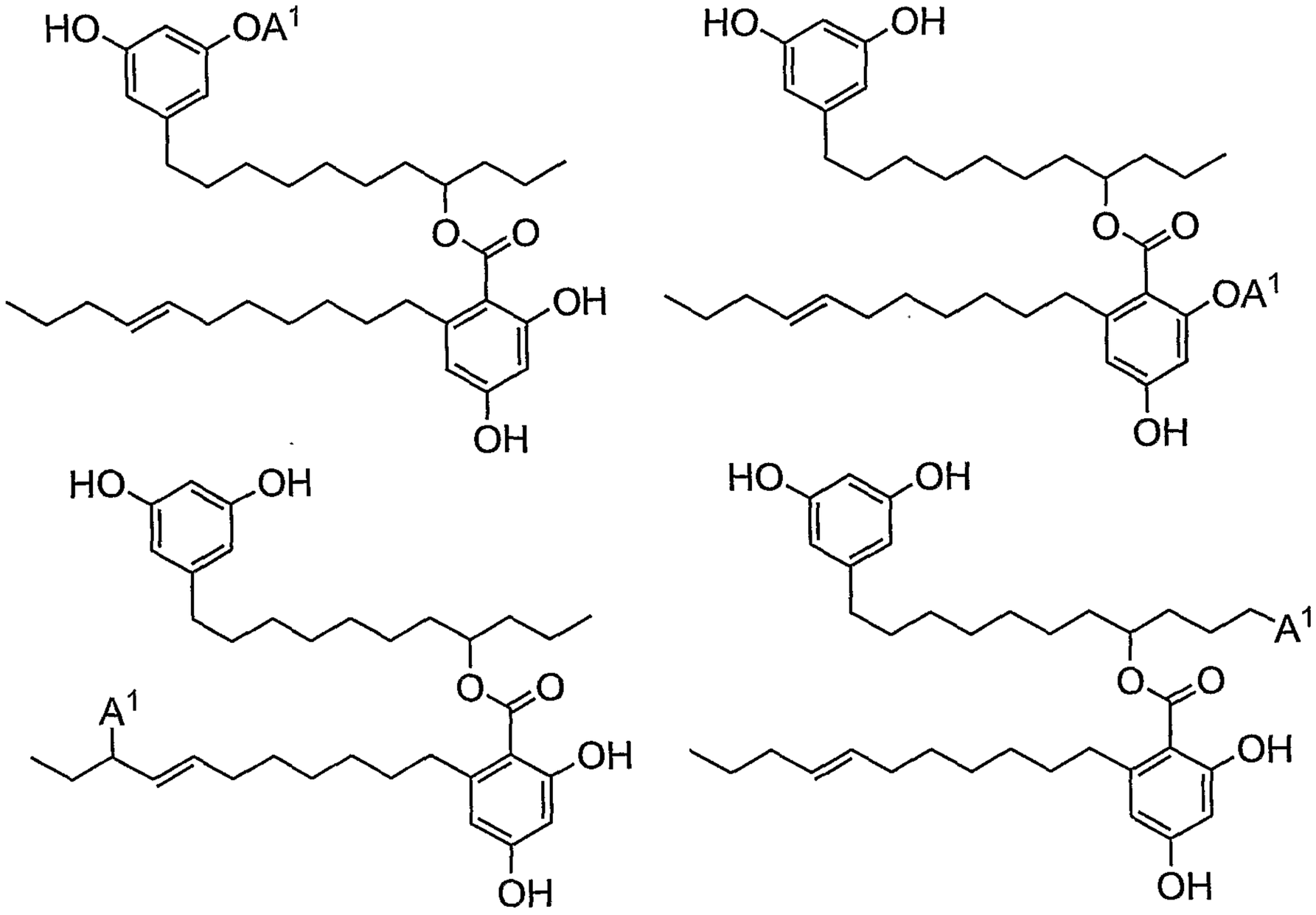
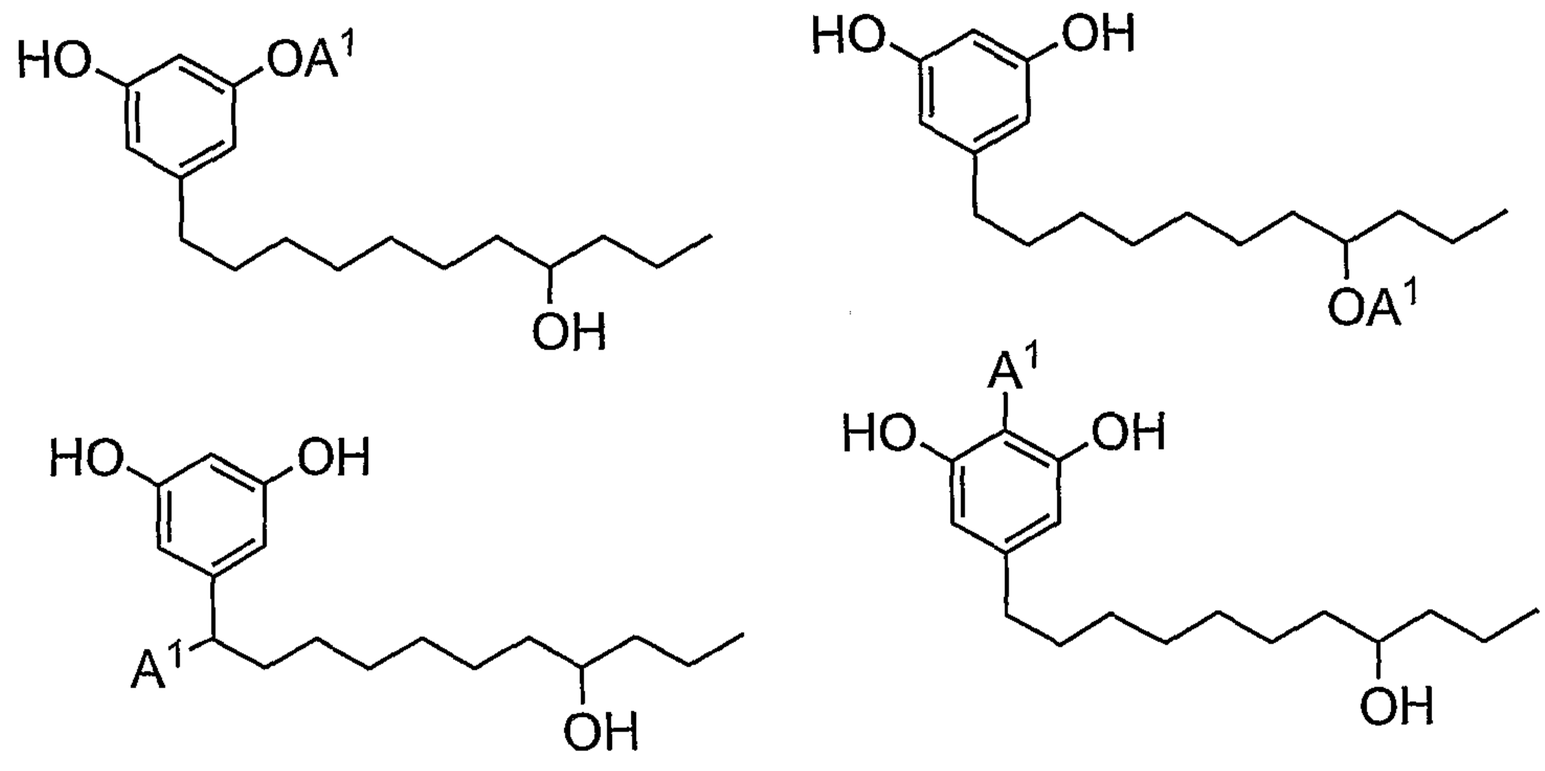
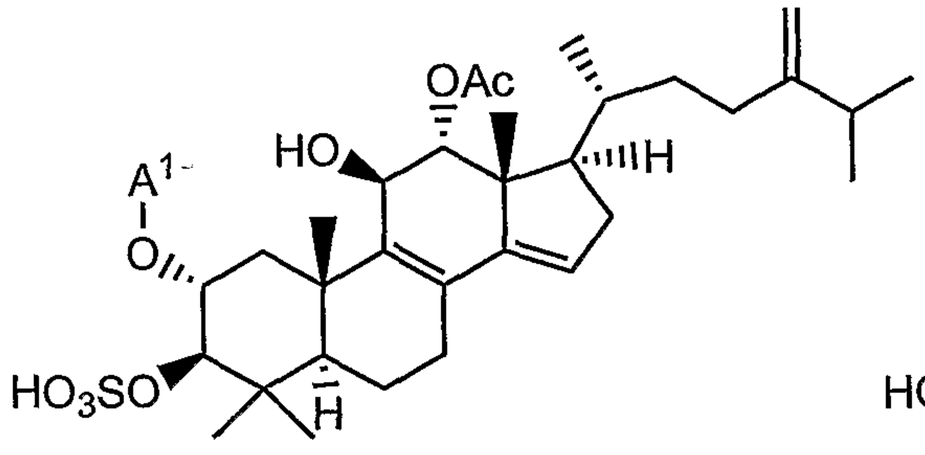
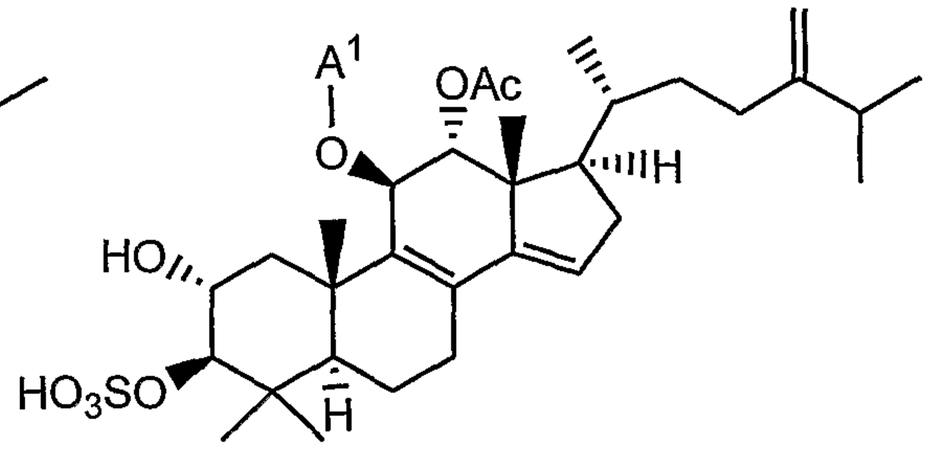
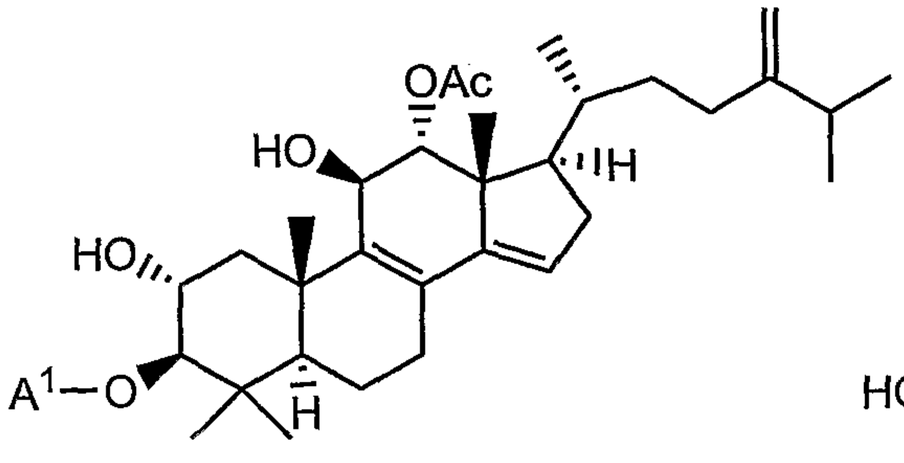
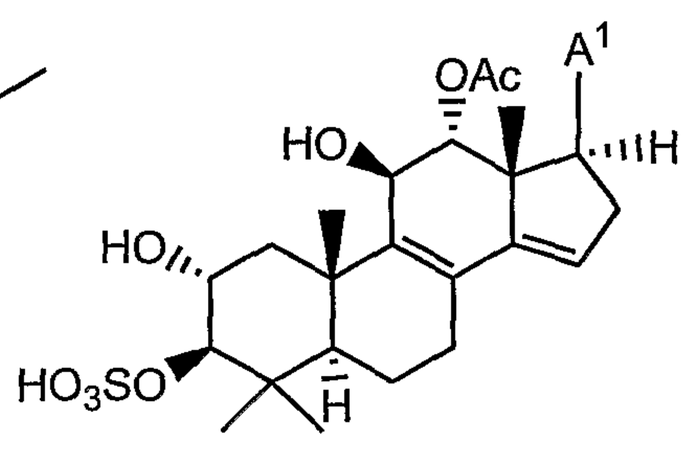
110. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXII structures:



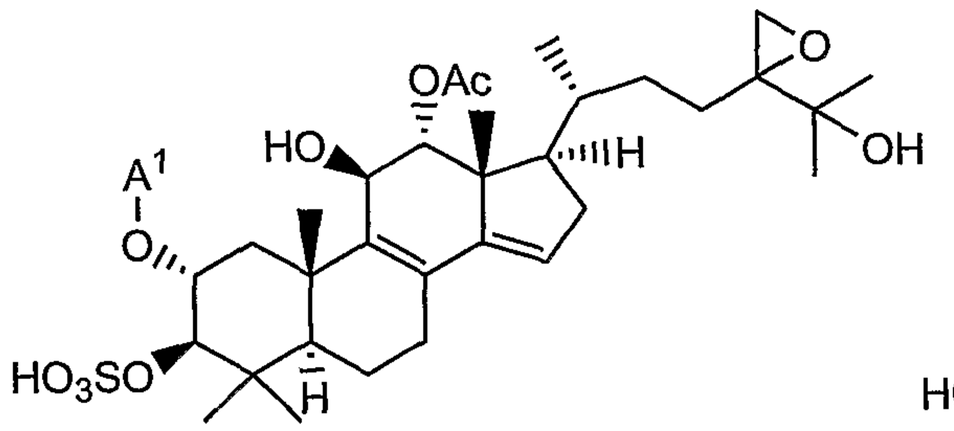
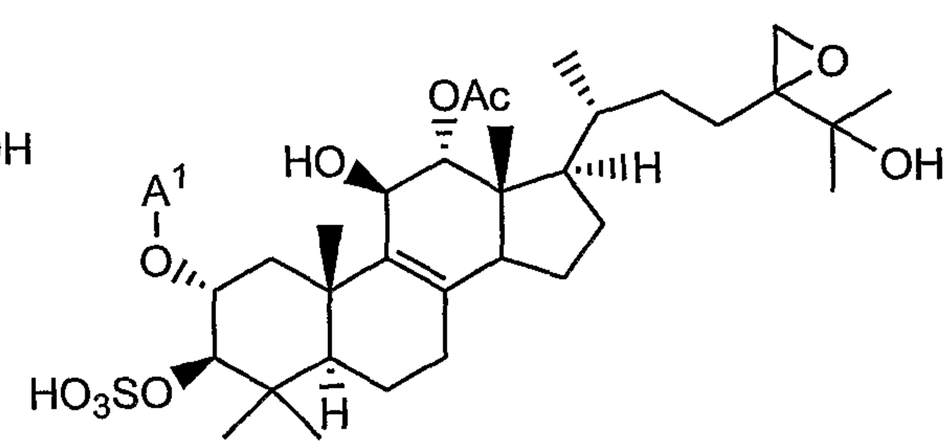
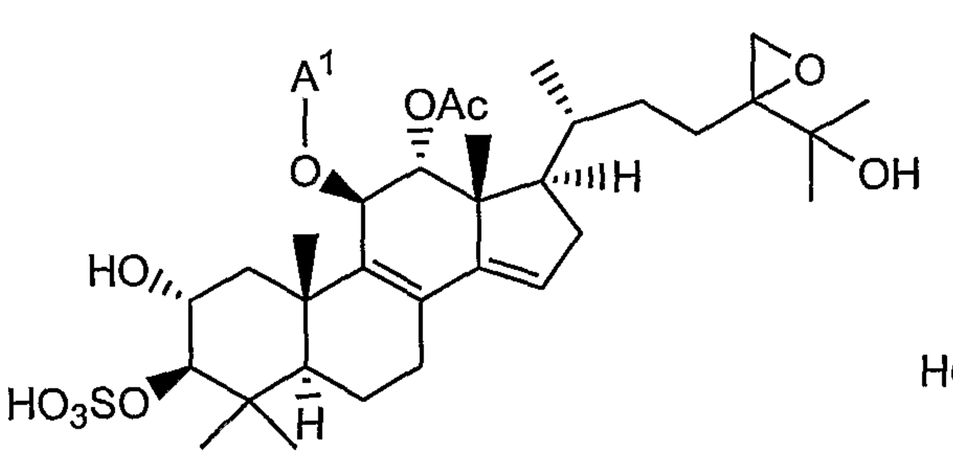
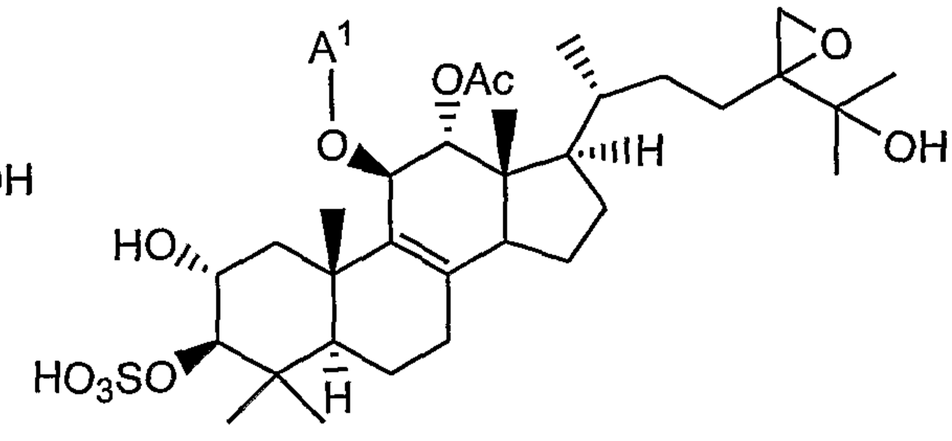
111. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXII structures:



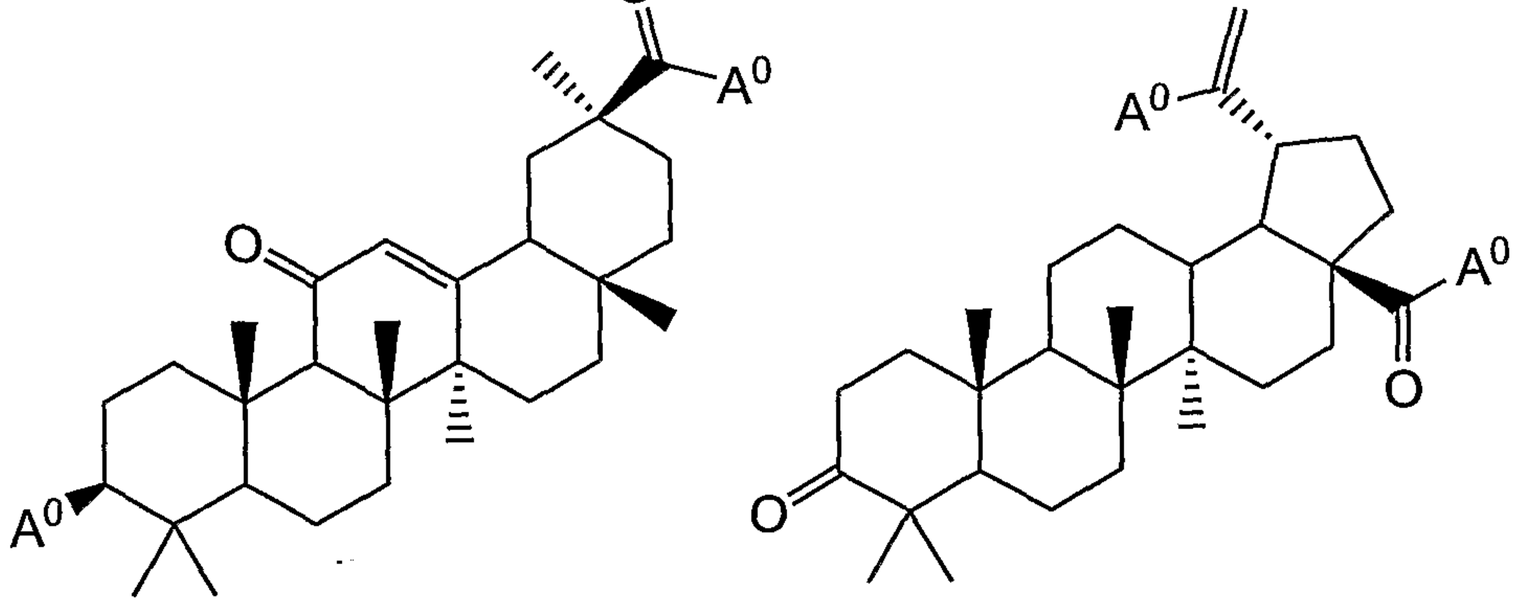
112. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXIII structures:

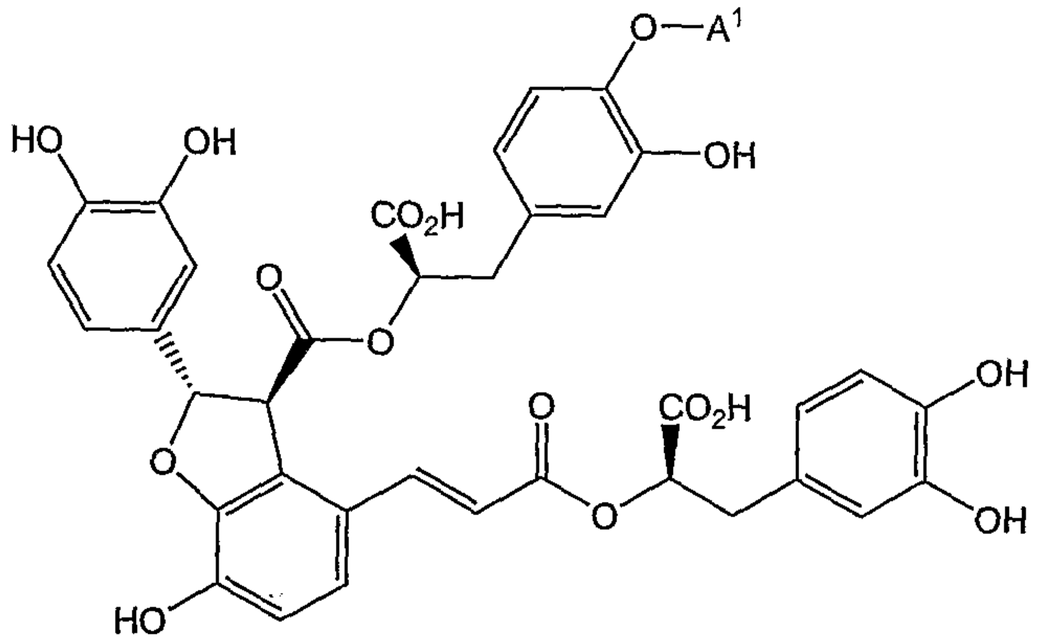
113. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXIII structures:

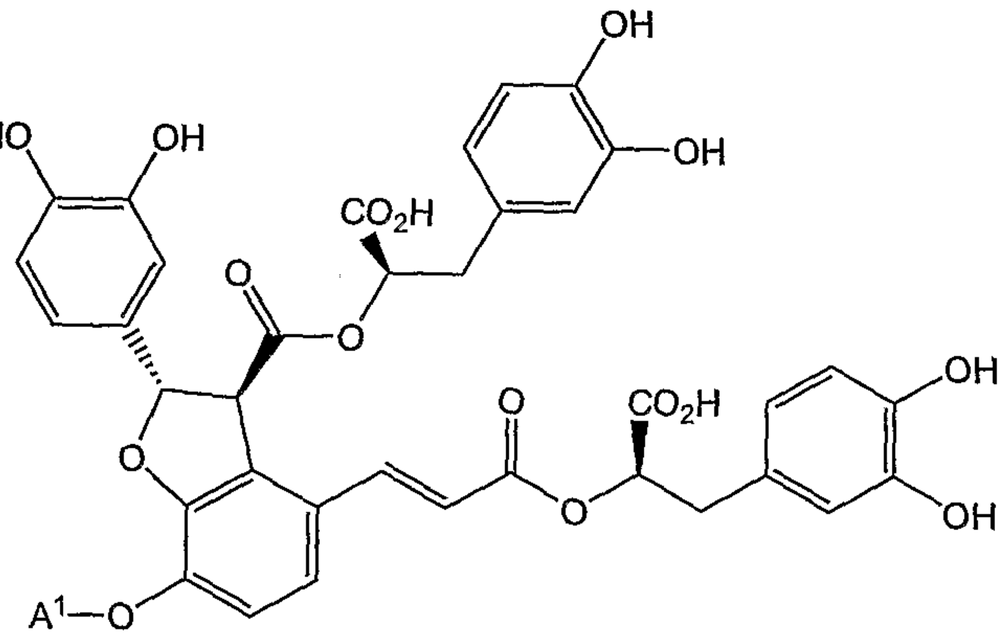





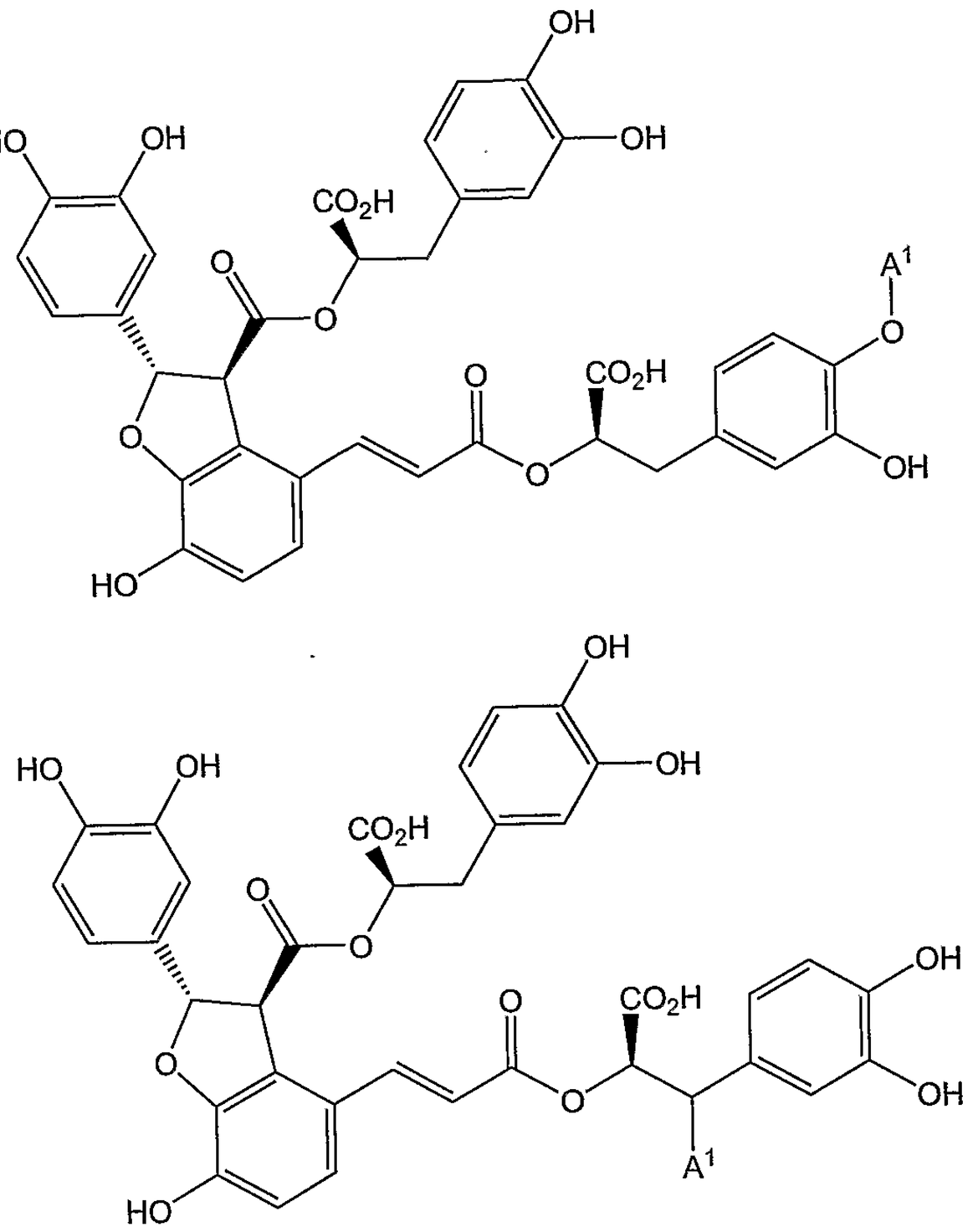
114. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXIV structures:



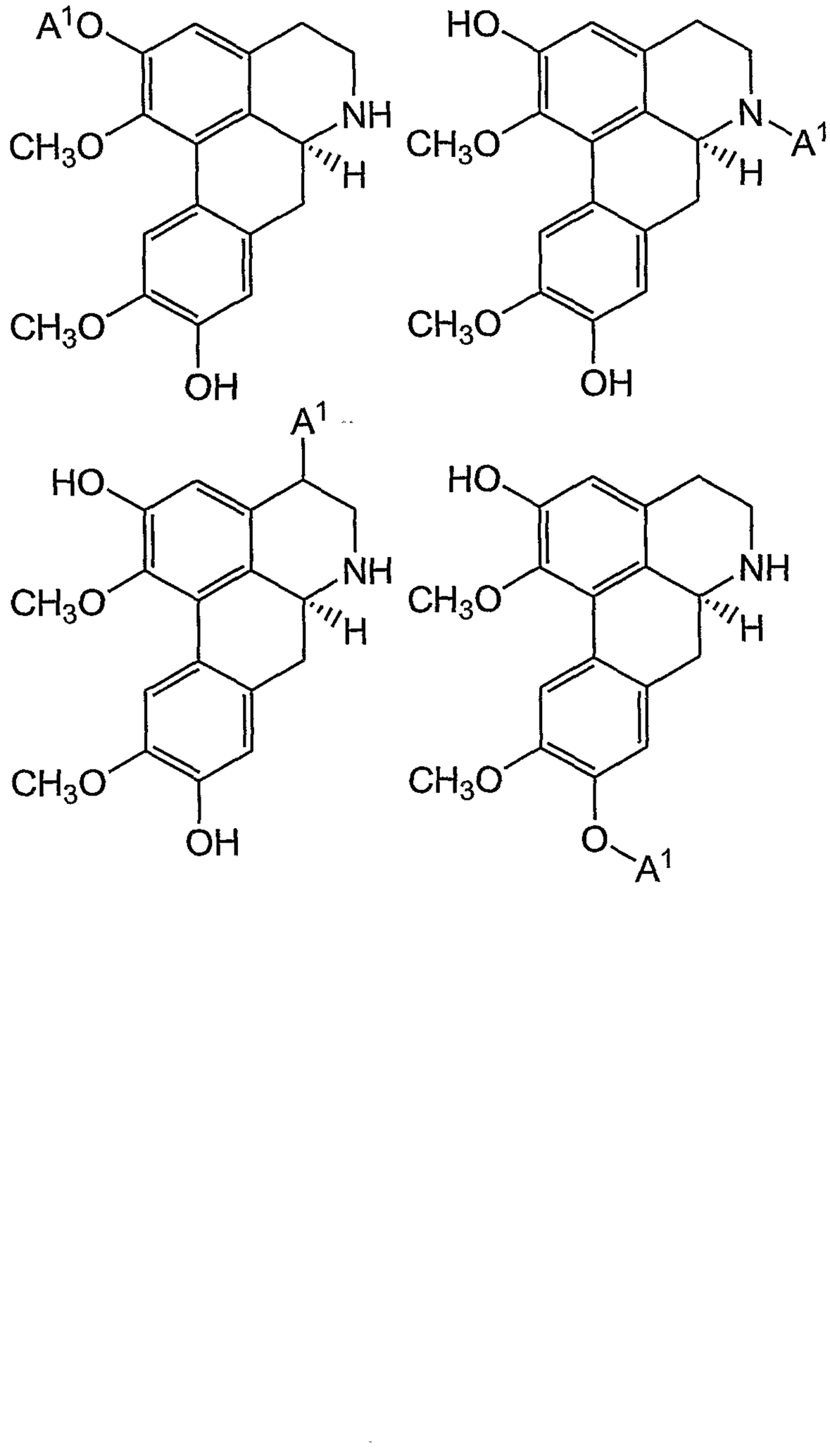
115. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXIV structures:



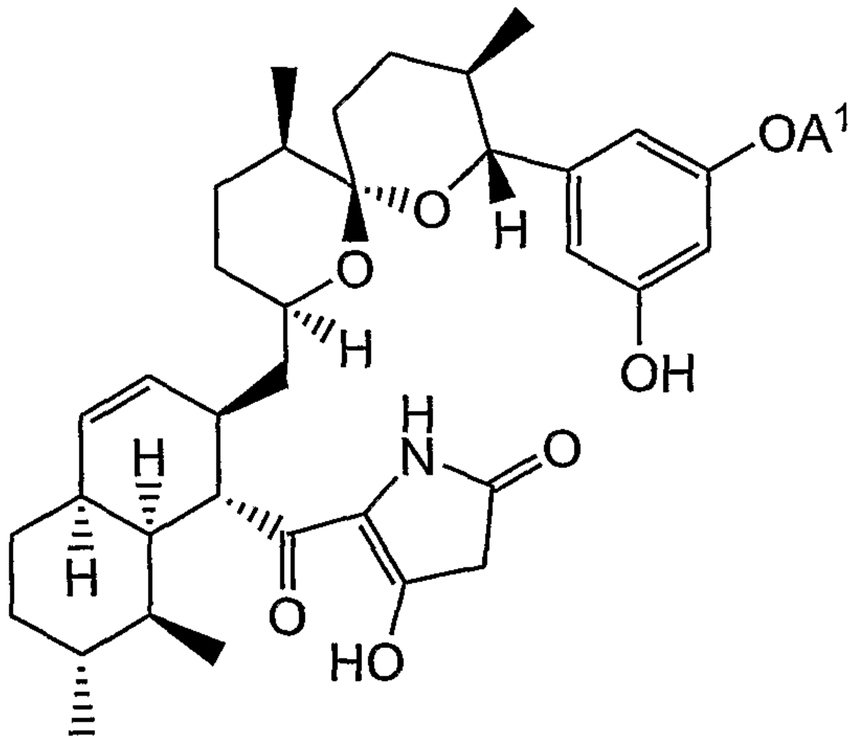


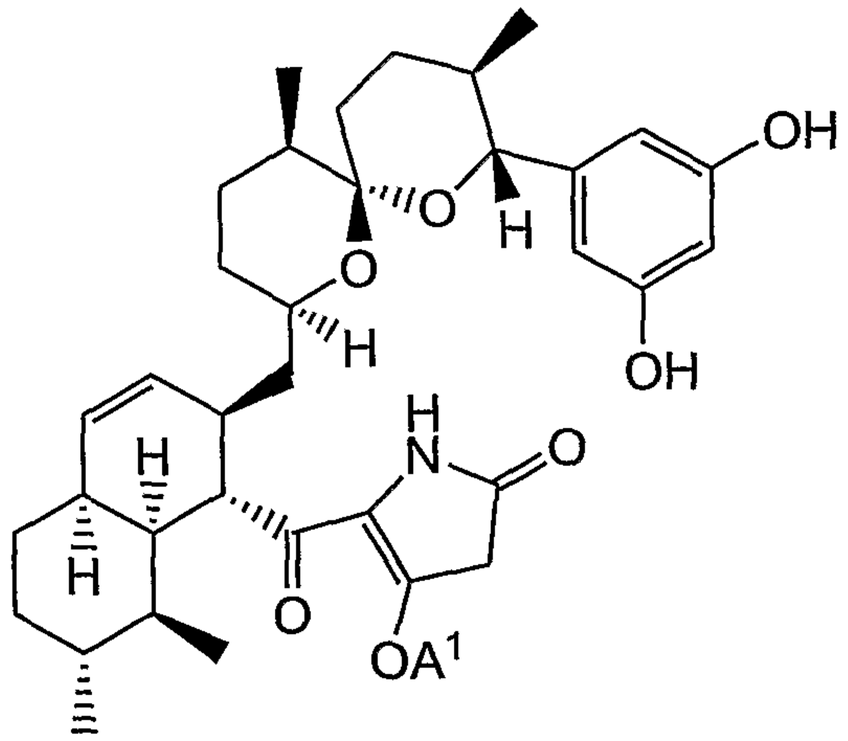

HO
OH
CO2H
O
O
O
O
CO2H
A1
O
OH
HO
OH
OH
HO
OH
CO2H
O
O
O
O
CO2H
OH
OH
A1
HO

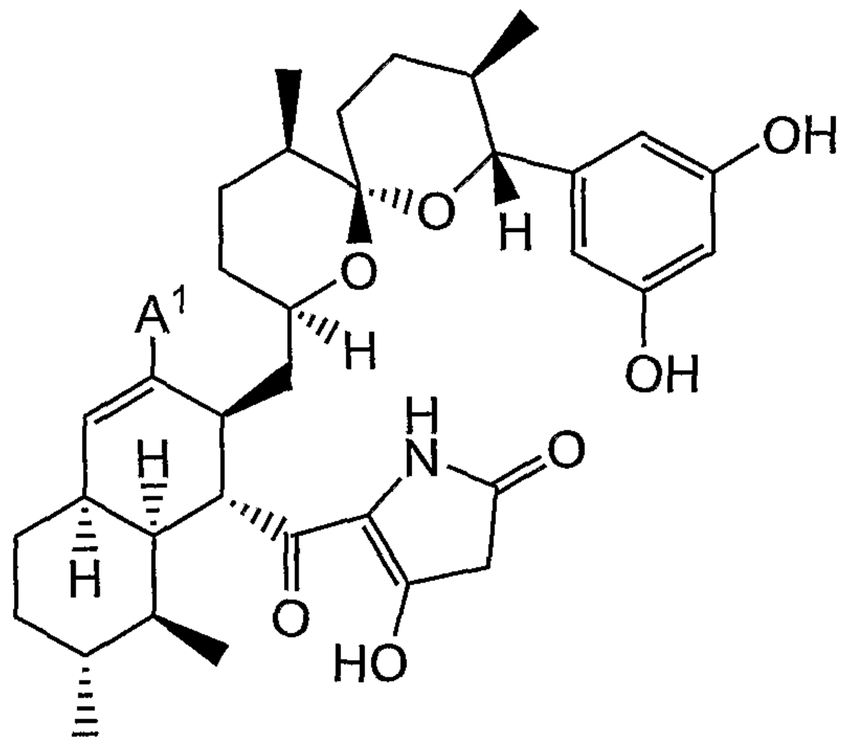
116. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXIV structures:

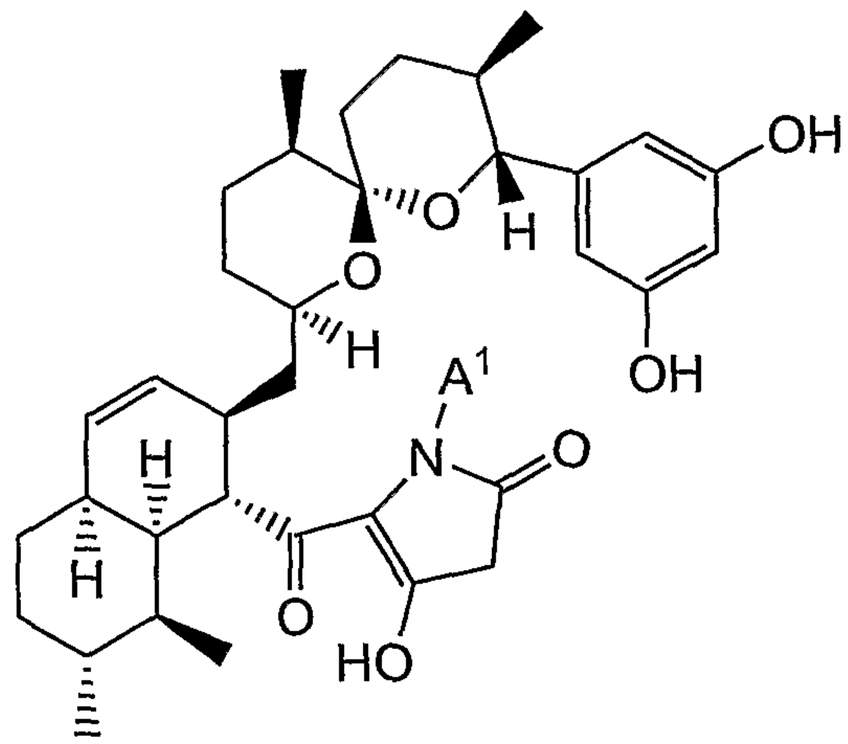


117. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXV structures:

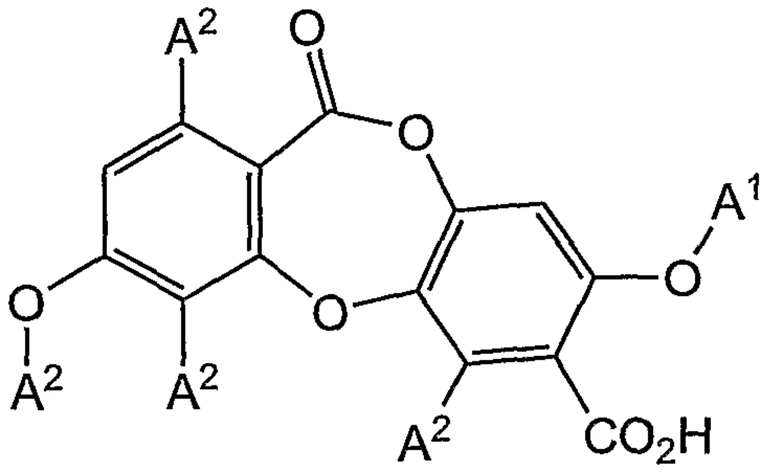


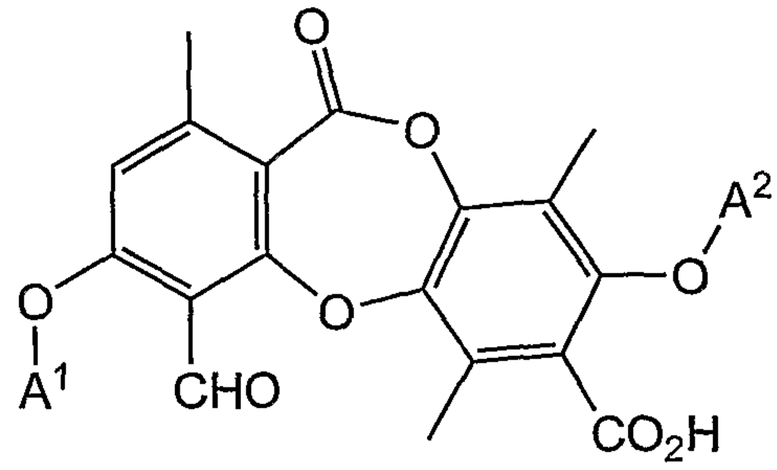


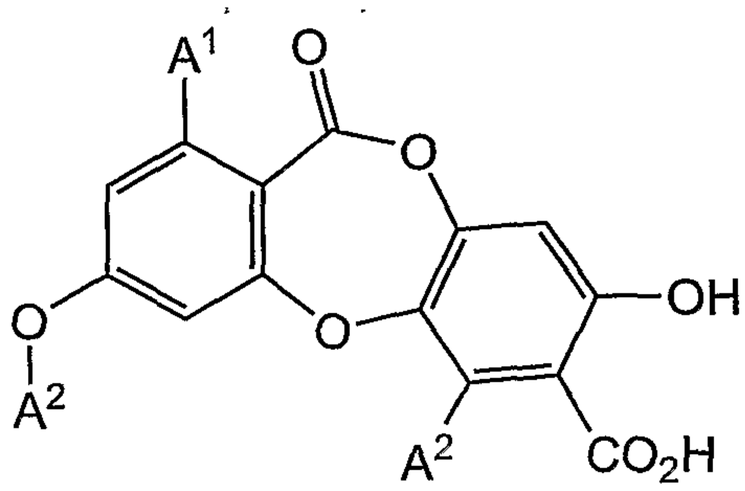


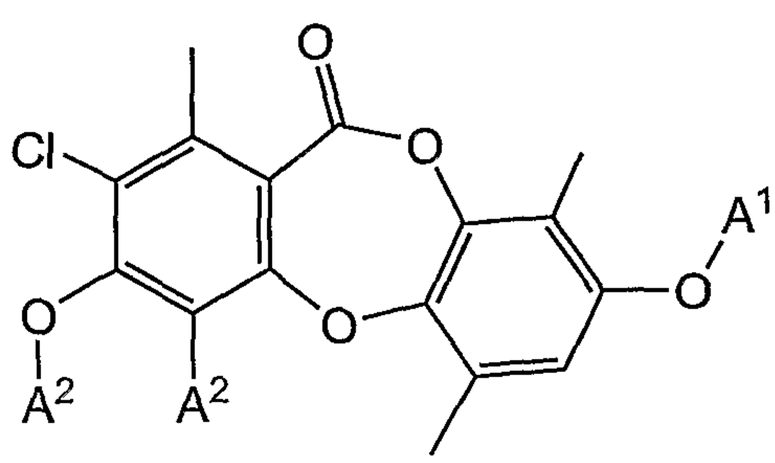


118. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXVI structures:

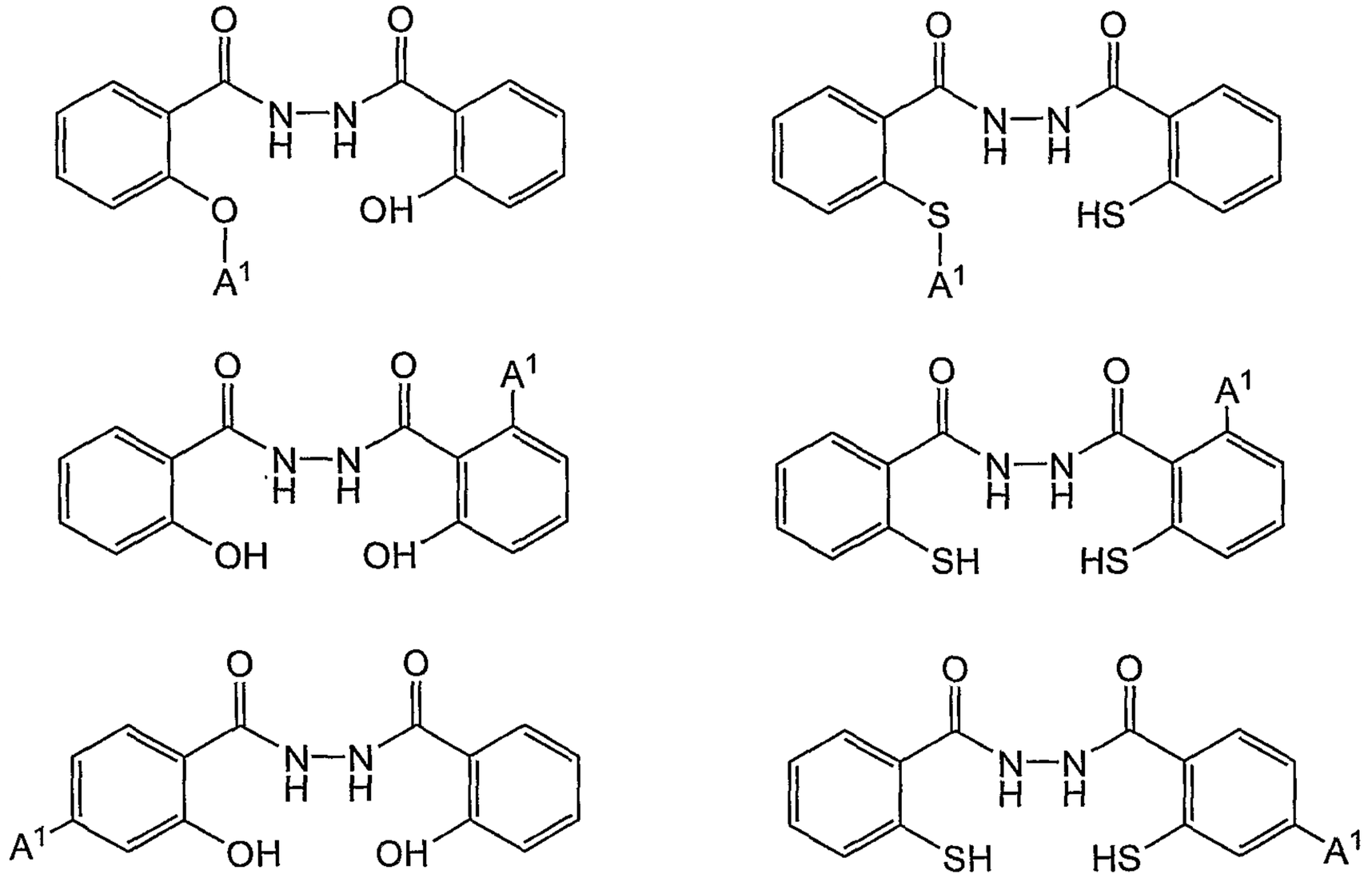






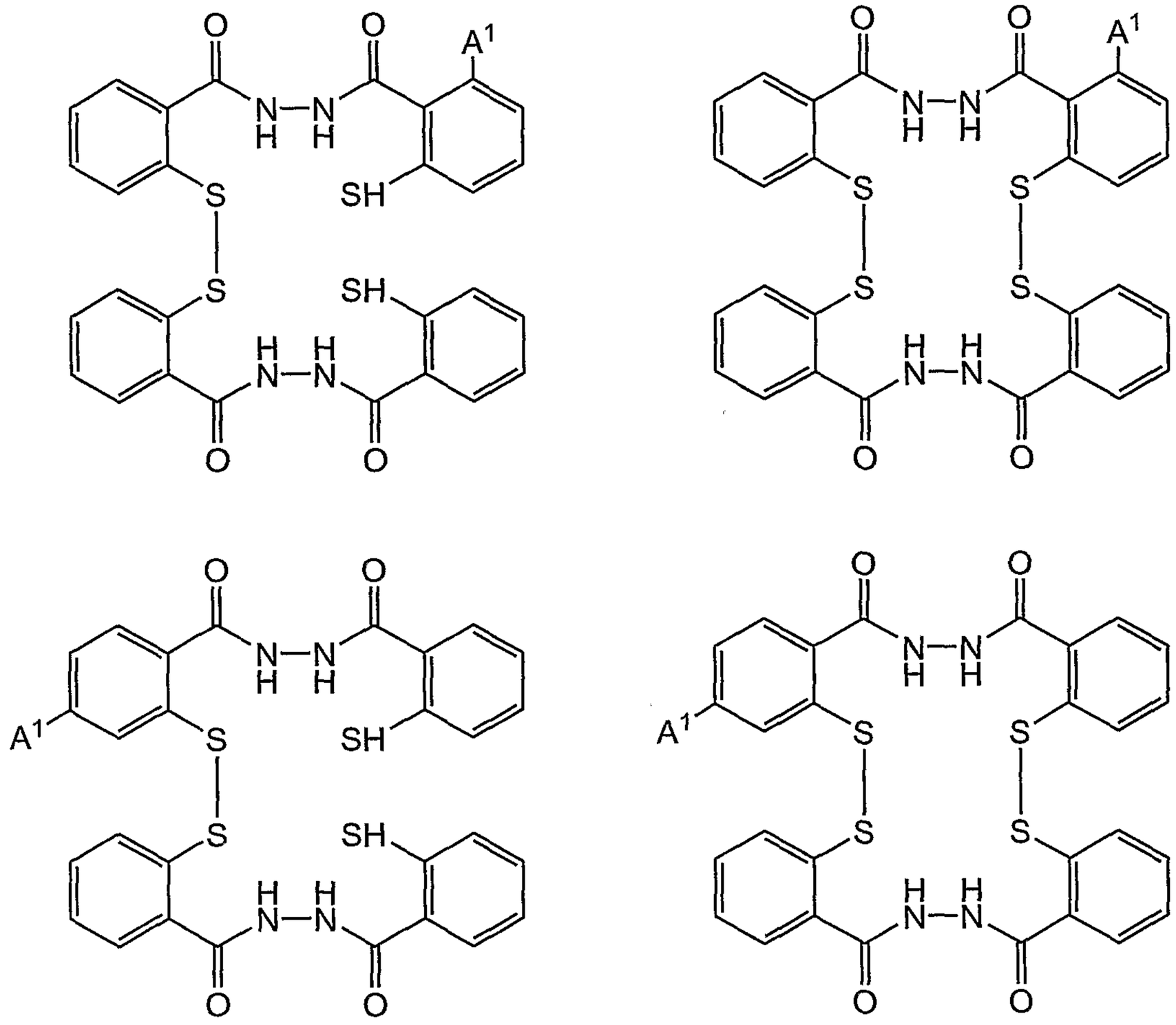


119. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXVI structures:



