PRE-ORGANIZED TRICYCLIC INTEGRASE INHIBITOR COMPOUNDS

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV) infection and related diseases are a major public health problem worldwide. A virally encoded integrase protein mediates specific incorporation and integration of viral DNA into the host genome. Integration is necessary for viral replication. Accordingly, inhibition of HIV integrase is an important therapeutic pursuit for treatment of HIV infection of the related diseases.

Human immunodeficiency virus type 1 (HIV-1) encodes three enzymes which are required for viral replication: reverse transcriptase, protease, and integrase. Although drugs targeting reverse transcriptase and 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, etal *N. Engl. J. Med.* (1998) 338:853-860; Richman, D. D. *Nature* (2001) 410:995-1001). There is a need for new agents directed against alternate sites in the viral life cycle. Integrase has emerged as an attractive target, because it is necessary for stable infection and homologous enzymes are lacking in the human host (LaFemina, etal *J. Virol.* (1992) 66:7414-7419). The function of integrase is to catalyze integration of proviral DNA, resulting from the reverse transcription of viral RNA, into the host genome, by a stepwise fashion of endonucleolytic processing of proviral DNA within a cytoplasmic preintegration complex (termed 3'-processing or "3'-P") with specific DNA sequences at the end of the HIV-1 long terminal repeat (LTR) regions, followed by

translocation of the complex into the nuclear compartment where integration of 3'-processed proviral DNA into host DNA occurs in a "strand transfer" (ST) reaction (Hazuda, etal *Science* (2000) 287:646-650; Katzman, etal *Adv. Virus Res.* (1999) 52:371-395; Asante-Applah, etal *Adv. Virus Res.* (1999) 52:351-369). Although numerous agents potently inhibit 3'-P and ST in extracellular assays that employ recombinant integrase and viral long-terminal-repeat oligonucleotide sequences, often such inhibitors lack inhibitory potency when assayed using fully assembled preintegration complexes or fail to show antiviral effects against HIV-infected cells (Pommier, etal *Adv. Virus Res.* (1999) 52:427-458; Farnet, etal *Proc. Natl. Acad. Sci. U.S.A.* (1996) 93:9742-9747; Pommier, etal *Antiviral Res.* (2000) 47:139-148.

Certain HIV integrase inhibitors have been disclosed which block integration in extracellular assays and exhibit good antiviral effects against HIV-infected cells (Anthony, etal WO 02/30426; Anthony, etal WO 02/30930; Anthony, etal WO 02/30931; WO 02/055079; Zhuang, etal WO 02/36734; US 6395743; US 6245806; US 6271402; Fujishita, etal WO 00/039086; Uenaka etal WO 00/075122; Selnick, etal WO 99/62513; Young, etal WO 99/62520; Payne, etal WO 01/00578; Jing, etal *Biochemistry* (2002) 41:5397-5403; Pais, etal *Jour. Med. Chem.* (2002) 45:3184-94; Goldgur, etal *Proc. Natl. Acad. Sci. U.S.A.* (1999) 96:13040-13043; Espeseth, etal *Proc. Natl. Acad. Sci. U.S.A.* (2000) 97:11244-11249).

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, etal *Jour. Med. Chem.* (2002) 45:841-852) of conformationally-restrained cinnamoyl-type integrase inhibitors (Artico, etal *Jour. Med. Chem.* (1998) 41:3948-3960) have correlated hydrogen-bonding interactions to the inhibitory activity differences among the compounds.

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

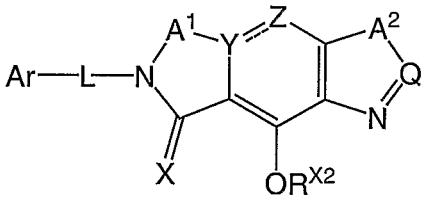
the inhibitory drug with its intracellular target, while minimizing intercellular redistribution of the drug, e.g. to neighboring cells, is often difficult or inefficient.

Most agents currently administered parenterally to a patient 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 which allow accumulation or retention of biologically active agents inside cells.

SUMMARY OF THE INVENTION

The present invention provides compositions and methods for inhibition of HIV integrase.

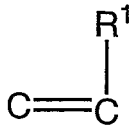
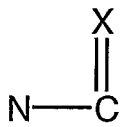
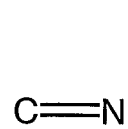
In one aspect, the invention comprises a compound having the structure:



wherein:

A^1 and A^2 are 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;

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

Y=Z is  ,  , or  ;

L is selected from a bond, O, S, S–S, S(=O), $S(=O)_2$, $S(=O)_2NR$, 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, 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;

X is selected from O, S, NH, NR, N–OR, $N–NR_2$, $N–CR_2OR$ and $N–CR_2NR_2$;

Ar is selected from 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;

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

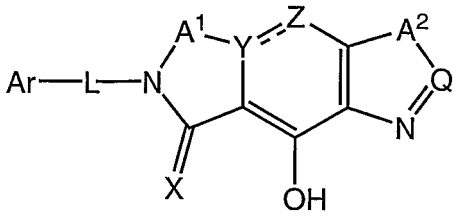
R is independently selected from H, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl, polyethyleneoxy, phosphonate, phosphate, and a prodrug moiety;

R^{X2} is independently selected from H, 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, polyethyleneoxy, phosphonate, phosphate, a prodrug, a pharmaceutically acceptable prodrug, a prodrug moiety, a protecting group, and a phosphonate prodrug moiety;

and the salts, solvates, resolved enantiomers and purified diastereomers thereof;

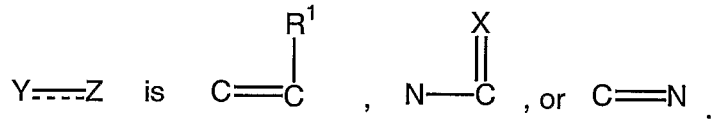
with the proviso that when Y=Z is C=C(OH), X is O, A^1 is C(=O), A^2 is $C(R^2)=C(R^3)$, and Q is CH, then L is not a bond.

In one aspect, the invention includes tricyclic compounds represented by the following structure:



The compounds of the invention share a tricyclic scaffold and a potential active site or metal binding motif defined by the lower side of the Formula above including the amide-type functionality, i.e. N-C(=X), of the left ring, the aromatic hydroxyl of the middle ring, and the nitrogen of the right ring. The compounds of the invention have binding functionality, e.g. nitrogen, hydroxyl, and X-carbonyl, in a pre-organized configuration which may confer optimized inhibitory properties against HIV integrase.

A^1 and A^2 are each and independently a moiety forming a five, six, or seven membered ring. Q is N, substituted nitrogen (NR), CH, or substituted carbon. L is a bond or a linker connecting a ring atom of Ar to N. X is O, S, NH, or substituted nitrogen (NR). Ar is a carbocycle, aryl or heteroaryl group. R is a substituent including H, alkyl, aryl, heteroaryl and substituted forms thereof, as well as polyethyleneoxy, phosphonate, phosphate, or a prodrug moiety. The 5 and 6 positions are represented in the structure above by Y and Z respectively. The chemical bond between Y and Z may be a single bond, a double bond, or a bond with enolic, tautomeric character, depending on the substituent on Z, i.e. R^1 or X. The Y and Z substructure is represented wherein:



The compounds of the invention may include prodrug moieties covalently attached at any site. The prodrug moiety may be a phosphonate group.

The invention also includes a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

The invention also includes a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of an AIDS

treatment agent selected from an HIV inhibitor agent, an anti-infective agent, and an immunomodulator. The HIV inhibitor agent may include an HIV-protease inhibitor, a nucleoside reverse transcriptase inhibitor, or a non-nucleoside reverse transcriptase inhibitor.

The invention also includes methods of preventing the proliferation of HIV virus, treating AIDS, delaying the onset of AIDS or ARC symptoms, and generally inhibiting HIV integrase. The methods comprise administering to a mammal infected with HIV (HIV positive) an amount of a compound of the invention, in a therapeutically effective dose or administration to inhibit the growth of HIV infected cells of the mammal.

In another aspect of the invention, the activity of HIV integrase is inhibited by a method comprising the step of treating a sample suspected of containing HIV virus with a compound or composition of the invention.

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

This invention also includes methods of increasing cellular accumulation, bioavailability, or retention of drug compounds, thus improving their therapeutic and diagnostic value, by administering a phosphonate prodrug form of a compound of the invention.

Another aspect of the invention provides a method for inhibiting the activity of HIV integrase comprising the step of contacting a sample suspected of containing HIV virus with the composition embodiments of the invention.

In other aspects, novel methods for the synthesis, analysis, separation, isolation, crystallization, purification, characterization, resolution of isomers including enantiomers and diastereomers, and testing of the compounds of this invention are provided.

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 descriptions, structure 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:

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, and nitrogen substituents. These substituents may be part of a prodrug moiety. As defined herein, "phosphonate" and "phosphonate group" include molecules with phosphonic acid, phosphonic monoester, phosphonic diester, phosphonamidate, phosphondiamidate, 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.

"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 prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy. A "prodrug" is thus a covalently modified analog of a therapeutically-active compound.

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 etal (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4,816,570, 4,968,788, 5,663,159 and 5,792,756. 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) $-CH_2OC(=O)C(CH_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-CH_2OC(=O)OC(CH_3)_3$.

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. Exemplary phosphonate prodrug moieties include by way of example and not limitation groups of the structure A^3.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (DeLambert etal (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 etal (1992) *J. Chem. Soc. Perkin Trans. I* 2345; Brook etal WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier etal 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 etal (1993) *Antiviral Res.*, 22: 155-174; Benzaria etal (1996) *J. Med. Chem.* 39: 4958). Cyclic phosphonate esters have also been described as prodrugs of phosphorus-containing compounds (Erion etal, 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, which is incorporated herein by reference. 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. Exemplary protecting groups include by way of example and

not limitation groups of the structure R^X other than hydrogen.

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 metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1–C_4 alkyl). Physiologically acceptable salts of an hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound of 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(CH3)C(CH3)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_2 $CH_2CH_2CH_2$CH=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≡CH),

The terms "alkylene" and "alkyldiyl" each refer 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, i.e. double carbon-carbon bond moiety. 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, i.e. triple carbon-carbon bond moiety. 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. Typical aryl groups include, but are not limited to, radicals derived from benzene, substituted benzene, naphthalene, anthracene, biphenyl, and the like.

"Heteroaryl" means a monovalent aromatic radical of one or more carbon atoms and one or more atoms selected from N, O, S, or P, derived by the removal of one hydrogen atom from a single atom of a parent aromatic ring system. Heteroaryl groups 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). Heteroaryl bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 hetero atoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The heteroaryl group may be bonded to the drug scaffold through a carbon, nitrogen, sulfur, phosphorus or other atom by a stable covalent bond.

Heteroaryl groups include, for example: pyridyl, dihydropyridyl isomers, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl.

"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.

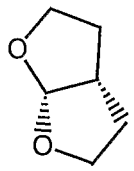
Substituted substituents such as "substituted alkyl", "substituted aryl", "substituted heteroaryl" and "substituted arylalkyl" mean alkyl, aryl, and arylalkyl respectively, in which one or more hydrogen atoms are each independently replaced with a substituent. Typical substituents include, but are not 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.

"Heterocycle" means a saturated, unsaturated or aromatic ring system including at least one N, O, S, or P. Heterocycle thus include heteroaryl groups. Heterocycle as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A. "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in

particular Volumes 13, 14, 16, 19, and 28; Katritzky, Alan R., Rees, C.W. and Scriven, E. "Comprehensive Heterocyclic Chemistry" (Pergamon Press, 1996); 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-indazoly, 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 system 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. Carbocycle thus includes some aryl groups.

"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. Linkers include L interposed between Ar and the nitrogen of the tricyclic compounds of the invention. The structures herein may refer to linkers as "link" or "L". Linkers may also be interposed between a phosphorus-containing A^3 group and the R^1, R^2, R^3, or R^4 position of the compounds of the invention. Linkers include, but are not limited to moieties such as 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 also include 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.

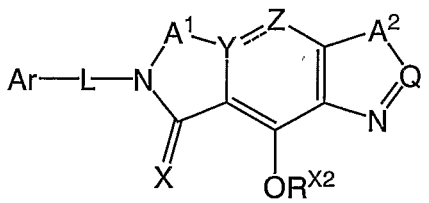
"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

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 COMPOUNDS

Novel tricyclic compounds with inhibitory activity against HIV integrase are described, including any pharmaceutically acceptable salts thereof.

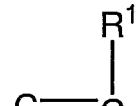
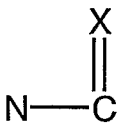
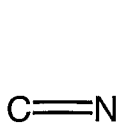
In one aspect, the invention comprises a compound having the structure:



wherein:

A^1 and A^2 are 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;

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

Y⁼⁼⁼Z is  ,  , or  ;

L is selected from a bond, O, S, S–S, S(=O), $S(=O)_2$, $S(=O)_2NR$, 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, 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;

X is selected from O, S, NH, NR, N–OR, $N–NR_2$, $N–CR_2OR$ and $N–CR_2NR_2$;

Ar is selected from 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;

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 is independently selected from H, 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, polyethyleneoxy, phosphonate, phosphate, and a prodrug moiety;

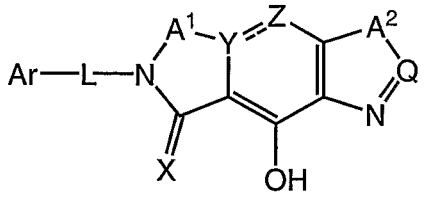
R^{X2} is independently selected from H, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl,

polyethyleneoxy, phosphonate, phosphate, a prodrug, a pharmaceutically acceptable prodrug, a prodrug moiety, a protecting group, and a phosphonate prodrug moiety;

and the salts, solvates, resolved enantiomers and purified diastereomers thereof;

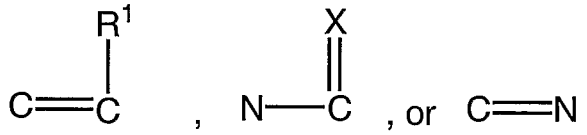
with the proviso that when Y=Z is C=C(OH), X is O, A^1 is C(=O), A^2 is $C(R^2)=C(R^3)$, and Q is CH, then L is not a bond.

In one aspect, the compounds are pre-organized with constrained conformations that include an active form for inhibition of nuclear integration of reverse-transcribed HIV DNA. The invention includes tricyclic compounds represented by the following structure:



A^1 and A^2 are each and independently any moiety forming a five, six, or seven membered ring. A^1 and A^2 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  .

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, 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.

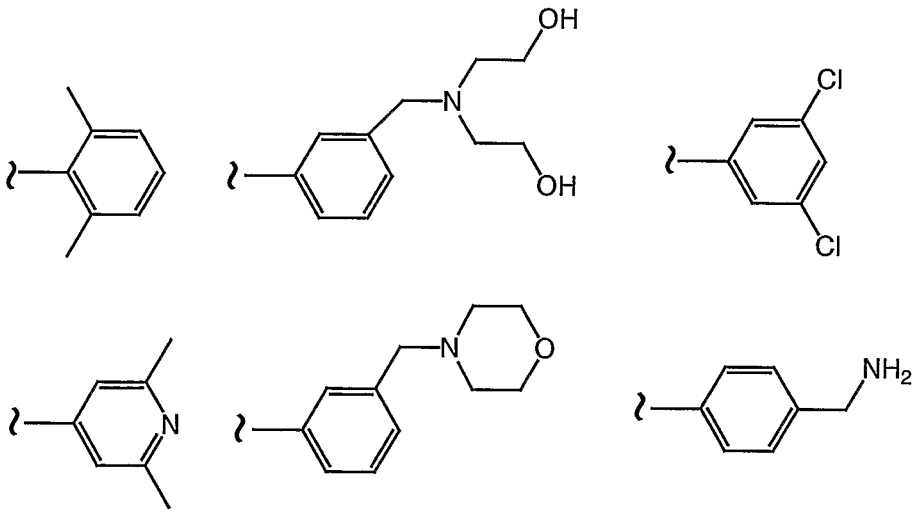
X may be O, S, NH, NR, N–OR, N–NR_2, N–CR_2OR or N–CR_2NR_2.

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.

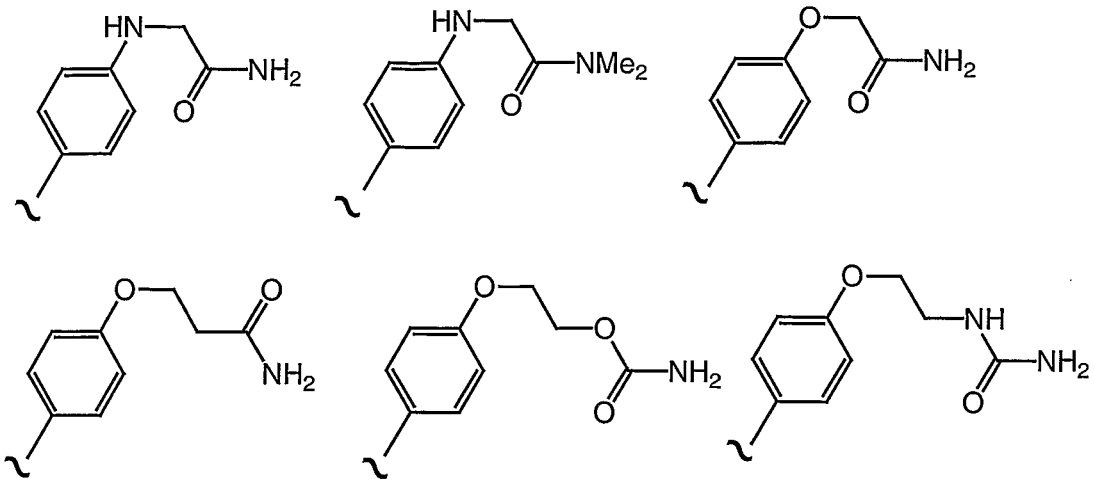
For example, Ar may be C_3–C_{12} carbocycle, C_3–C_{12} substituted carbocycle, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, or C_2–C_{20} substituted heteroaryl.

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:

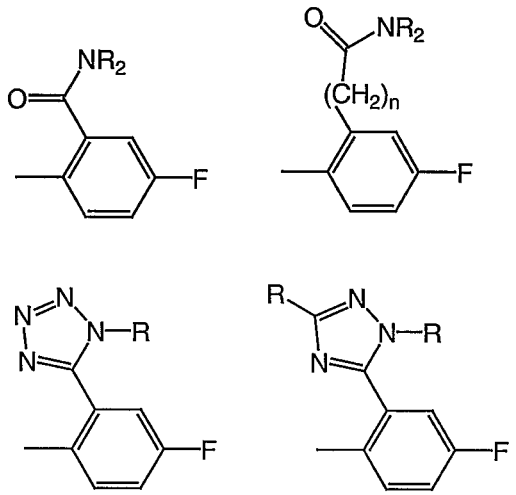


Other examples of substituted phenyl groups include:



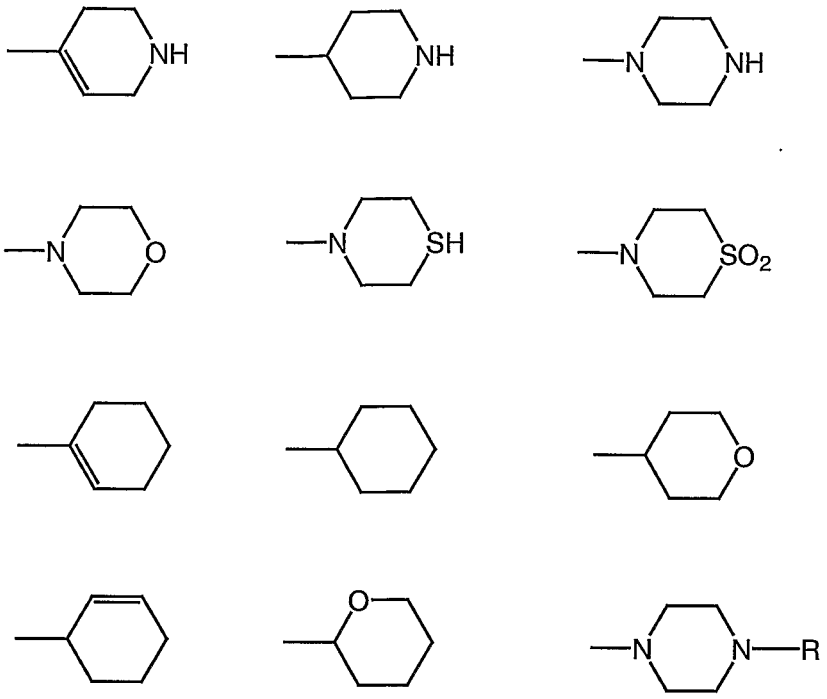
where a wavy line ~, in any orientation, indicates the covalent attachment site to L.

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

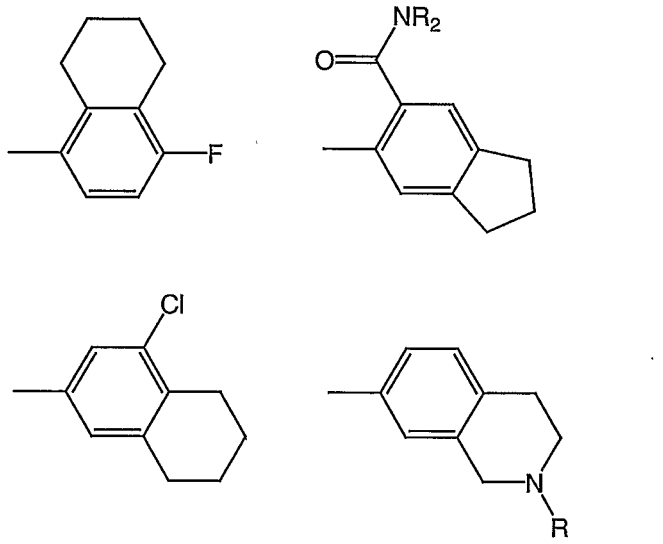


where n is 1 to 6.

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:

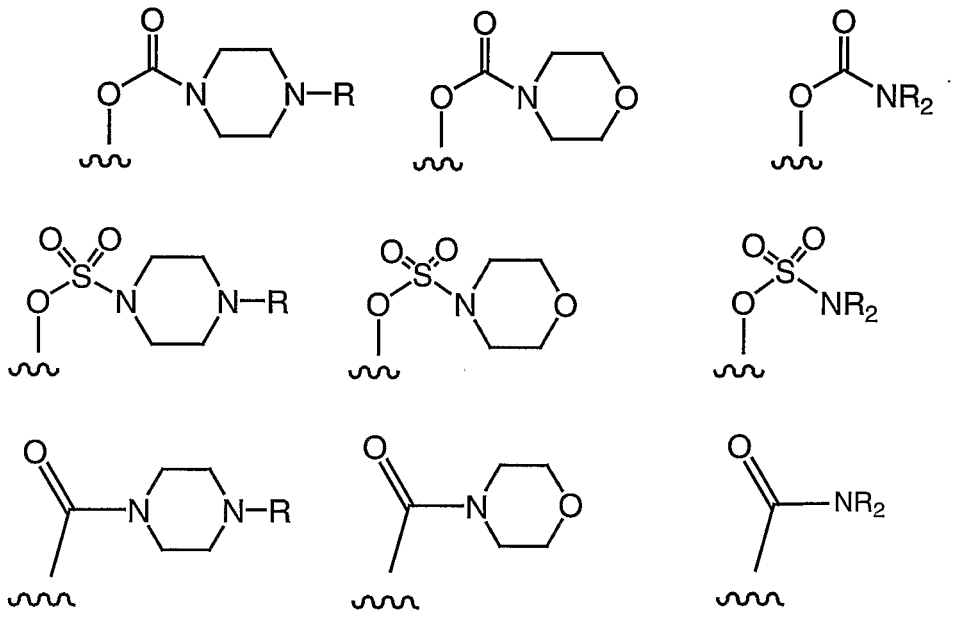


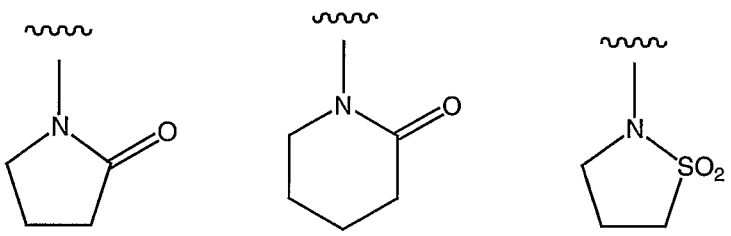
R^1, R^2, R^3, and R^4, and substituents of Ar, may independently be H, F, Cl, Br, I, OH, amino ($-NH_2$), ammonium ($-NH_3^+$), alkylamino, dialkylamino, trialkylammonium, C_1-C_8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, C_1-C_8 alkylsulfonate, C_1-C_8 alkylamino, 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

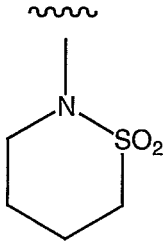
($-C(=O)NR_2$), 5-7 membered ring lactam, 5-7 membered ring lactone, nitrile (–CN), azido ($-N_3$), nitro ($-NO_2$), C_1–C_8 alkoxy (–OR), C_1–C_8 trifluoroalkyl, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_3–C_{12} carbocycle, C_3–C_{12} substituted carbocycle, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl, phosphonate, phosphate, polyethyleneoxy, and a prodrug moiety.

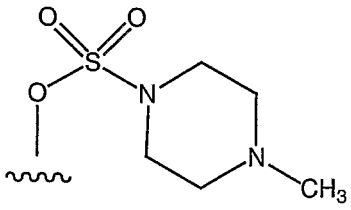
R^1, R^2, R^3, and R^4 also include: $-OC(=O)OR$, $-OC(=O)NR_2$, $-OC(=S)NR_2$, $-OC(=O)NRNR_2$, $-OC(=O)R$, $-C(=O)OR$, $-C(=O)NR_2$, $-C(=O)NRNR_2$, $-C(=O)R$, $-OSO_2NR_2$ (sulfamate), $-NR_2$, $-NRSO_2R$, $-NRC(=S)NR_2$, –SR, –S(O)R, $-SO_2R$, $-SO_2NR_2$ (sulfonamide), $-OSO_2R$ (sulfonate), $-P(=O)(OR)_2$,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

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





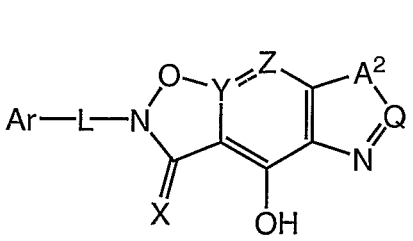


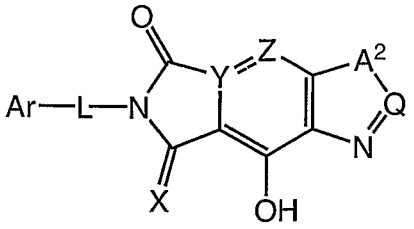


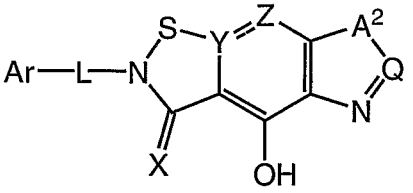
where the wavy line indicates the point of covalent attachment on the tricyclic structure.

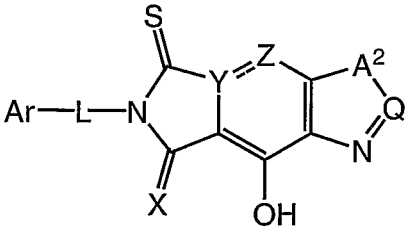
R may be independently selected from H, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, C_2–C_{20} substituted heteroaryl, polyethyleneoxy, phosphonate, phosphate, and a prodrug moiety. Two R groups may form a ring, such as when the two R groups are bonded to a nitrogen atom and form a ring such as aziridinyl, azetidinyl, pyrrolidinyl, pyrazinyl, imidazolyl, piperidyl, piperazinyl, pyridinium, or morpholino.

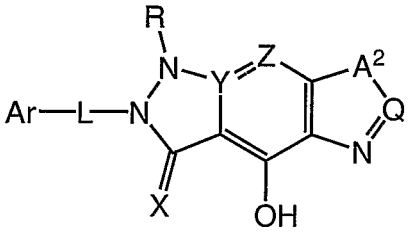
The following embodiments of A^1 and A^2 in the compounds of the invention include but are not limited to the following structures. Various embodiments of A^1 form 5-membered rings in the exemplary structures:

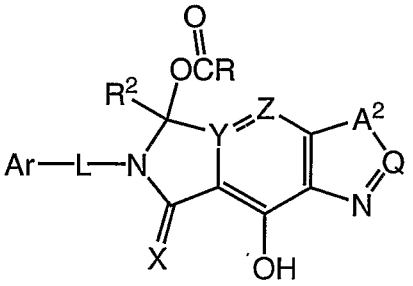


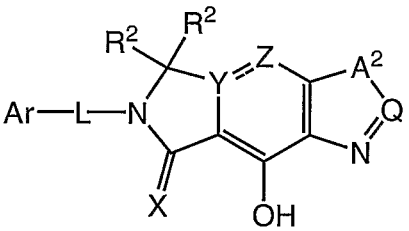


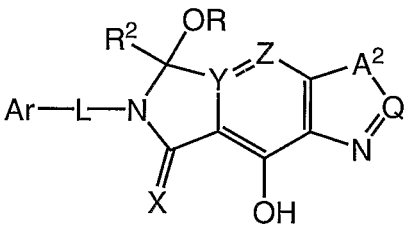


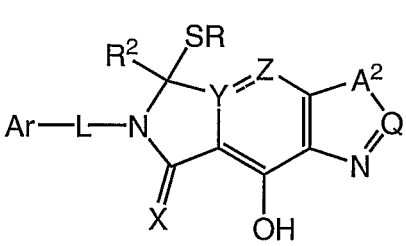


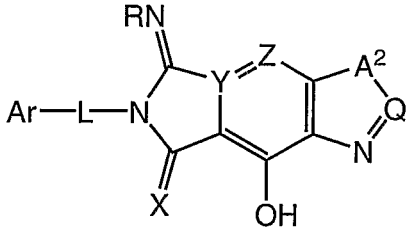




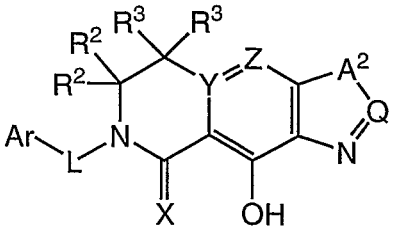
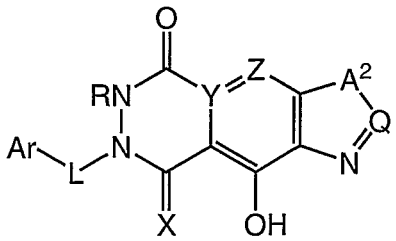
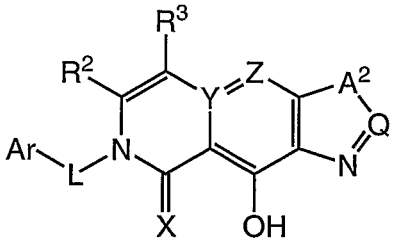
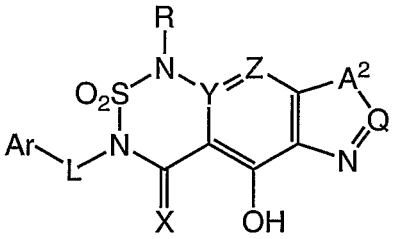
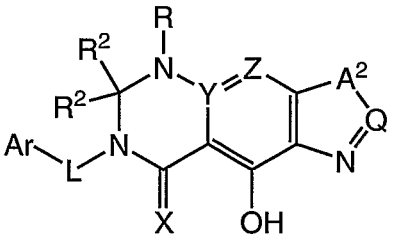
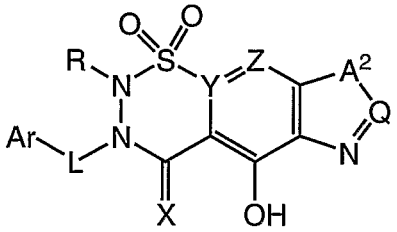
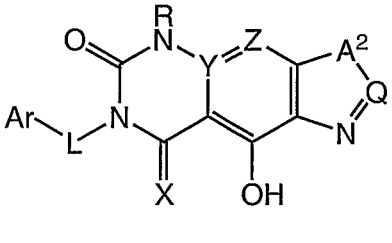
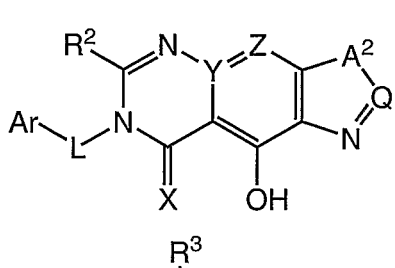
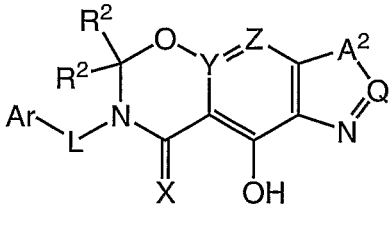
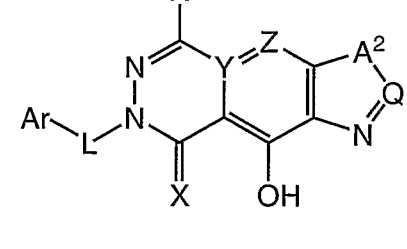




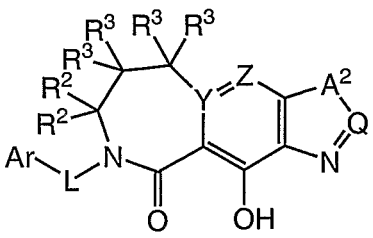


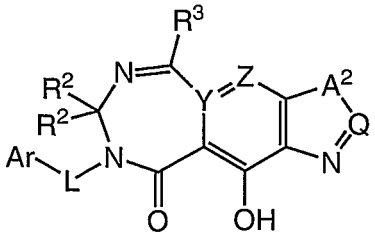


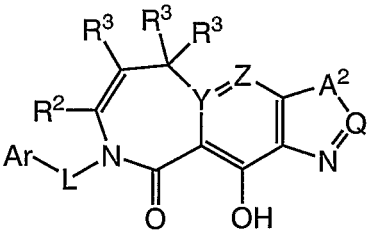
Various embodiments of A^1 form 6-membered rings in the exemplary structures:

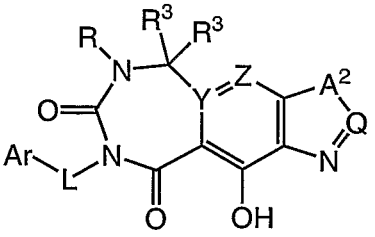











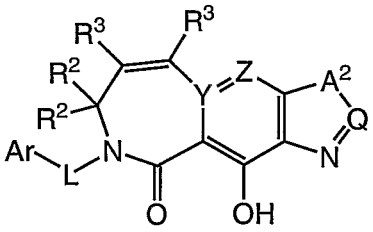
Various embodiments of A^1 form 7-membered rings in the exemplary structures:

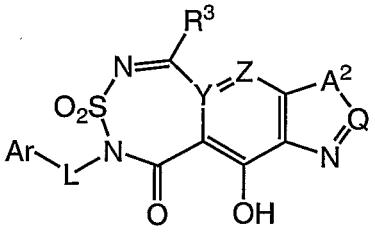


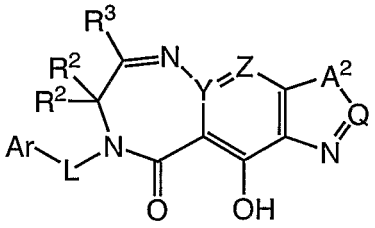




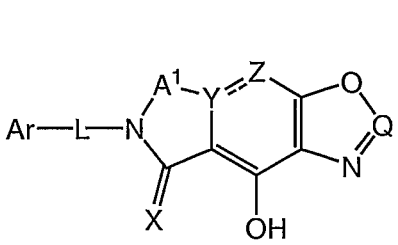


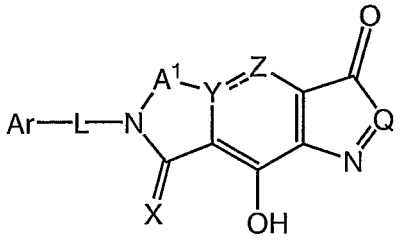


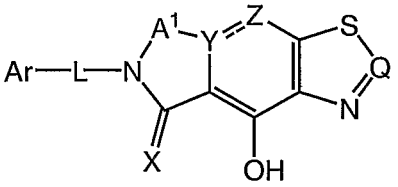


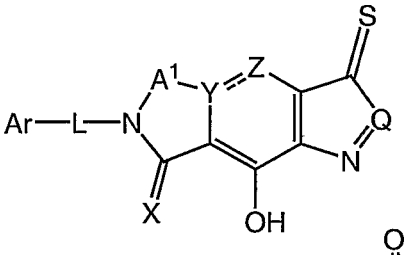


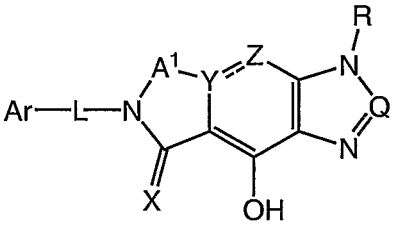
Various embodiments of A^2 form 5-membered rings in the exemplary structures:

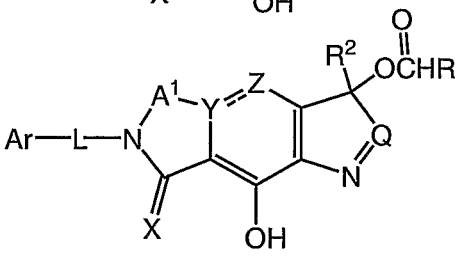


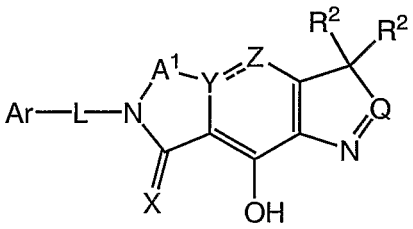


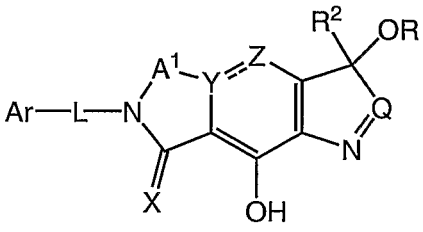


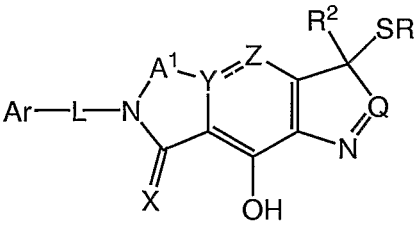




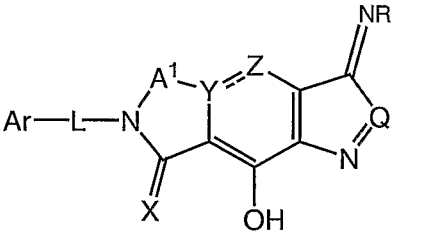




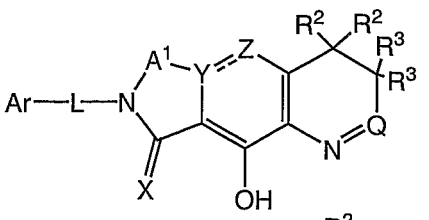


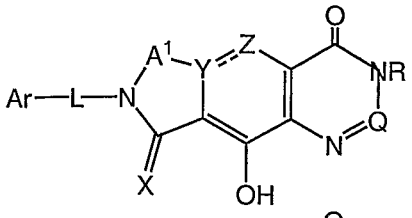


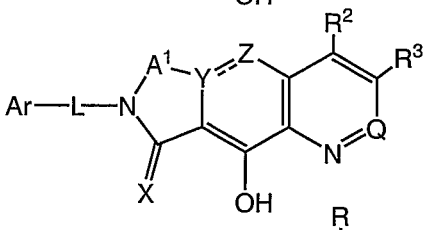
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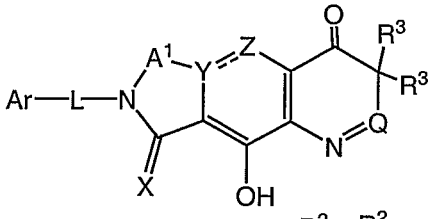


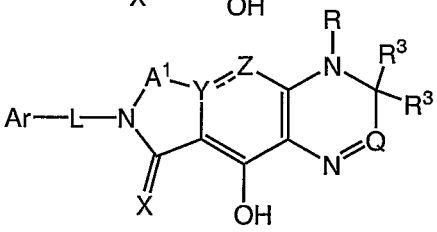
Other various embodiments of A^2 form 6-membered rings in the exemplary structures:

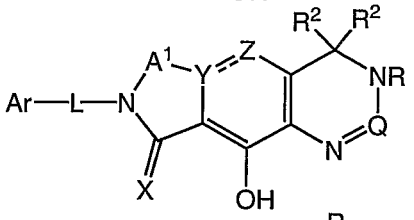


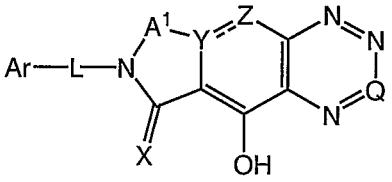


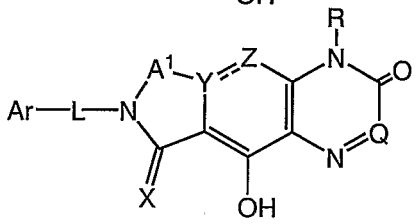




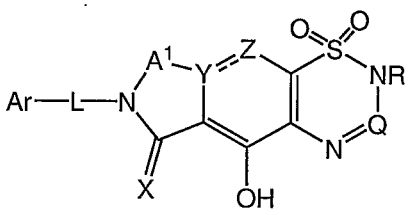




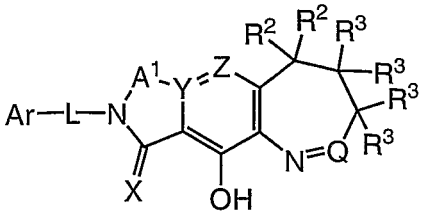


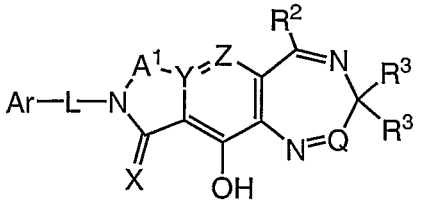


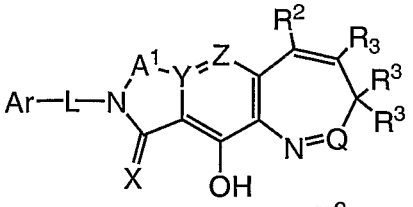
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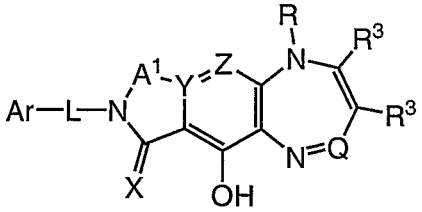


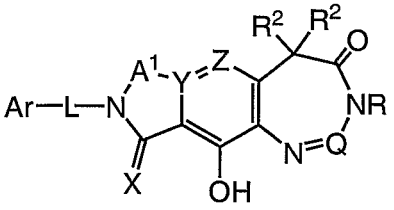
Other various embodiments of A^2 form 7-membered rings in the exemplary structures:

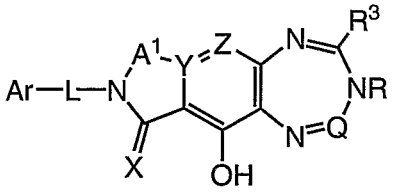




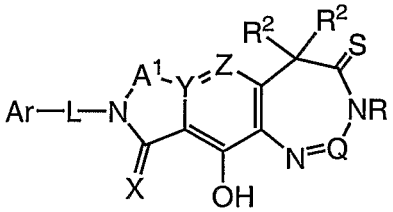




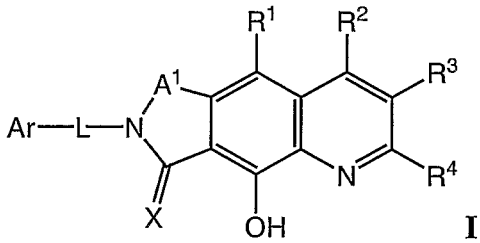




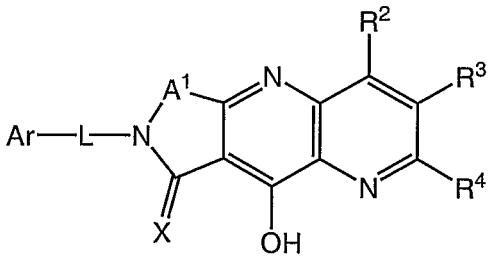
and



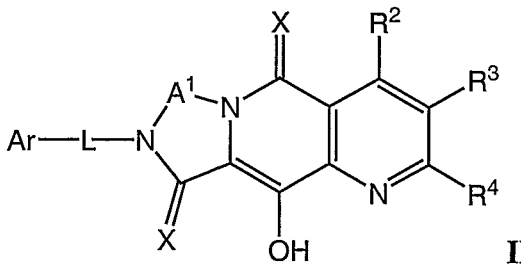
Compounds of the invention include Formulas I-IV, represented by the following structures:



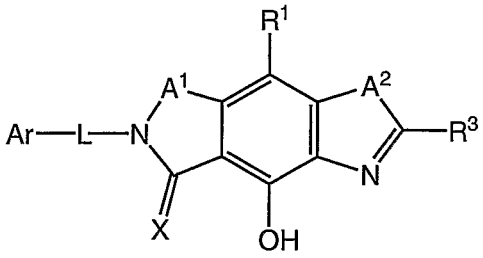
I



II

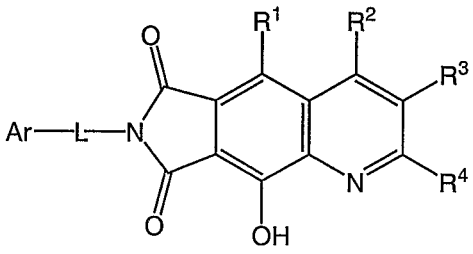


III

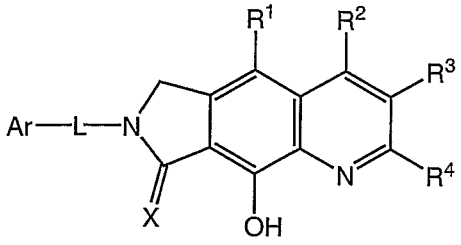


IV

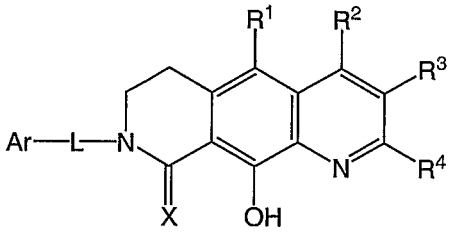
Formula I compounds thus include the following succinimide structure:



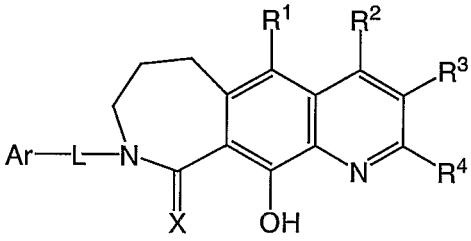
Embodiments of Formula I also include Ia-c where A is CH_2, CH_2CH_2, and $CH_2CH_2CH_2$, respectively:



Ia

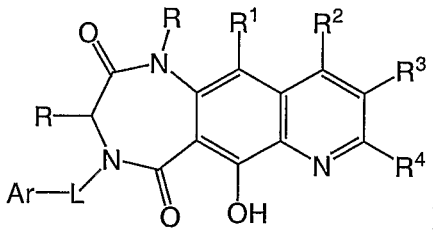


Ib



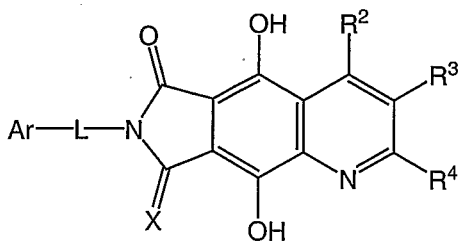
Ic

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



Id

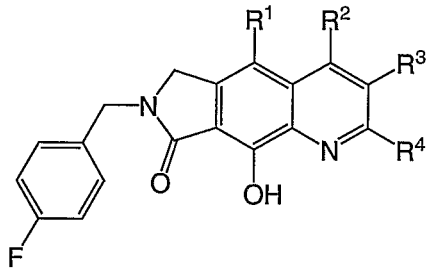
One aspect of the invention includes compounds with a cyclic imide group, e.g. 5,9-dihydroxy-pyrrolo[3,4-*g*]quinoline-6,8-dione (Myers, etal U.S. Patent No. 5,252,560; Robinson, U.S. Patent No. 5,854,275), where A is C(=O) and X is O, as in formula Ie:



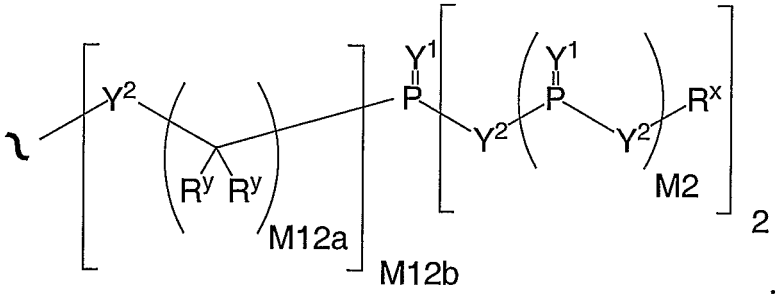
Ie

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:



R^1, R^2, R^3, or R^4 may independently comprise a phosphonate group or phosphonate prodrug moiety. A tricyclic integrase inhibitor compound of the invention may include one or more phosphonate group or phosphonate prodrug moiety. For example, R^1, R^2, R^3, or R^4 may comprise the structure A^3, where A^3 is:



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

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

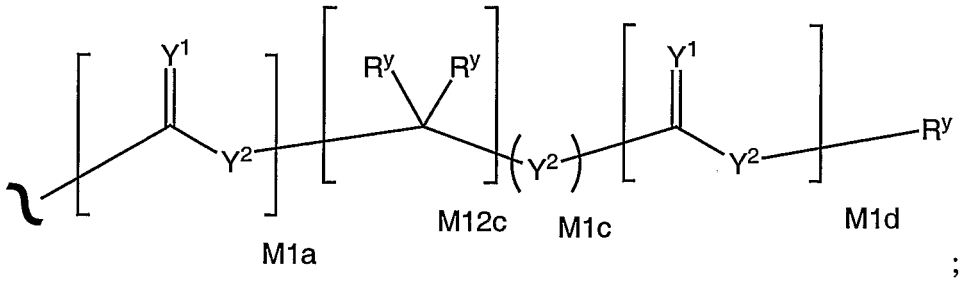
M2 is 0, 1 or 2.

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

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

R^y is independently H, C_1–C_6 alkyl, C_1–C_6 substituted alkyl, aryl, substituted aryl, or a protecting group. 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_6 alkyl, C_1–C_6 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, or a protecting group, or the formula:

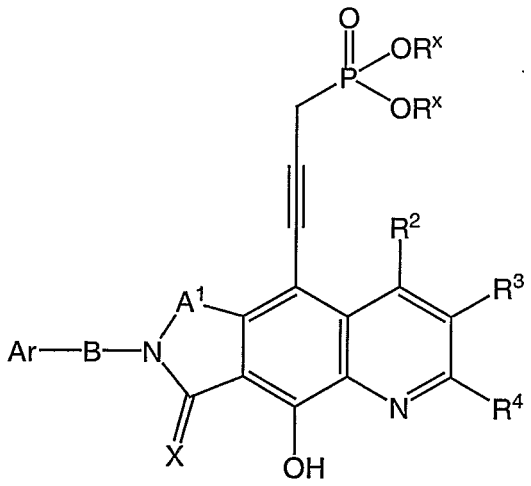


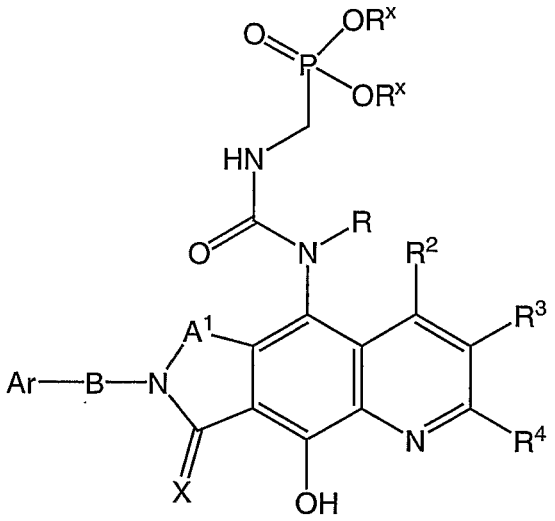
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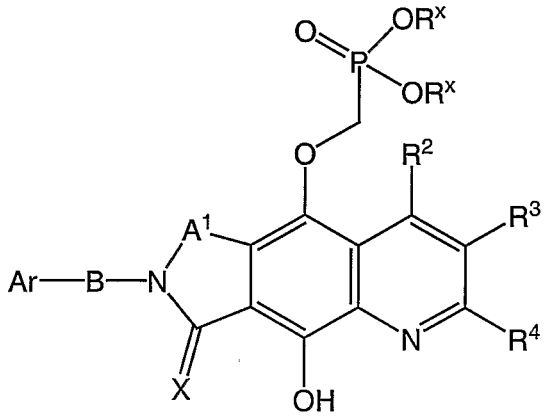
M1a, M1c, and M1d are independently 0 or 1.

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

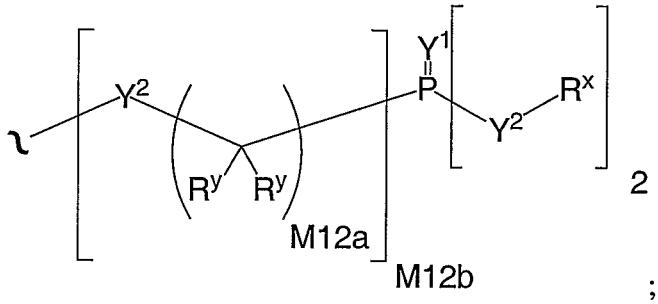
A linker may be interposed between positions R^1, R^2, R^3 or R^4 and substituent A^3. The linker may be O, S, NR, N–OR, C_1–C_{12} alkylene, C_1–C_{12} substituted alkylene, C_2–C_{12} alkenylene, C_2–C_{12} substituted alkenylene, C_2–C_{12} alkynylene, C_2–C_{12} substituted alkynylene, C(=O)NH, C(=O), $S(=O)_2$, $C(=O)NH(CH_2)_n$, 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 in the exemplary structures:





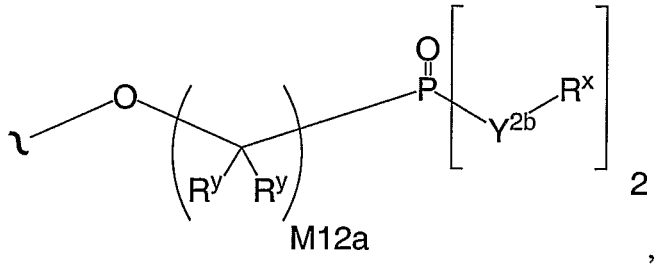


Embodiments of A^3 include where M2 is 0, such as:

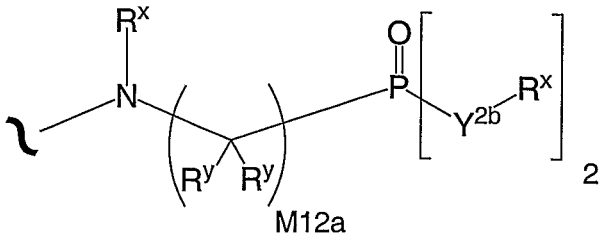


M12a M12b ;

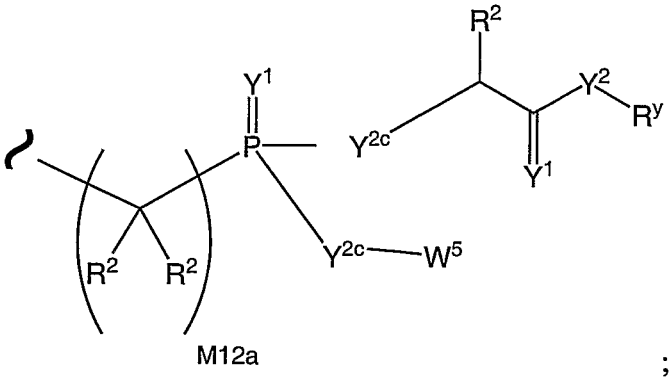
and where M12b is 1, Y^1 is oxygen, and Y^{2b} is independently oxygen (O) or nitrogen ($N(R^x)$) such as:



M12a , and



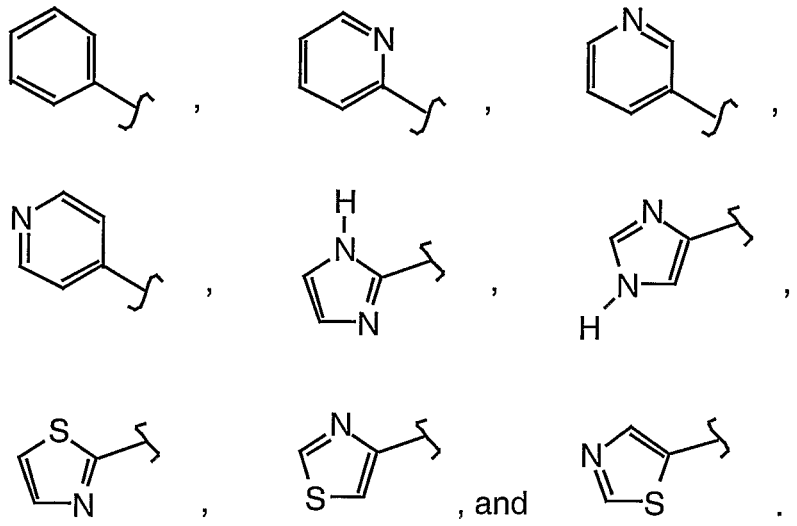
An embodiment of A^3 includes:



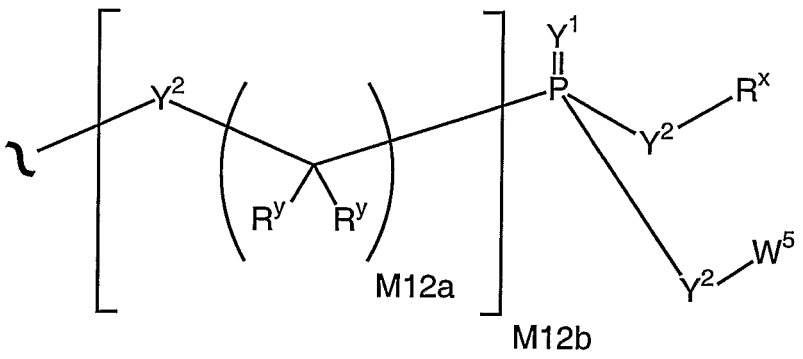
;

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^1 may be H and n may be 1.