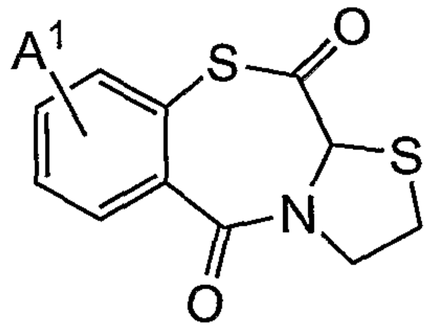
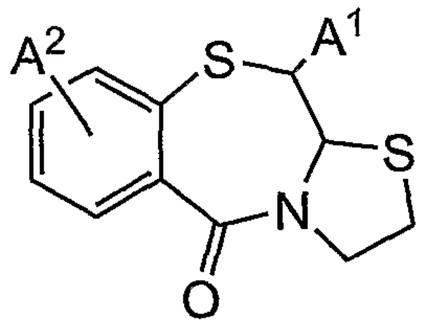
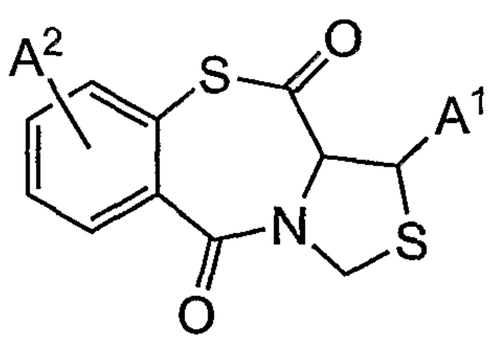
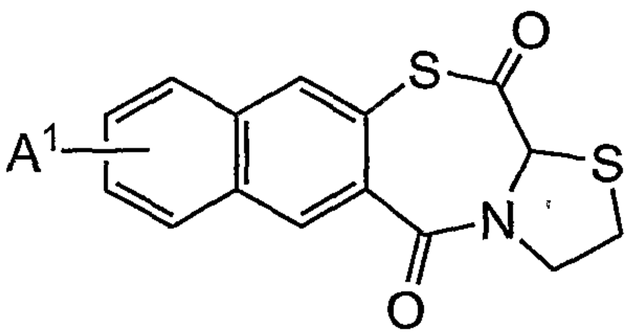
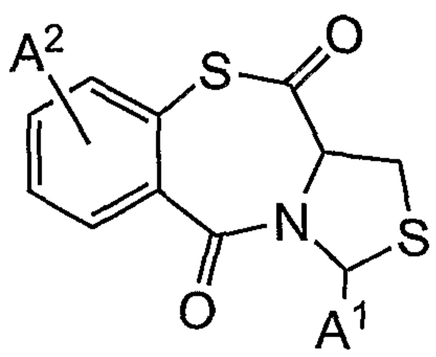
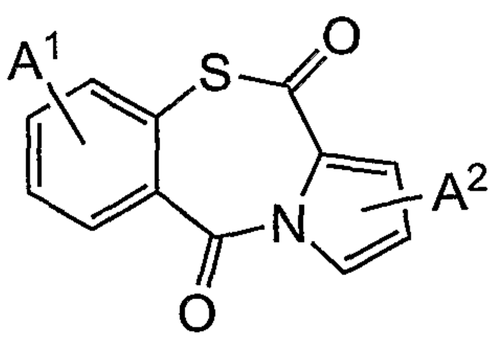
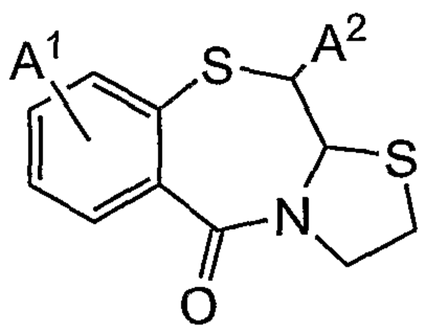
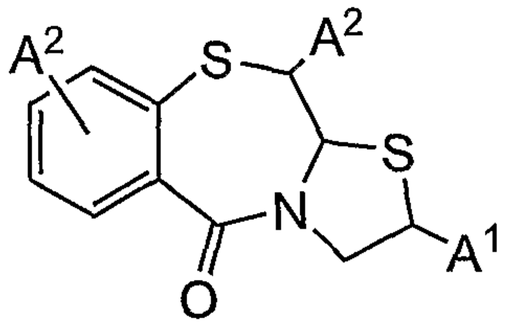
where each of the phenyl rings, N, S, or hydroxyl oxygen atoms in the structures above may be independently substituted with A^0 groups.

120. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXVI structures:



where each of the phenyl rings, N, S, or hydroxyl oxygen atoms in the structures above may be independently substituted with A^0 groups.

121. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXVIII structures:

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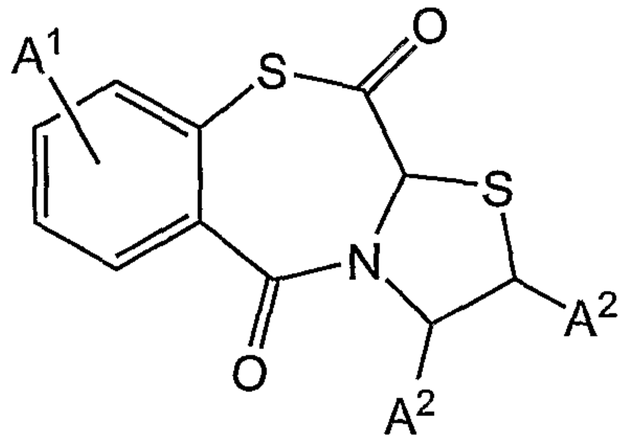
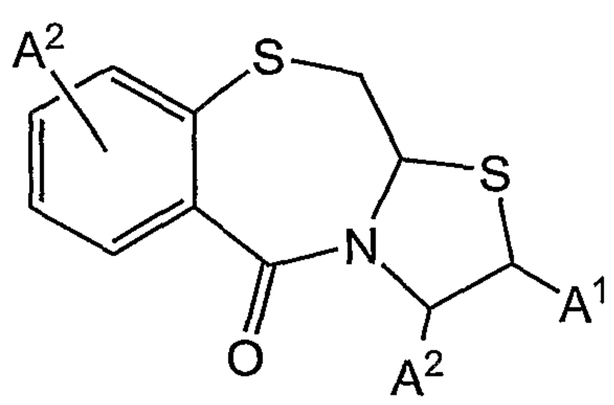
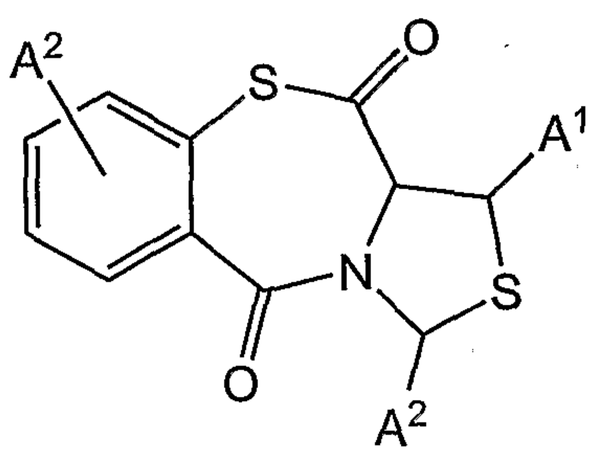
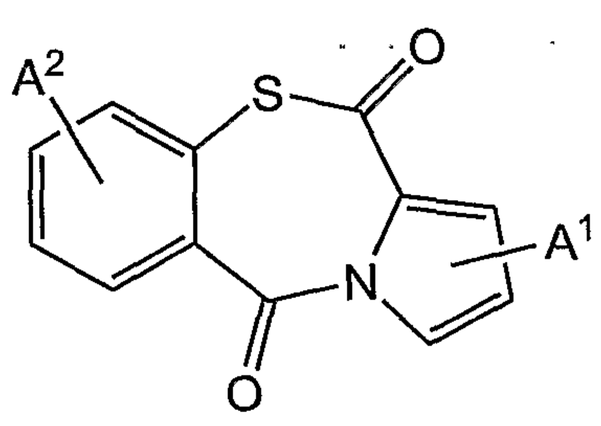
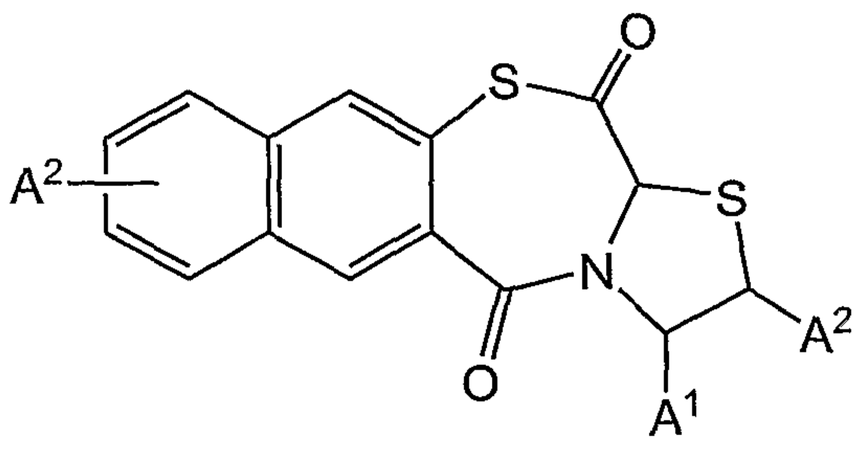
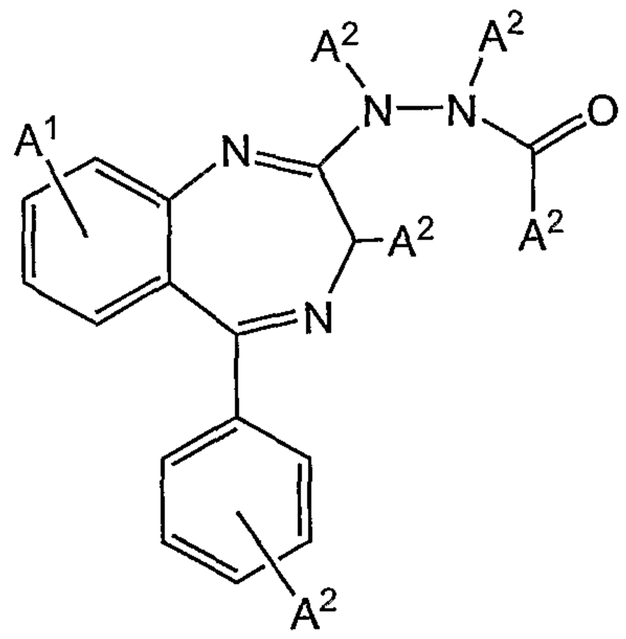
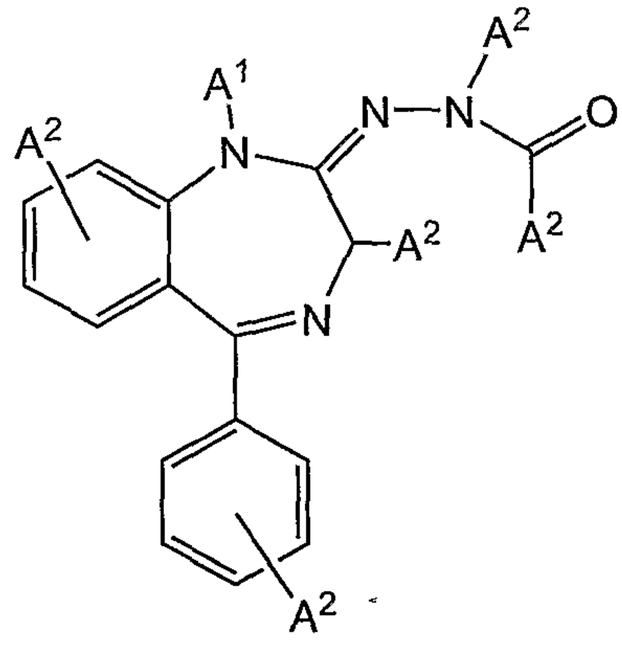
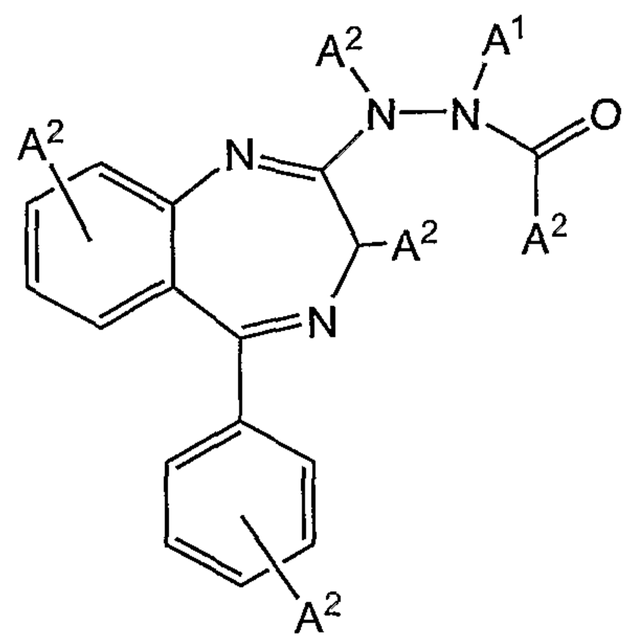
122. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXVIII structures:

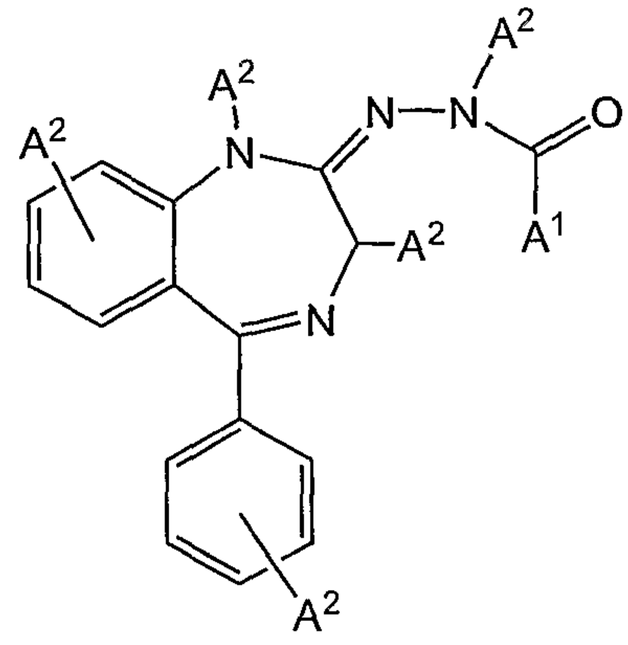






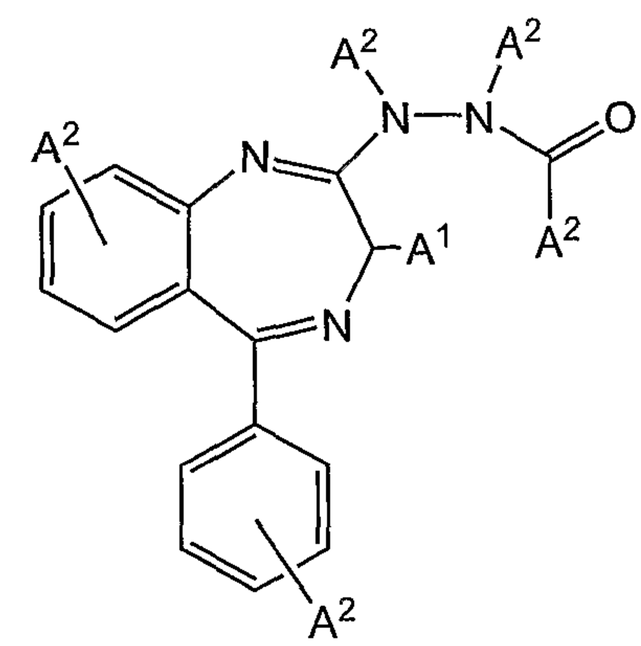
123. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXIX structures:

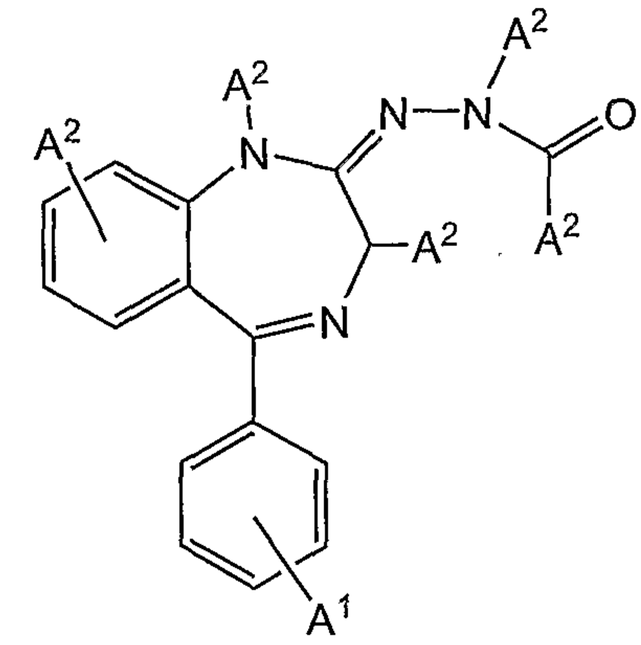




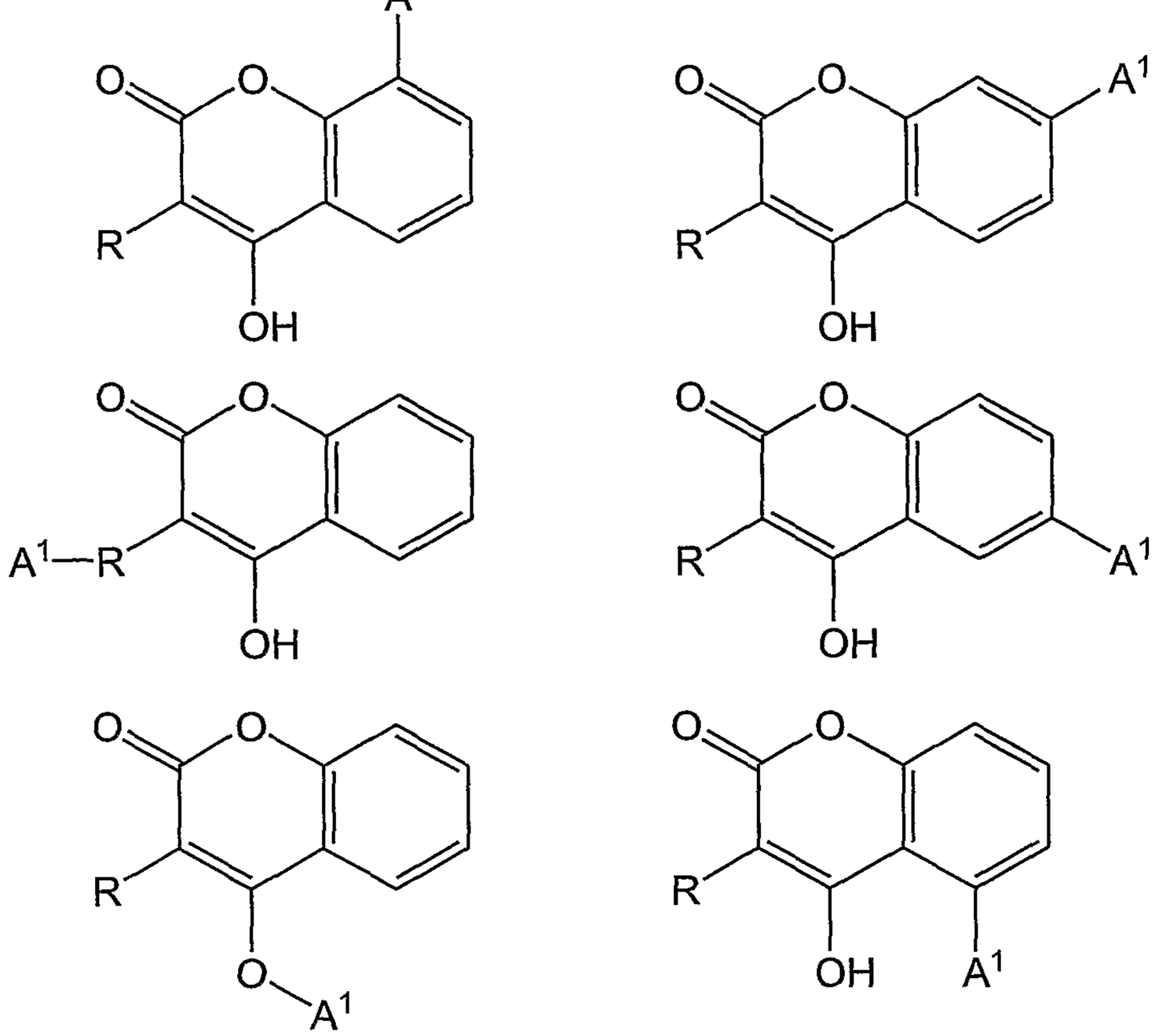




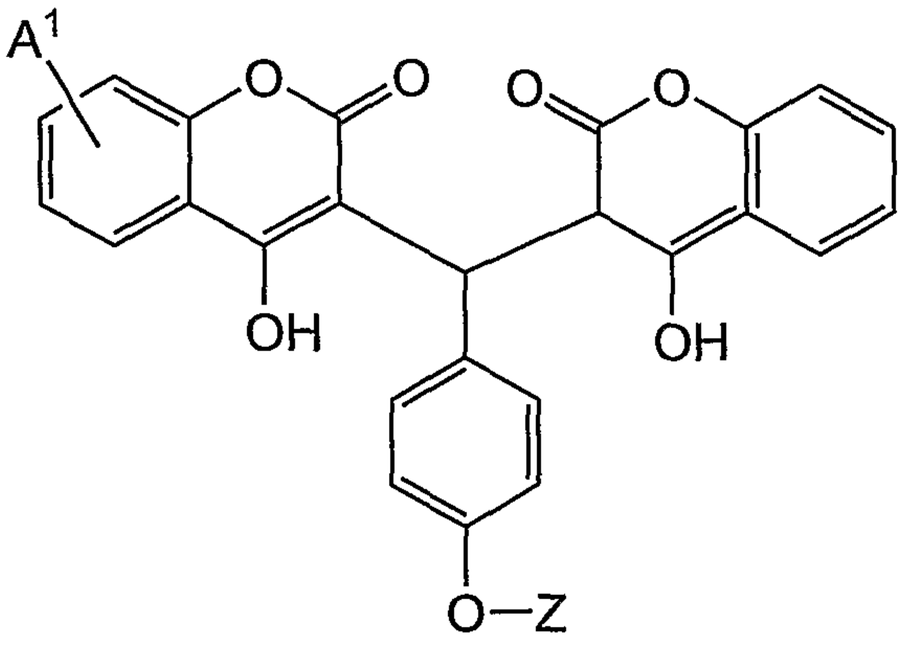


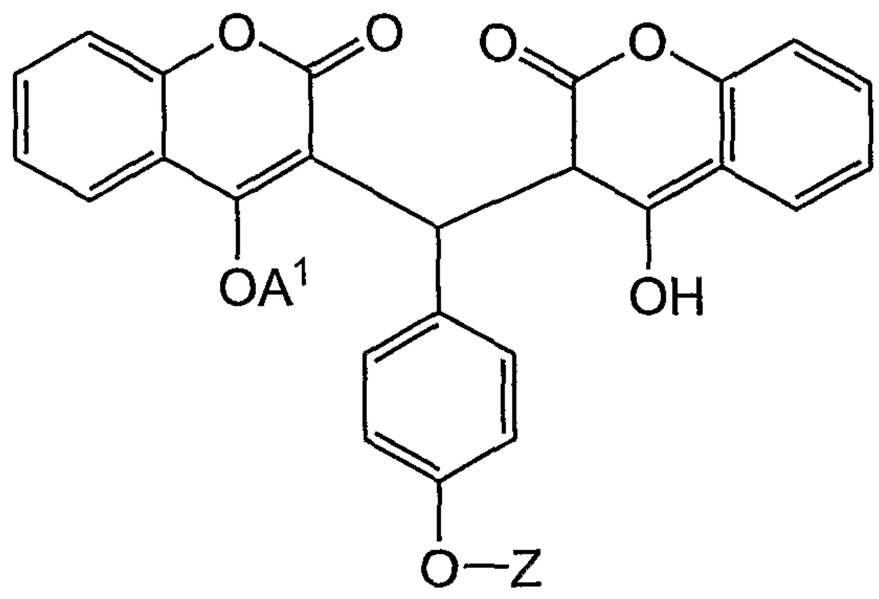


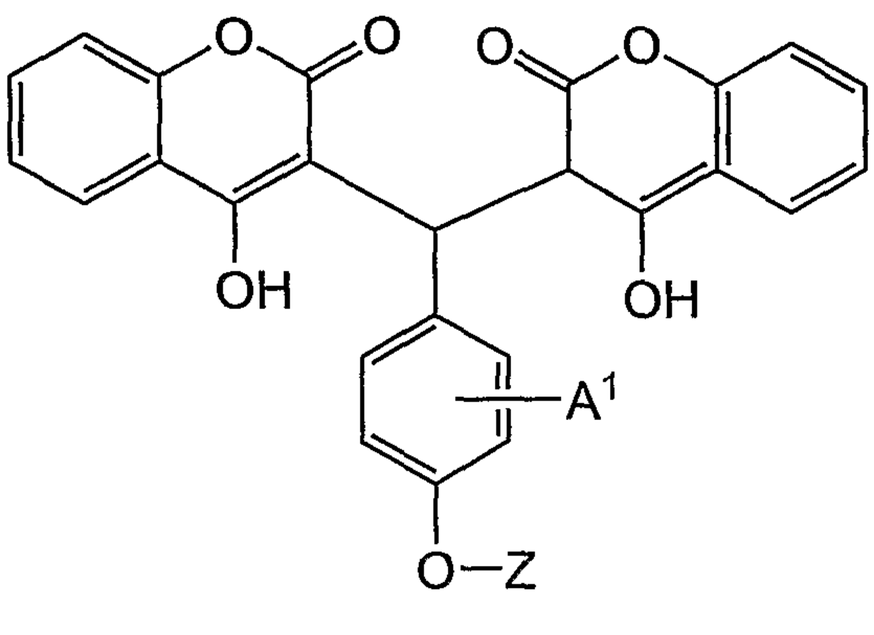
124. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXX structures:

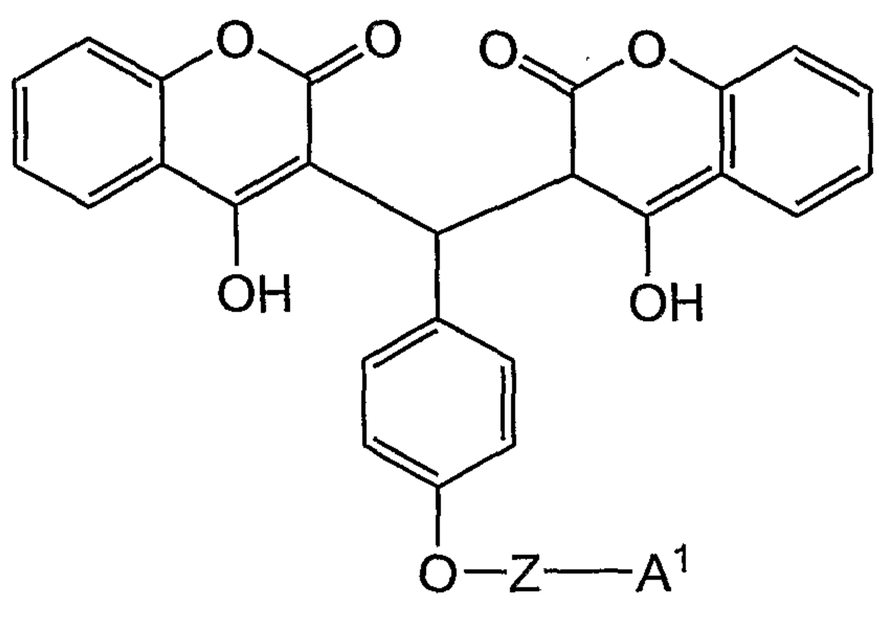


where R is H, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_2–C_{18} alkenyl, C_2–C_{18} substituted alkenyl, C_2–C_{18} alkynyl, C_2–C_{18} substituted alkynyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, or C_2–C_{20} substituted heteroaryl; and









where Z is $-C(O)Ar$ or $-SO_2R$; and Ar is C_3–C_{12} carbocycle, C_3–C_{12} substituted carbocycle, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, or C_2–C_{20} substituted heteroaryl.

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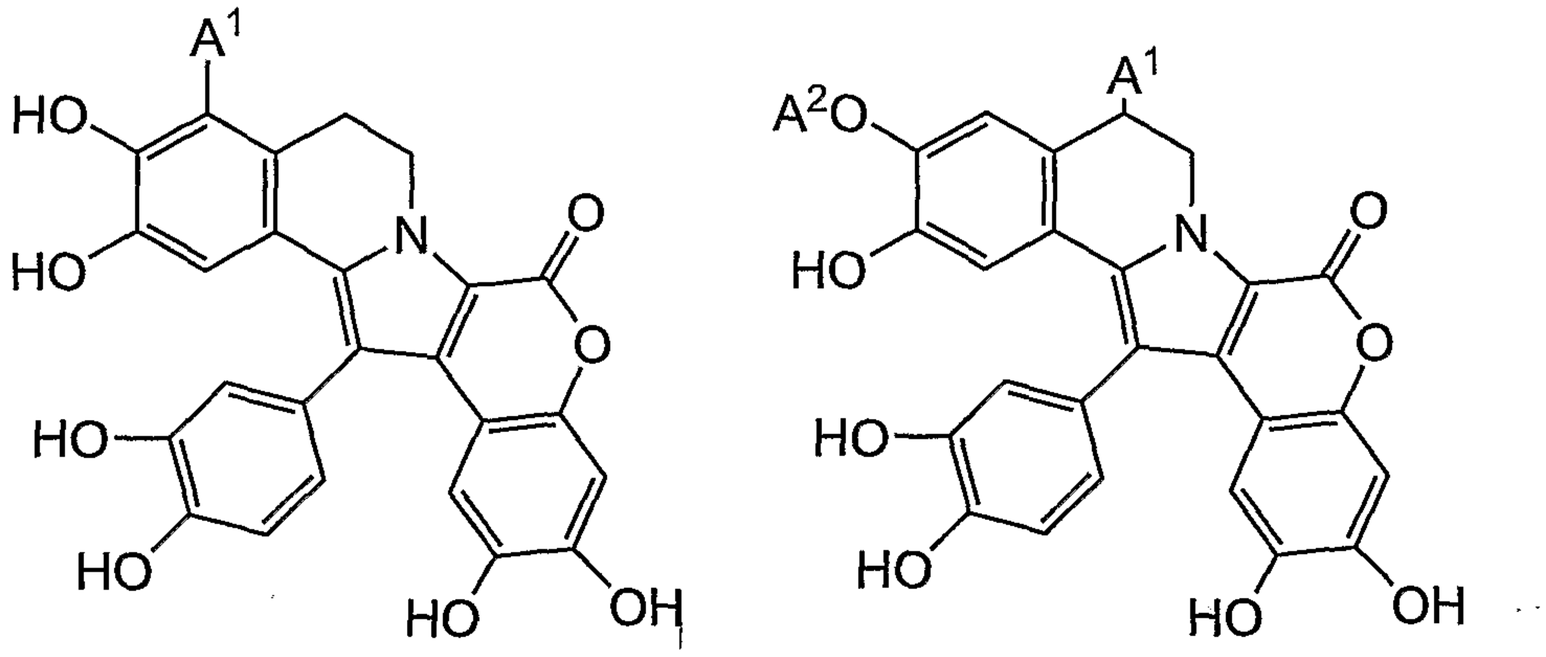
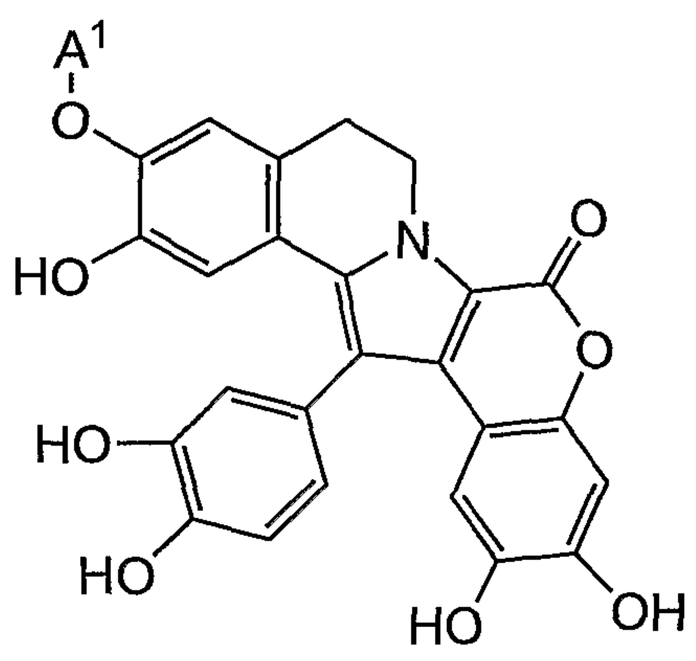
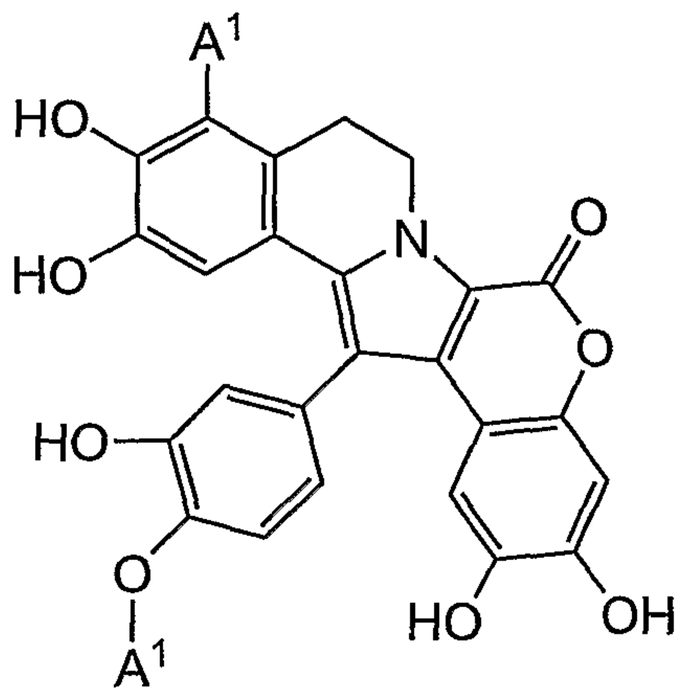
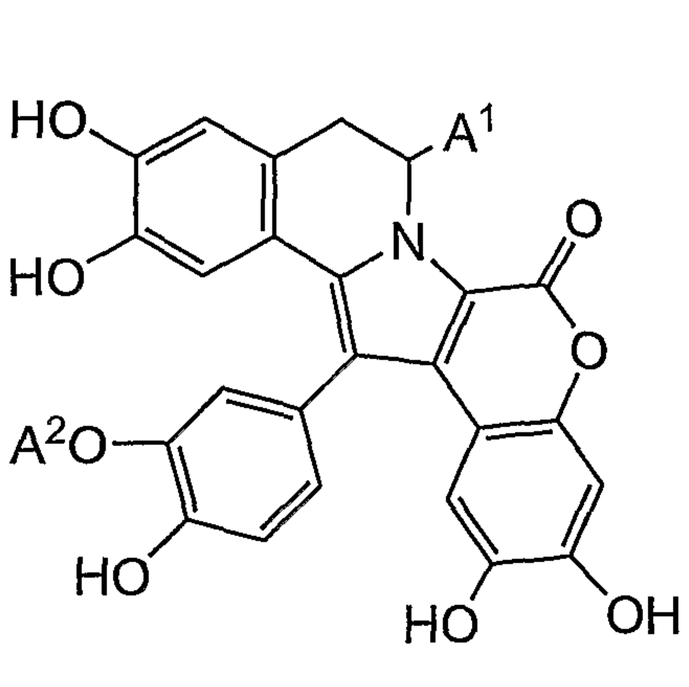
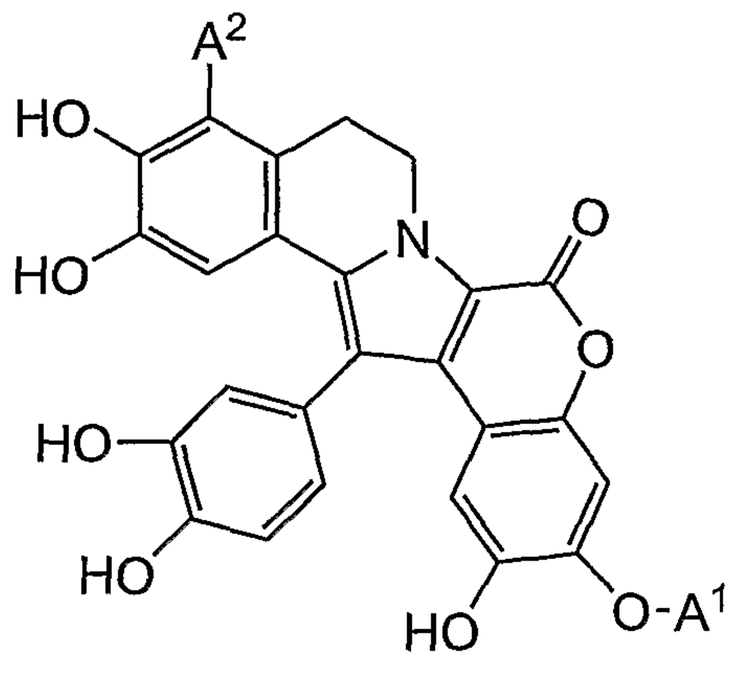
125. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXX structures:



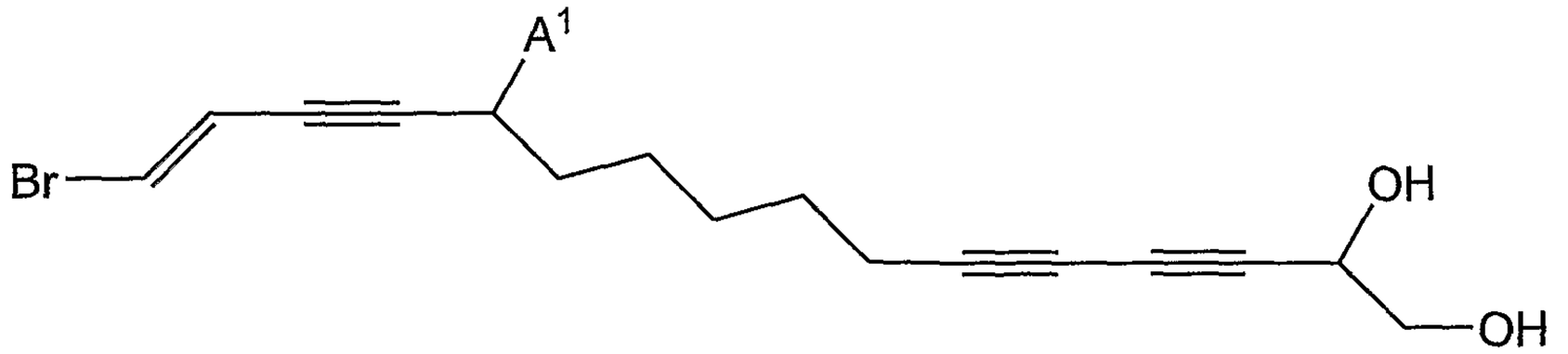


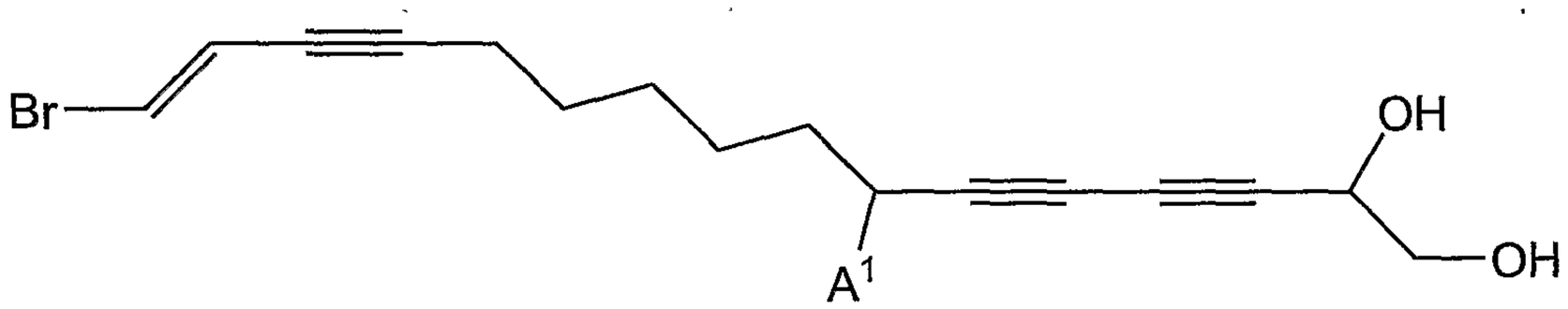


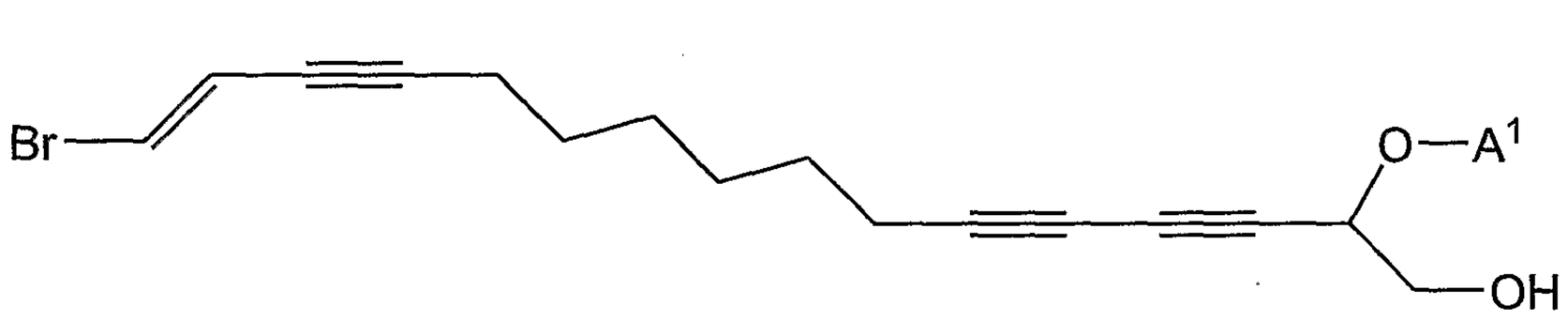


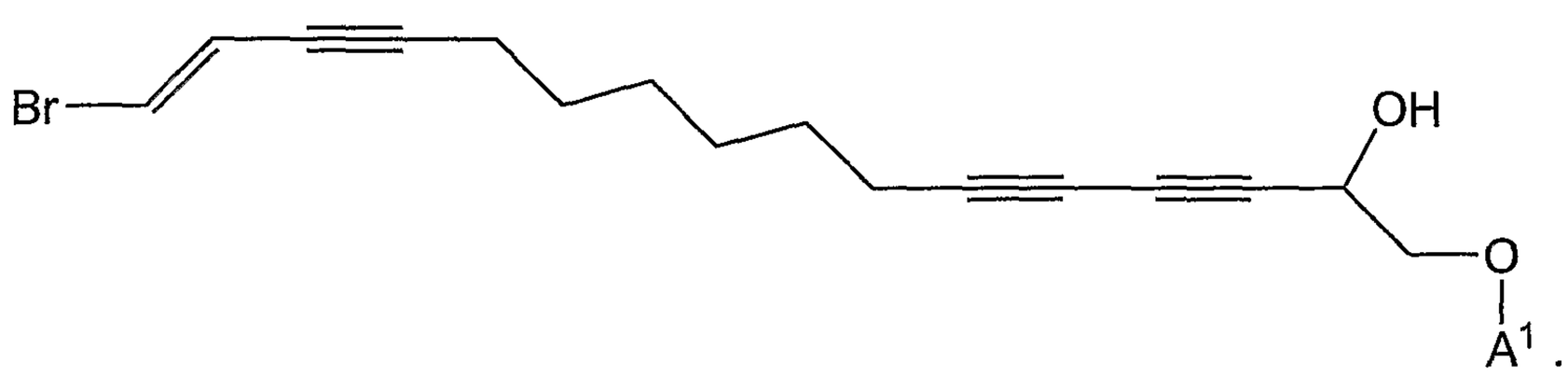


126. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXI structures:









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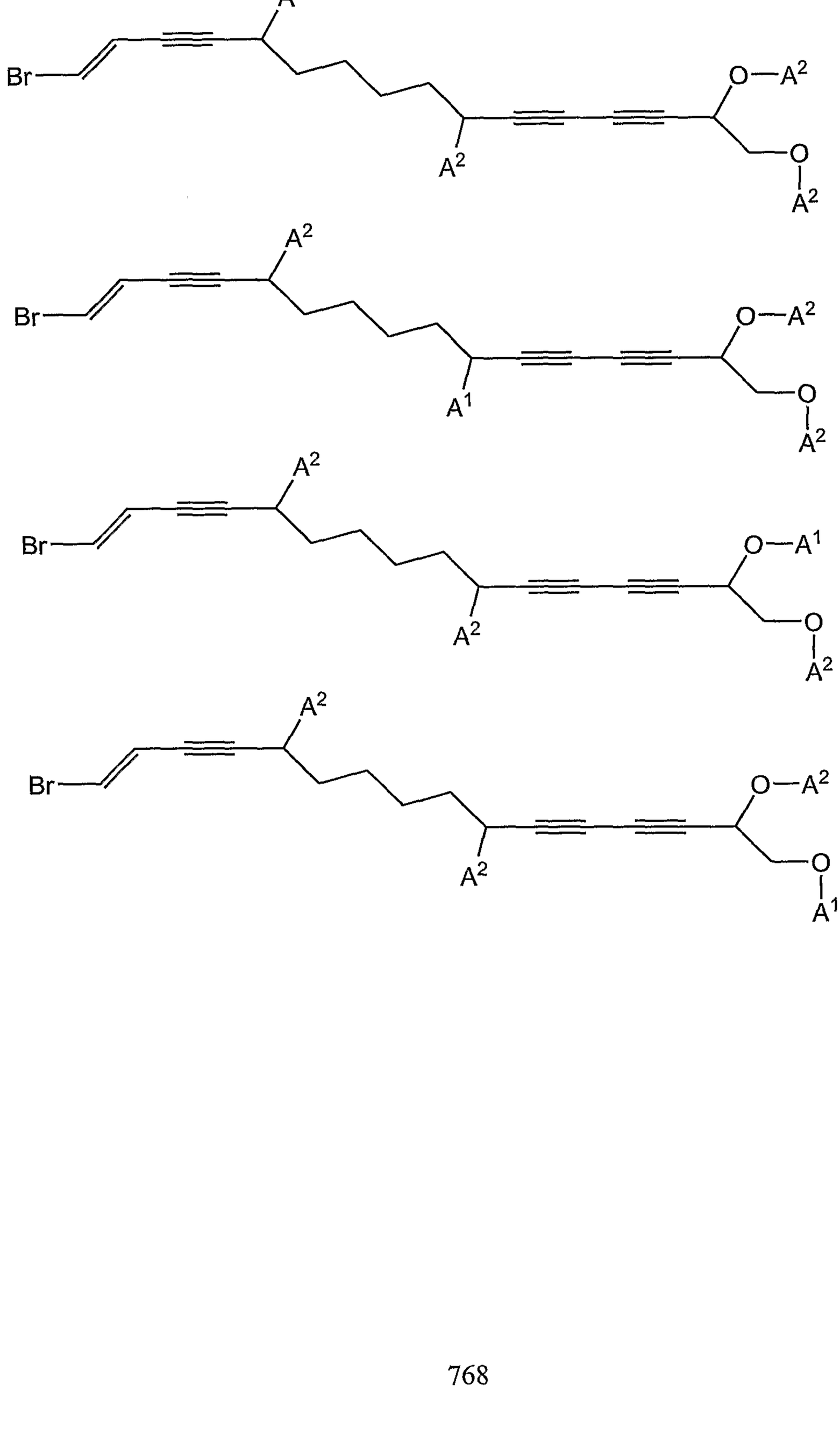
127. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXI structures:



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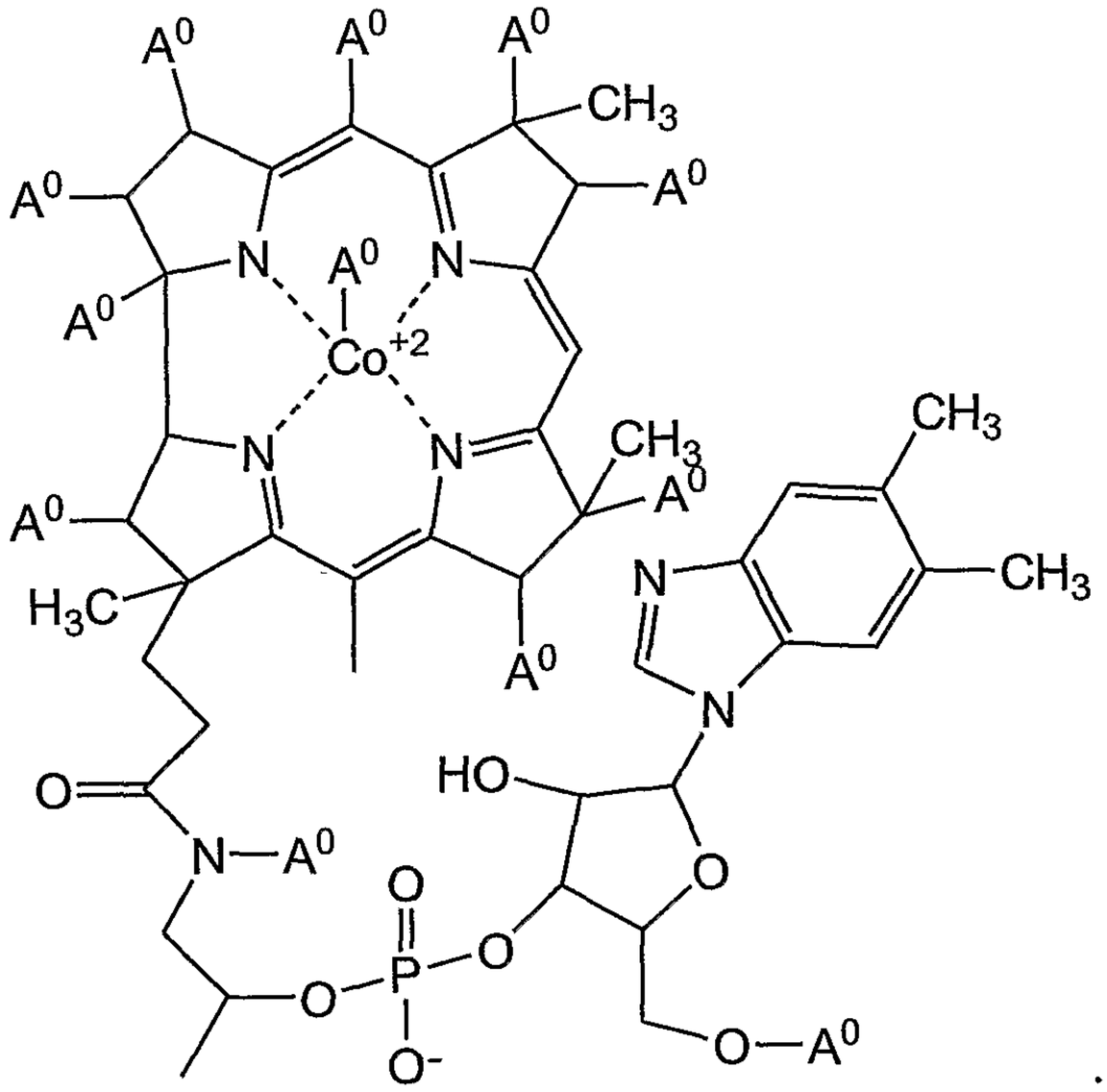
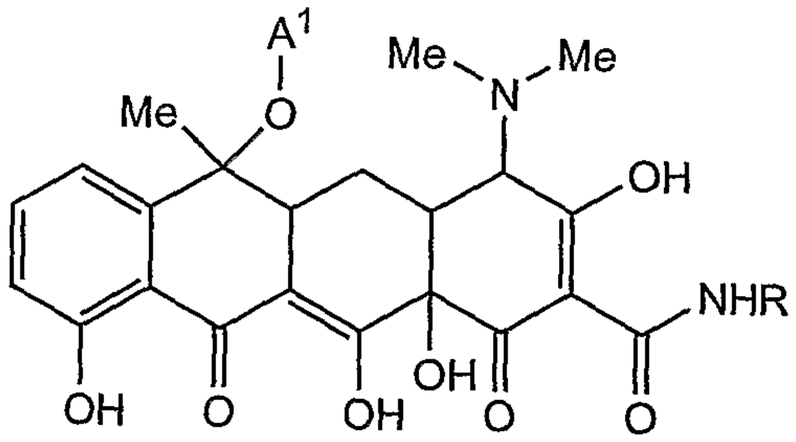
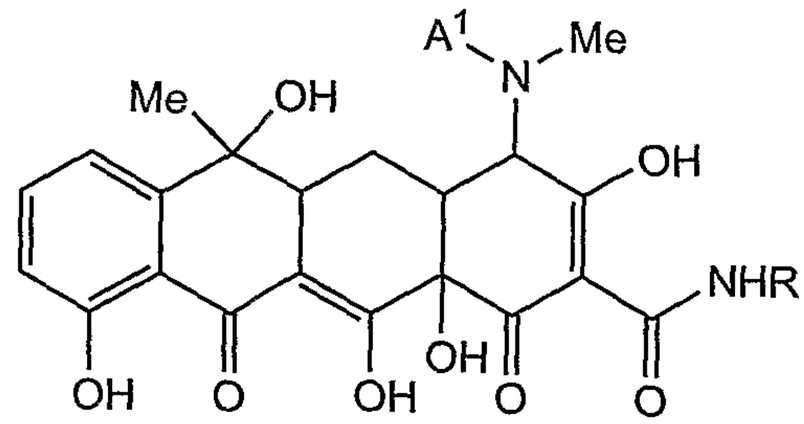
128. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXII structures:

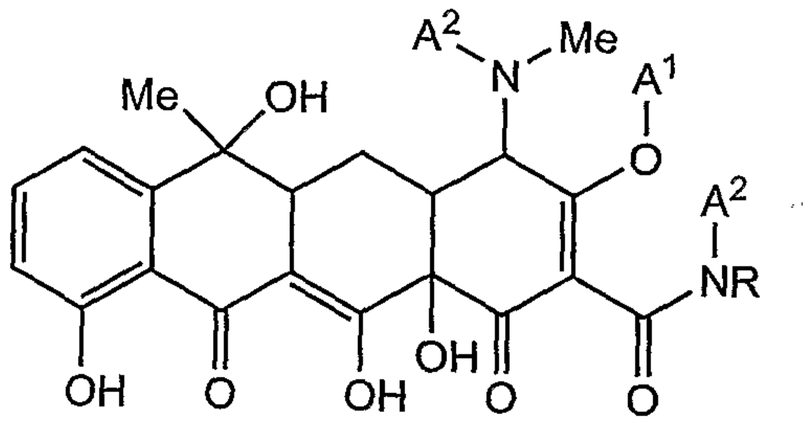


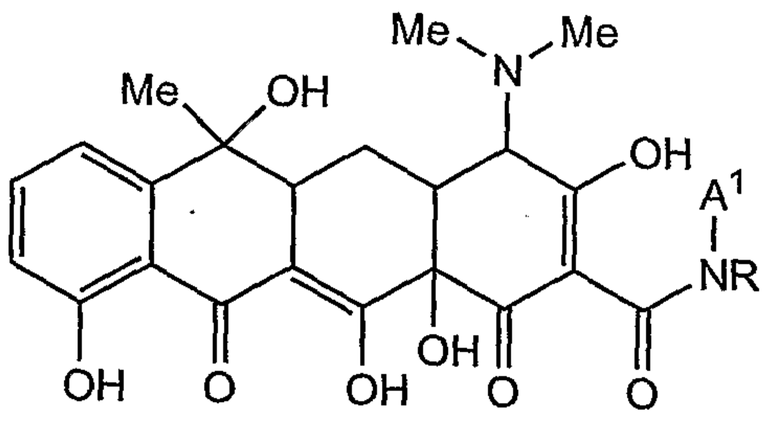
129. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXII structures:

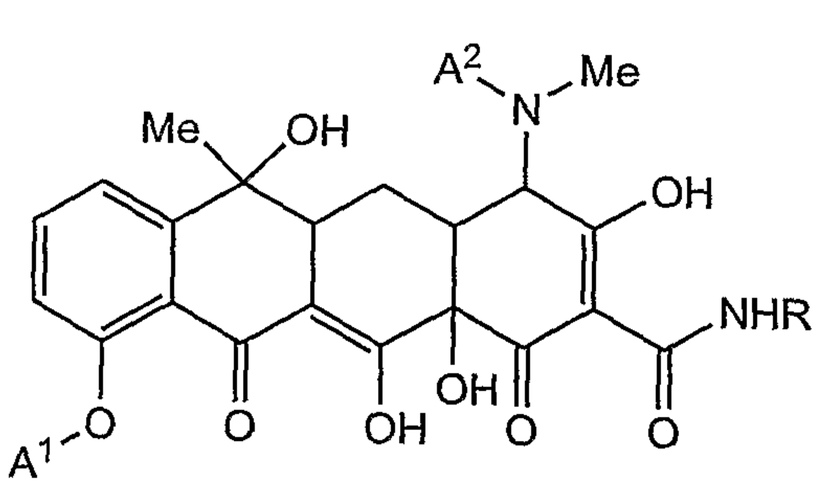
130. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXIII structures:

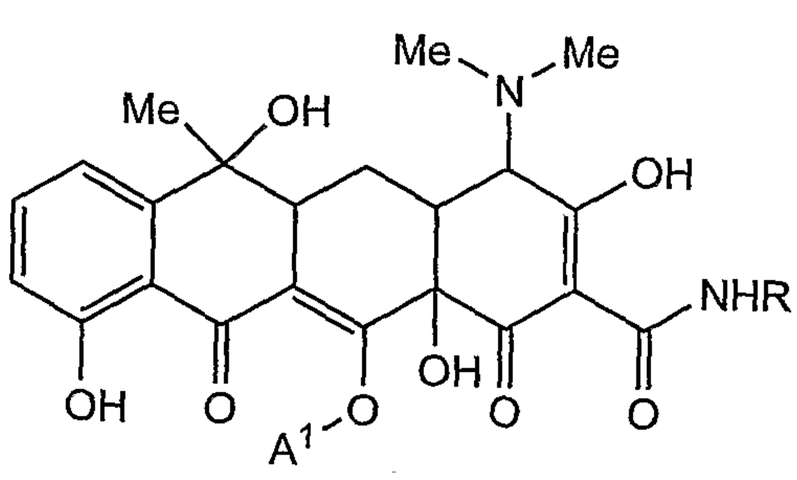

A1
Me
N
Me
Me
O
OH
NHR
OH
O
OH
O
O


A1
N
Me
Me
OH
OH
NHR
OH
O
OH
O
O

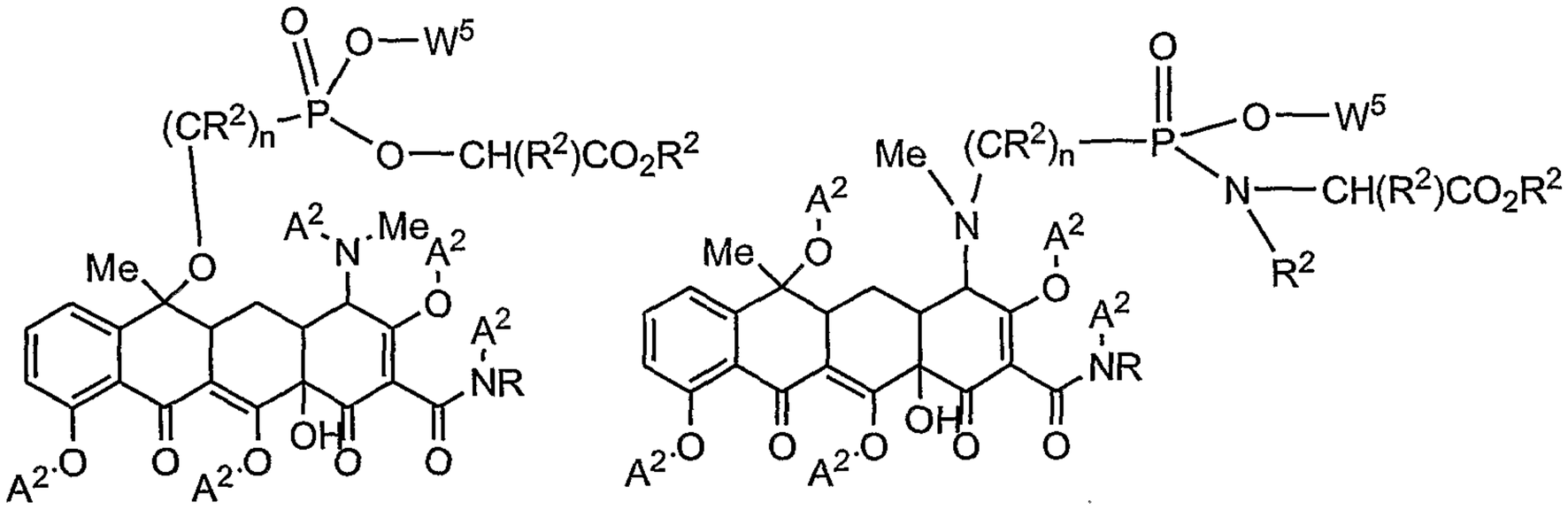

A2
N
Me
Me
OH
A1
O
A2
NR
OH
O
OH
O
O

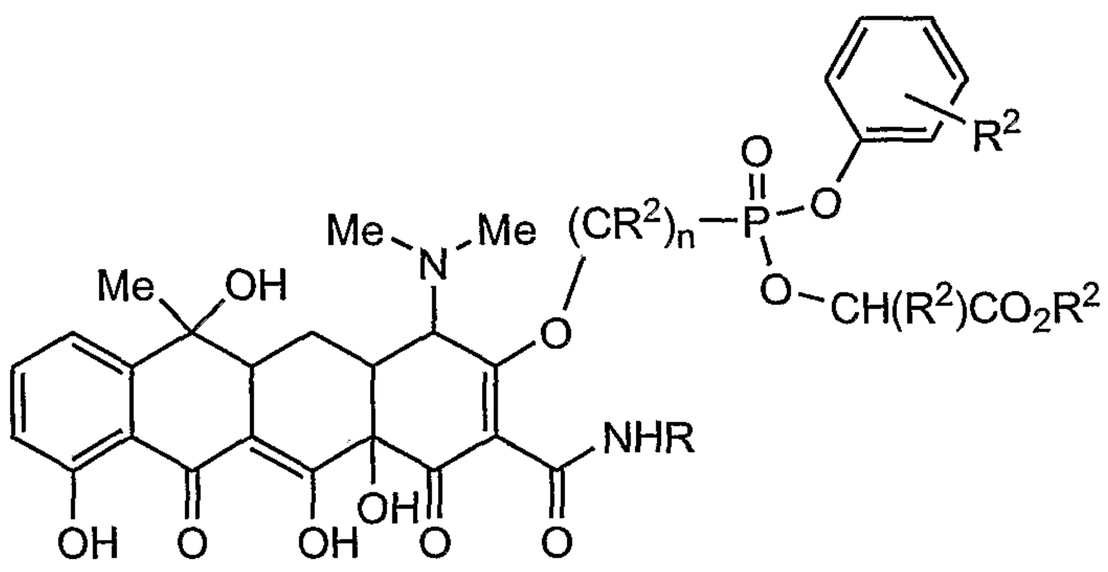

Me
N
Me
Me
OH
OH
A1
NR
OH
O
OH
O
O

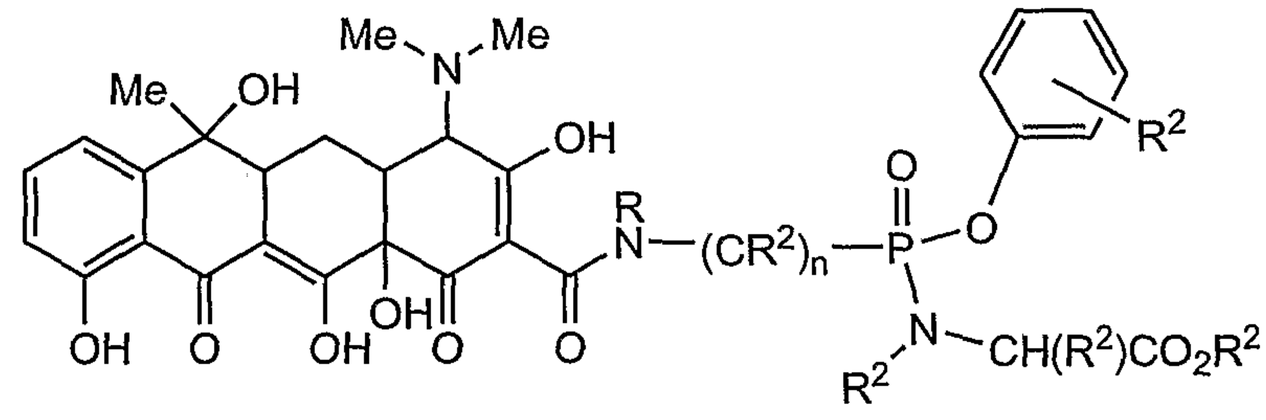

A2
N
Me
Me
OH
OH
NHR
A1
O
O
OH
O
O

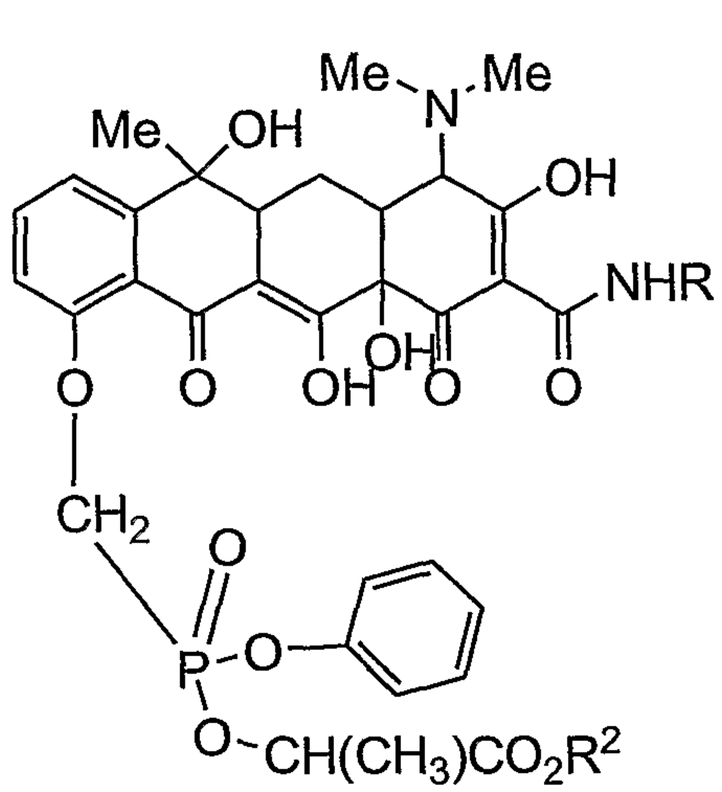

Me
N
Me
Me
OH
OH
NHR
OH
O
A1
O
OH
O
O

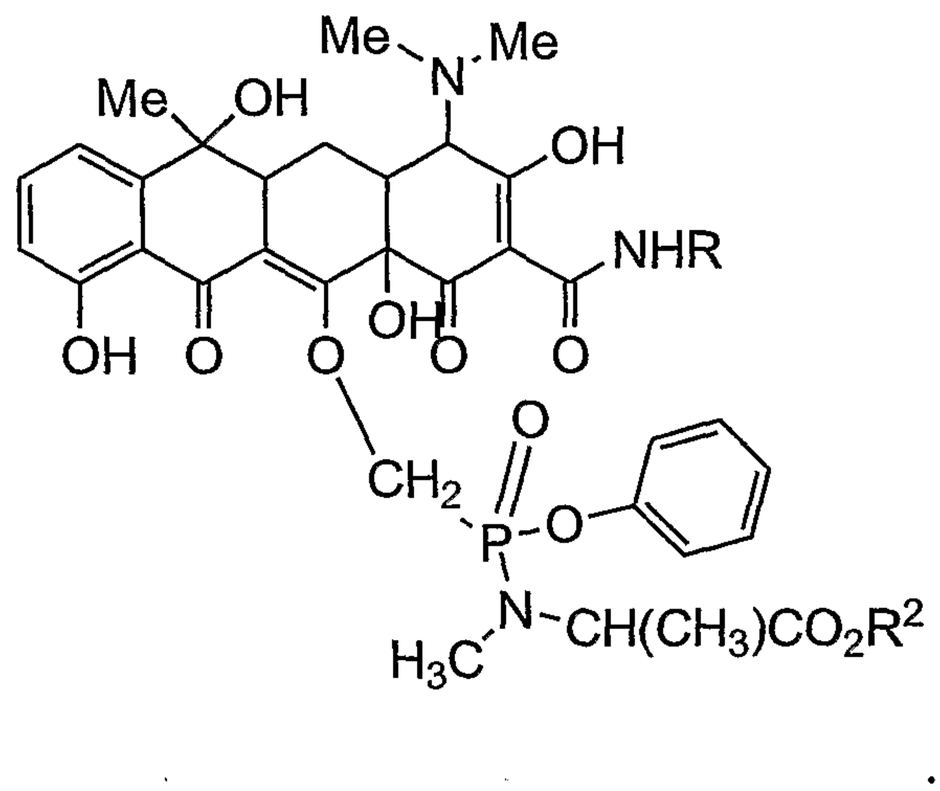
131. An HIV integrase inhibitor compound of claim 130 selected from the Formula XXXIII structures:



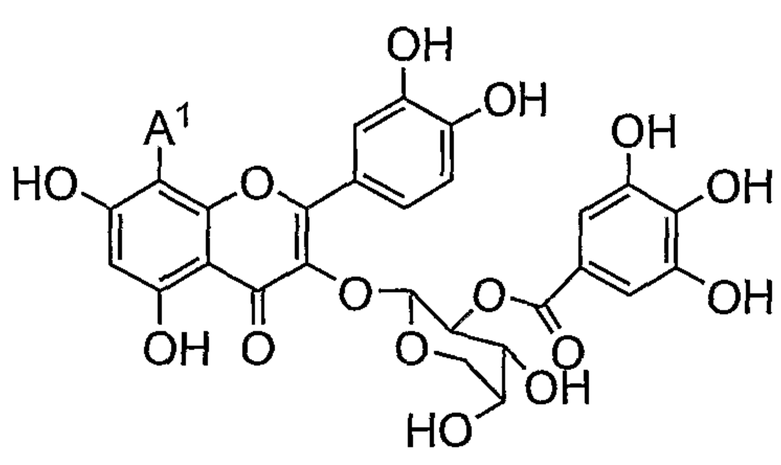


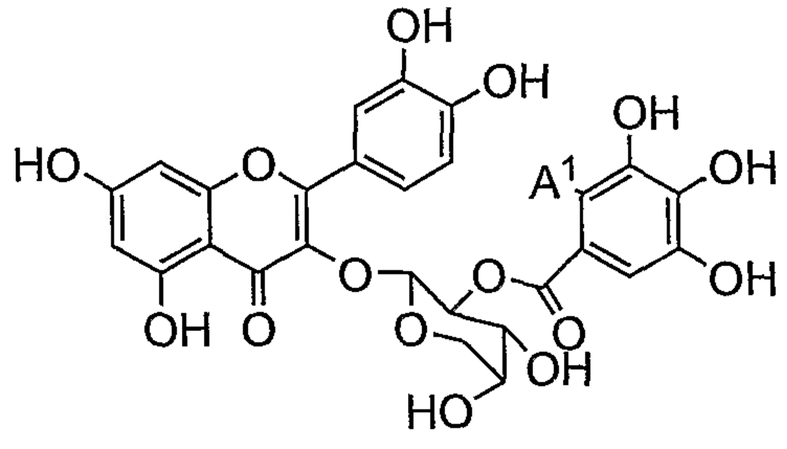


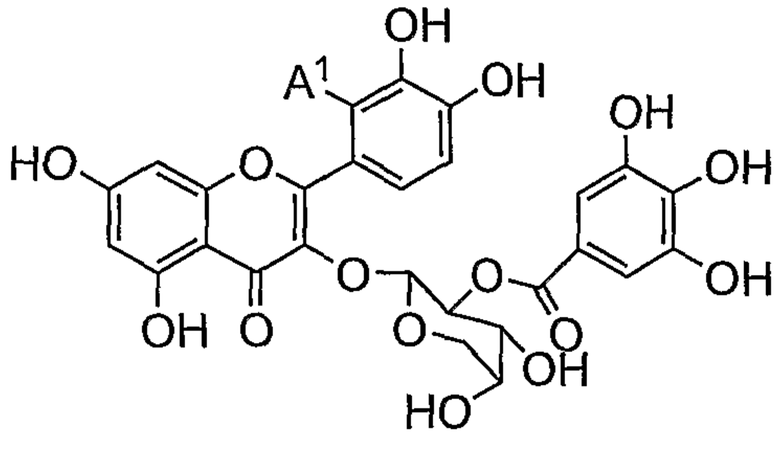


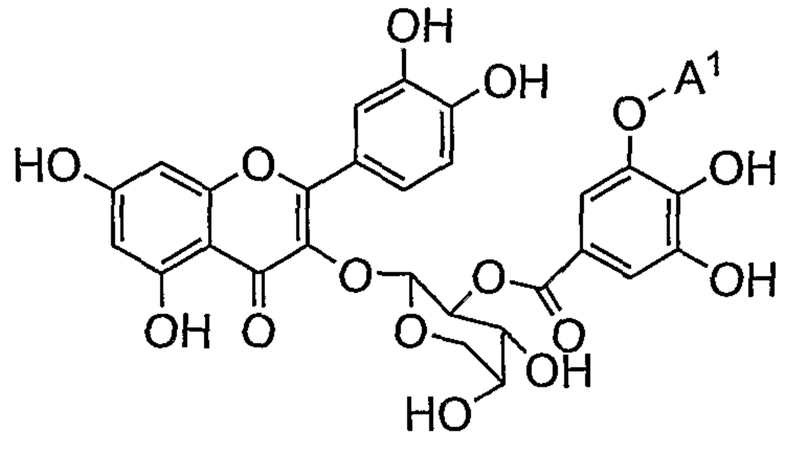


132. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXIII structures:









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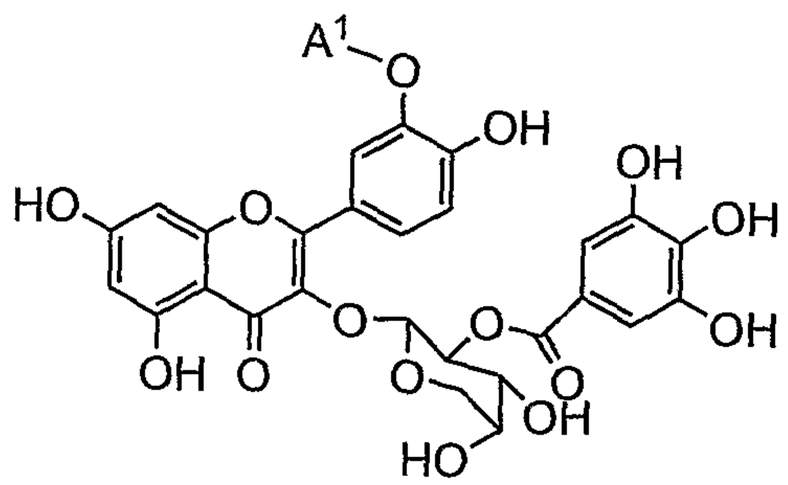
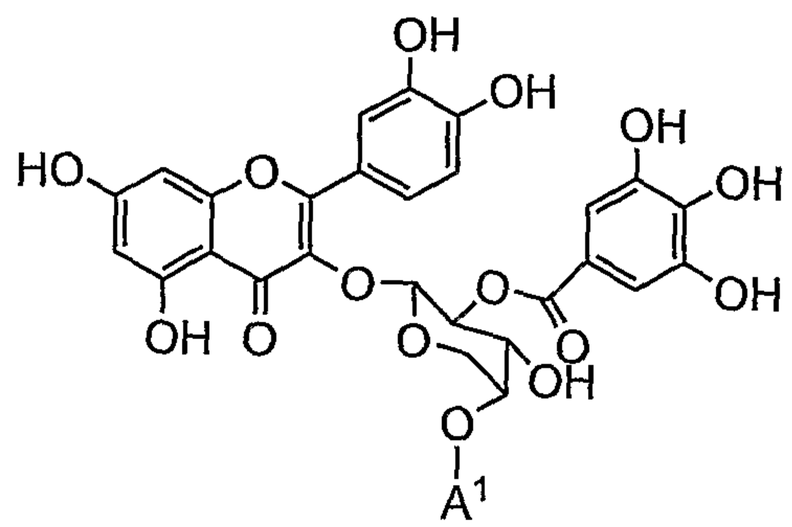
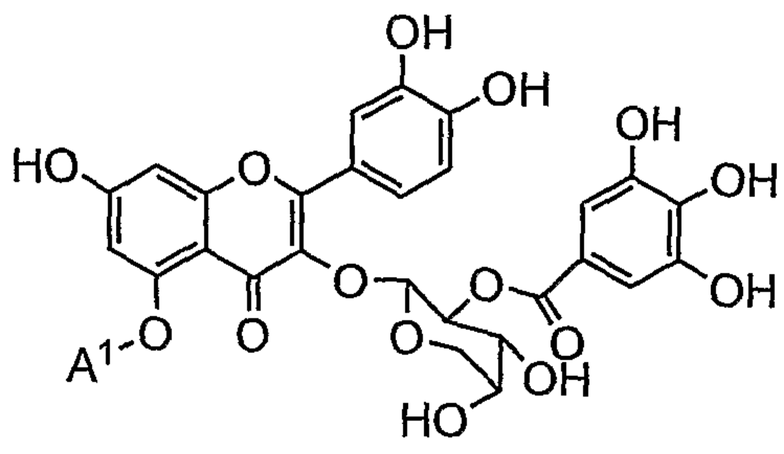
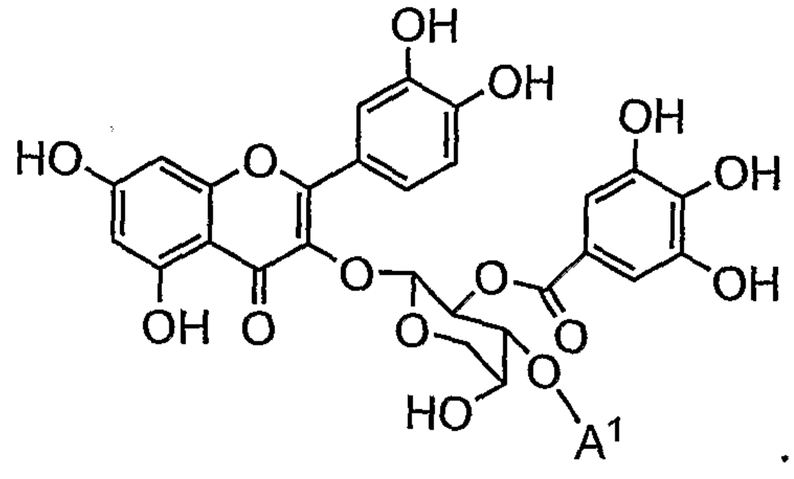
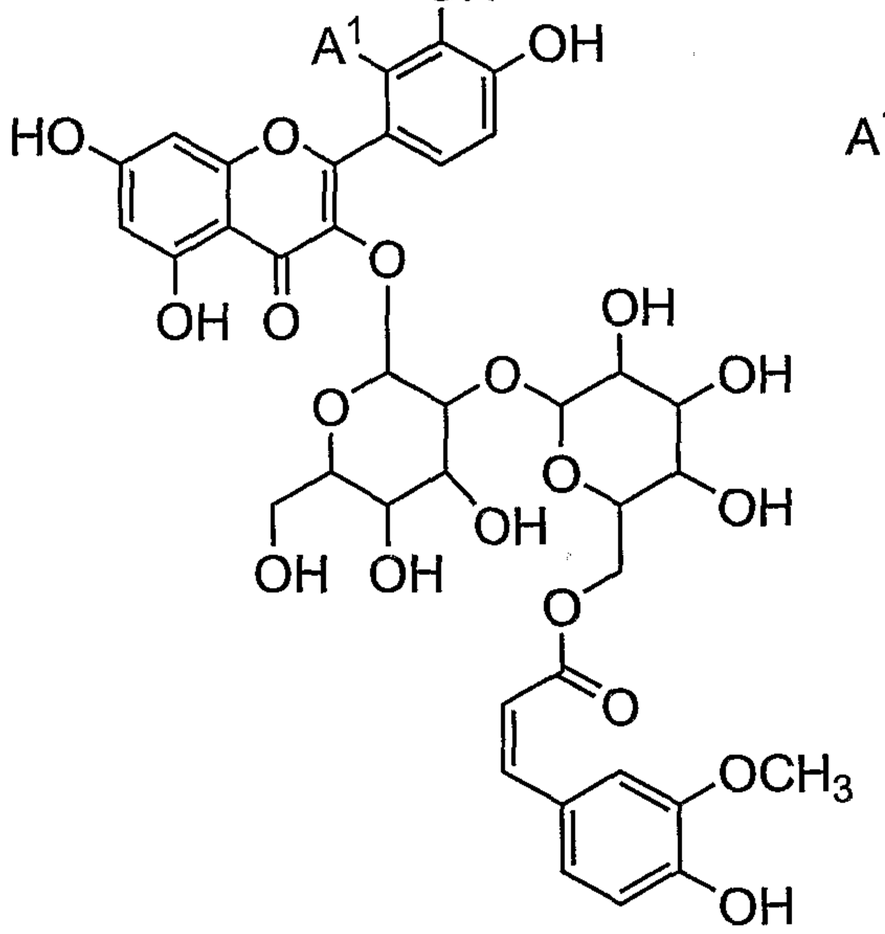


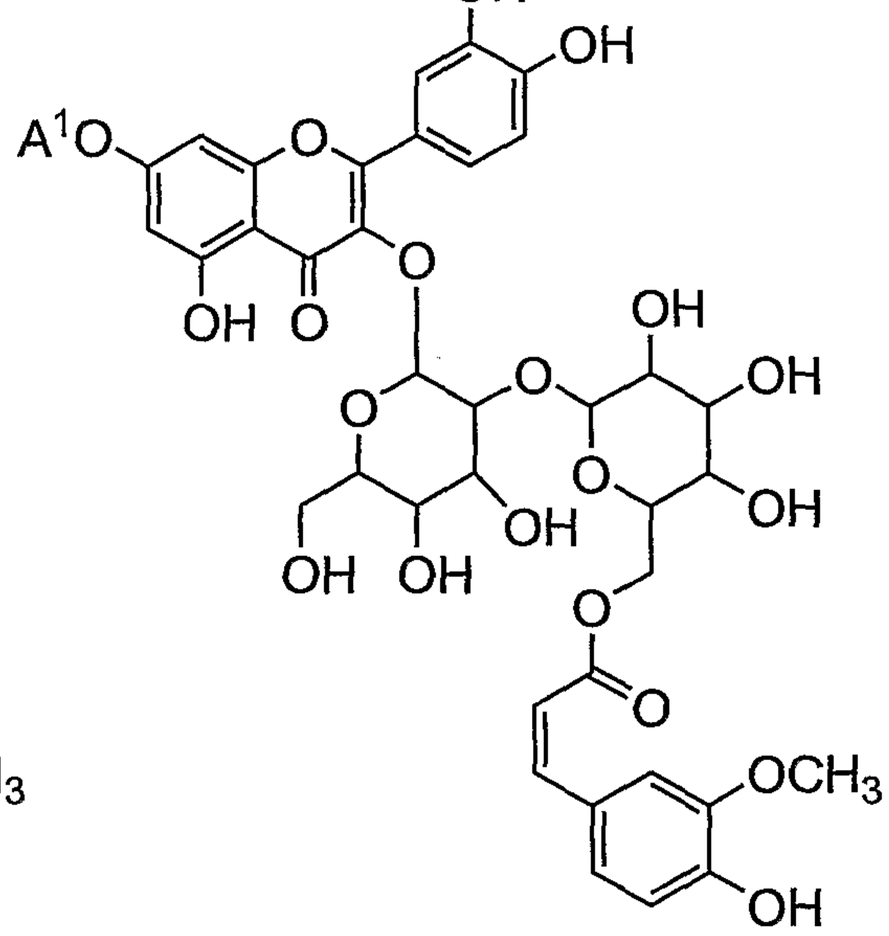


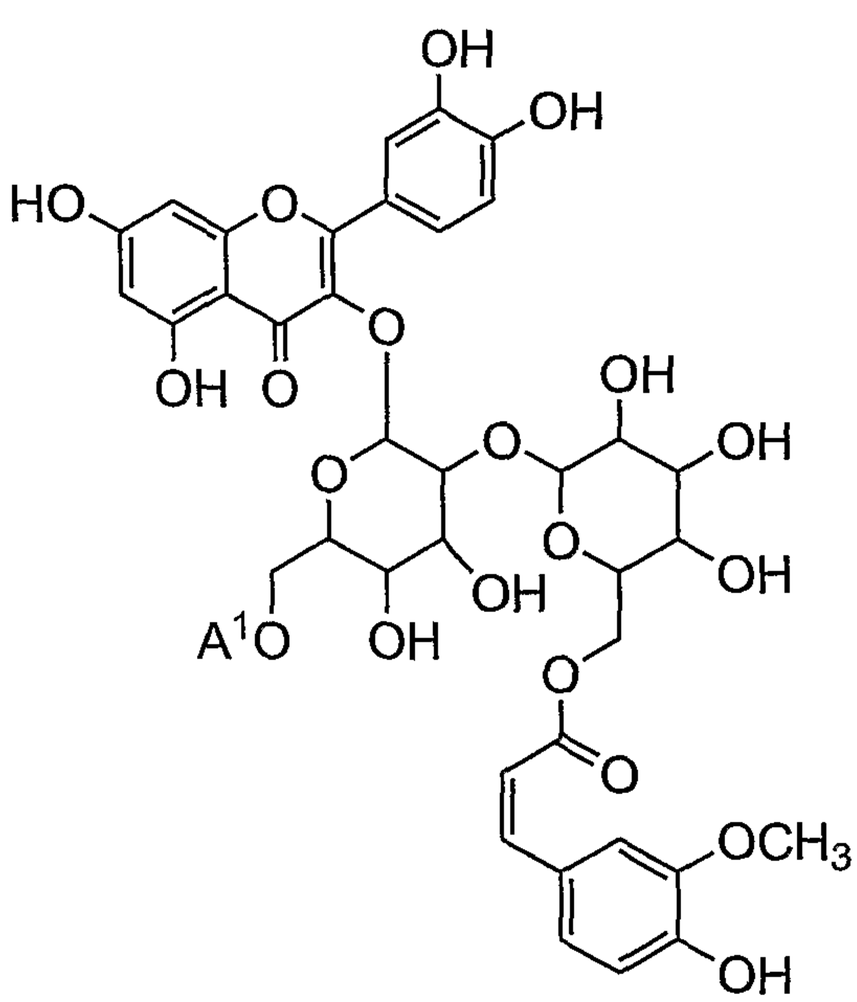


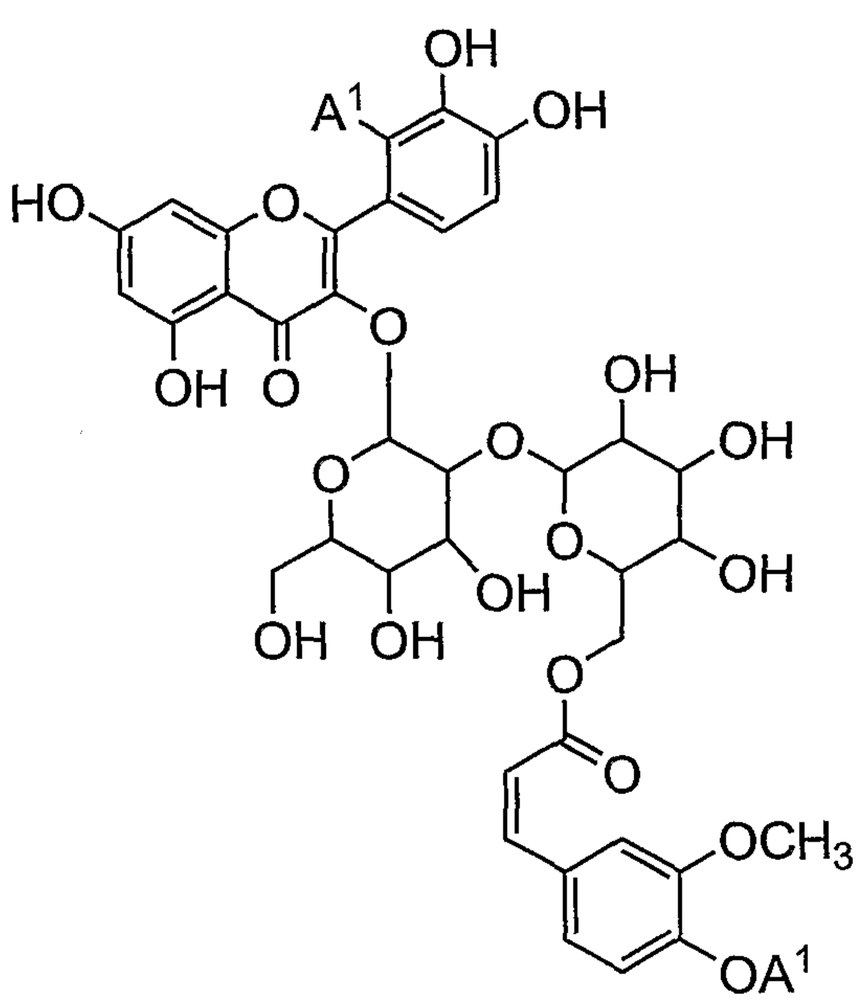


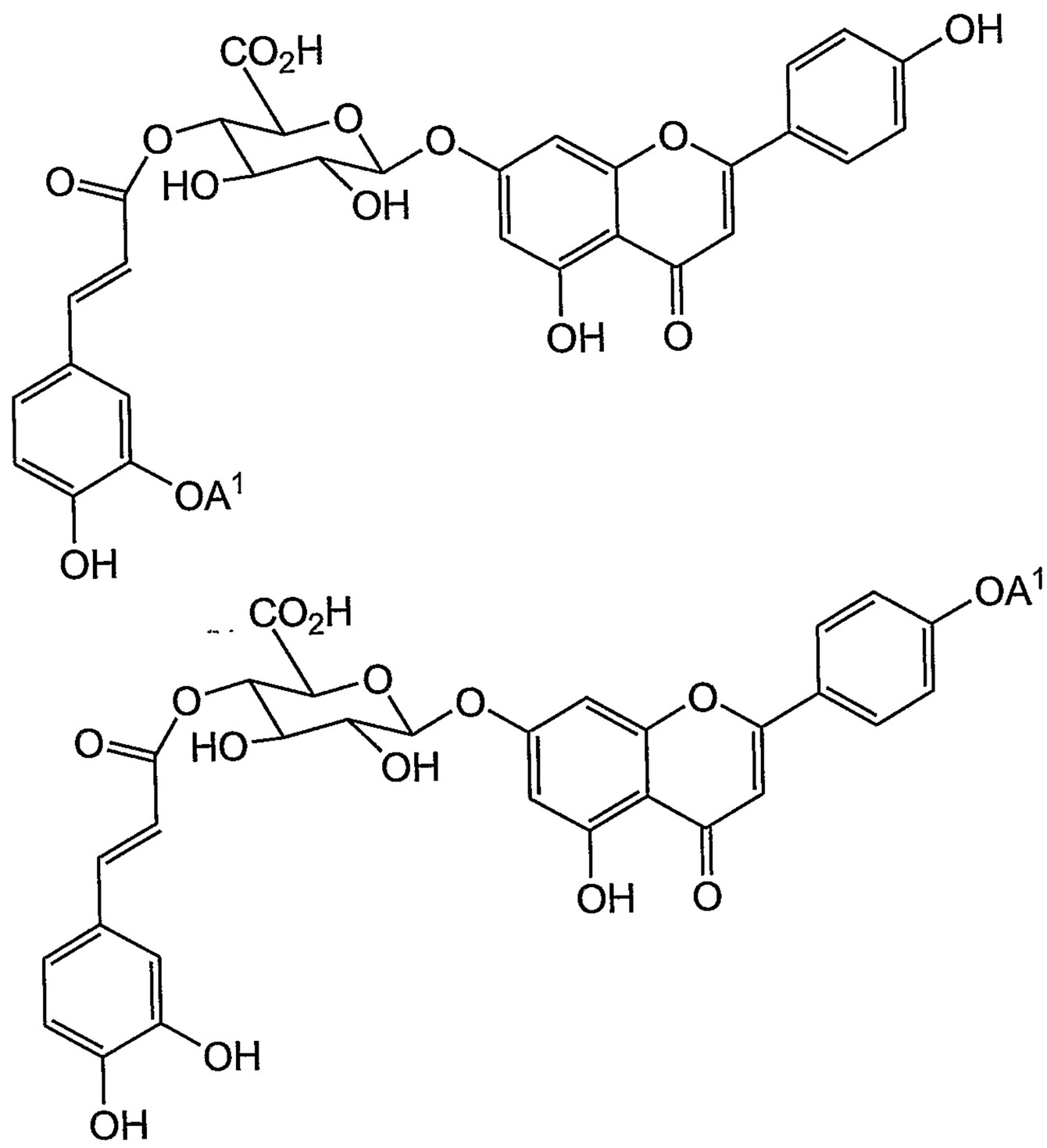
133. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXIII structures:

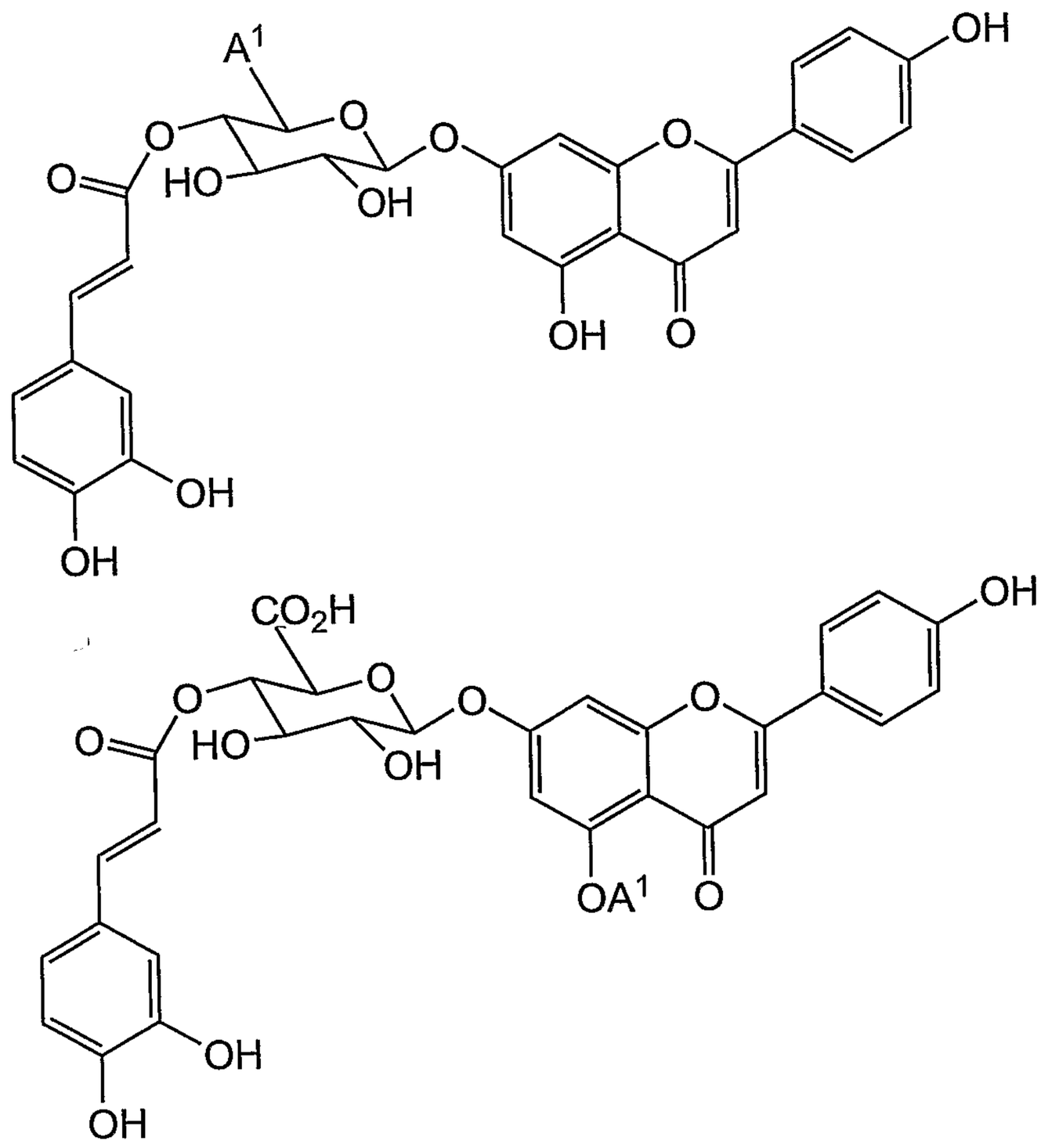




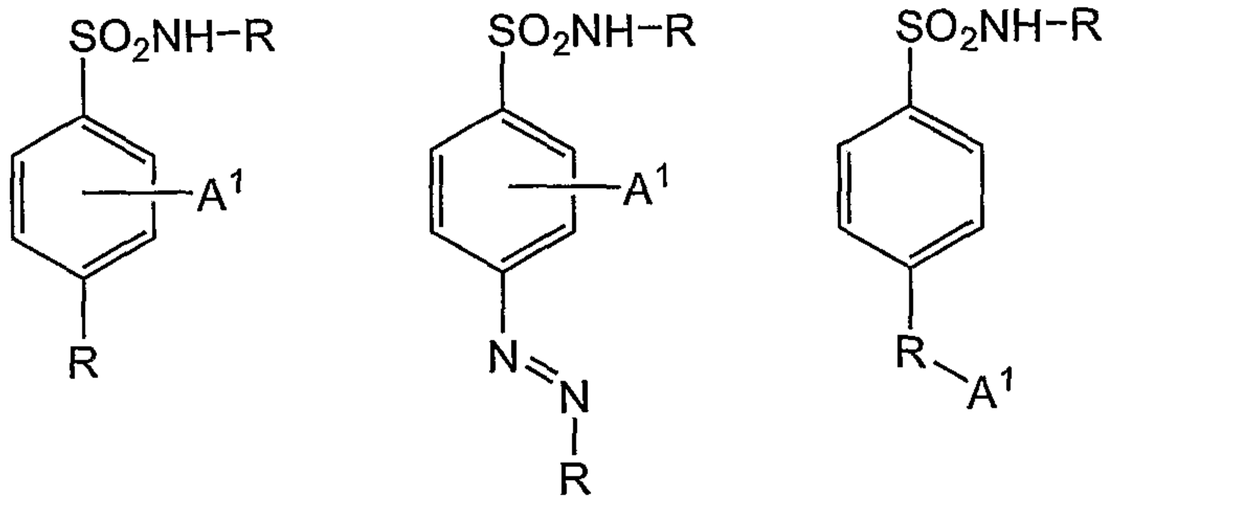


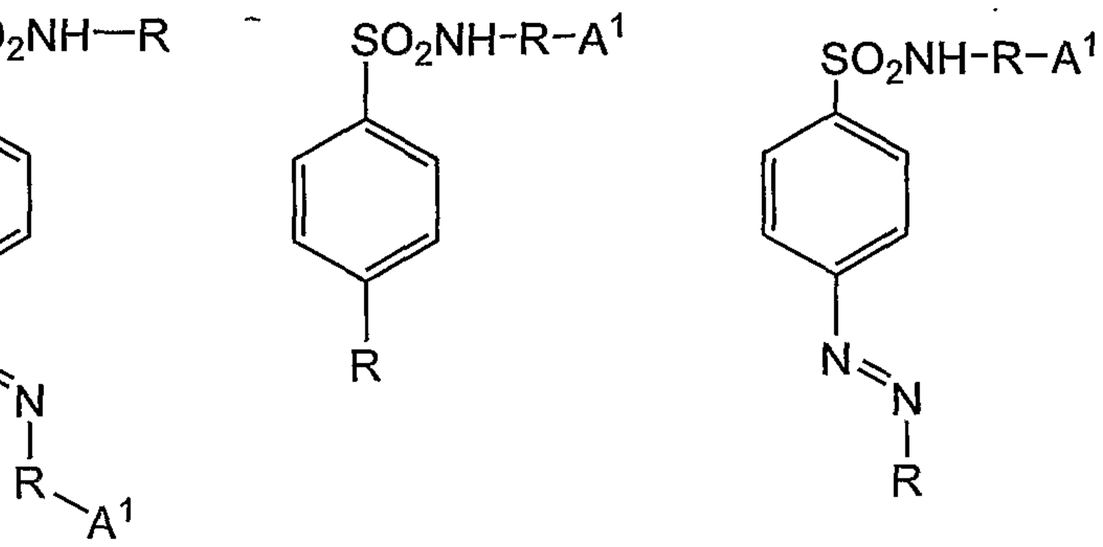



CO2H
O
O
O
HO
OH
OH
O
OH
O
OA1
OH
CO2H
O
O
O
HO
OH
OH
O
OA1
OH
O
OH
OH


A1
O
O
O
HO
OH
O
OH
OH
OH
O
OH
OH
CO2H
O
O
O
HO
OH
O
OA1
O
OH
OH

134. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXIV structures:





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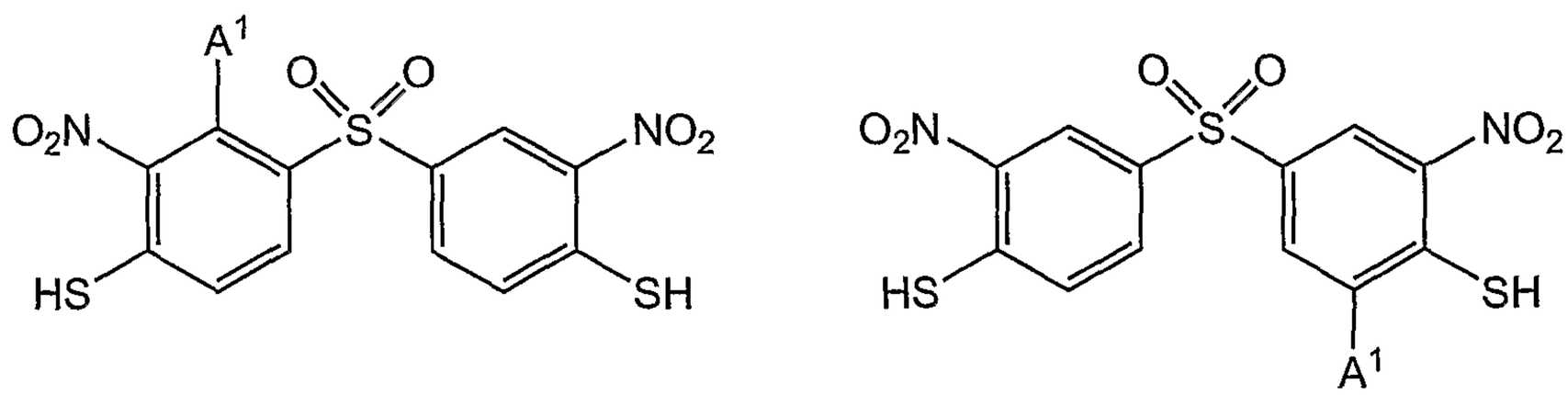
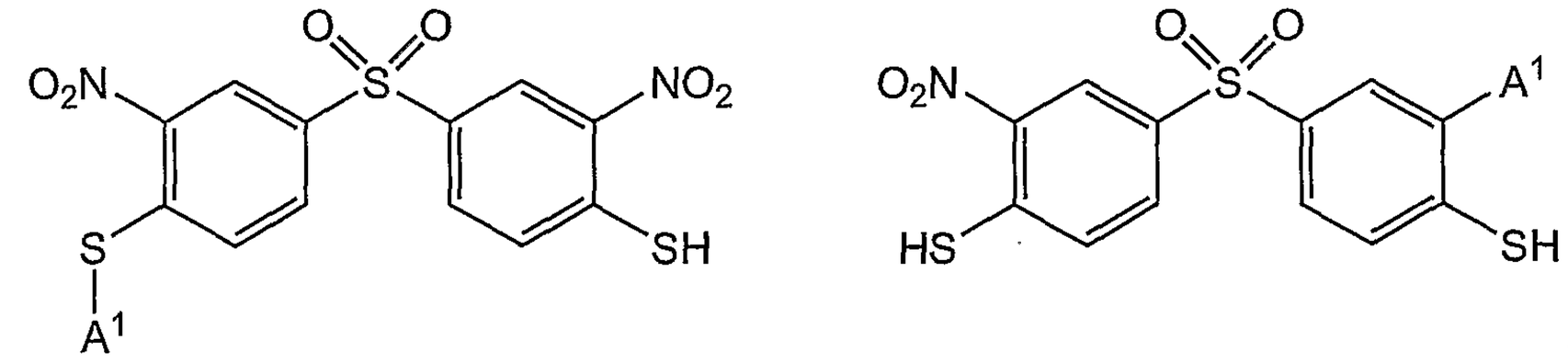
135. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXIV structures:





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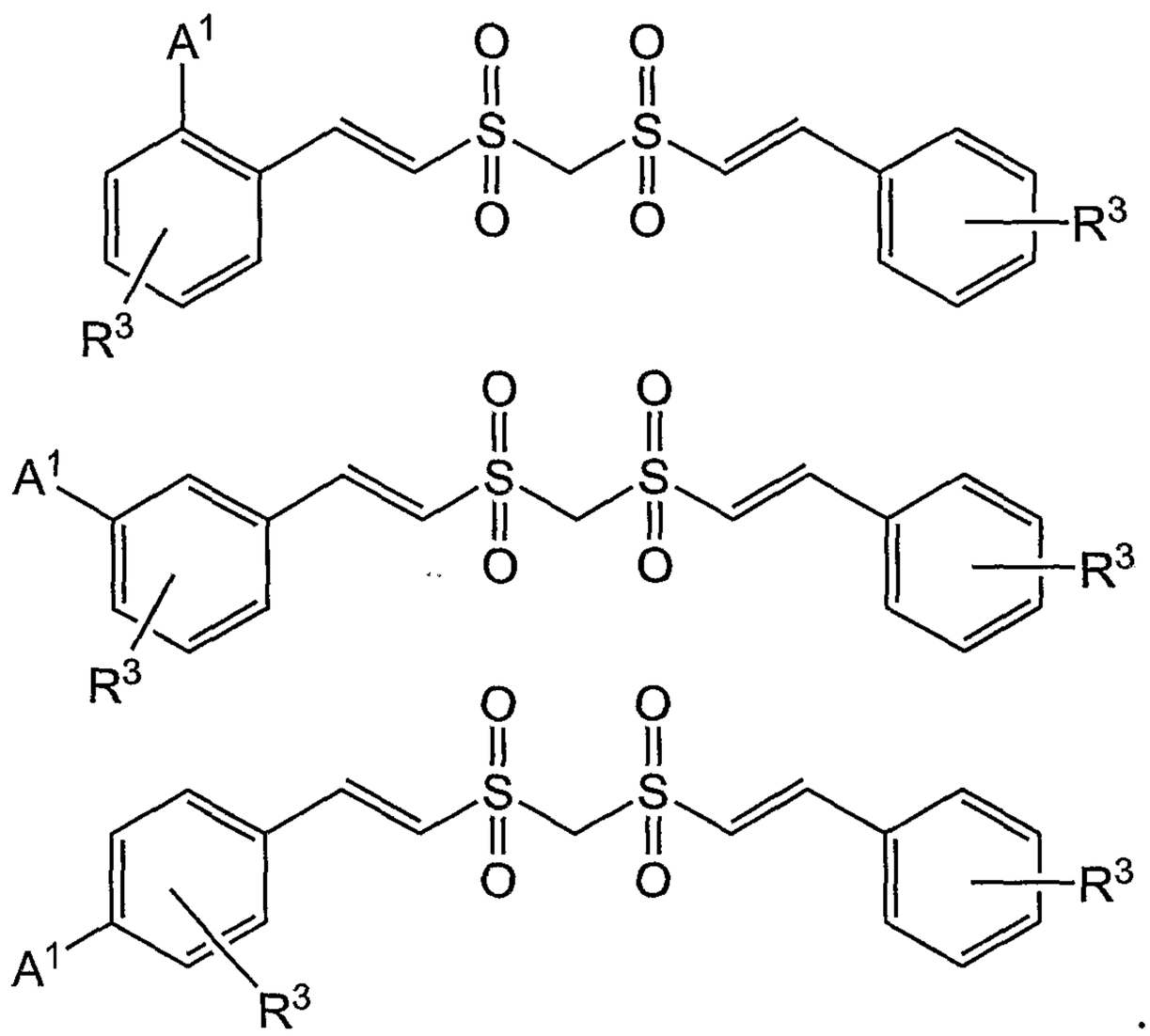
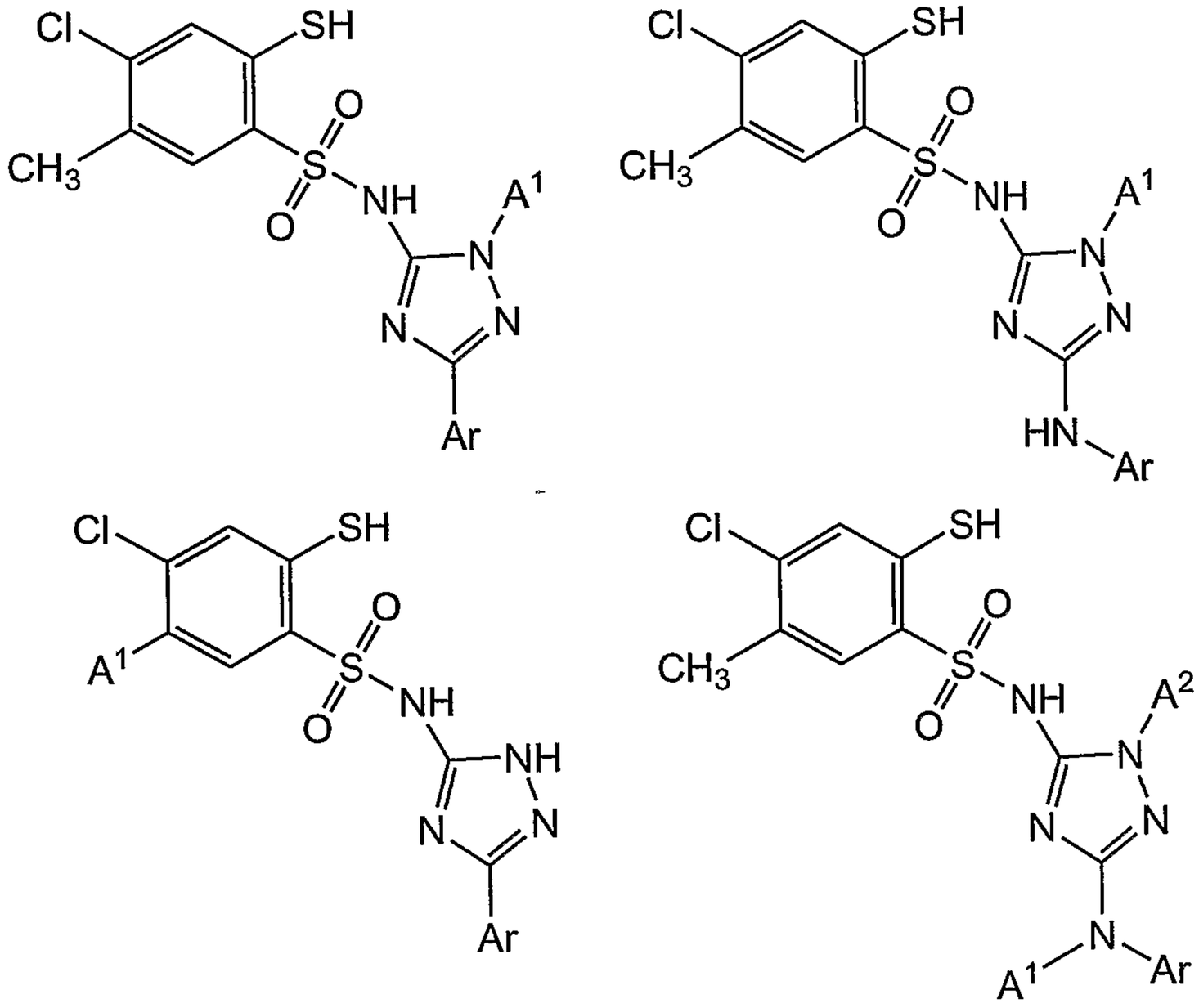
136. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXIV structures:

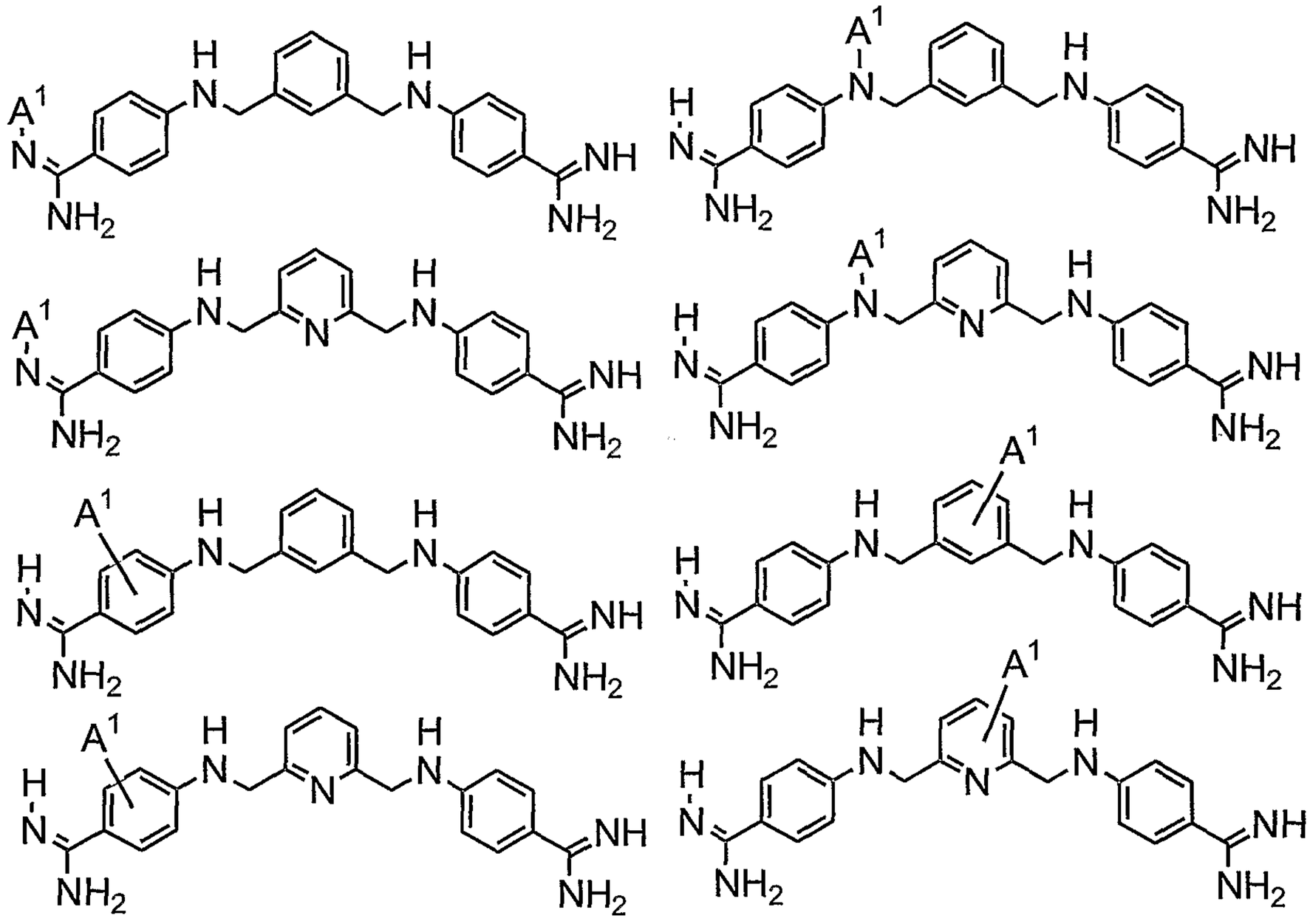


137. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXIV structures:

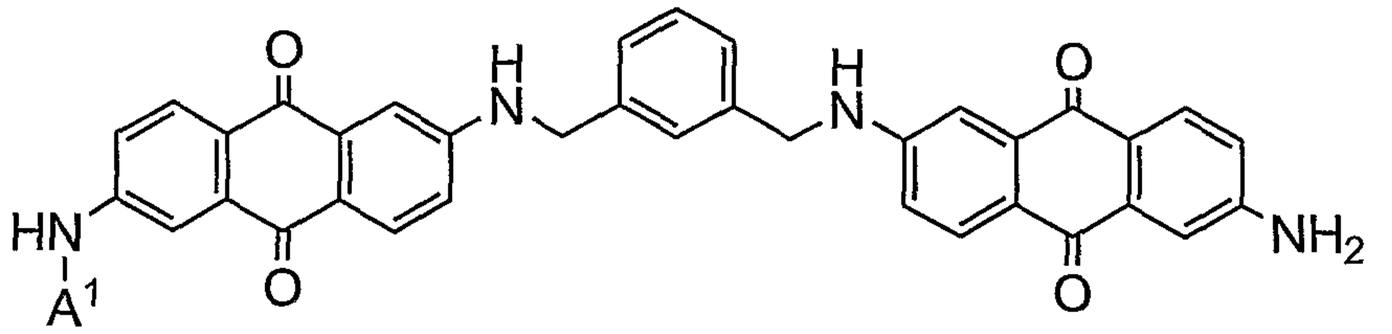


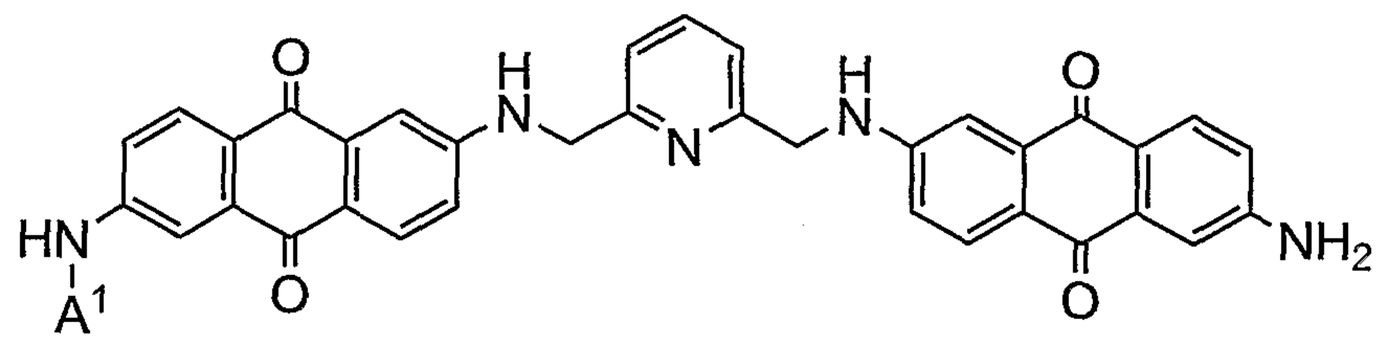
where Ar is carbocycle or heterocycle.