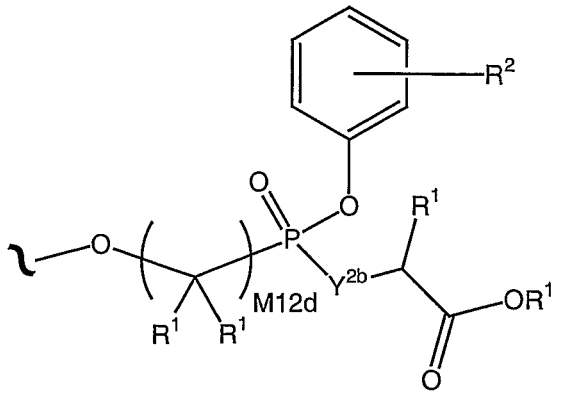
W^5 also includes, but is not limited to, aryl and heteroaryl groups such as:



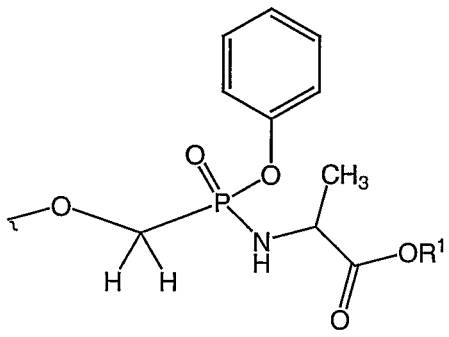
Another embodiment of A^3 includes:



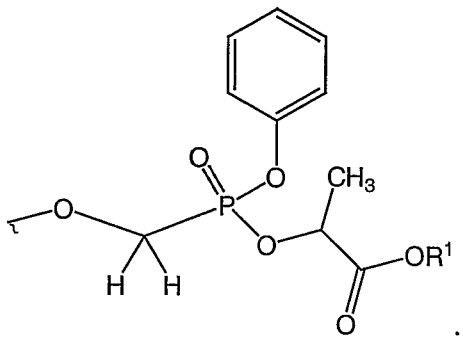
Such embodiments include:



where Y^{2b} is O or N(R^x); M12d is 1, 2, 3, 4, 5, 6, 7 or 8; R^1 is H or C_1–C_6 alkyl; and the phenyl carbocycle is substituted with 0 to 3 R^2 groups where R^2 is C_1–C_6 alkyl or substituted alkyl. Such embodiments of A^3 include phenyl phosphonamidate amino acid, e.g. alanate esters and phenyl phosphonate-lactate esters:

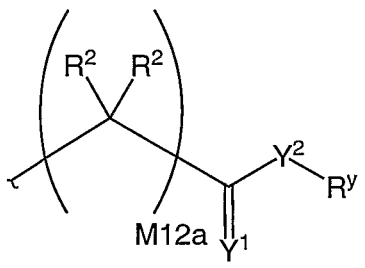


and

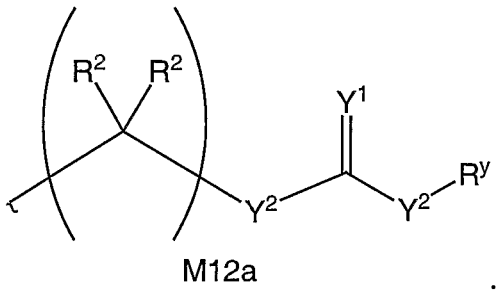


.

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



and



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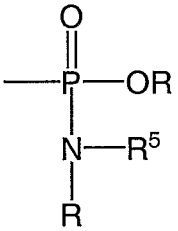
The compounds of the invention may also include one or more prodrug moieties located as a covalently-attached substituent at any location or site, e.g. Ar, L, X, A, R^1, R^2, R^3, R^4, or the 9-hydroxyl. One substituent which may be modified as a prodrug moiety is a phosphonate, phosphate, phosphinate or other phosphorus functionality (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). Prodrug moieties of

phosphorus functionality serve to mask anionic charges and decrease polarity. The phosphonate prodrug moiety may be an ester (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.

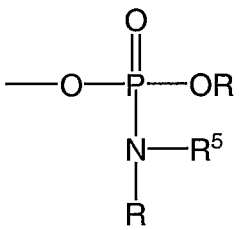
Compounds of the invention bearing one or more prodrug moieties may increase or optimize the bioavailability of the compounds as therapeutic agents. For example, bioavailability after oral administration may be preferred and depend on resistance to metabolic degradation in the gastrointestinal tract 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).

R^{X2} is independently selected from H, 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, polyethyleneoxy, phosphonate, phosphate, a prodrug, a pharmaceutically acceptable prodrug, a prodrug moiety, a protecting group, and a phosphonate prodrug moiety; preferably H, a prodrug or a protecting group; more preferably, H or a prodrug; more preferably yet R^{X2} is H.

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



phosphonamidate

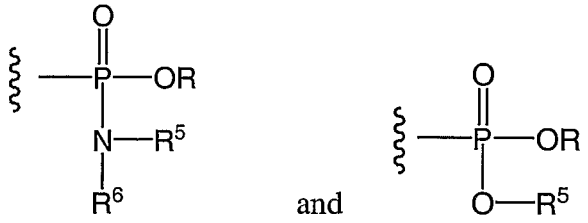


phosphoramidate

The phosphorus atom of the phosphonamidate group is bonded to a carbon atom. The nitrogen substituent R^5 may include an ester, an amide, or a carbamate functional group. For example, R^5 may be $-CR_2C(=O)OR'$ where R' is H, C_1–C_6 alkyl, C_1–C_6

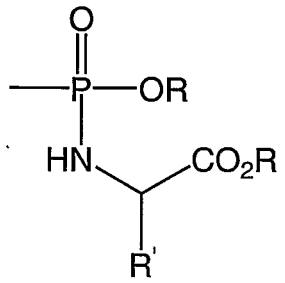
substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, or C_2–C_{20} substituted heteroaryl.

Exemplary embodiments of phosphonamidate and phosphoramidate prodrugs include:



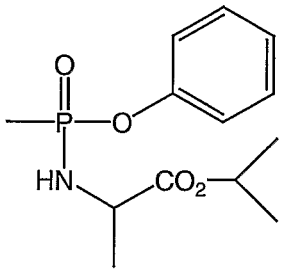
wherein R^5 is $-CR_2CO_2R^7$ where R^6 and R^7 are independently H or C_1–C_8 alkyl.

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:



Another embodiment of the invention is directed toward an HIV integrase inhibitor tricyclic compound of the invention which is 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. 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, or it is 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.

The compounds of the invention may have pre-organized binding modes which optimize the binding affinity of other, known HIV integrase inhibitors. During binding between the inhibitor and the active site of the target HIV integrase enzyme, the inhibitor may attain a low energy conformation (also called bound conformation) in order to interact within an active site. Generally, ligands of molecules with multiple rotational bonds exist in many potential conformational states, most of which are not able to bind to the active site. The greater the number of possible ligand conformations typically results in a greater decrease in efficiency of the entropy contribution to the free energy of binding, and will result in less favorable binding affinities. One aspect of designing pre-organized binding features in an integrase inhibitor compound is incorporating conformational constraints that reduces the total number of conformational states and places the inhibitor into a correct binding conformation (Lam , P.Y.S. et al. *J. Med. Chem*, (1996) 39:3514–3525; Chen, J.M. et al. *Biochemistry* (1998) 37:17735–17744; Chen, J.M. et al. *Jour. Amer. Chem. Soc.* (2000) 122:9648–9654; Chen, J.M. et al US 6187907; Chen, et al *Bio. Org. Med. Chem.*

Letters (2002) 12:1195–1198). Knowledge of one or more preferred, i.e. low-energy, binding conformations is important for rational structure design and avoid inactive lead compounds.

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.

The compounds 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 metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. The compounds of the invention may bear multiple positive or negative charges. The net charge of the compounds of the invention may be either positive or negative. Any associated counter ions are typically dictated by the synthesis and/or isolation methods by which the compounds are obtained. Typical counter ions include, but are not limited to ammonium, sodium, potassium, lithium, halides, acetate, trifluoroacetate, etc., and mixtures thereof. It will be understood that the identity of any associated counter ion is not a critical feature of the invention, and that the invention encompasses the compounds in association with any type of counter ion. Moreover, as the compounds can exists in a variety of different forms, the invention is intended to encompass not only forms of the compounds that are in association with counter ions (e.g., dry salts), but also forms that are not in association with counter ions (e.g., aqueous or organic solutions).

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound. In addition, salts may be formed from acid addition of certain organic and inorganic acids, e.g., HCl, HBr, H_2SO_4, H_3PO_4 or organic sulfonic acids, to basic centers, typically amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise compounds of

the invention in their unionized, 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, especially the naturally-occurring amino acids found as protein components. The amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

The compounds of the invention can also exist as tautomeric, resonance isomers in certain cases. Typically, the structures shown herein exemplify only one tautomeric or resonance form of the compounds. For example, hydrazine, oxime, hydrazone groups may be shown in either the syn or anti configurations. The corresponding alternative configuration is contemplated as well. All possible tautomeric and resonance forms are within the scope of the invention.

One enantiomer of a compound of the invention can be separated substantially free of its opposing enantiomer by 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). Separation of diastereomers formed from the racemic mixture can be accomplished 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 enantiomers. Alternatively, enantiomers can be separated directly under chiral conditions, method (3).

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 may be reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S.

(1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111).

By method (3), a racemic mixture of two asymmetric 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) "Optical resolution of dihydropyridine enantiomers by High-performance liquid chromatography using phenylcarbamates of polysaccharides as a chiral stationary phase", *J. of Chromatogr.* 513:375-378).

Enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

SYNTHESIS OF HIV-INTEGRASE INHIBITOR COMPOUNDS

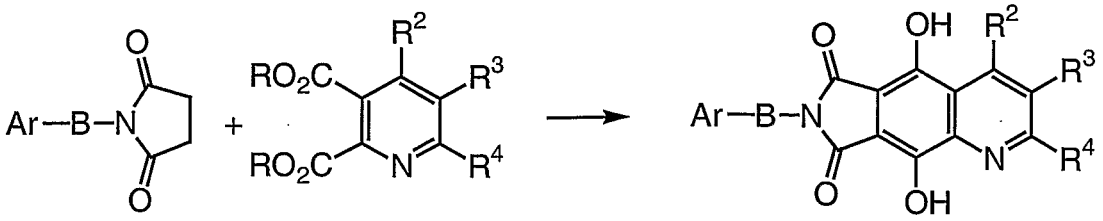
The compounds of the invention may be prepared by a variety of synthetic routes and methods known to those skilled in the art. The invention also relates to methods of making the compounds of the invention. The compounds are prepared by any of the applicable techniques of organic synthesis. Many such 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.

A number of exemplary methods for the preparation of the compounds, Formulas I-IV, of the invention are provided herein. These methods are intended to illustrate the nature of such preparations 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.

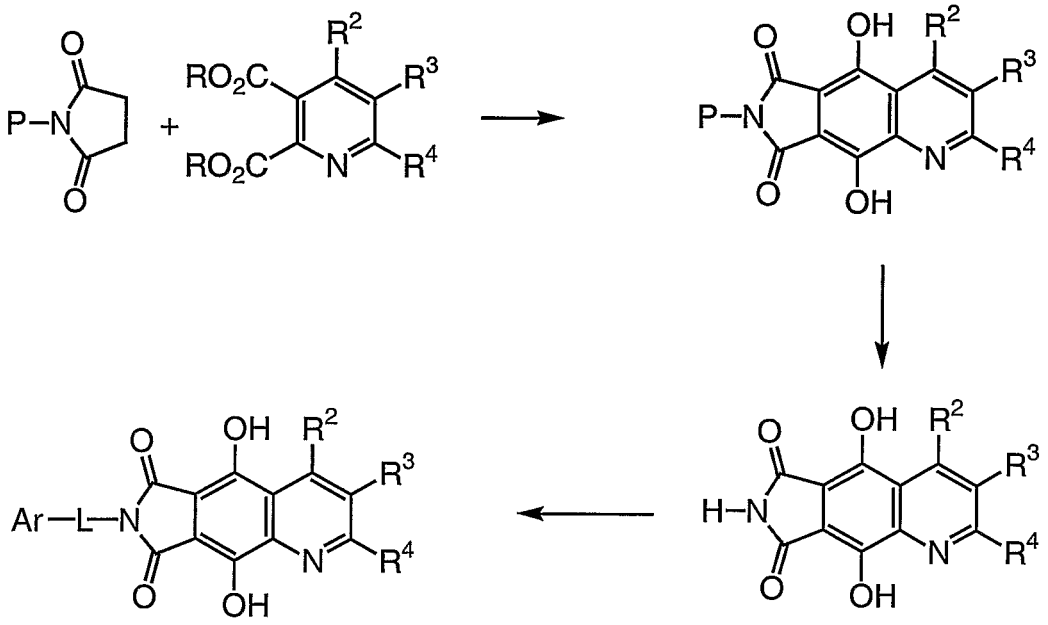
Formula I compounds

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.



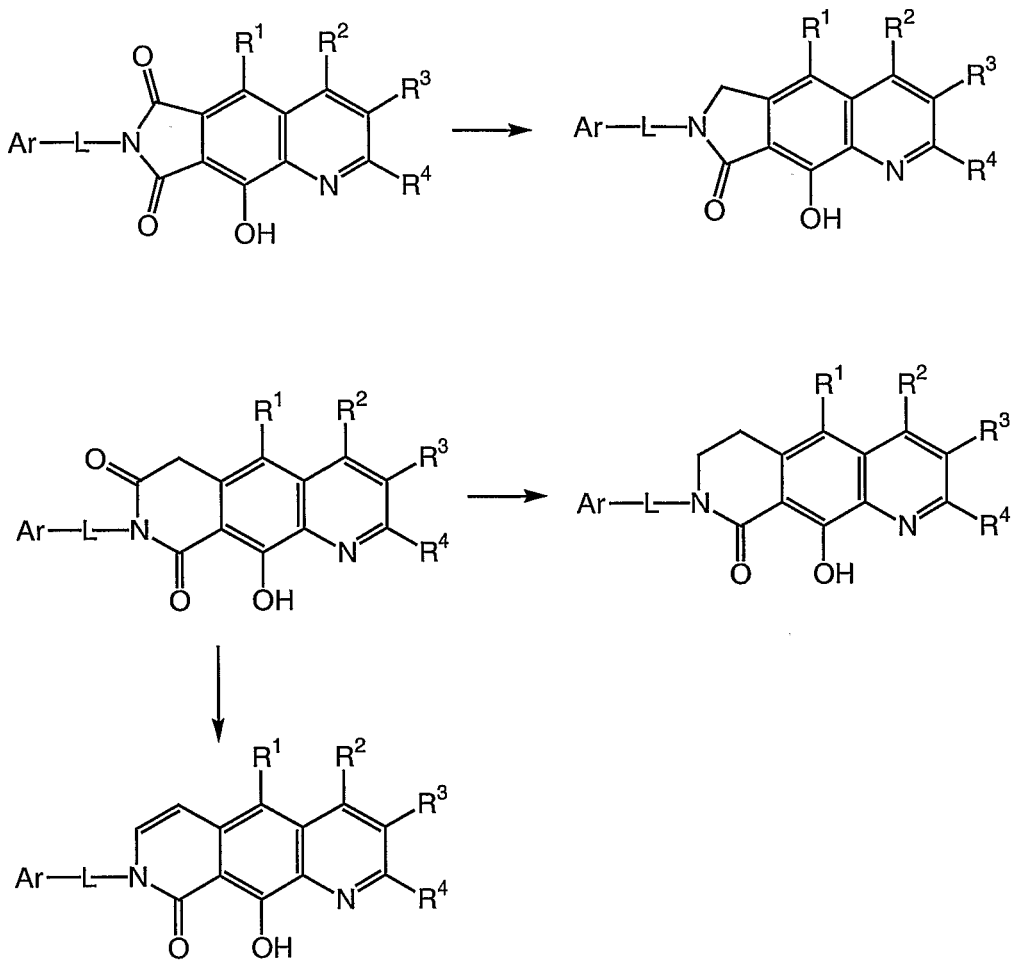
Scheme 1

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.



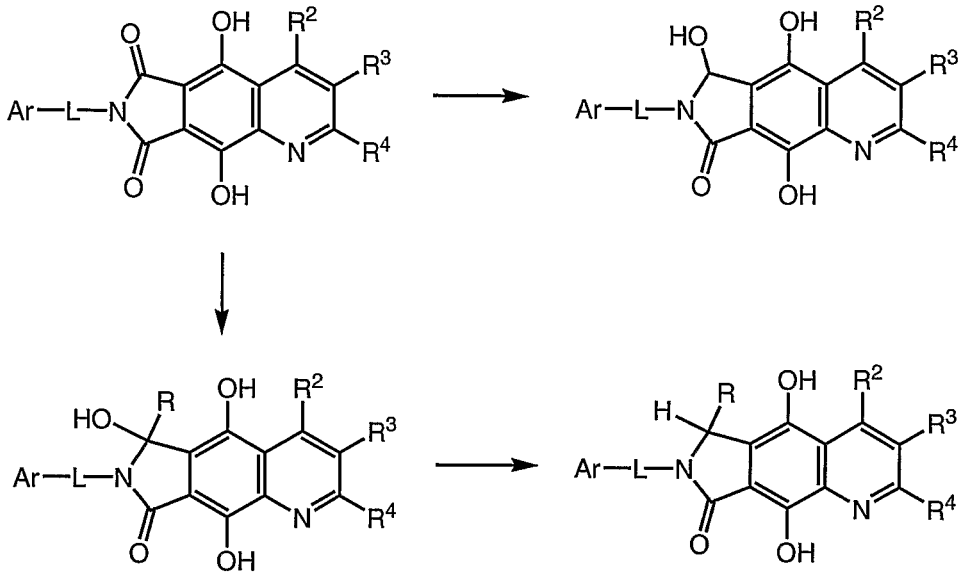
Scheme 2

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:



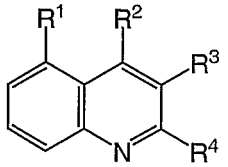
Scheme 3

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.

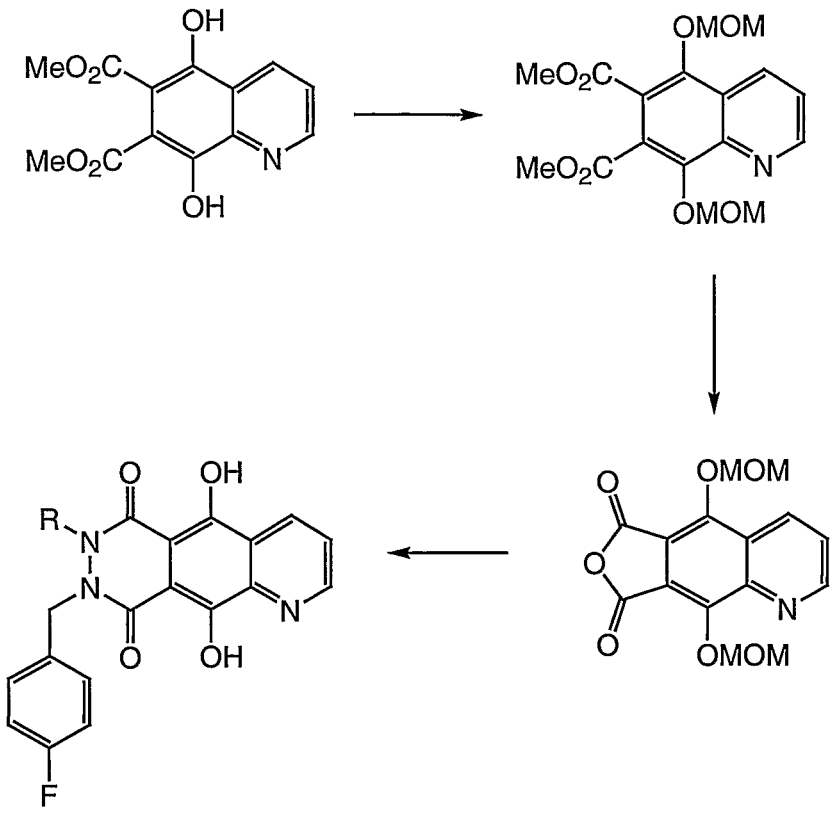


Scheme 4

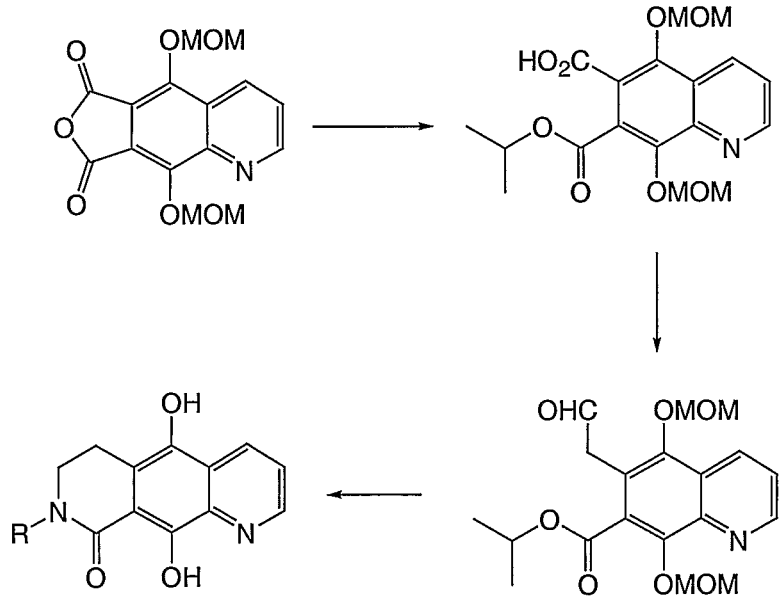
Another synthetic route to the compounds of the invention proceeds through substituted quinoline intermediates (Clemence, etal U.S. Patent No. 5,324,839; Billhardt-Troughton, etal U.S. Patent No. 5,602,146; Matsumura, *J. Amer. Chem. Soc.* (1935) 57:124-128) having the general formula:

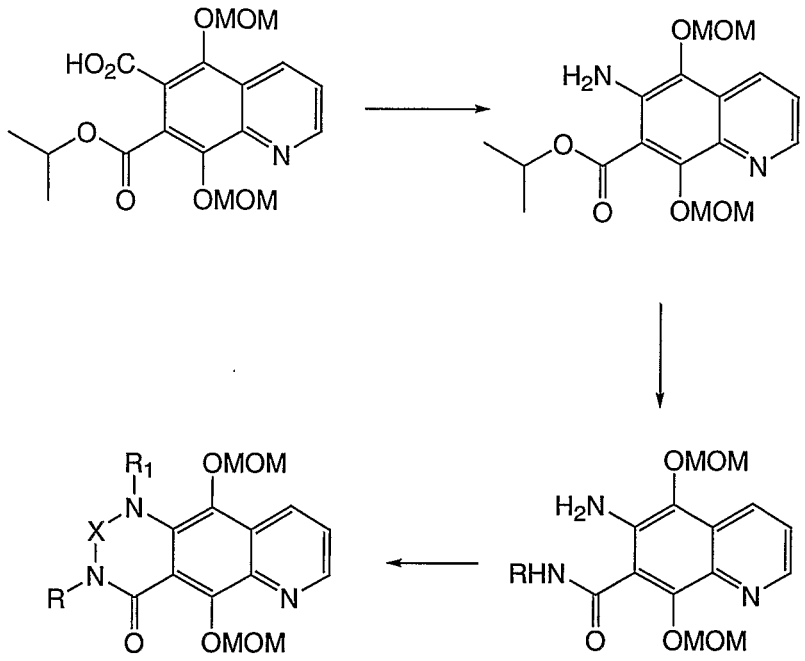


5,8-Dihydroxy quinoline compounds may be elaborated according to Scheme 5:



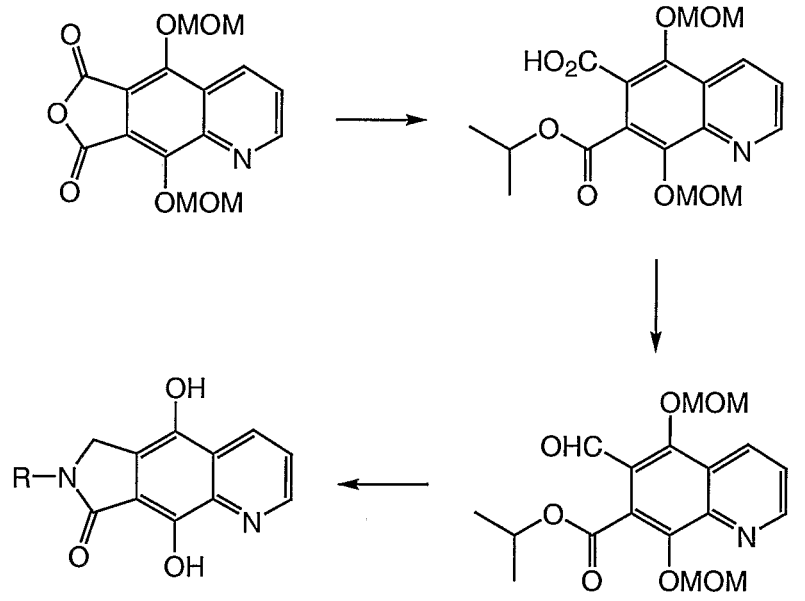
Scheme 5





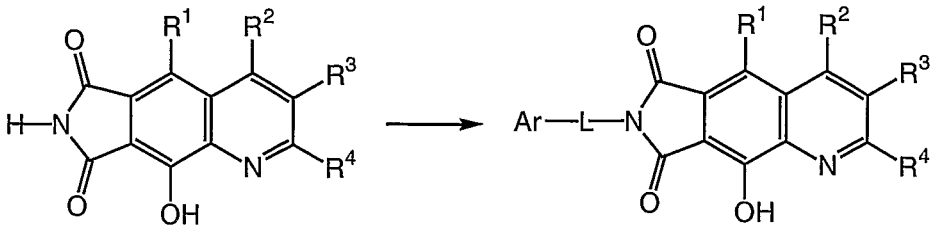
Scheme 6

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



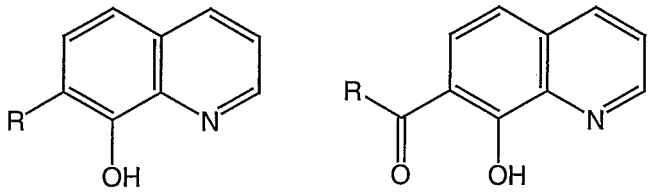
Scheme 7

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

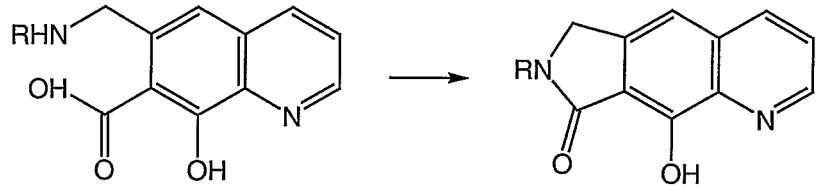


The Ar–L group may be attached as one reactant group, for example as an alkylating reagent like benzyl bromide (Ar = phenyl, L = CH_2) or a sulfonating reagent, like 4-methoxyphenyl sulfonyl chloride (Ar = 4-methoxyphenyl, L = $S(=O)_2$. Alternatively, the Ar–L group may be attached by a multi step process. 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:

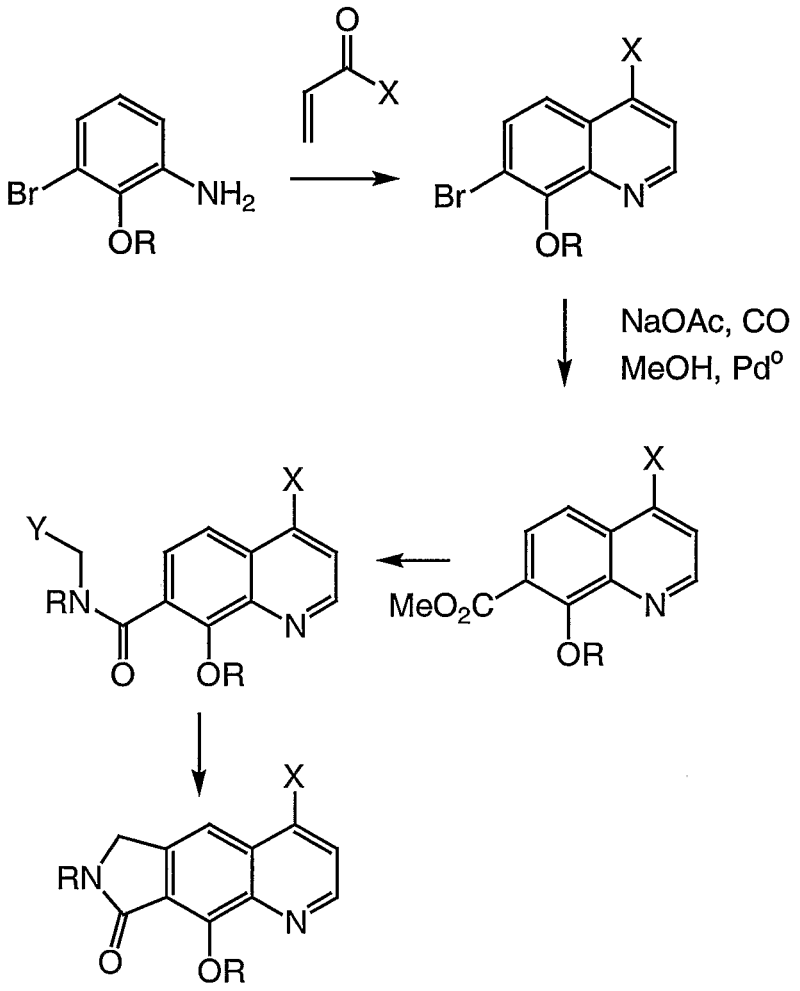


Annulation of the third, 5-7 membered ring can be conducted by appropriate selection of aryl substituents on the quinoline ring system, utilizing known synthetic transformations to give compounds of Formula I. For example, methods for coupling carboxylic acids and other activated acyl groups with amines 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:



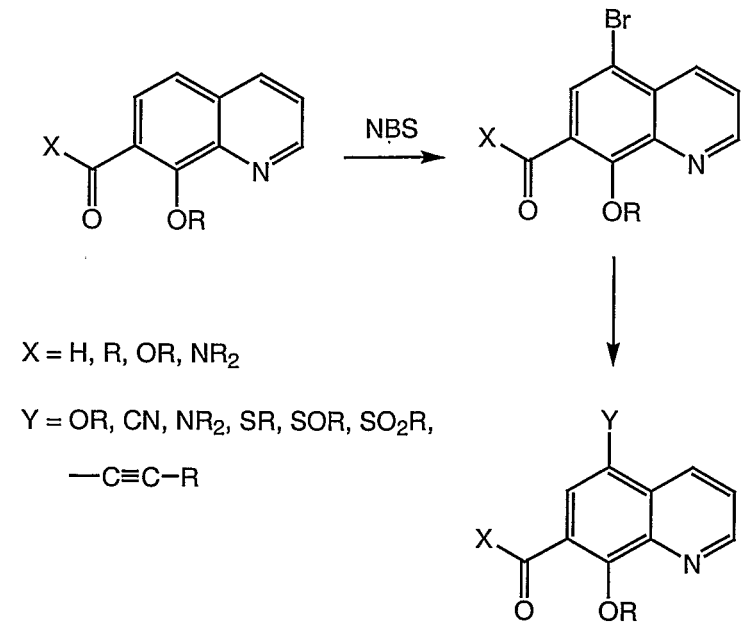
Scheme 8 below shows another synthetic route to compounds of the invention, i.e. Formula I. This route proceeds by cyclization of a 2-O-protected, 3 halo-aniline compound with an α,β-unsaturated carbonyl compound to give a functionalized quinoline. The α,β-

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.



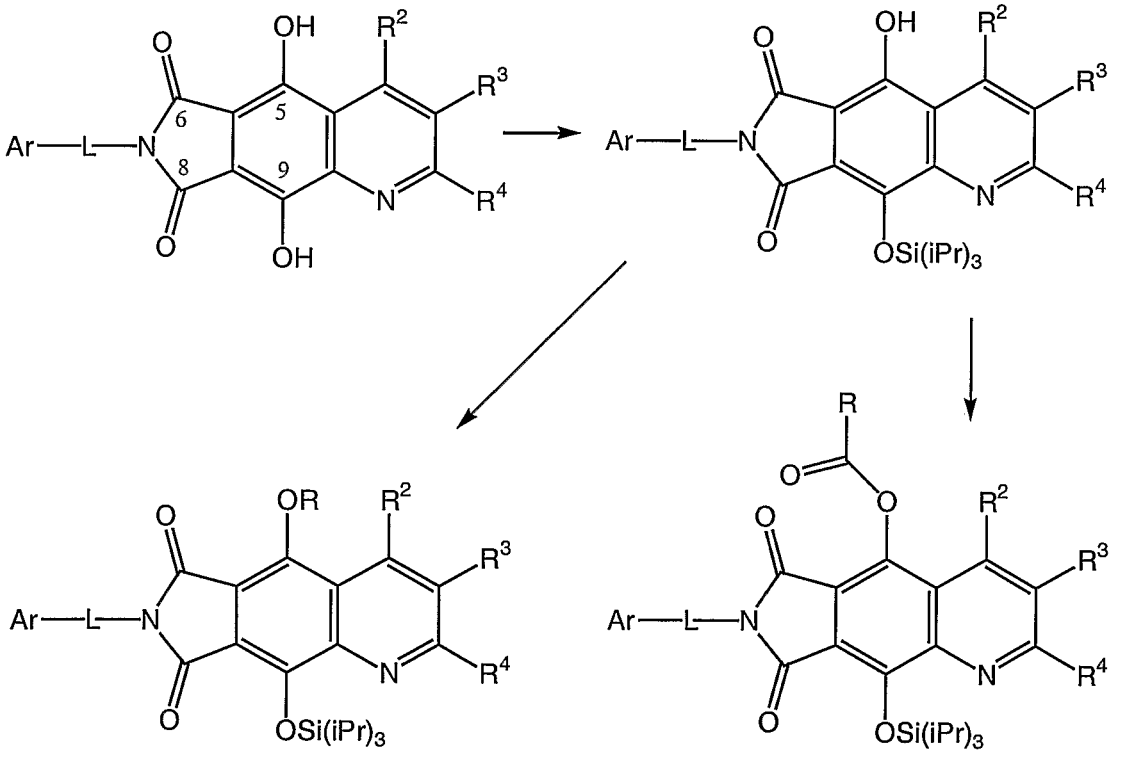
Scheme 8

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

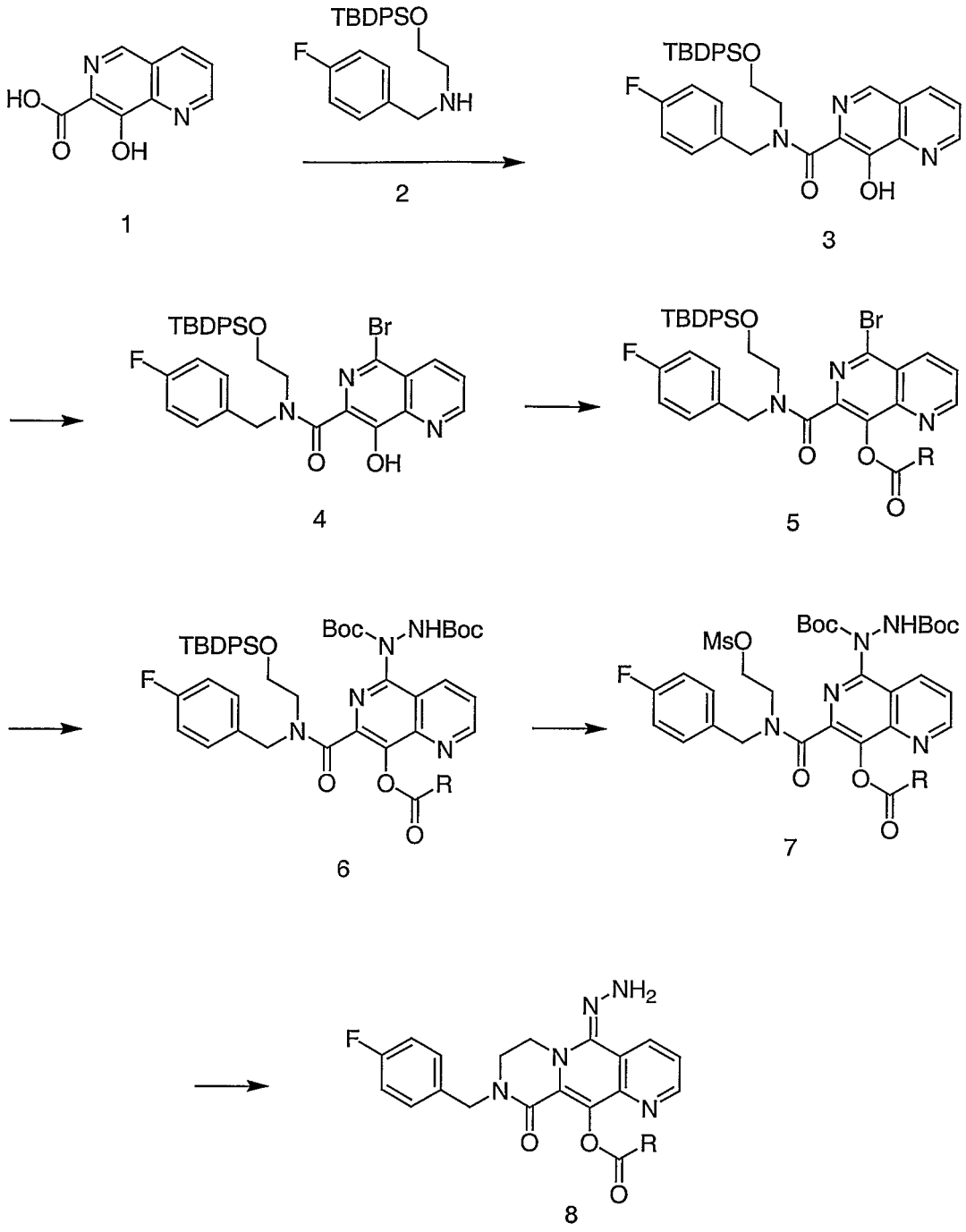
Formula I compounds with a 5,9-dihydroxy-pyrrolo[3,4-g]quinoline-6,8-dione were prepared by selective protection of the C9 phenol in 5,9-dihydroxy-pyrrolo[3,4-g]quinoline-6,8-dione. The C9 phenol was protected with a TIPS group and the C5 phenol could then be alkylated or acylated (Scheme 10).



Scheme 10

Formula III compounds

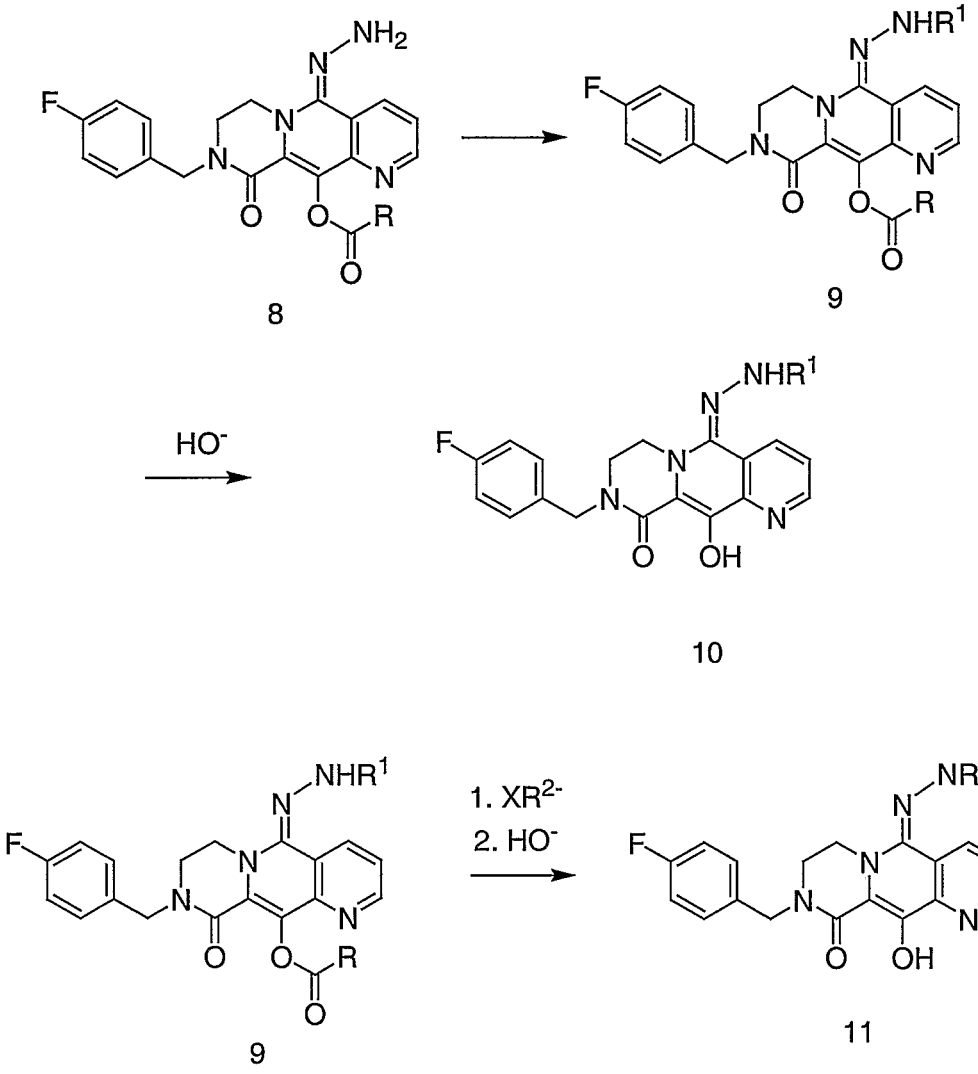
Formula III compounds may be prepared by the following methods in Schemes 11-14:



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**.



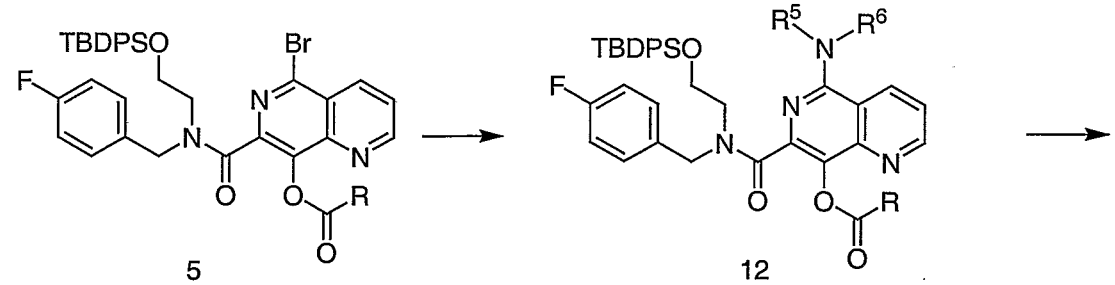
8 9 10 9 11

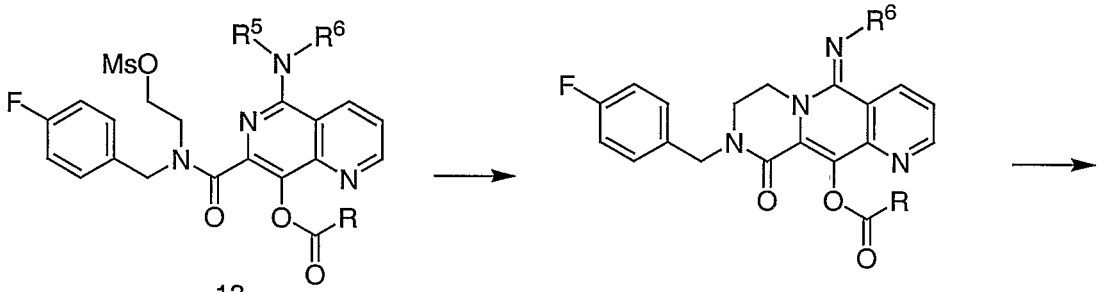
Scheme 12

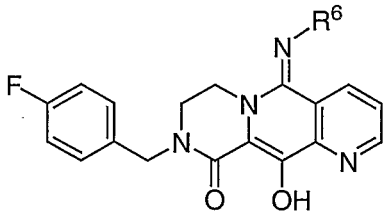
Compound **8** is converted to many different derivatives, e.g. carbazones **9** (R^1 = COR^3) are generated by reaction with acid chlorides or activated carboxylic acids. Carbamates **9** (R^1 = $COOR^3$) are obtained upon reaction of **8** with chloro formates $ClCOOR^3$. Semicarbazones **9** (R^1 = $CONR^2R^3$) 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**.



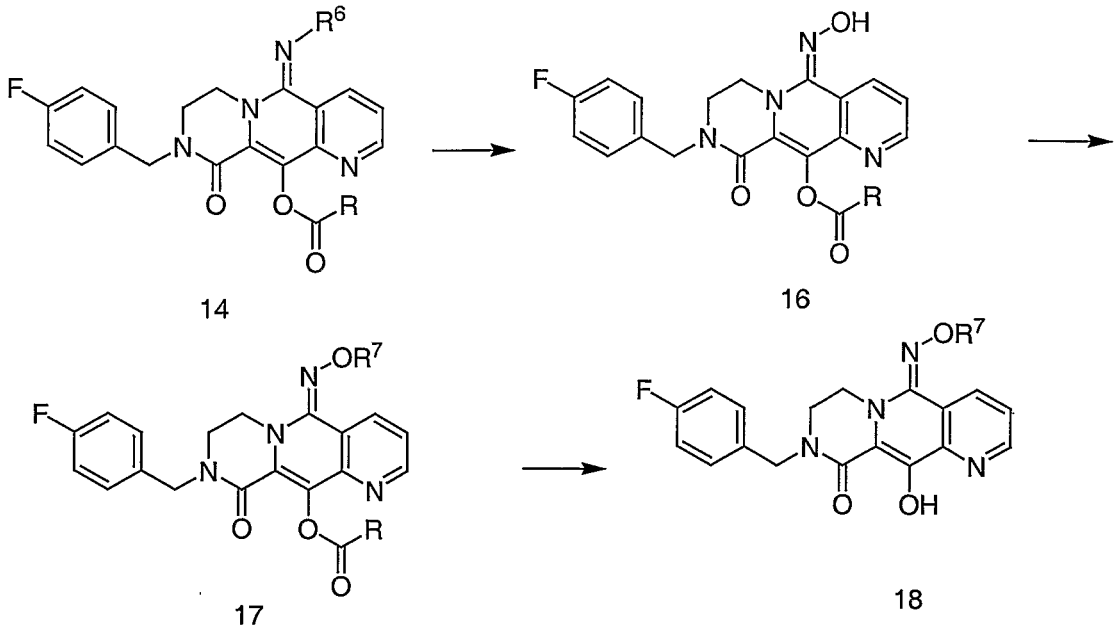




Scheme 13

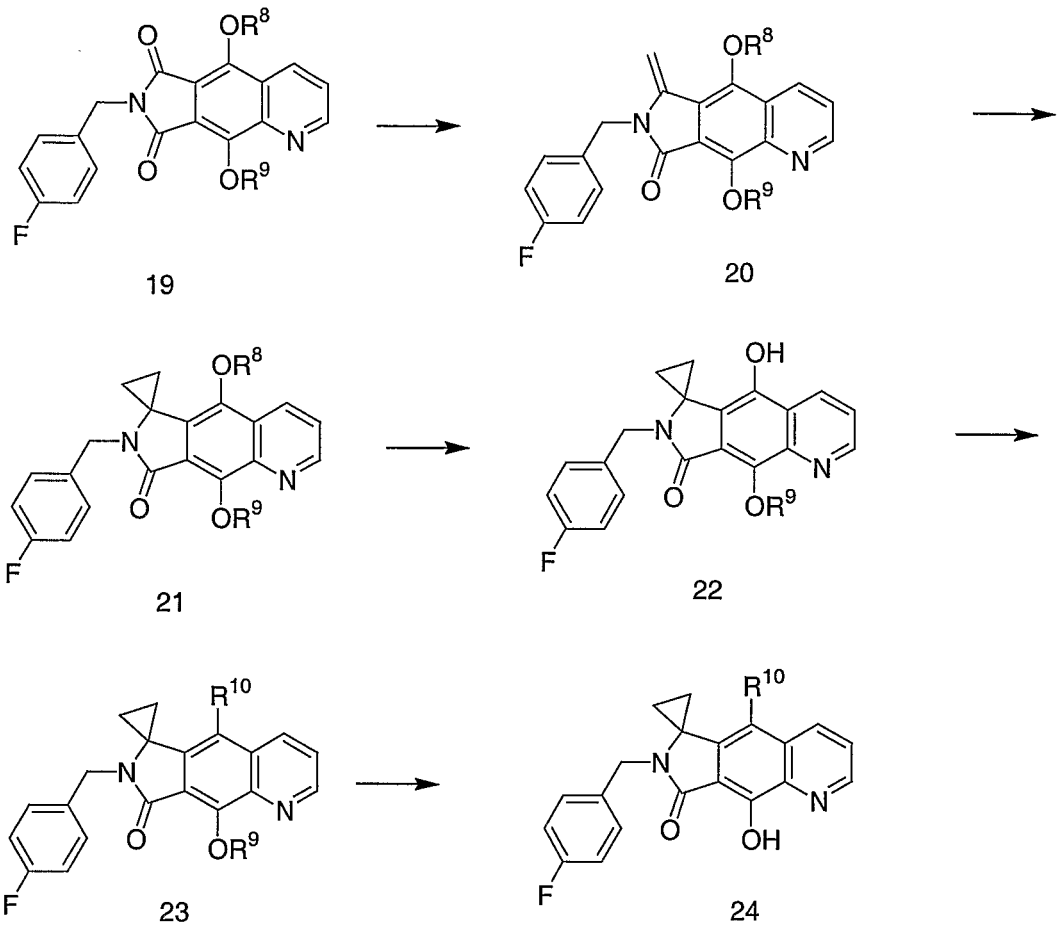
Compound **5** from Scheme 11 is reacted with a substituted hydroxyamine or amine (R^5 = Boc; R^6 = OR^a or alkyl) in a manner similar to that described by L.A., Carpino et al, Org. Lett., 3, 2001, 2793-2795 to give derivative **12**. After transforming the silyl protected hydroxyl in **12** to a leaving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



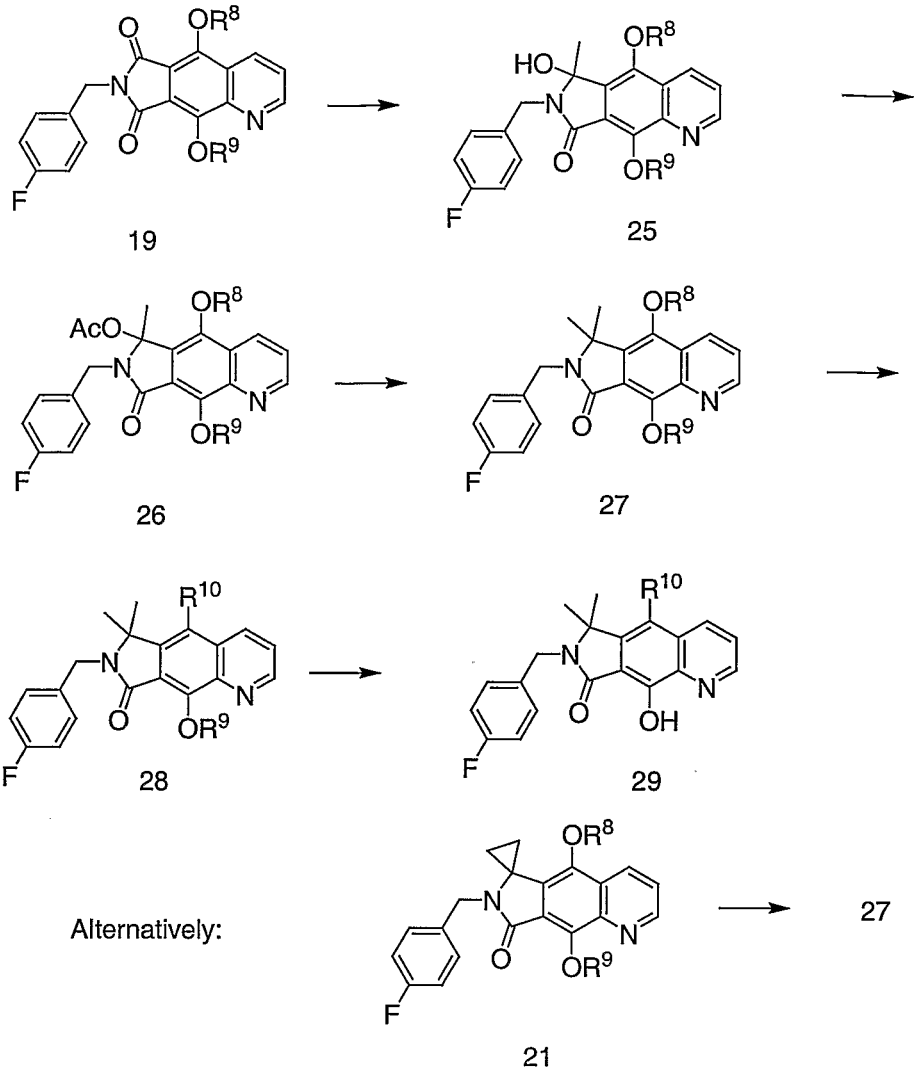
Scheme 14

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** (R^7: $C(=O)NR^2R^3$) 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: $SO_2NR^1R^2$).



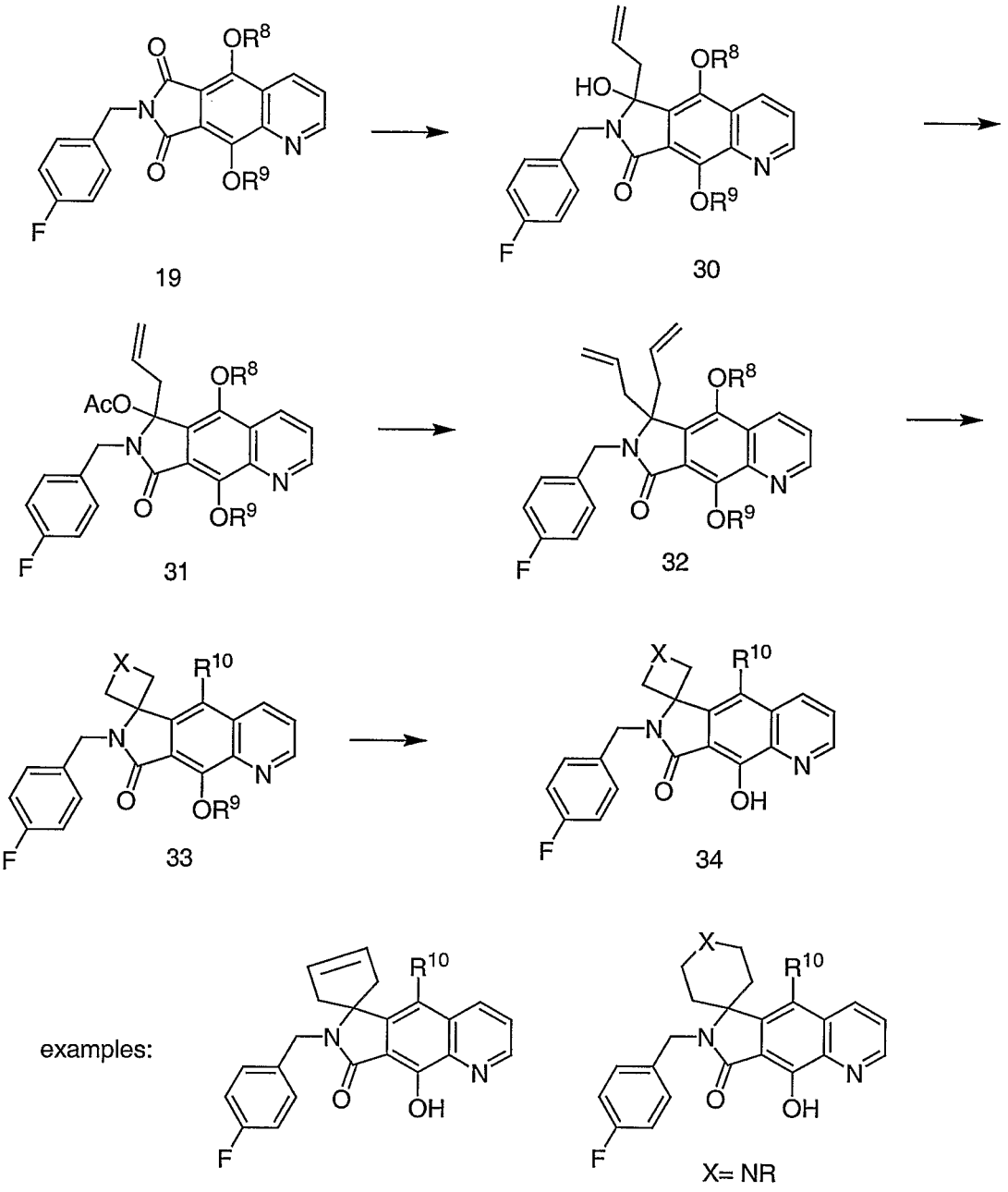
Scheme 15

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**.



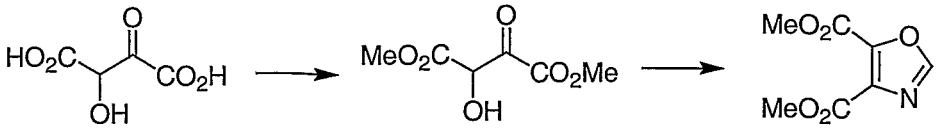
Scheme 16

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**.



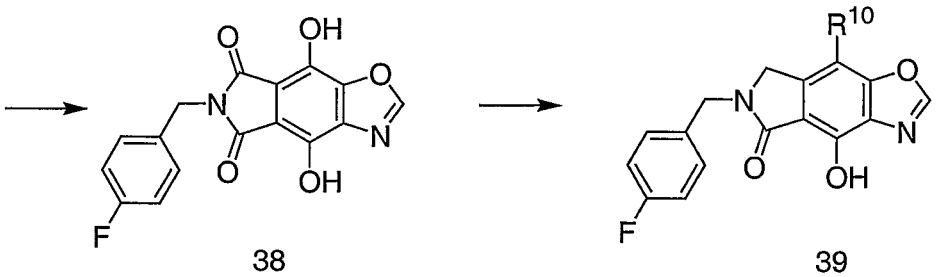
Scheme 17

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.



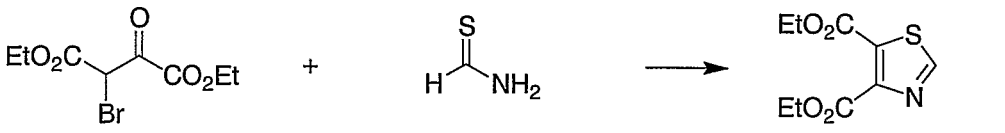
35 36 37

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



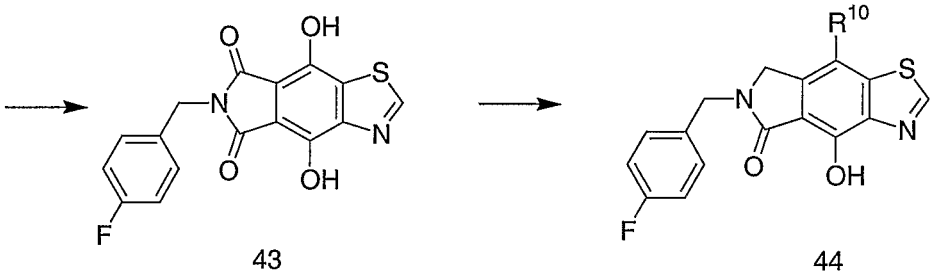
38 39

Scheme 18



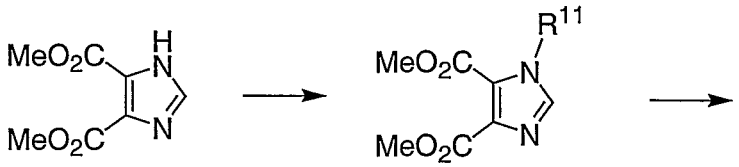
40 41 42

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



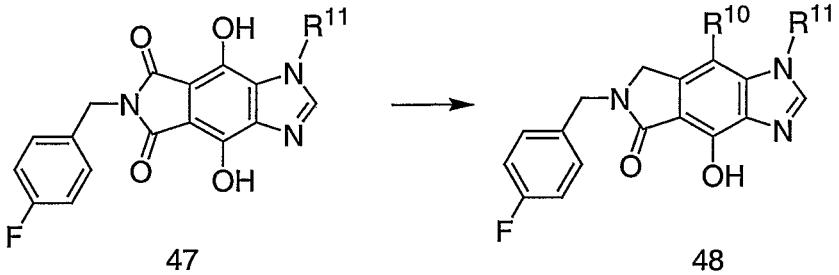
43 44

Scheme 19



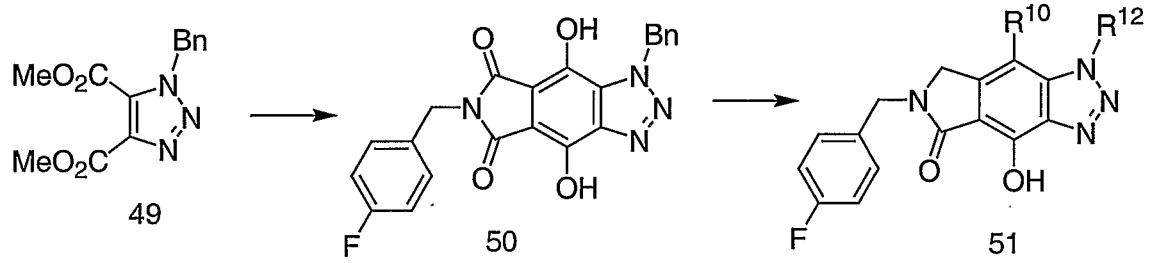
45 46

TCI-US



47 48

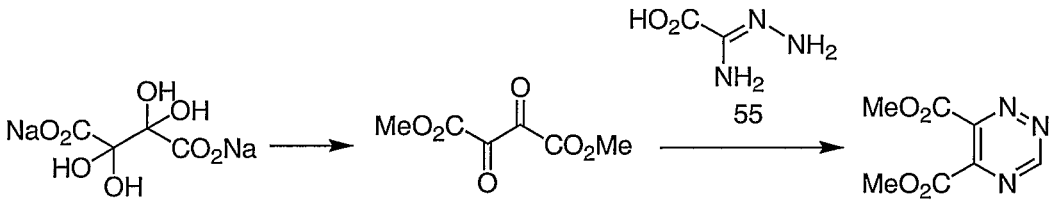
Scheme 20



49 50 51

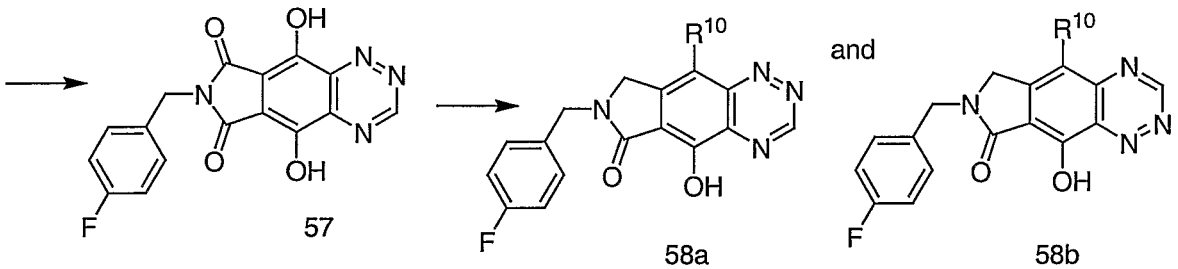
Lancaster

Scheme 21



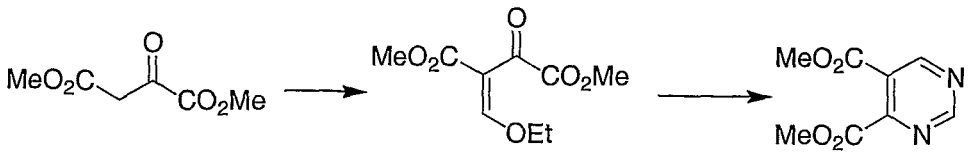
53 54 55 56

Pfaltz-Bauer JACS, 112, 1990, 8126 JOC, 23, 1958, 1931



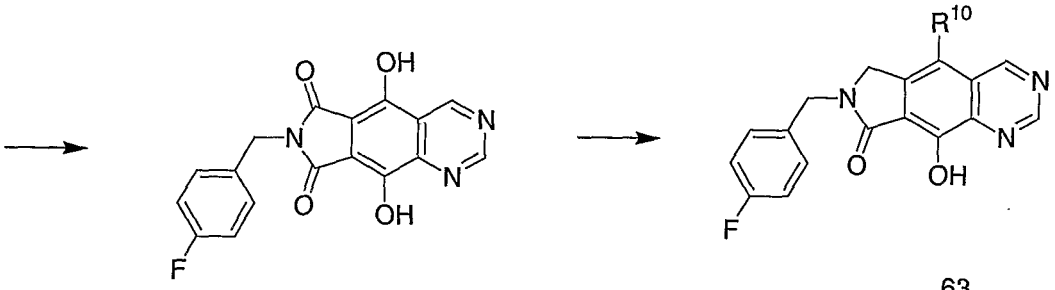
57 58a and 58b

Scheme 22



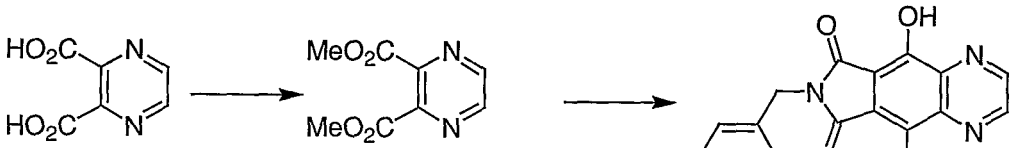
59 60 61

Aldrich J. Het. Chem., 30, 1993, 1597



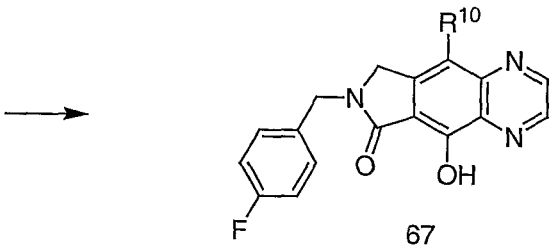
62 63

Scheme 23



64 65 66

Aldrich



67

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.

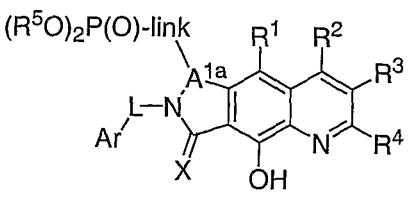
The intermediate compounds **Iaa** to **IVcc** incorporate a phosphonate moiety $(R^5O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Chart **2** illustrates examples of the linking groups present in the structures **Iaa** - **IVcc**.

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.

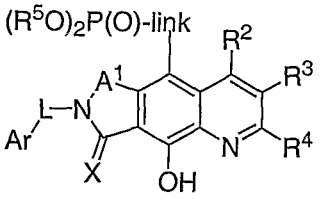
The methods described for the introduction of phosphonate substituents are, with modifications made by one skilled in the art, transferable within the substrates **I** - **V**. For example, reaction sequences which produce the phosphonates **Iaa** are, with appropriate modifications, applicable to the 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.

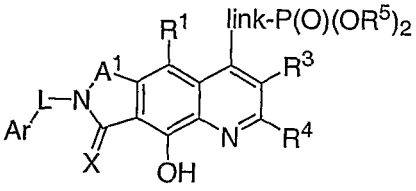
Chart 1. Structures of the phosphonate esters Iaa - IVcc.



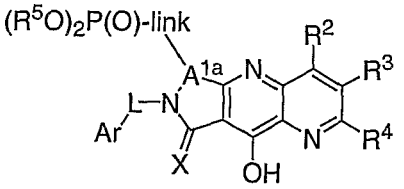
Iaa



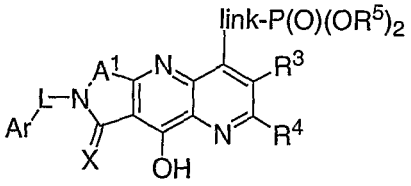
Ibb



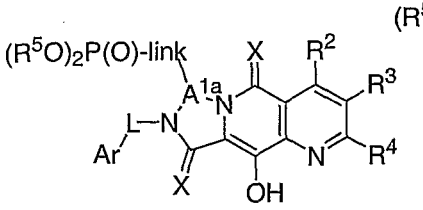
Icc



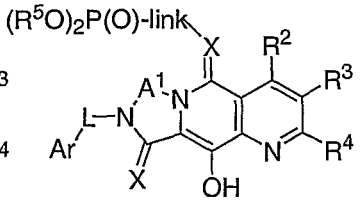
IIaa



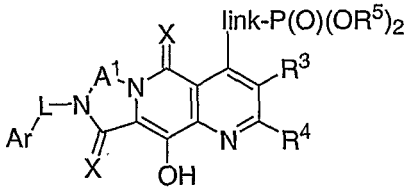
IIcc



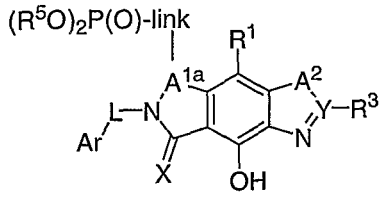
IIIaa



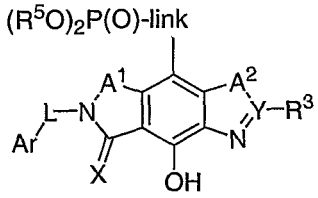
IIIbb



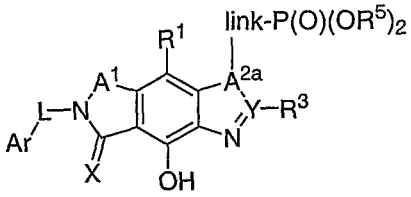
IIIcc



IVaa

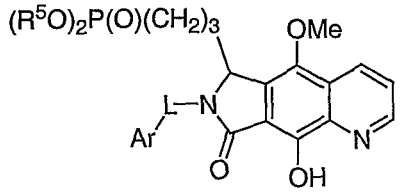


IVbb

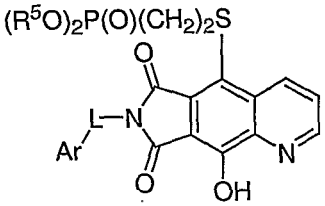


IVcc

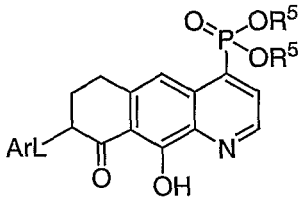
Chart 2 Examples of phosphonate linkages



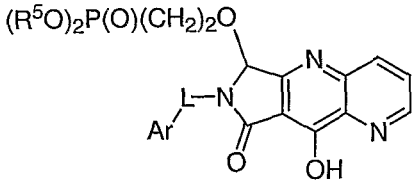
Iaa



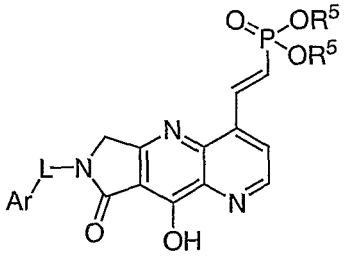
Ibb



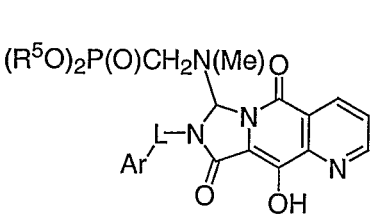
Icc



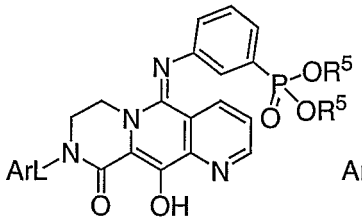
IIaa



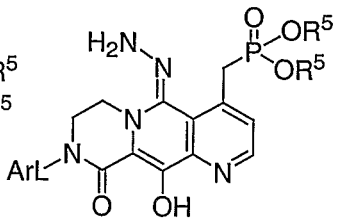
IIcc



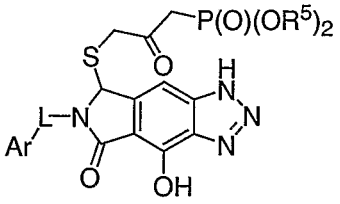
IIIaa



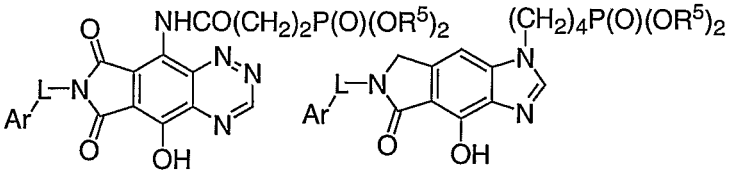
IIIbb



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°C, 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°C 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 carbinol **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 carbinol 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°C, 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°C to produce the carbinol **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 carbinols **A4.5** and **A4.9**, different carbinols **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,

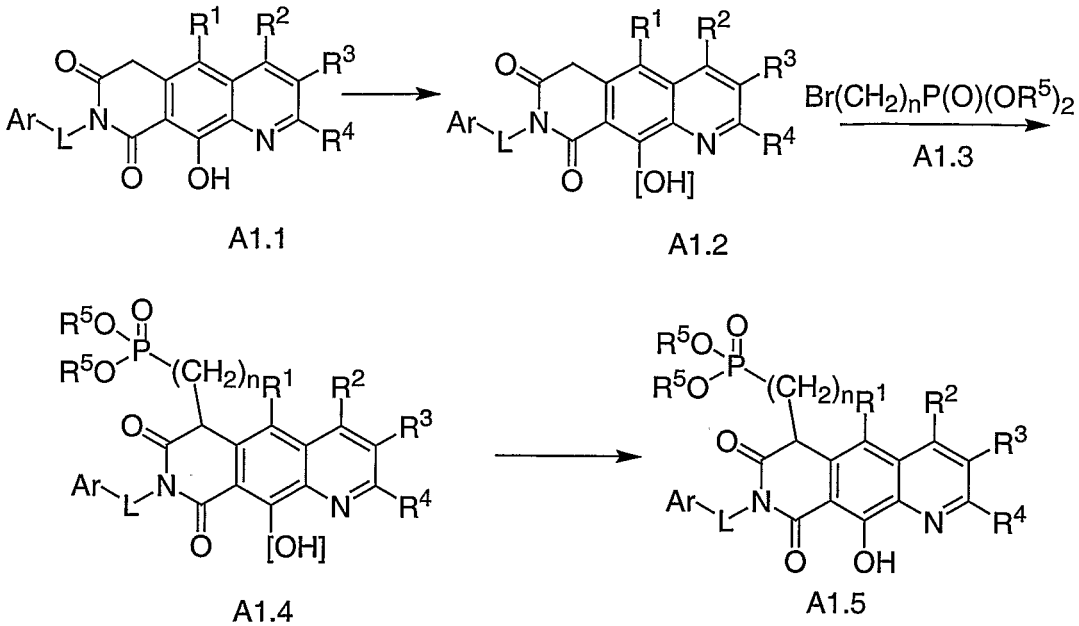
for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, 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**.

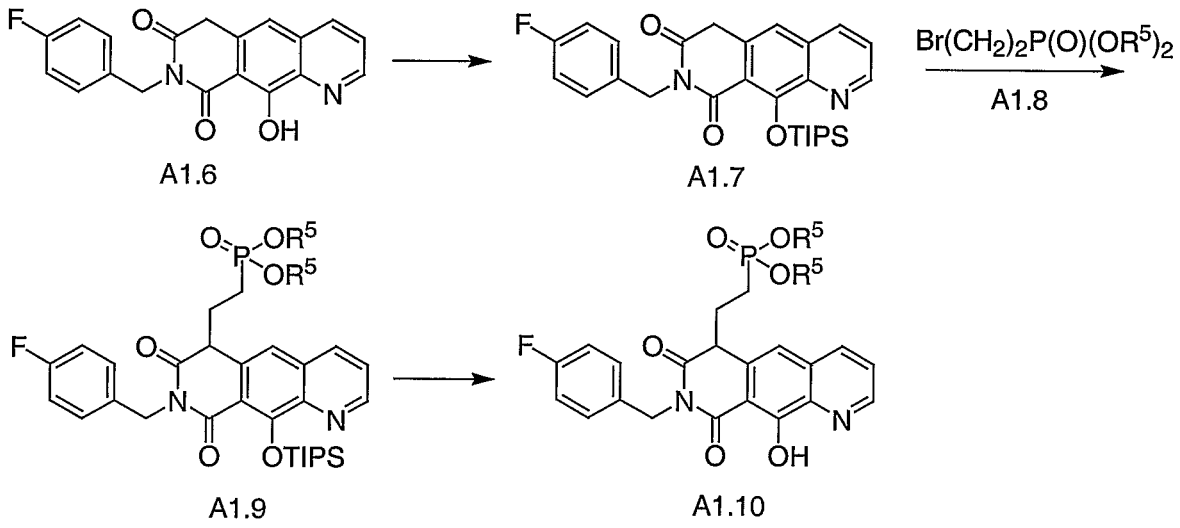
Using the above procedures, but employing, in place of the amine **A3.7**, different amines **A5.2**, and/or different aldehydes **A5.3**, and/or different carboxylic acids **A5.5**, the corresponding products **A5.7** are obtained.

Scheme A1. Phosphonates Iaa.

Method

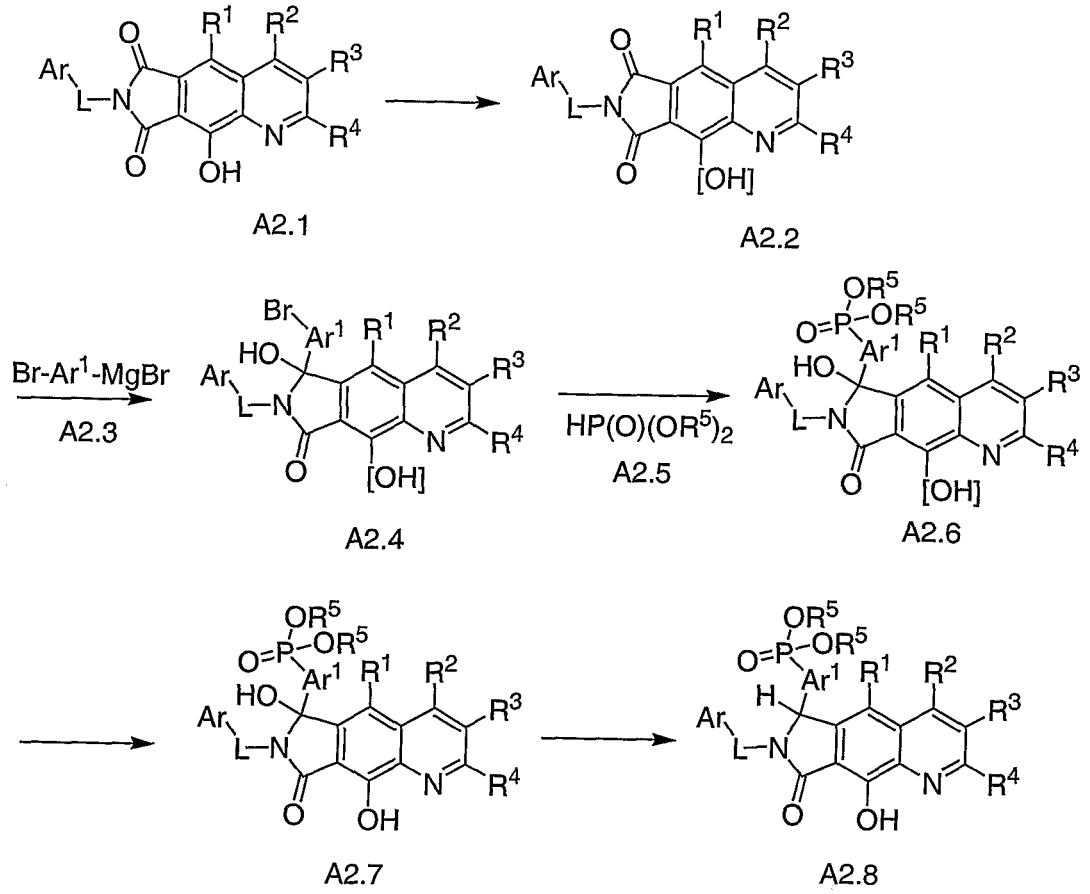


Example A1

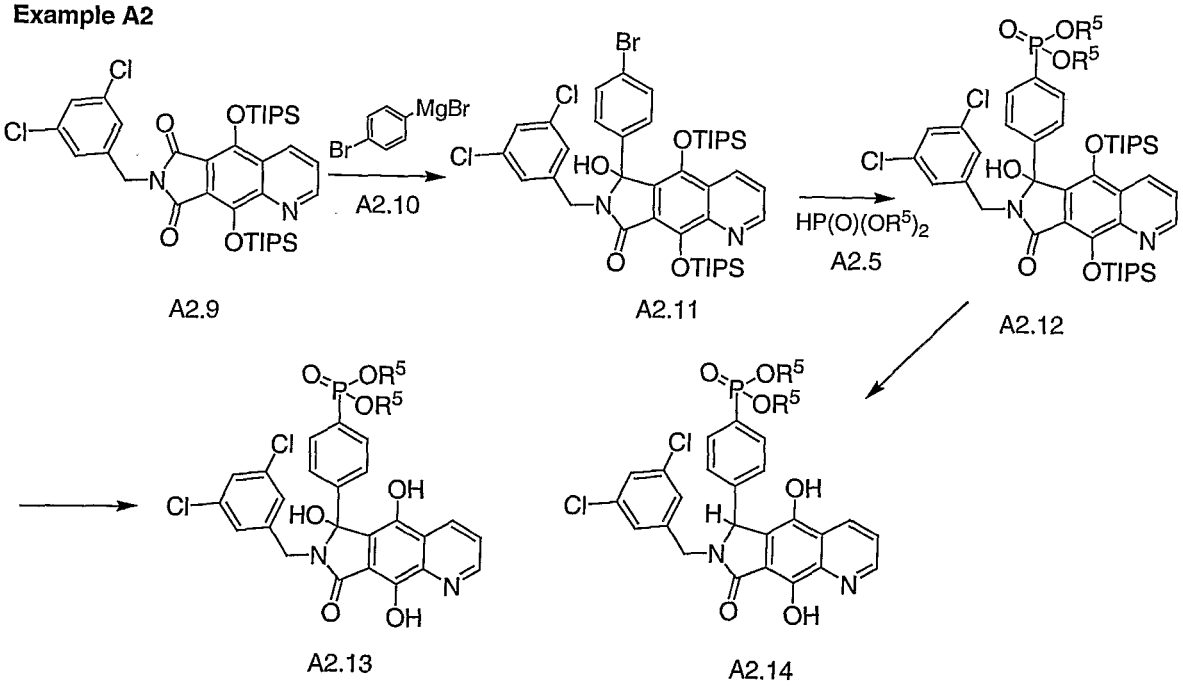


Scheme A2. Phosphonates Iaa.