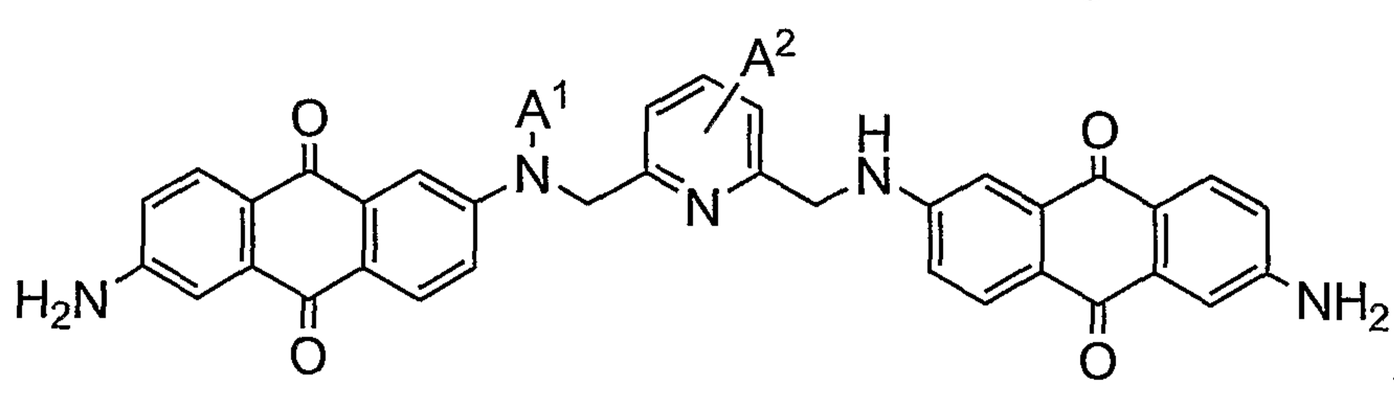
138. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXV structures:



139. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXV structures:







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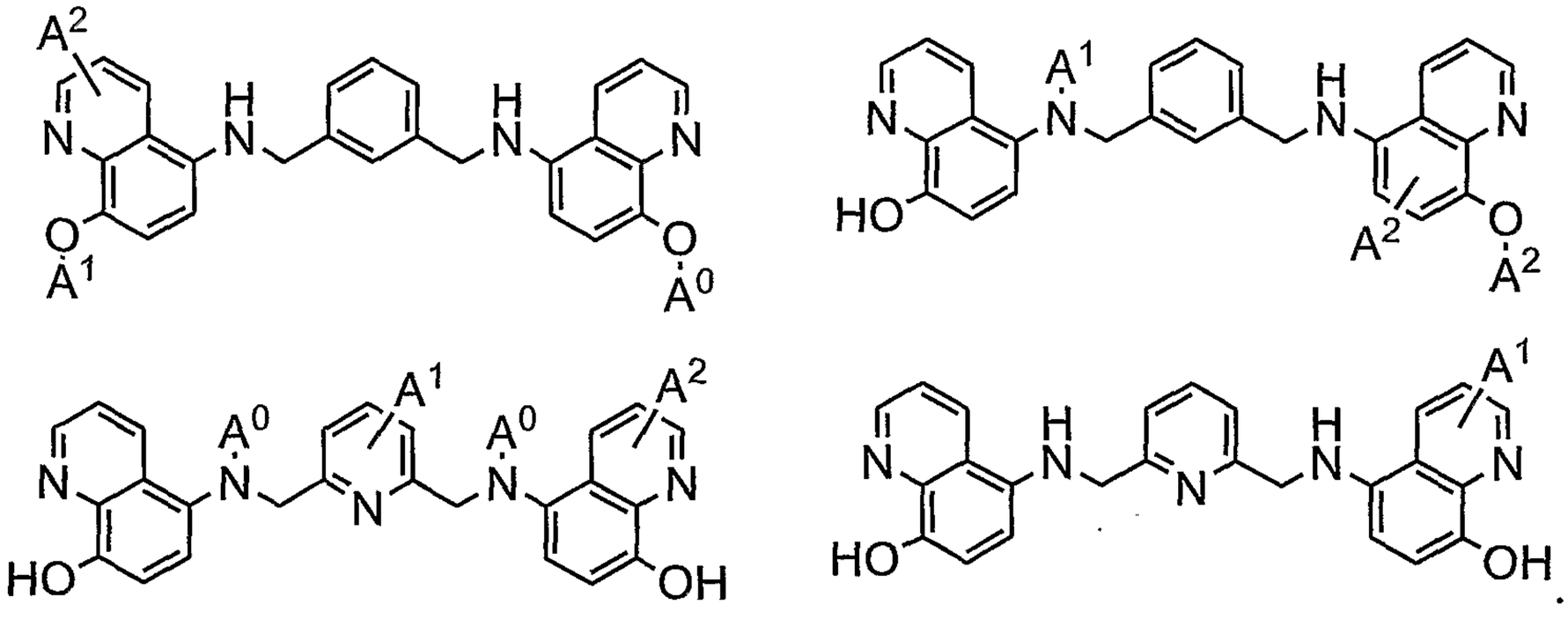
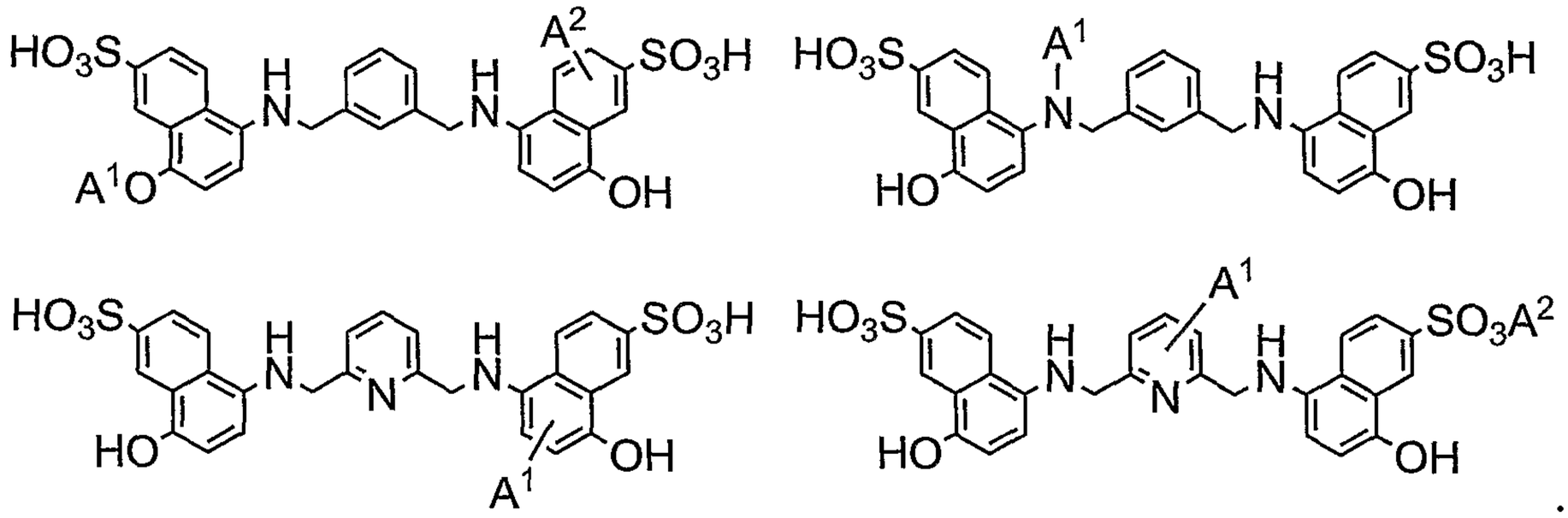
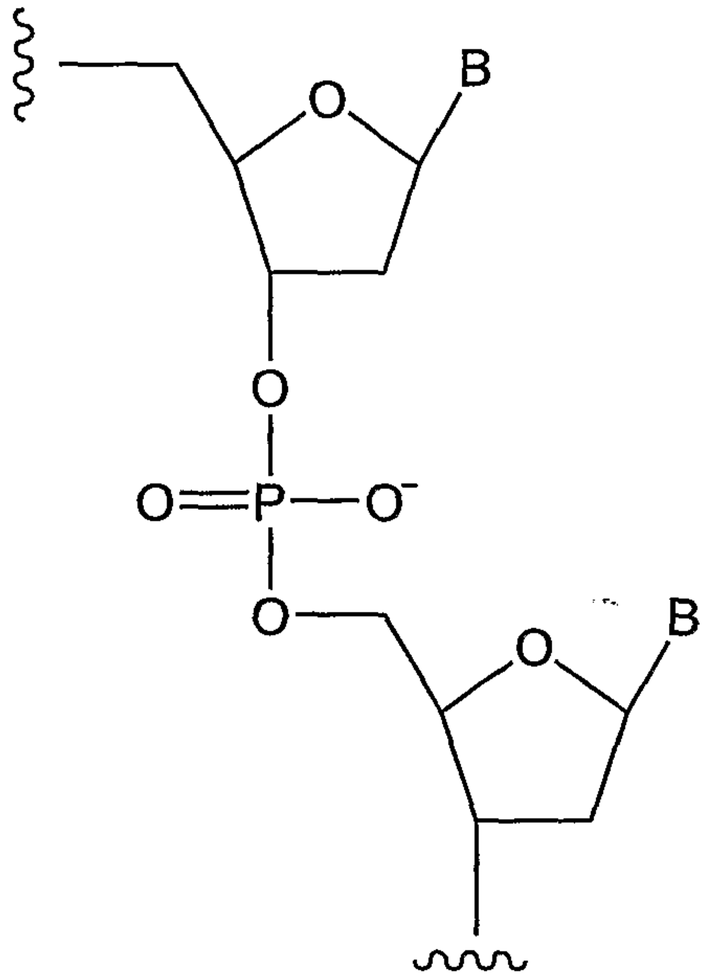
140. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXV structures:



141. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXV structures:

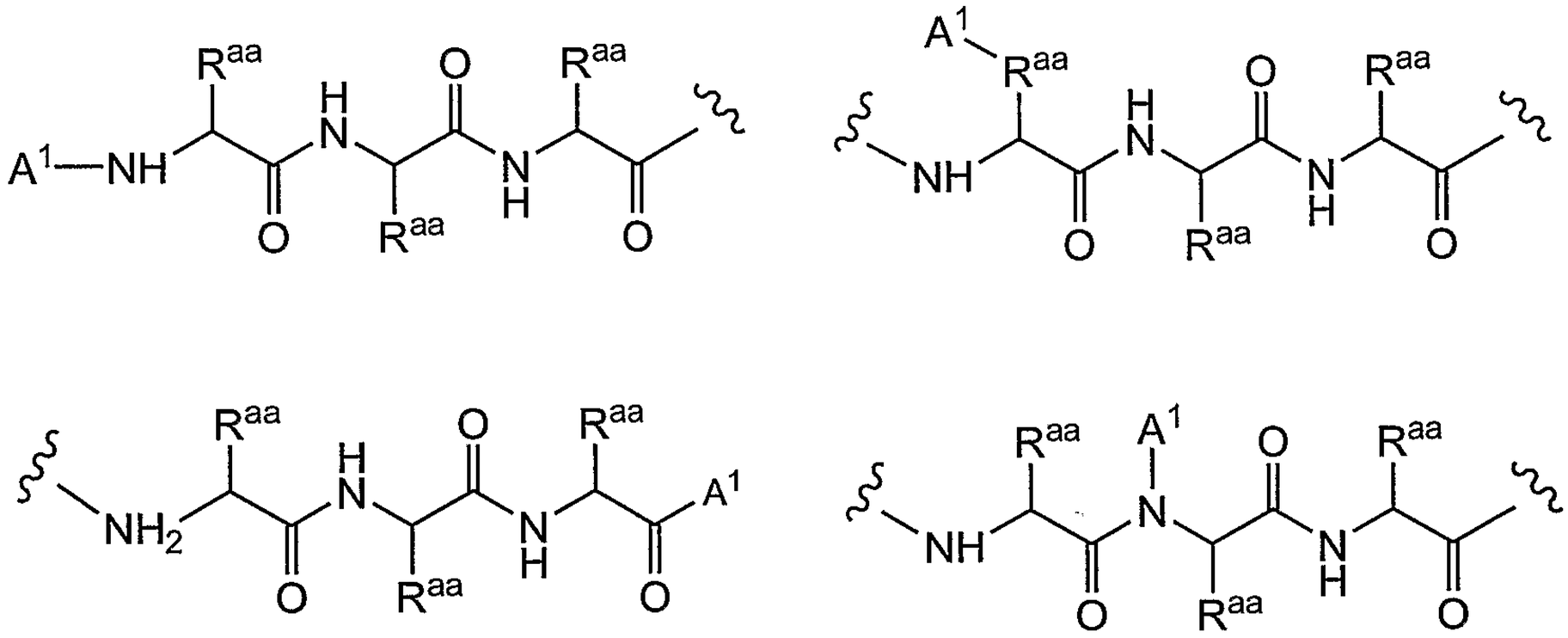


142. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXVI structure:



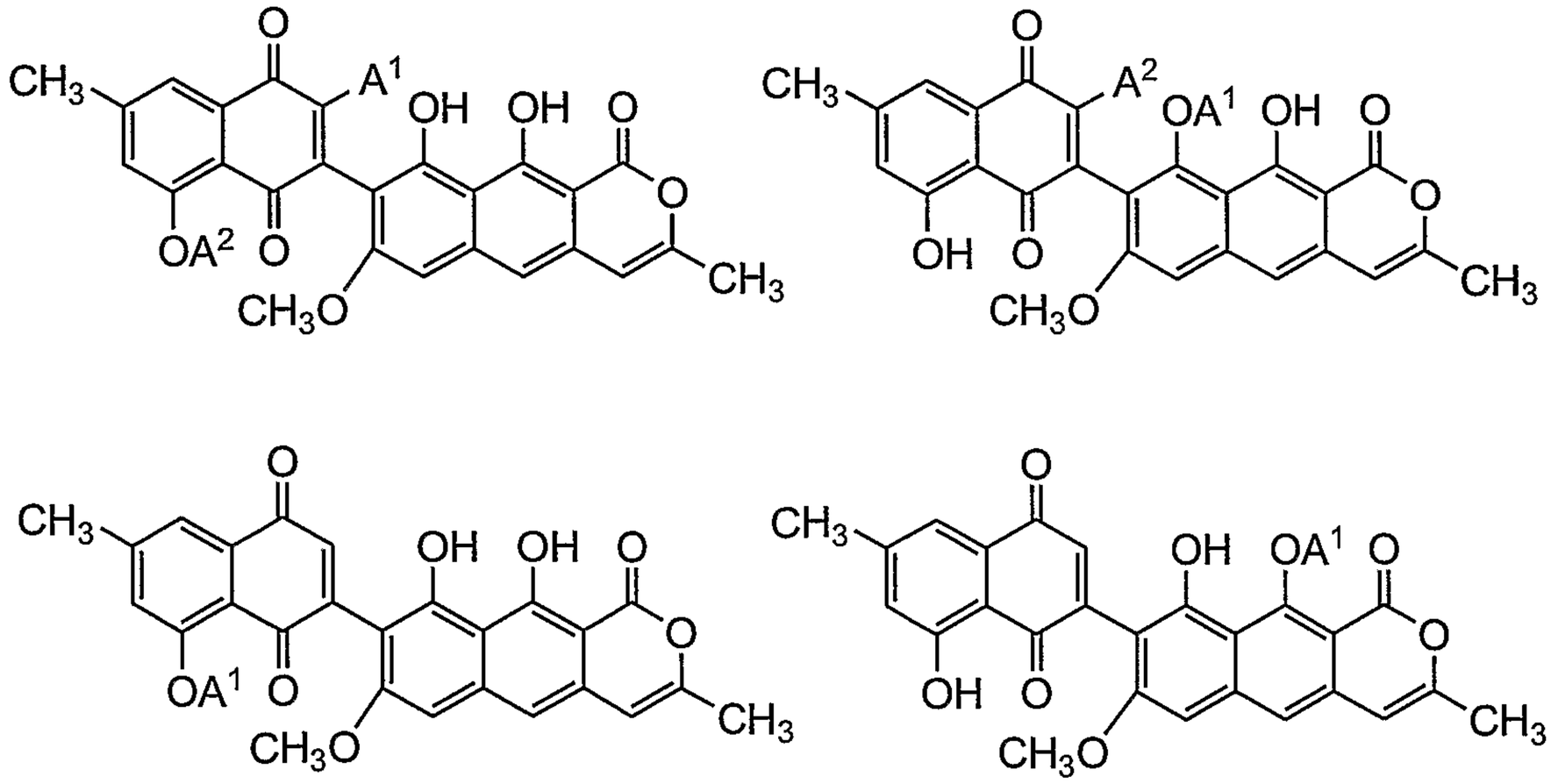
wherein the wavy lines indicate additional nucleotide units in the molecule; B is a nucleobase, and the Formula XXXVI compound comprises at least one A^1 group covalently attached at the 5' terminus, the 3' terminus, an internucleotide phosphate linkage, a sugar, or a nucleobase moiety.

143. An HIV integrase inhibitor compound of claim 2 comprising the Formula XXXVII structures:

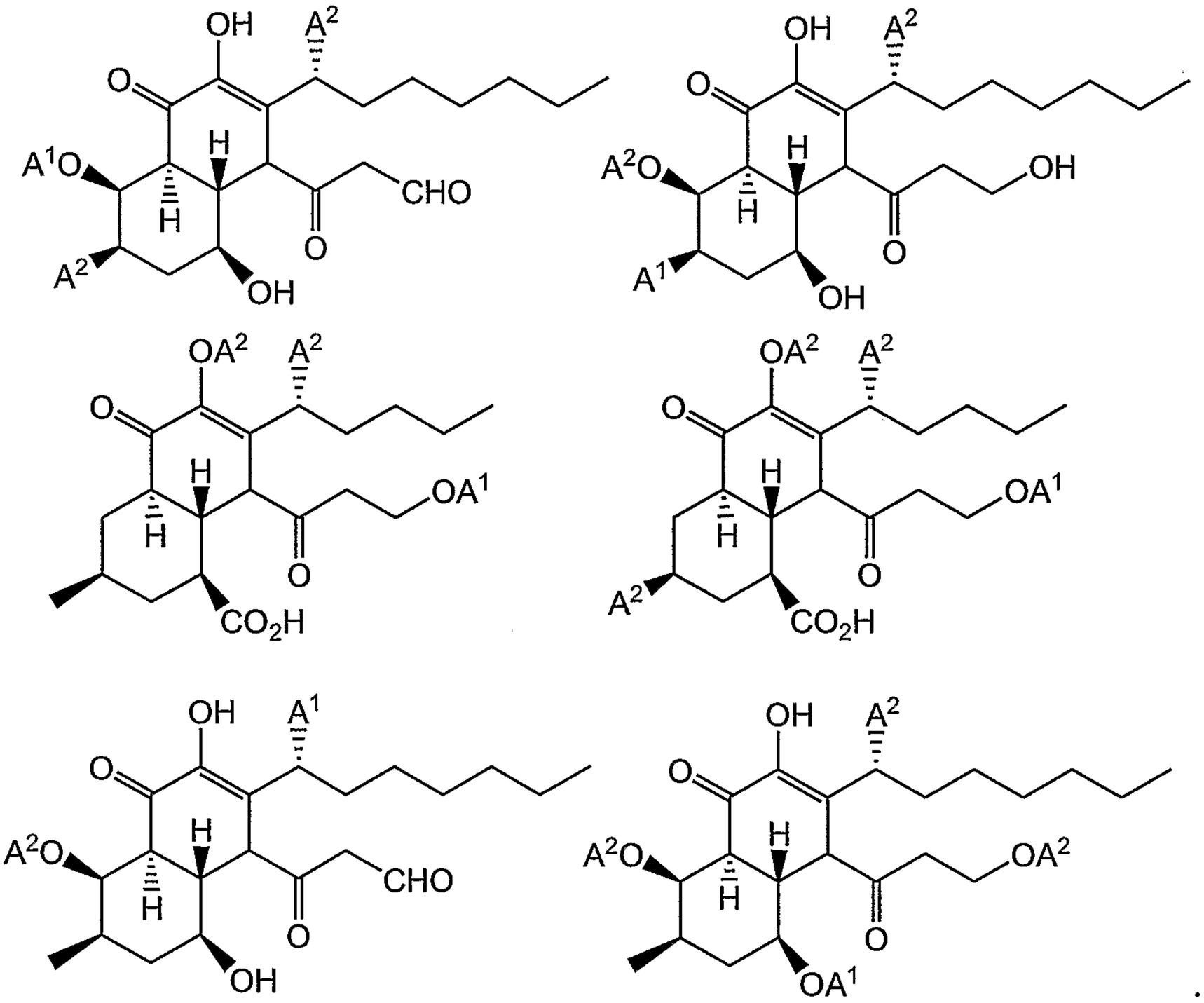


where R^{aa} is an amino acid side chain.

144. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXVIII structures:

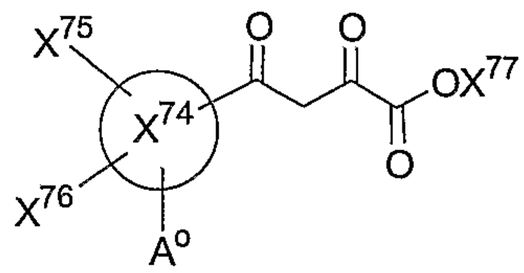


145. An HIV integrase inhibitor compound of claim 2 selected from the Formula XXXIX structures:

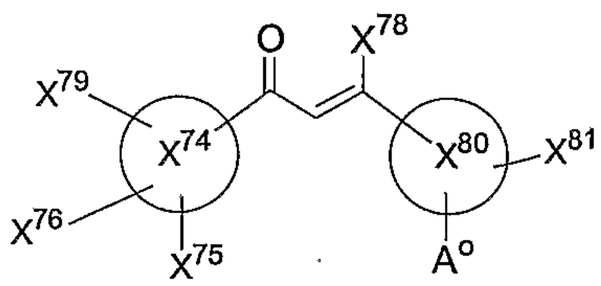


146. An HIV integrase inhibitor compound of claim 2 wherein the compound is not 4-(3-benzyl-phenyl)-2-hydroxy-4-oxo-but-2-enoic acid, 1-[5-(4-fluoro-benzyl)-furan-2-yl]-3-hydroxy-3-(1H-[1,2,4]triazol-3-yl)-propenone, or 5-(1,1-dioxo-1l6-[1,2]thiazinan-2-yl)-8-hydroxy-quinoline-7-carboxylic acid 4-fluoro-benzylamide comprising one or more covalently attached A^0 groups.

147. An HIV integrase inhibitor compound of claim 2 wherein the compound is not:



wherein X^{74} (-X^{75}, -X^{76}) is not phenyl substituted with benzyl and X^{77} is not hydrogen; or the compound is not:



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wherein X^{74} (-X^{75}, -X^{76} , -X^{79}) is not furan substituted with p-fluorobenzyl, when X^{78} is hydroxy, and X^{80} (-X^{81}) is *1H*-[1,2,4]triazole.

148. An HIV integrase inhibitor compound of claim 1 comprising a phosphonate prodrug and capable of accumulating in human PBMC.

149. The compound of claim 148 wherein the bioavailability of the compound or an intracellular metabolite of the compound in human PBMC is improved when compared to the analog of the compound not having the phosphonate or phosphonate prodrug.

150. The compound of claim 148 wherein the intracellular half-life of the compound or an intracellular metabolite of the compound in human PBMC is improved when compared to the analog of the compound not having the phosphonate or phosphonate prodrug.

151. The compound of claim 150 wherein the half-life is improved by at least about 50%.

152. The compound of claim 150 wherein the half-life is improved by at least about 100%.

153. The compound of claim 150 wherein the intracellular half-life of a metabolite of the compound in human PBMC is improved when compared to an analog of the compound not having the phosphonate or phosphonate prodrug.

154. The compound of claim 152 wherein the half-life is improved by at least about 50%.

155. The compound of claim 152 wherein the half-life is improved by at least about 100%.

156. The compound of claim 152 wherein the half-life is improved by greater than 100%.

157. A pharmaceutical composition comprising a therapeutically effective amount of an HIV integrase inhibitor compound of claim 1 and a pharmaceutically acceptable carrier.

158. The pharmaceutical composition of claim 157 further comprising a therapeutically effective amount of an AIDS treatment agent selected from an HIV inhibitor agent, an anti-infective agent, and an immunomodulator.

159. The pharmaceutical composition of claim 158 wherein the HIV inhibitor agent is an HIV-protease inhibitor.

160. The composition of claim 159 wherein the HIV inhibitor agent is a nucleoside reverse transcriptase inhibitor.

161. The composition of claim 159 wherein the HIV inhibitor agent is a non-nucleoside reverse transcriptase inhibitor.

162. A process for making a pharmaceutical composition comprising combining an HIV integrase inhibitor compound of claim 1 and a pharmaceutically acceptable carrier.

163. A method of inhibiting HIV integrase, comprising the administration to a mammal in need of such treatment of a therapeutically effective amount of an HIV integrase inhibitor compound of claim 1.

164. A method of treating infection by HIV, or of treating AIDS or ARC, comprising administration to a mammal in need of such treatment of a therapeutically effective amount of an HIV integrase inhibitor compound of claim 1.

165. Method of treating a disorder affecting white blood cells, comprising: administering an HIV integrase inhibitor compound of claim 1 comprising phosphonate prodrug to a patient in need of white-blood-cell targeting.

166. Method of targeting a compound to white blood cells, comprising:

selecting an HIV integrase inhibitor compound having a desired pharmaceutical activity and having a first structure;

modifying said first structure by replacing one or more atom of said first structure with an organic substituent comprising a phosphonate group or incipient phosphonate group to provide a compound having a second structure.

167. A method of manufacturing an HIV integrase inhibitor compound having both selectivity for white blood cells and a desired pharmaceutical activity, comprising:

chemically synthesizing a first molecule of claim 1 having a first structure containing a phosphonate or precursor phosphonate group, wherein said first structure differs from a second structure of a compound known to have said desired pharmaceutical activity by having at least one hydrogen atom of said second structure replaced by an organic substituent comprising a phosphonate group or incipient phosphonate group.

168. The method of claim 167, wherein said first molecule is synthesized by a series of chemical reactions in which a hydrogen of said second structure is replaced by said organic substituent.

169. The method of claim 167, wherein said first molecule is synthesized by a series of chemical reactions that never includes a molecule of said second structure.

170. Method of accumulating an HIV integrase inhibitor compound inside a white blood cell, comprising: administering to a sample a composition comprising a compound of claim 1.

171. The method of claim 170 wherein said sample is a human infected with HIV.

172. The method of claim 170 wherein said sample is a human at risk for infection with HIV.

173. A method for the treatment or prevention of the symptoms or effects of HIV infection in an animal which comprises administering to said animal a

formulation comprising a therapeutically effective amount of a compound according to claim 1.

174. The method of claim 173 wherein the compound is formulated with a pharmaceutically acceptable carrier.

175. The use of a compound of claim 1 to prepare a medicament for treatment or prophylaxis of HIV infection.

176. The compound of claim 1 for use in medical therapy or diagnosis.

177. The HIV integrase inhibitor compound of claims 1, 2, or 3 which does not have antiinflamatory activity.

178. The HIV integrase inhibitor compound of any of claims 1, 2, 3, and 177 which does not have immuno-modulatory activity.

179. The HIV integrase inhibitor compound of any of claims 1, 2, 3, 177, and 178 which does not have activity against metabolic diseases.

180. The HIV integrase inhibitor compound of any of claims 1, 2, 3, 177, 178, and 179 which does not have anticancer activity.

181. The HIV integrase inhibitor compound of any of claims 1, 2, 3, 177, 178, 179, and 180 which does not inhibit purine nucleoside phosphorylase.

182. The HIV integrase inhibitor compound of any of claims 1, 2, 3, 177, 178, 179, 180, and 181 which does not have anti-kinase activity.

183. The HIV integrase inhibitor compound of any of claims 1, 2, 3, 177, 178, 179, 180, 181, and 182 which does not have anti-metabolite activity.

184. The HIV integrase inhibitor compound of any of claims 1, 2, 3, 177, 178, 179, 180, 181, 182, and 183 which does not have anti-IMPDH activity.

185. The HIV integrase inhibitor compound of any of claims 1, 2, 3, 177, 178, 179, 180, 181, 182, 183, and 184 which does not have nucleoside activity.