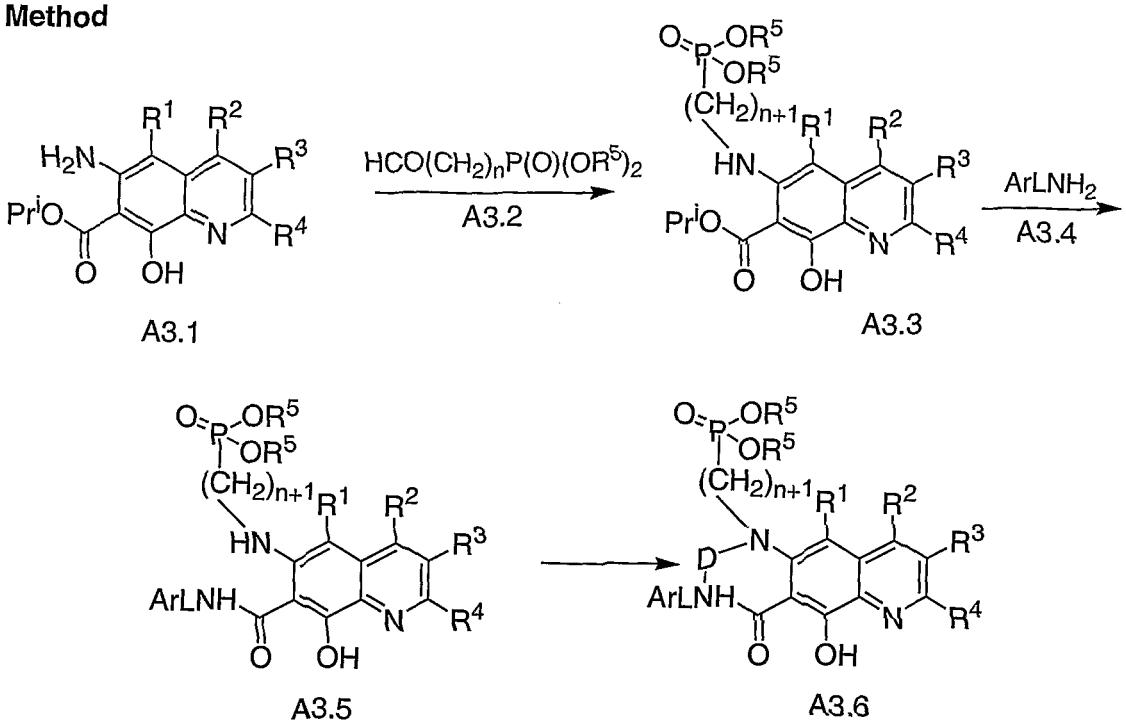
Method



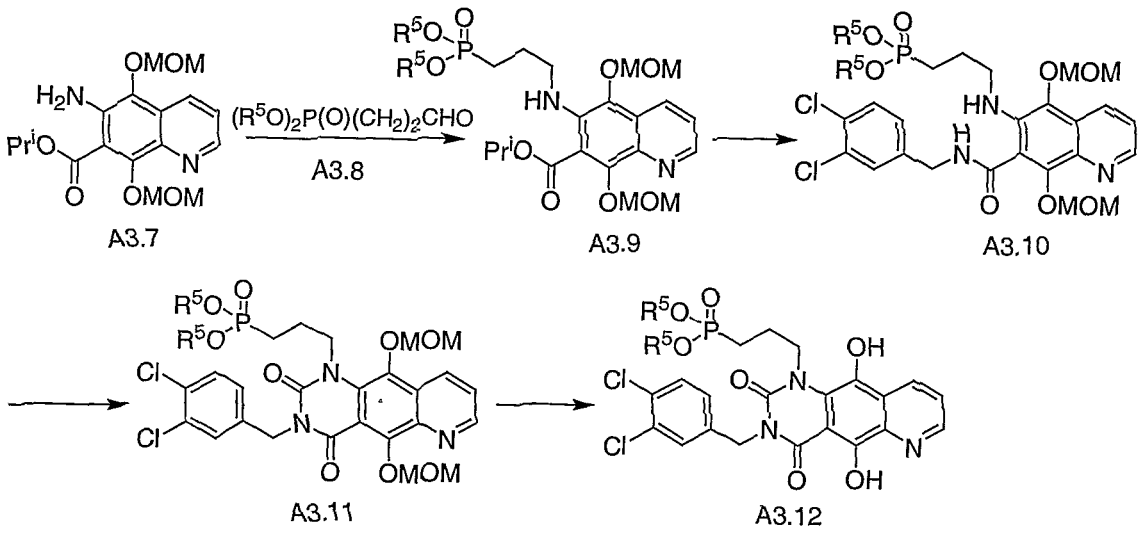
Example A2



Scheme A3. Phosphonates Iaa.
Method

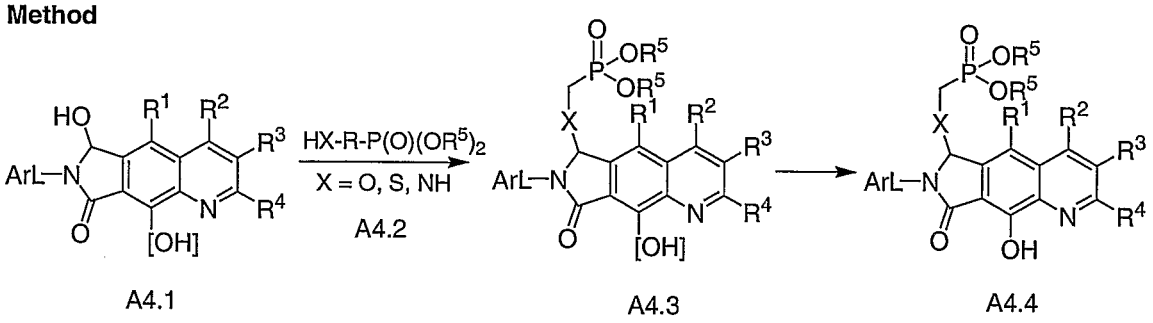


Example A3



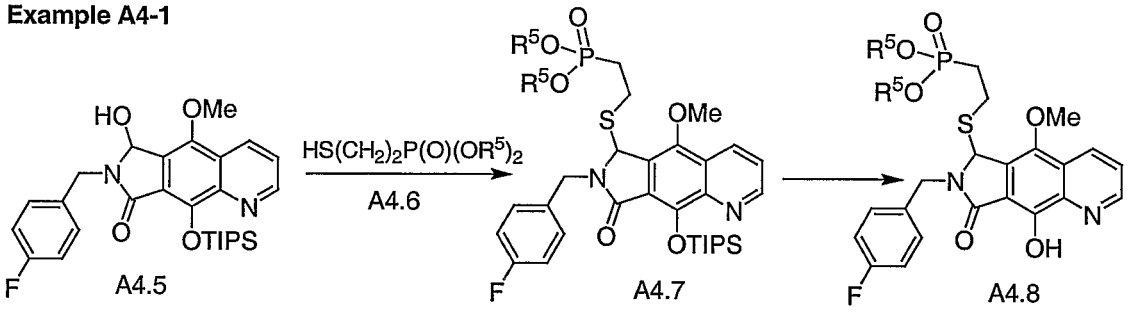
Scheme A4. Phosphonates Iaa.

Method



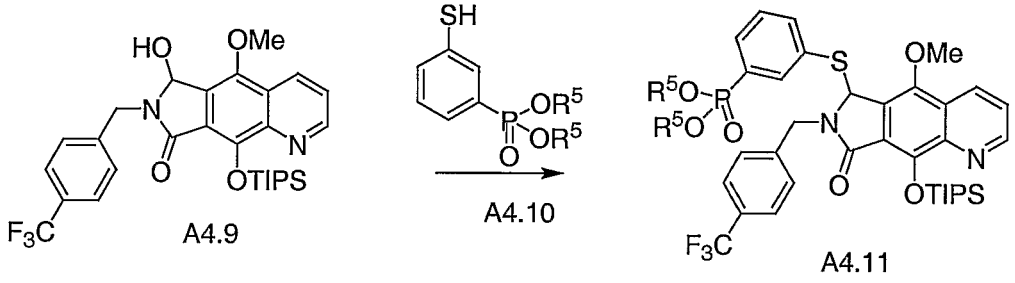
A4.1 A4.3 A4.4

Example A4-1

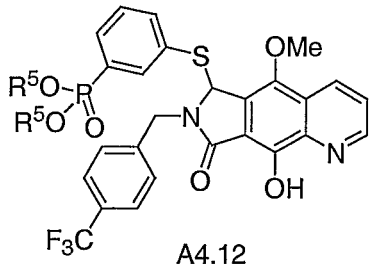


A4.5 A4.7 A4.8

Example A4-2

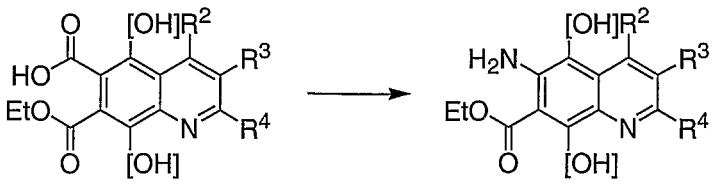


A4.9 A4.11

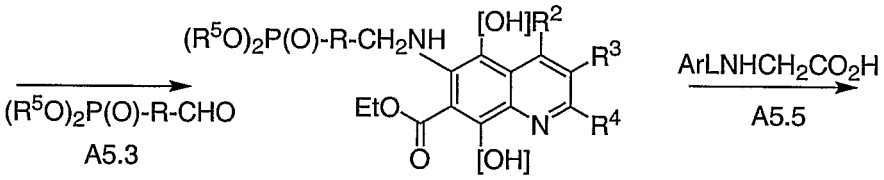


A4.12

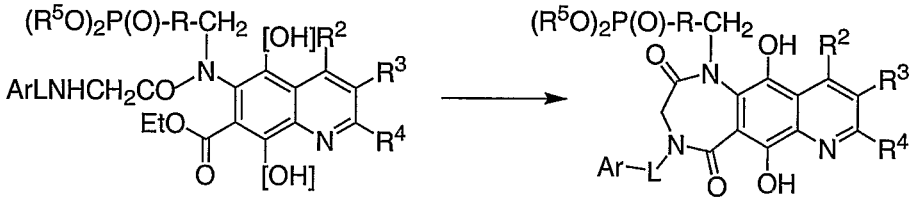
Scheme A5. Phosphonates Iaa.
Method



A5.1 A5.2

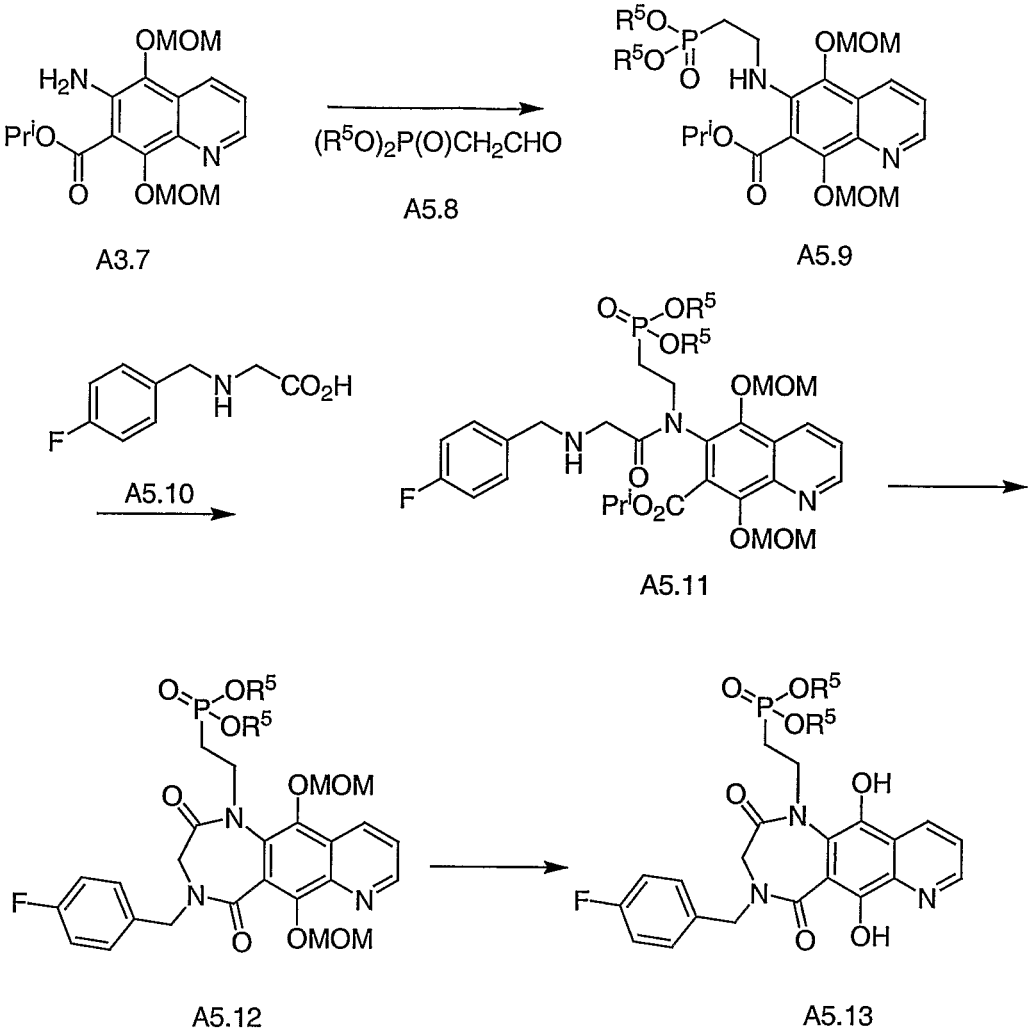


A5.3 A5.4 A5.5



A5.6 A5.7

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°C 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 a 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 carbinols, 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°C, 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°C 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 carbinols, 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 a 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°C-130°C 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°C 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 carbinol **A11.5**, different carbinols **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 carbinol 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 carbinol **A12.5**, different carbinols **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°C. 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 carbinol **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 carbinol **A16.6** is then converted into the substituted amine **A16.7**. The conversion is effected in two stages. In the first step, the carbinol 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

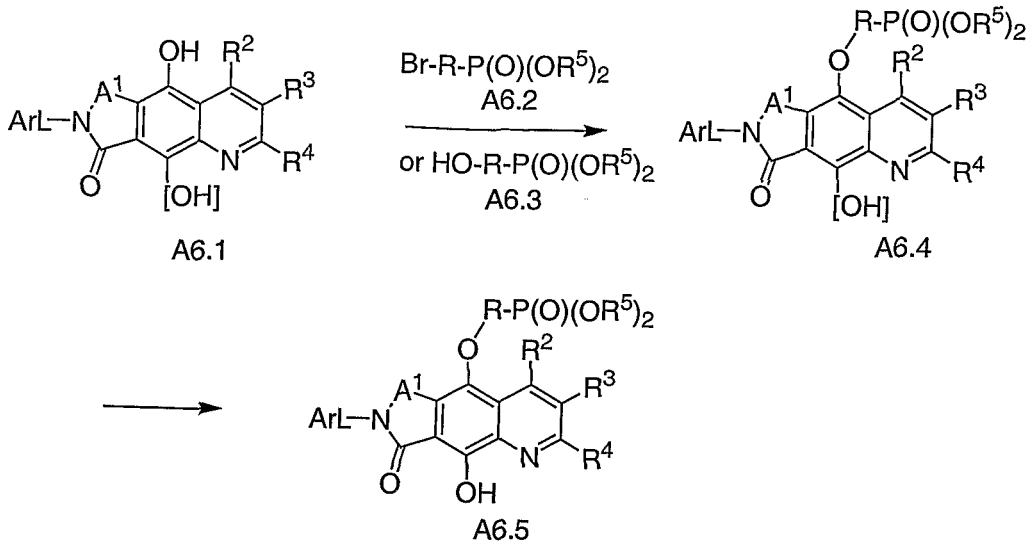
described above (Scheme **A5**). For example, the aminoester is heated in xylene at reflux temperature in the presence of a catalytic amount of sodium isopropoxide. The doubly protected azepin derivative **A16.8** is then selectively deprotected to give the phenol **A16.9**. The procedure for the selective 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**.

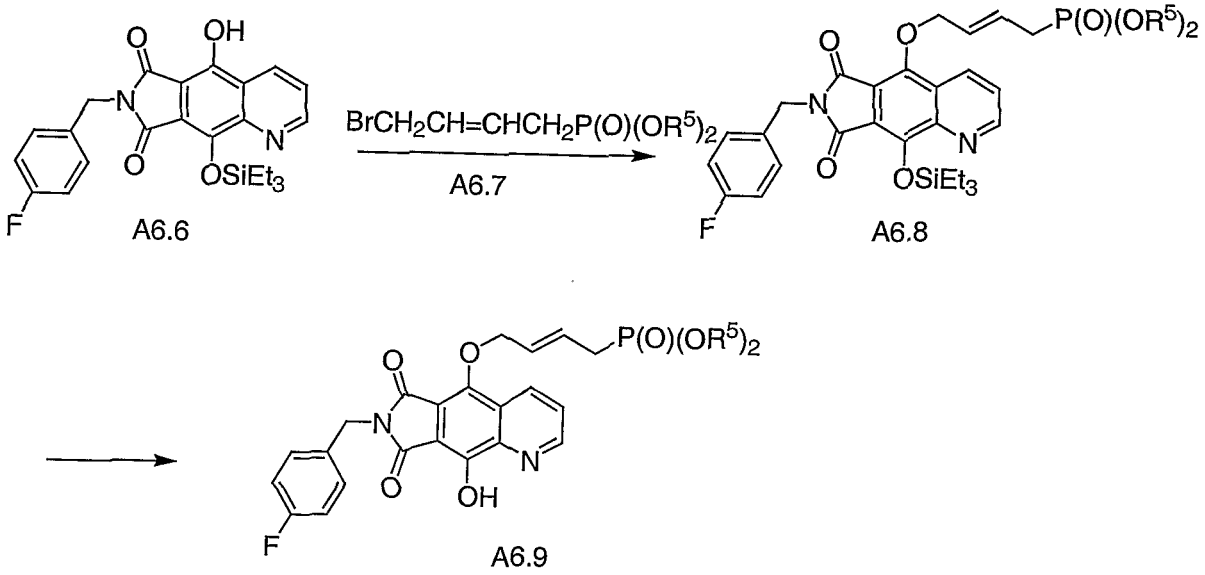
Using the above procedures, but employing, in place of the phenol **A16.12**, different phenols **A16.2**, and/or different hydroxyesters **A16.10**, and/or different amines $ArBNH_2$, the corresponding products **A16.11** are obtained.

Scheme A6. Phosphonates Ibb.

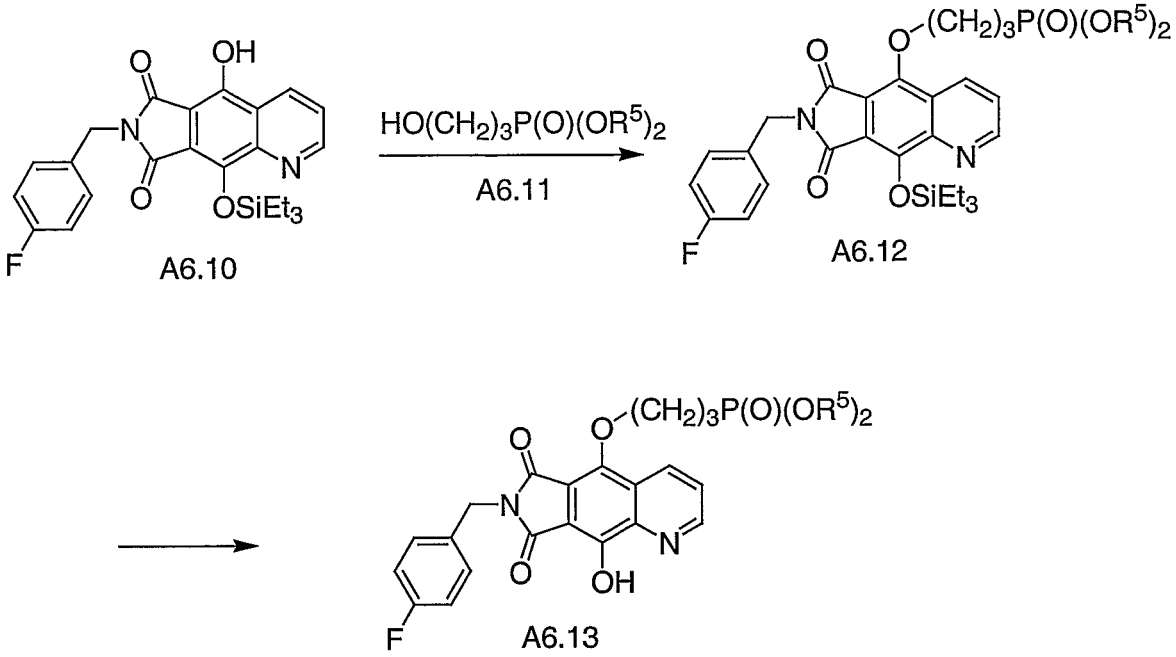
Method



Example A6-1

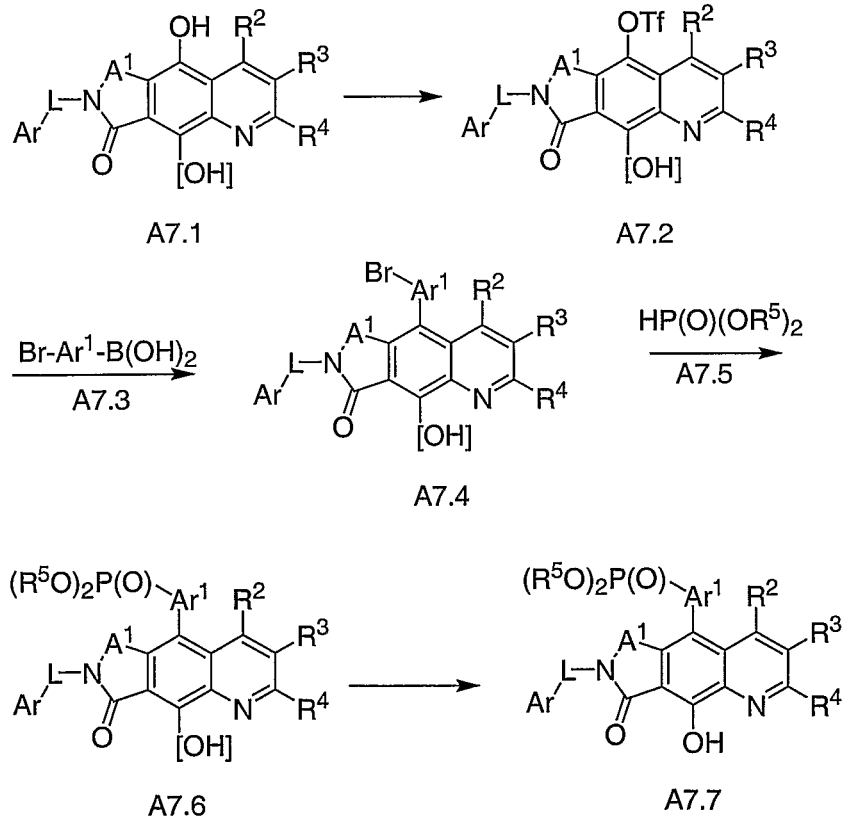


Example A6-2

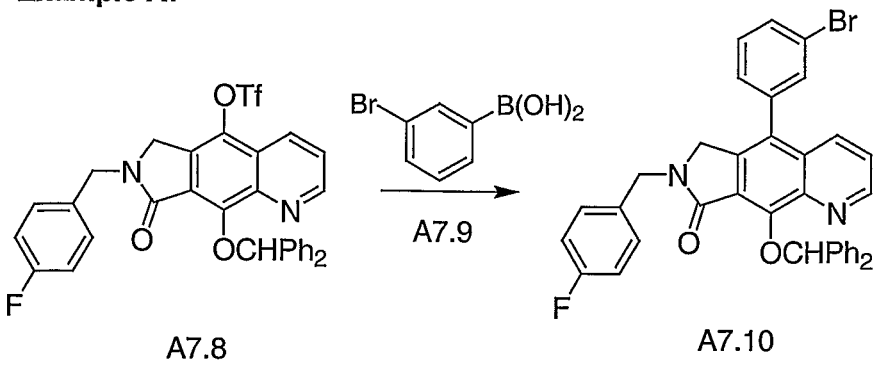


Scheme A7. Phosphonates Ibb.

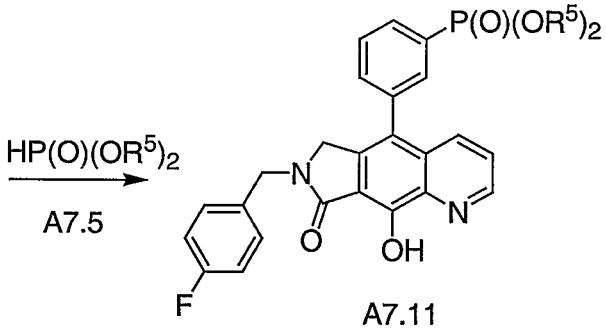
Method



Example A7



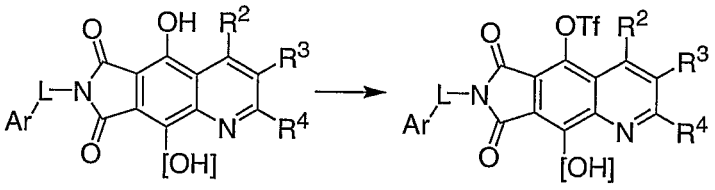
A7.8 A7.10



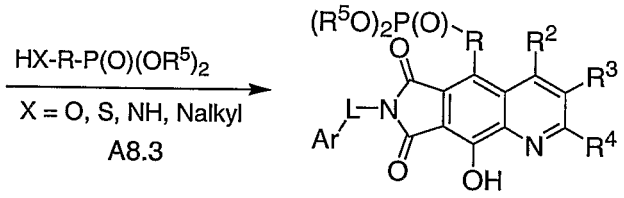
A7.11

Scheme A8. Phosphonates Ibb.

Method

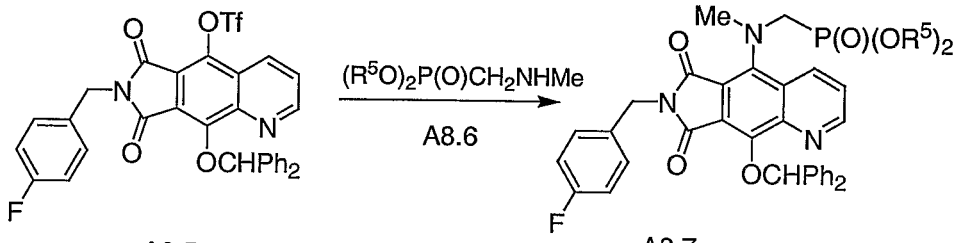


A8.1 A8.2

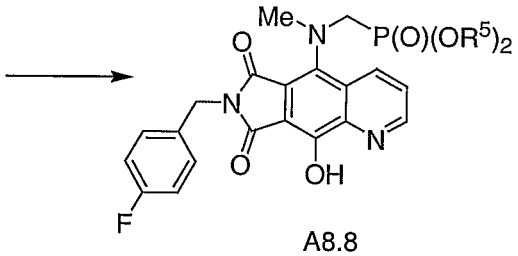


A8.3 A8.4

Example A8



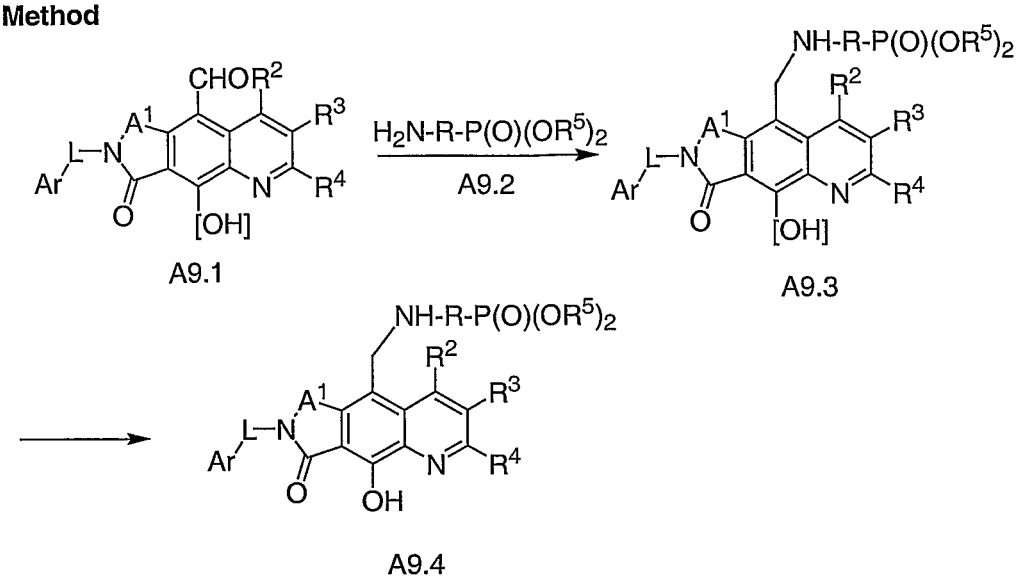
A8.5 A8.6 A8.7



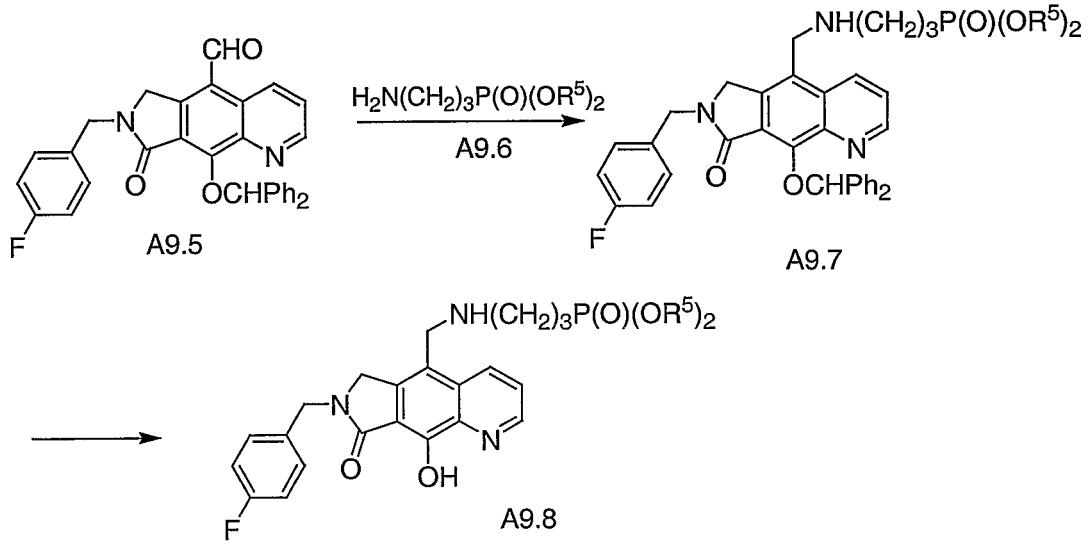
A8.8

Scheme A9. Phosphonates Ibb.

Method

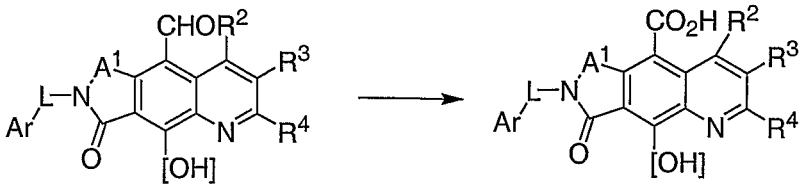


Example A9

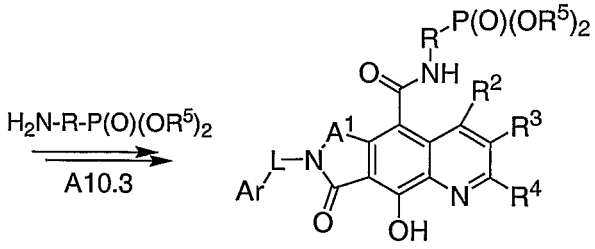


Scheme A10. Phosphonates Ibb.

Method

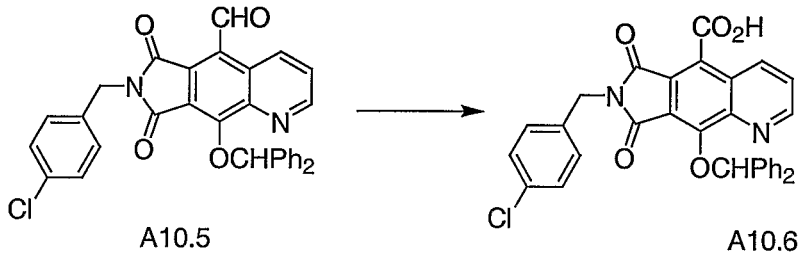


A10.1 A10.2

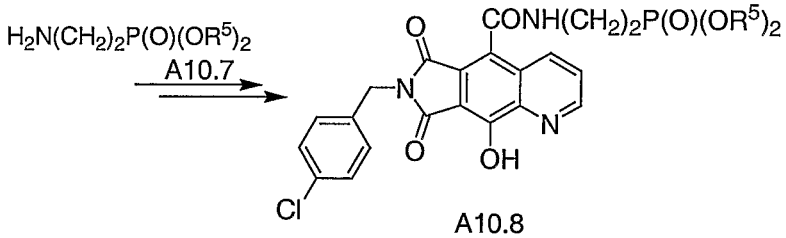


A10.4

Example A10



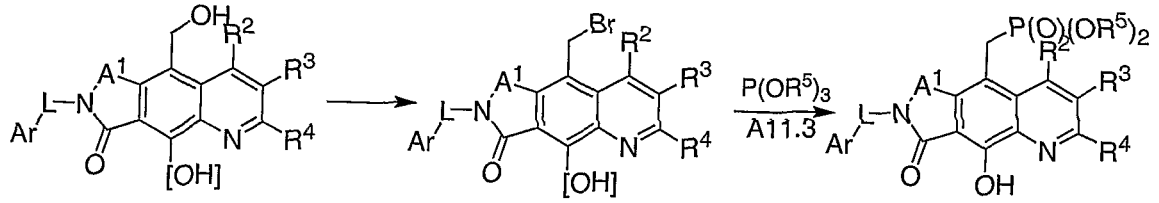
A10.5 A10.6



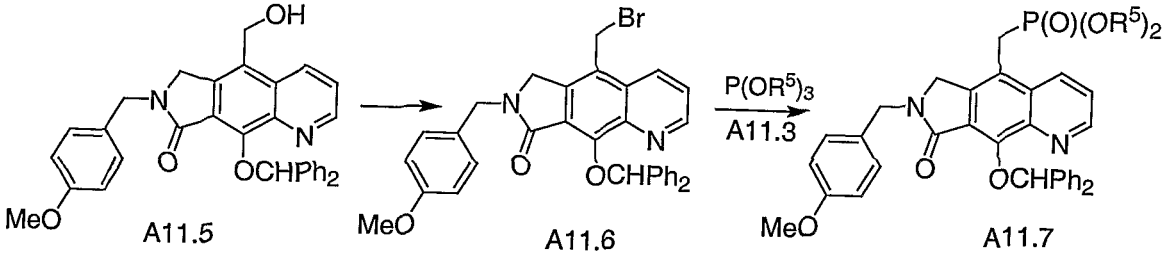
A10.8

Scheme A11. Phosphonates Ibb.

Method

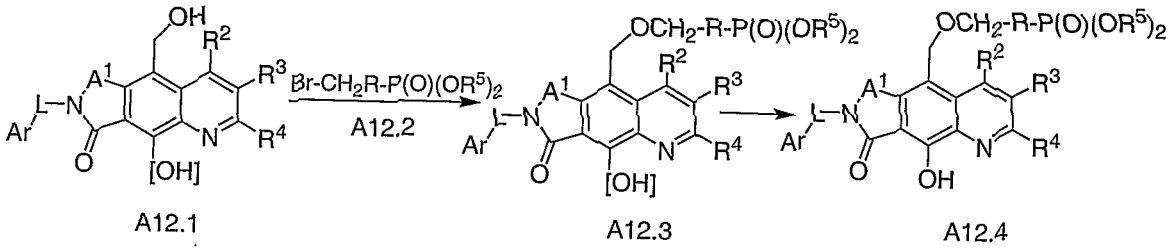


Example A11

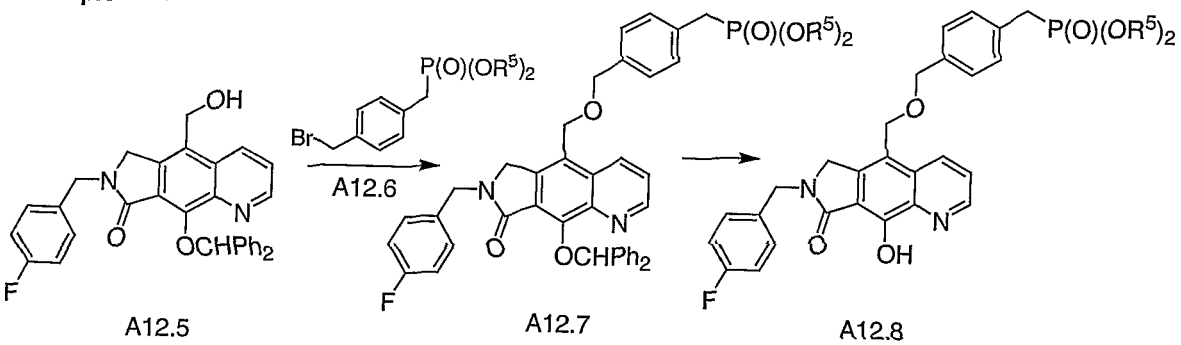


Scheme A12. Phosphonates Ibb.

Method

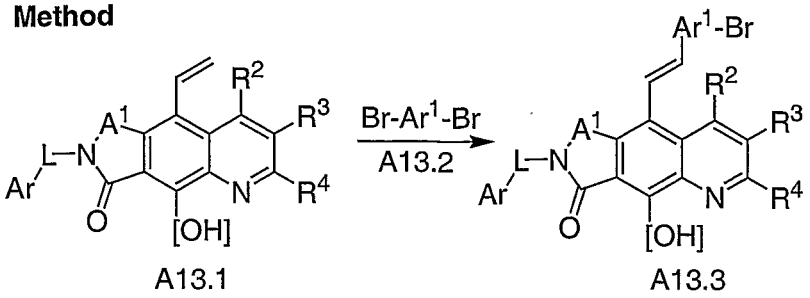


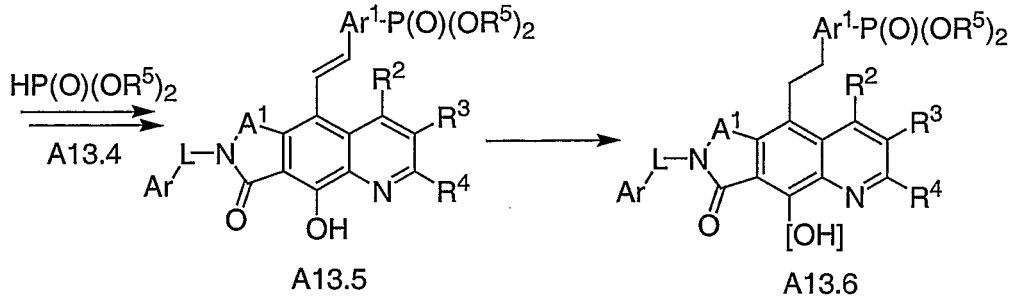
Example A12



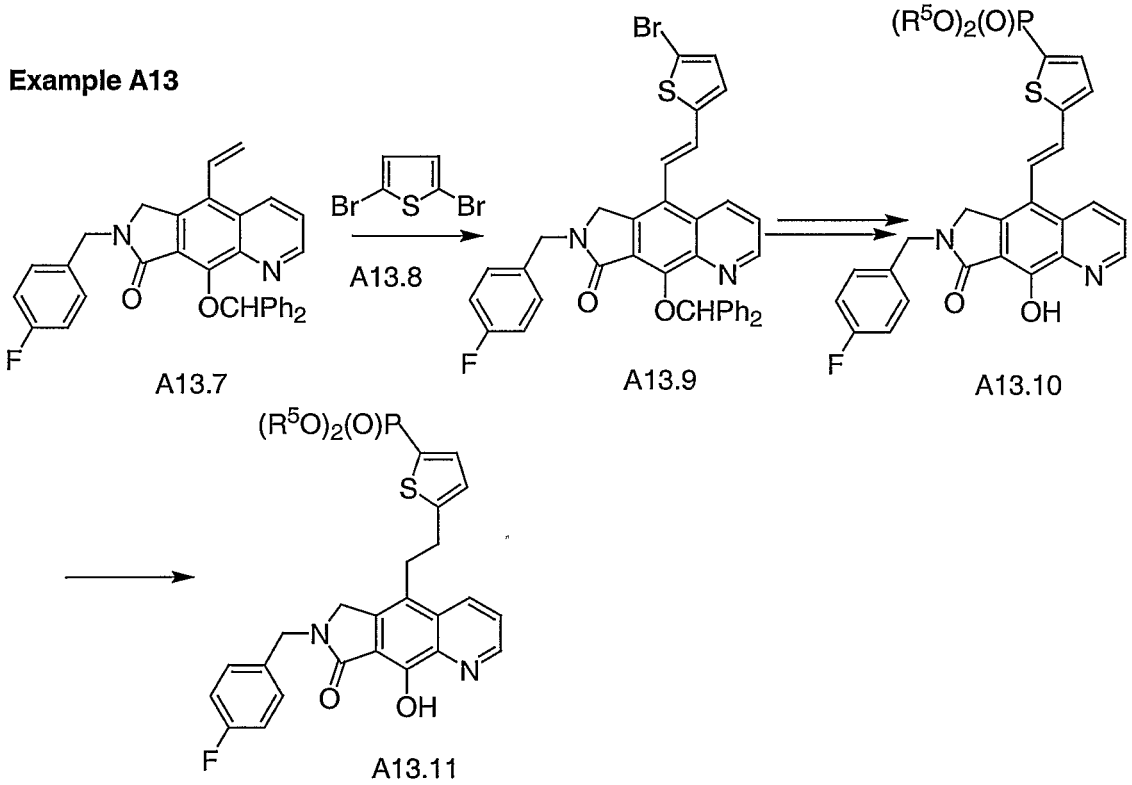
Scheme A13. Phosphonates Ibb.

Method



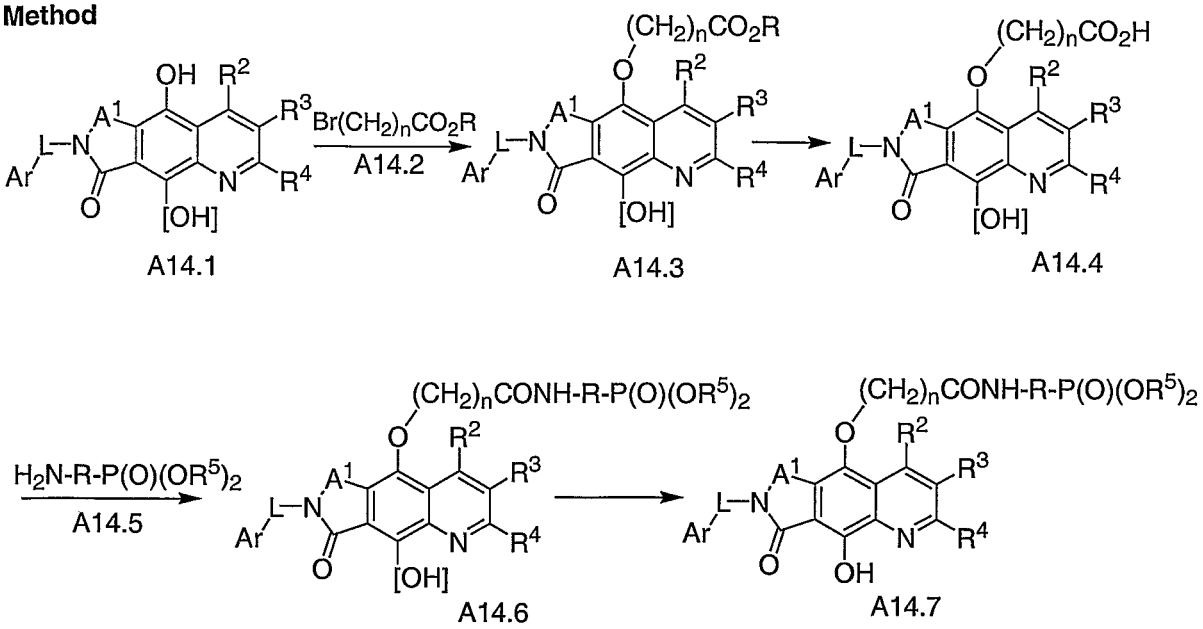


Example A13

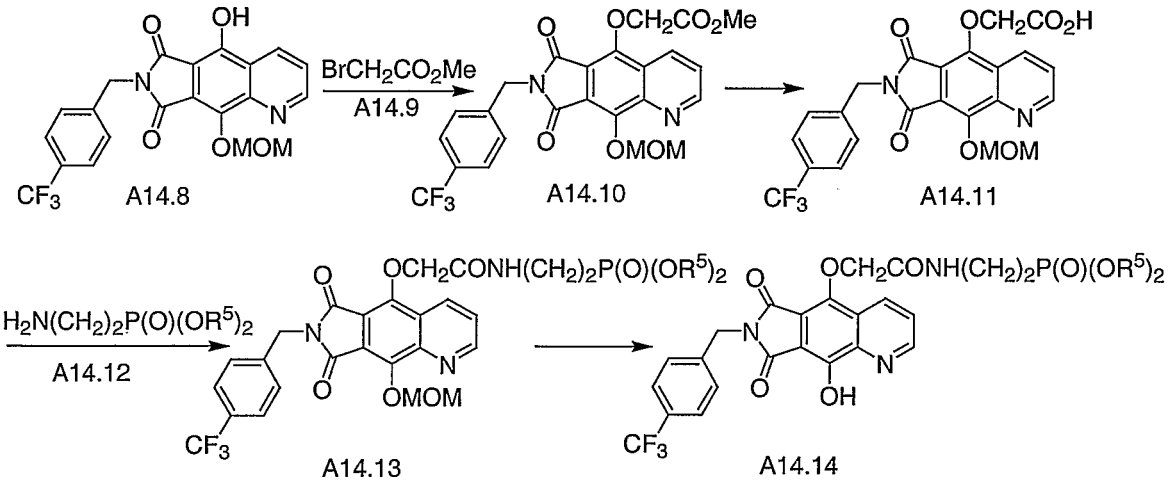


Scheme A14. Phosphonates Ibb.

Method

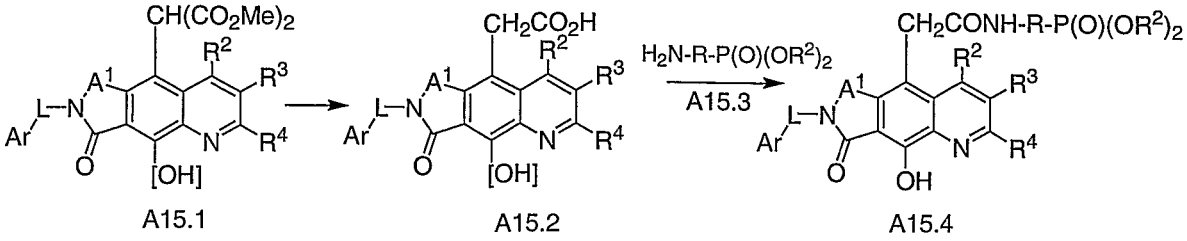


Example A14

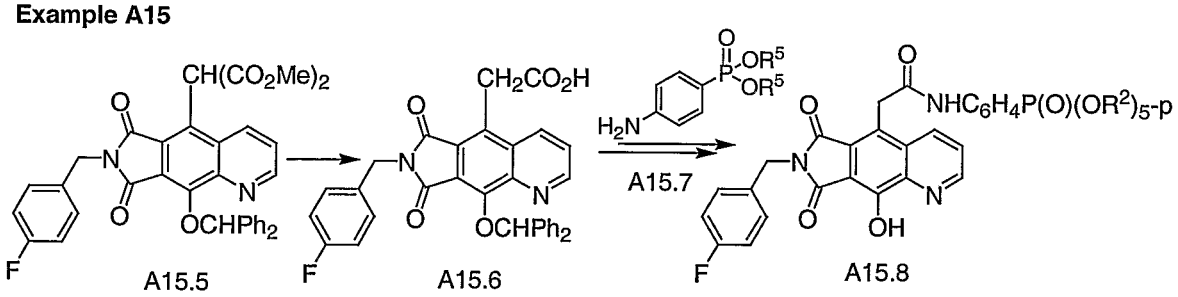


Scheme A15. Phosphonates Ibb.

Method

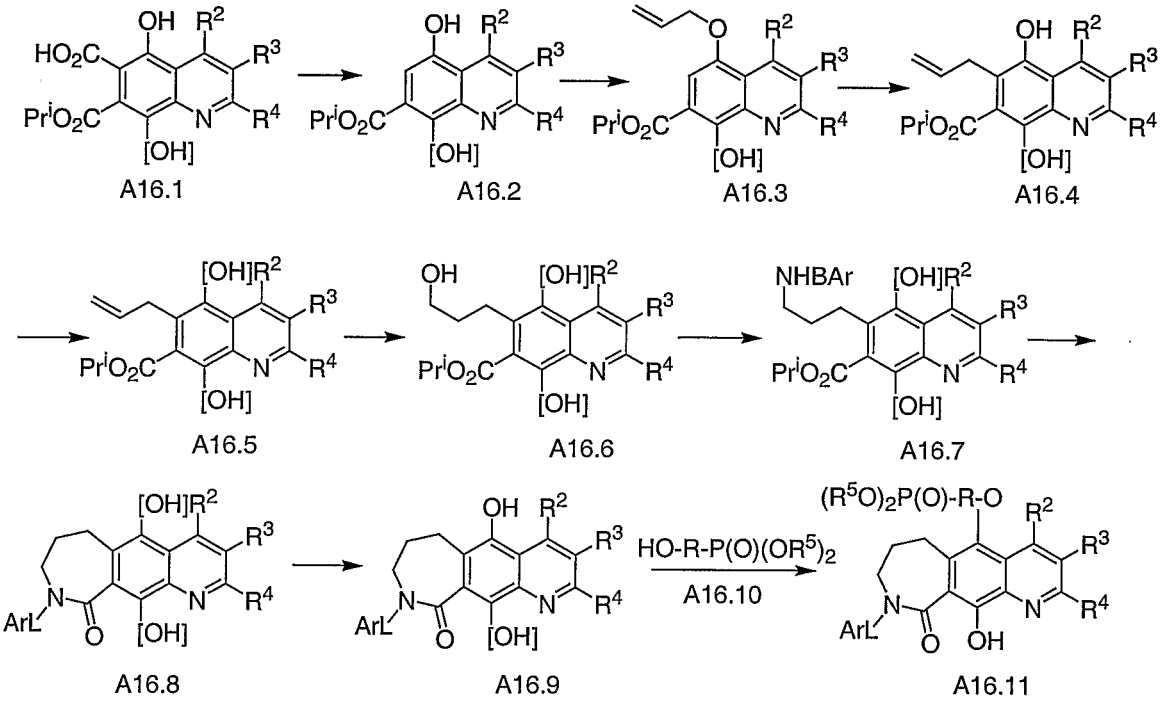


Example A15

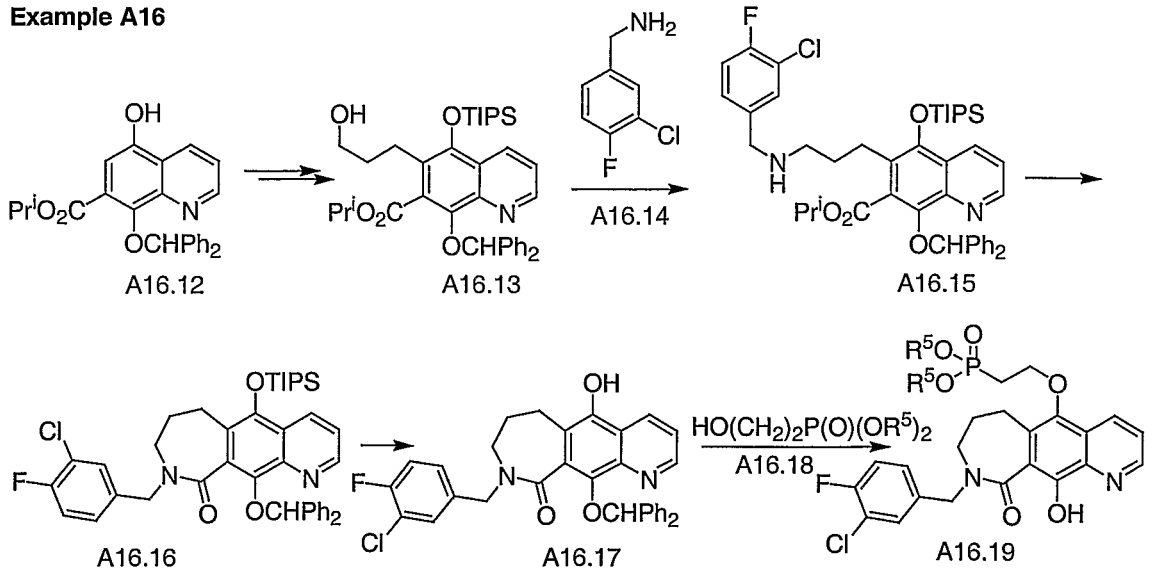


Scheme A16. Phosphonates Ibb.

Method



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°C, 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°C with an excess of a trialkyl phosphite to give after deprotection the phenolic phosphonate ester **A17.14**.

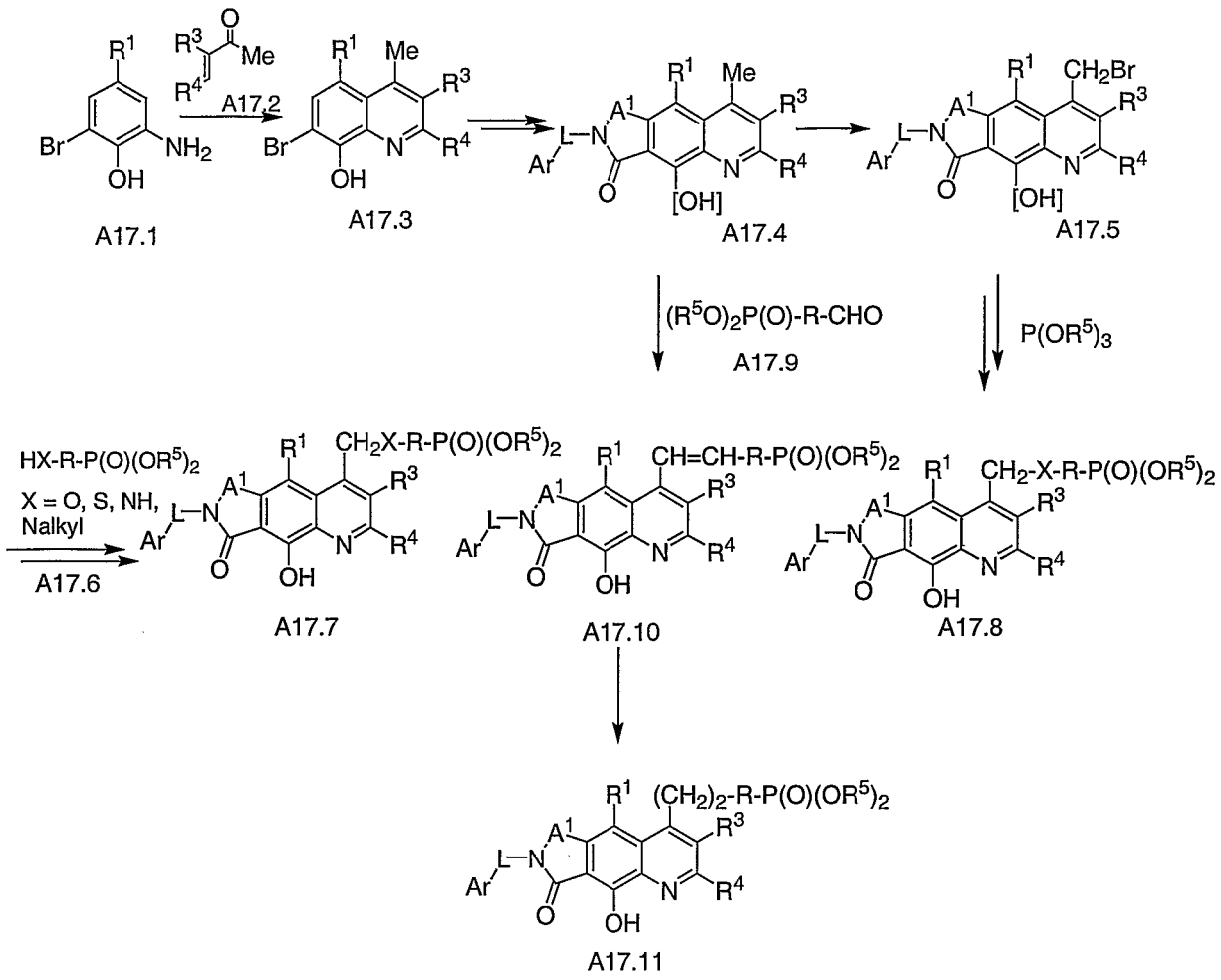
As a further example, 4-bromomethyl-7-(4-fluoro-benzyl)-9-triisopropylsilanyloxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **A17.15**, prepared by bromination of the corresponding methyl compound is reacted with a dialkyl 2-mercaptoethyl phosphonate **A17.16** (Zh. Obschei. Khim., 1973, 43, 2793) and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

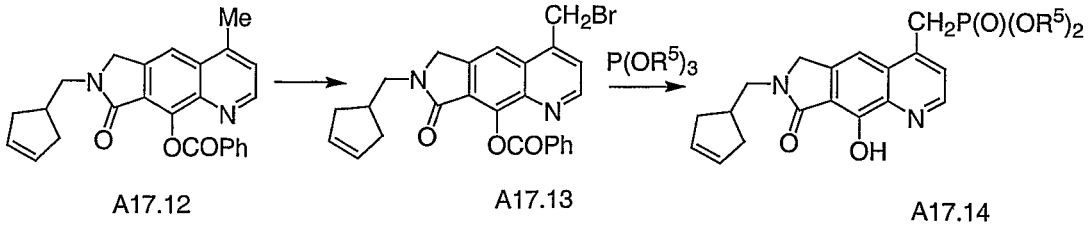
Using the above procedures, but employing, in place of the starting materials **A17.12**, **A17.15** and **A17.19**, different starting materials **A17.4** or **A17.5**, and/or different carbinols, thiols or amines **A17.6** or aldehydes **A17.9**, the corresponding products **A17.7**, **A17.8**, **A17.10**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

Scheme A17. Phosphonates Icc.

Method

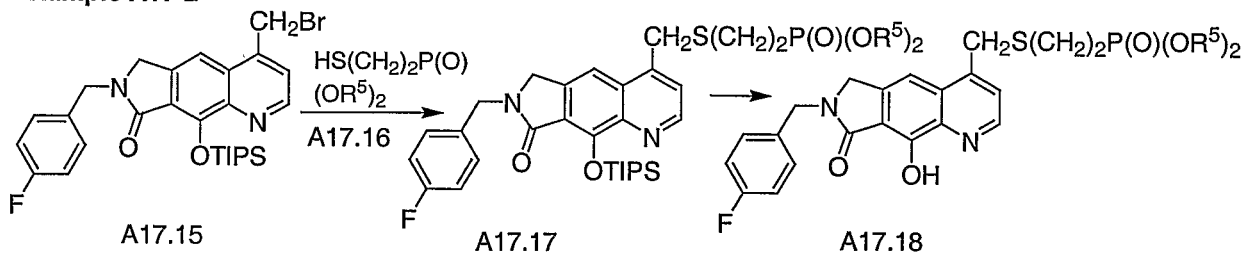


Example A17-1



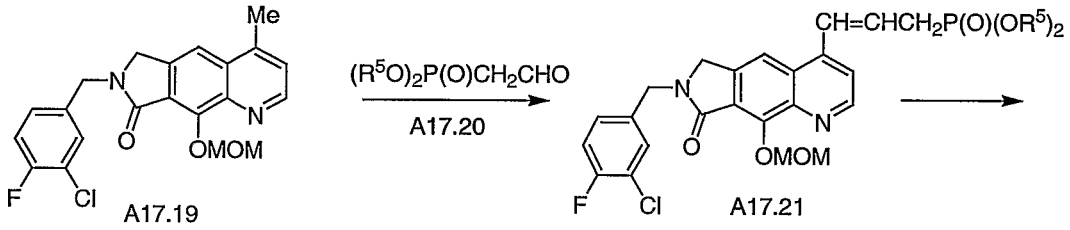
A17.12 A17.13 A17.14

Example A17-2

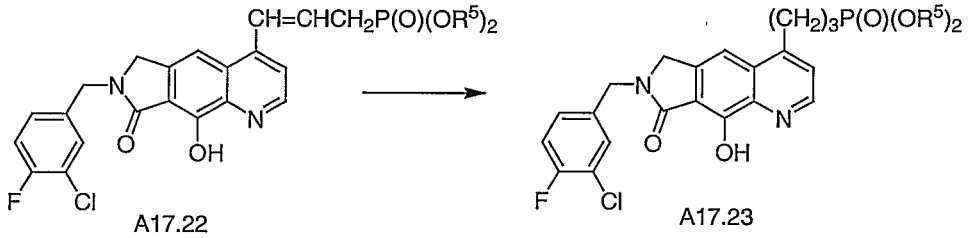


A17.15 A17.17 A17.18

Example A17-3



A17.19 A17.21



A17.22 A17.23

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°C. 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°C. 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°C 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.

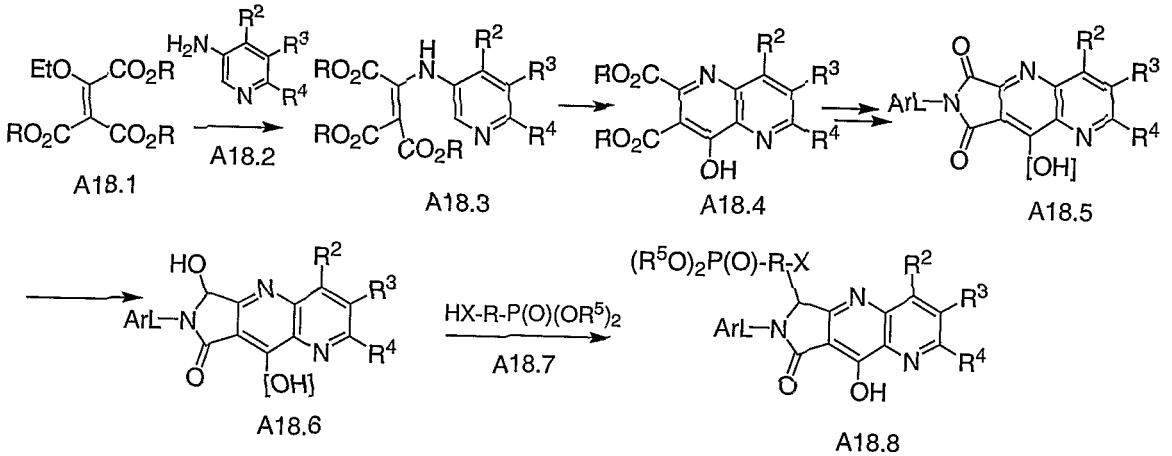
Scheme **A19** depicts the preparation of phosphonate esters of structure **IIaa** in which the phosphonate group is attached by means of variable carbon linkage, and the nucleus is a 1,3,5,9-tetraazaanthracene. In this procedure, the 1,5-naphthyridine **A18.4** is converted into the phenol-protected 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°C to give the cyclized product **A19.13**. Deprotection then yields the phenol **A19.14**.

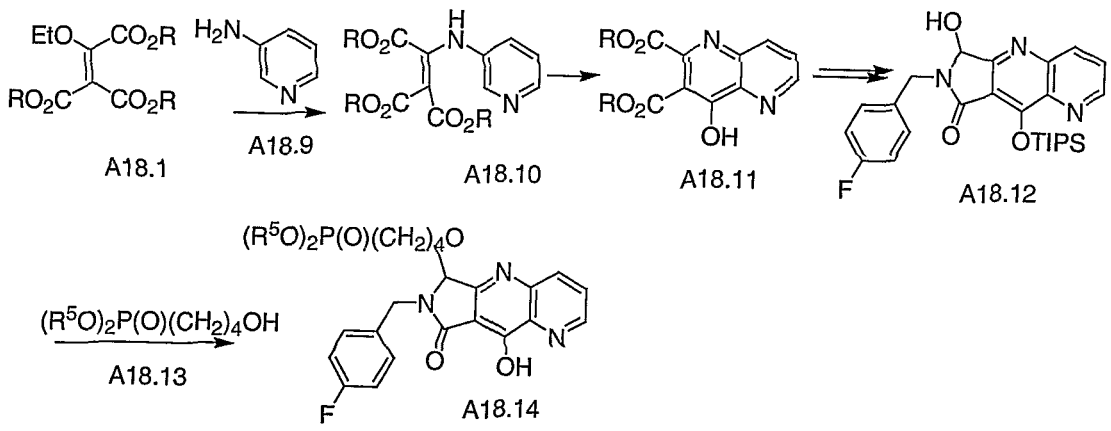
Using the above procedures, but employing, in place of the amine **A19.9**, different amines **A19.3**, and/or different formyl phosphonates **A19.4**, the corresponding products **A19.7** are obtained.

Scheme A18. Phosphonates IIaa.

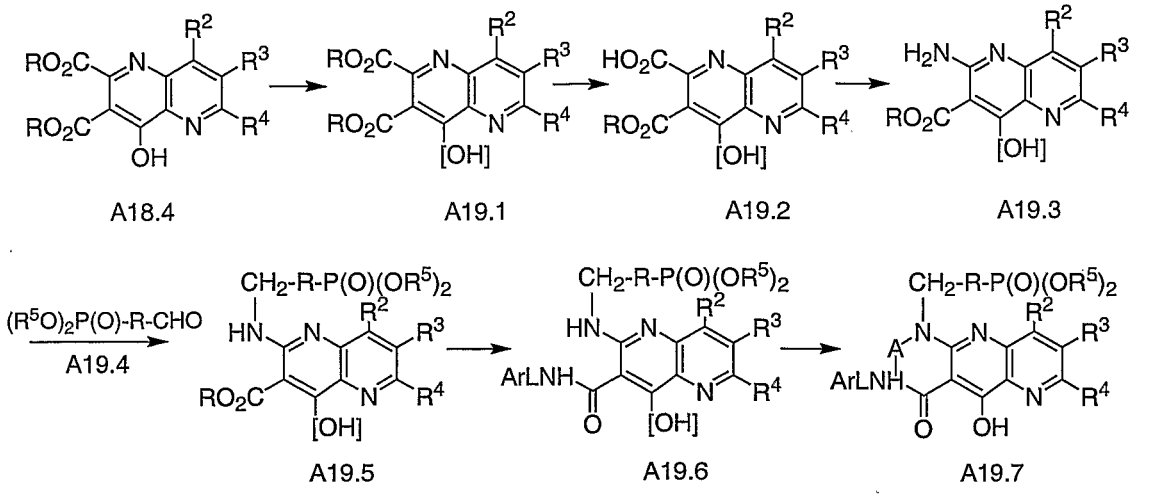
Method



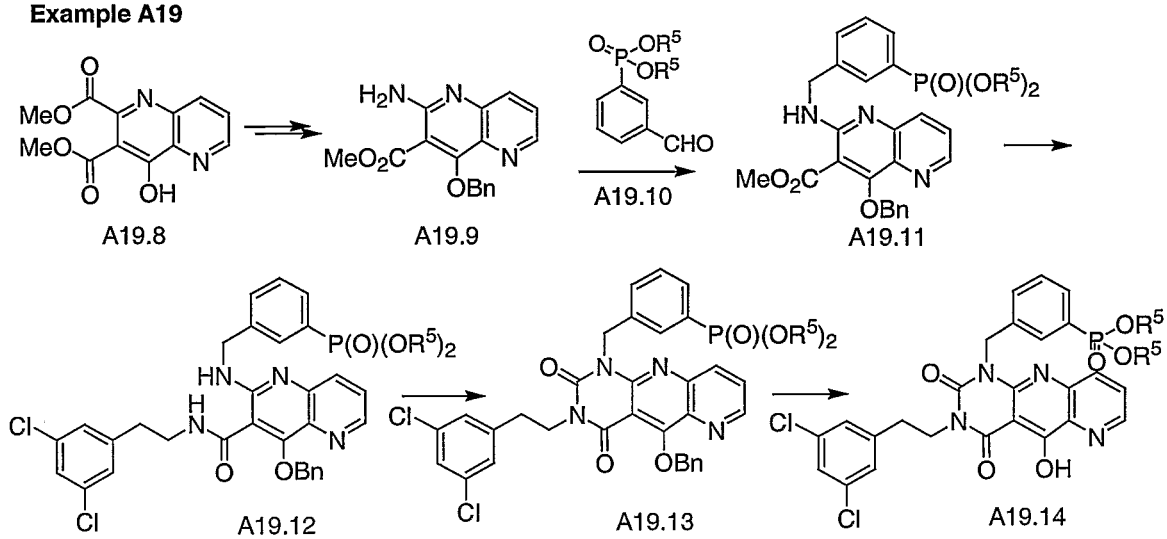
Example A18



Scheme A19. Phosphonates IIaa.
Method



Example A19



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°C with excess of a trialkyl phosphite to give after deprotection the phosphonate **A20.19**.

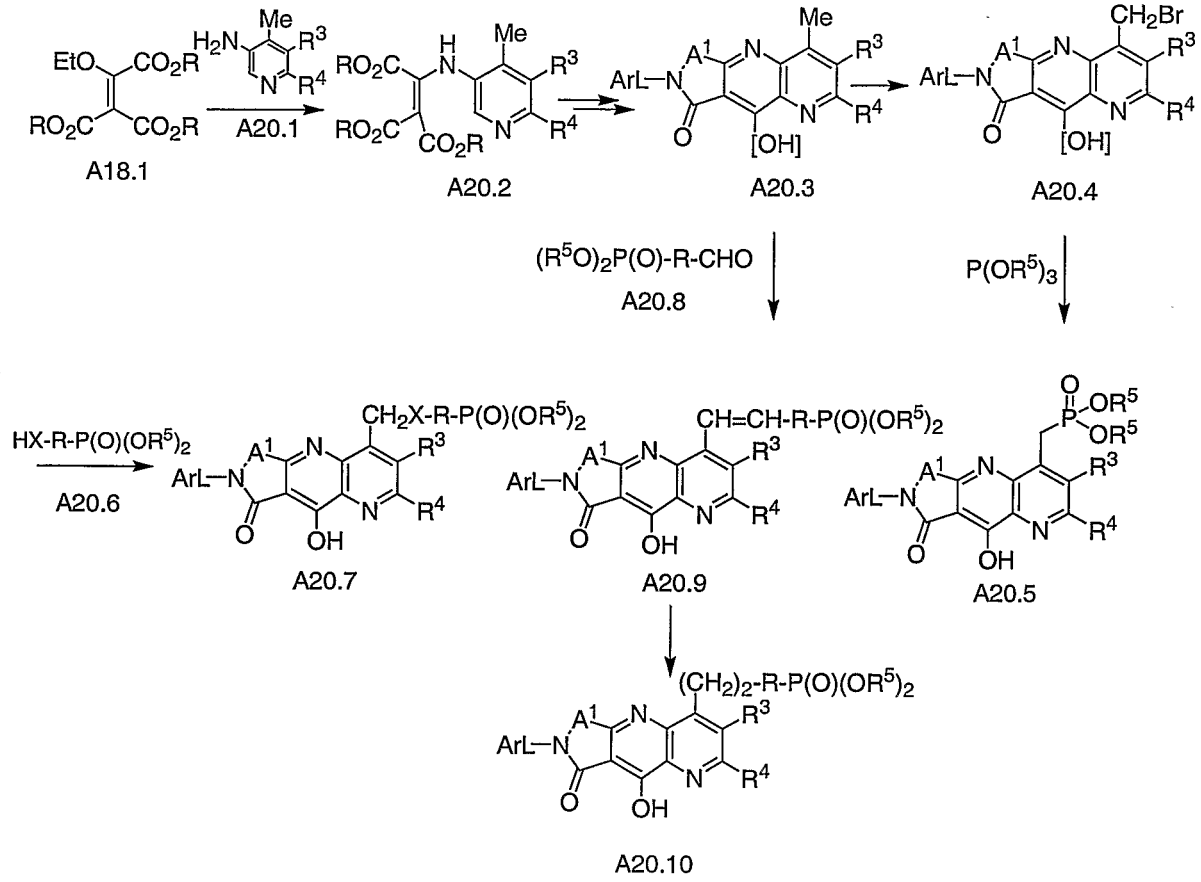
As a further example, 4-bromomethyl-7-(3-chloro-4-fluoro-benzyl)-9-triisopropylsilanyloxy-pyrrolo[3,4-b][1,5]naphthyridine-6,8-dione **A20.20**, prepared according to the procedures described above, is reacted in dimethylformamide solution with a dialkyl methylaminomethyl phosphonate **A20.21**(AsInEx)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

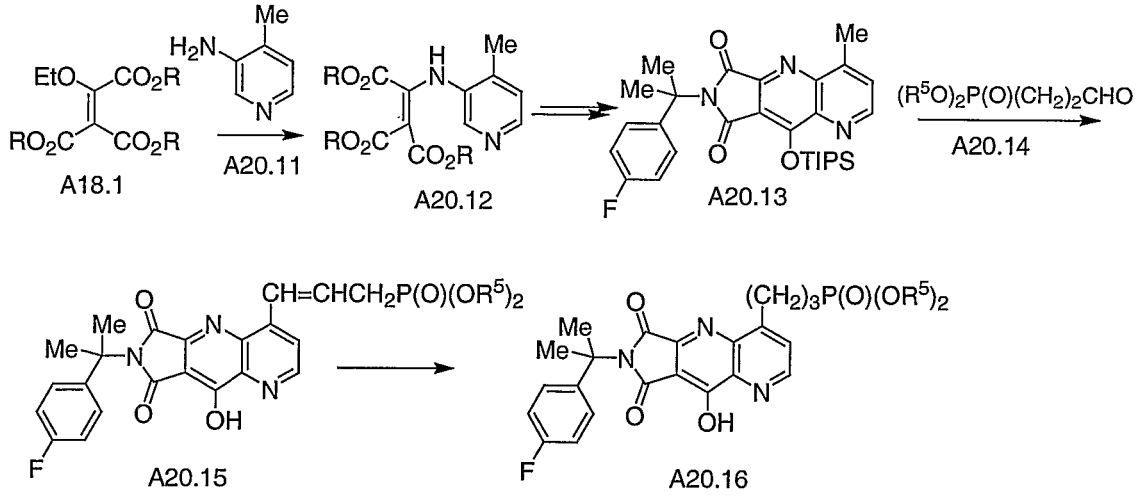
carbinols, thiols or amines **A20.6** or aldehydes **A20.8**, the corresponding products **A20.5**, **A20.7**, **A20.9** and **A20.10** are obtained.

Scheme A20. Phosphonates IIcc.

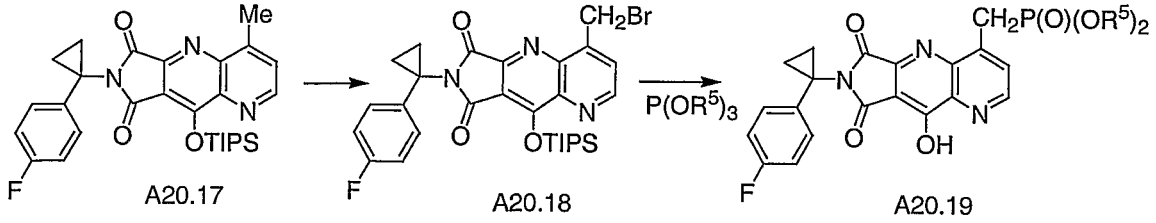
Method



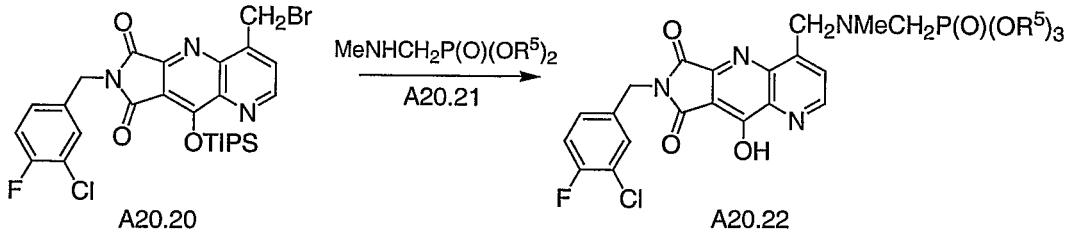
Example A20-1



Example A20-2



Example A20-3



Preparation of the intermediate phosphonate esters IIIaa.

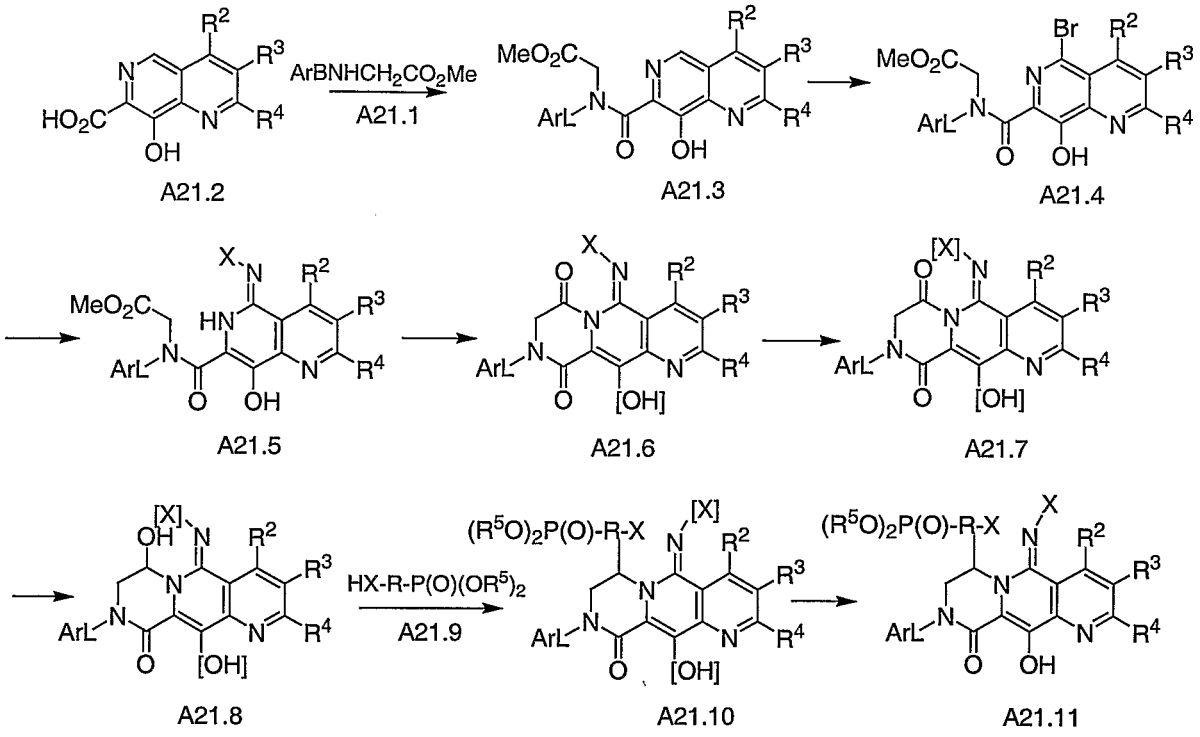
Scheme **A21** illustrates methods for the preparation of phosphonates of structure **IIIaa** in which the phosphonate group is attached by means of a heteroatom and a variable carbon link. In this sequence, a carbomethoxymethyl derivative of the amine $ArBNH_2$, **A21.1** is coupled with the 1,6-naphthyridine 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-

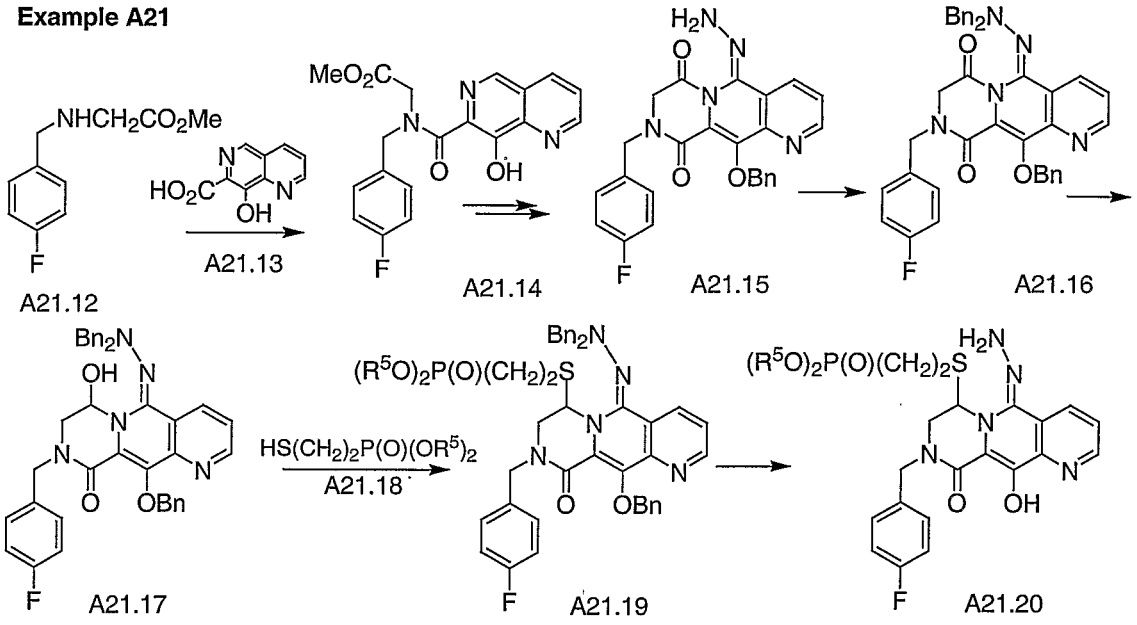
carboxylic acid **A21.13**, (WO 0230930) in the presence of diisopropyl carbodiimide, to form [(4-fluoro-benzyl)-(8-hydroxy-[1,6]naphthyridine-7-carbonyl)-amino]-acetic acid methyl ester **A21.14**. The latter compound is then transformed, by bromination, displacement and cyclization, as described above 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 carbinol **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°C 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**.

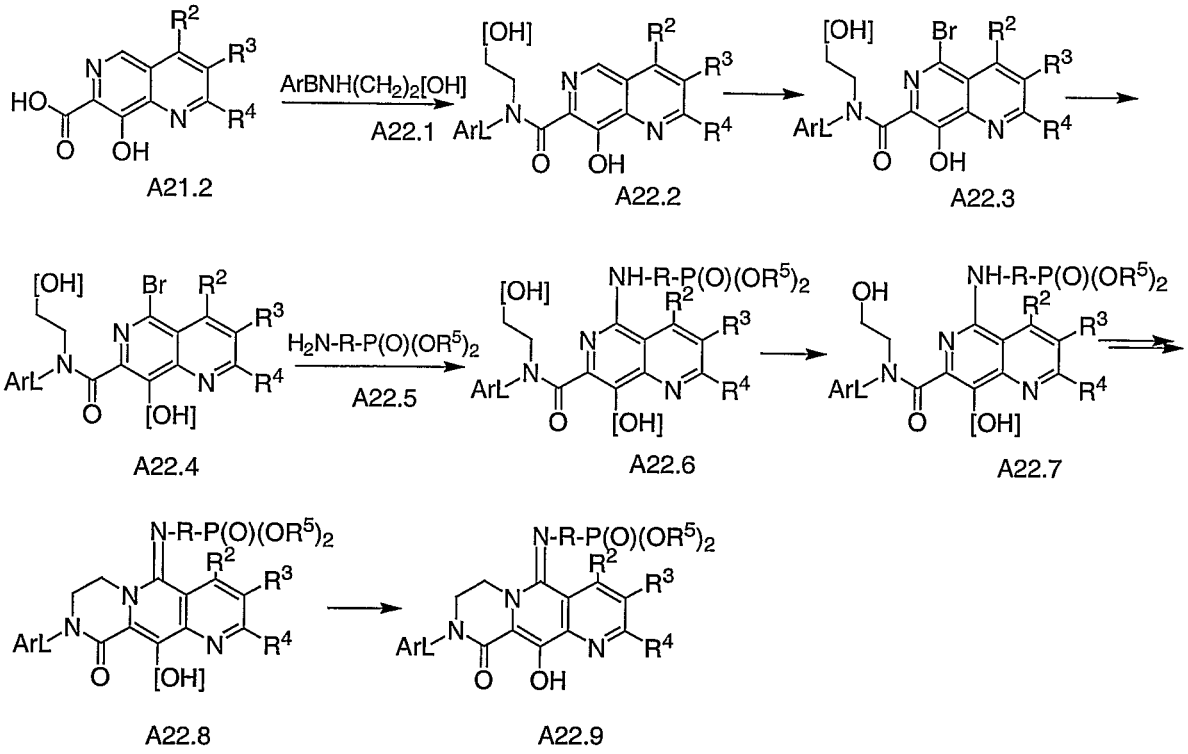
Using the above procedures, but employing, in place of the hydrazone **A23.7**, different hydrazones **A23.1**, and/or different bromophosphonates **A23.2**, or formyl phosphonates **A23.4** the corresponding products **A23.3**, **A23.5** and **A23.6** are obtained.

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**.

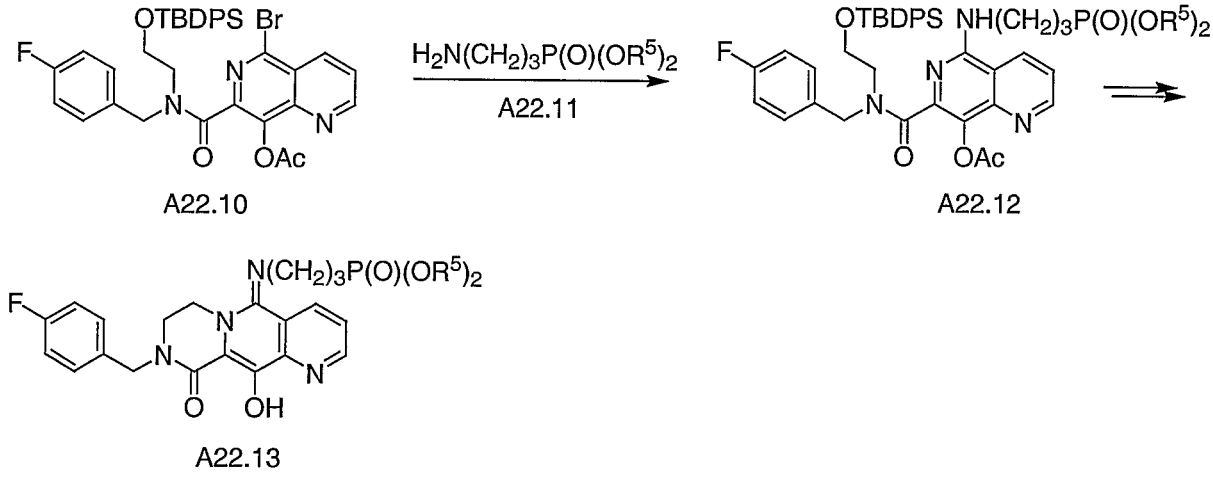
For example, acetic acid 7-(4-fluoro-benzyl)-10-hydroxyimino-8-oxo-6,7,8,10-tetrahydro-5H-1,7,10a-triaza-anthracen-9-yl ester **A24.5** (Scheme 14) is reacted in dimethylformamide solution with one molar equivalent of sodium hydride, followed by the addition of one molar equivalent of a dialkyl 4-(bromomethyl)phenyl 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. Phospnonates IIIbb.
Method

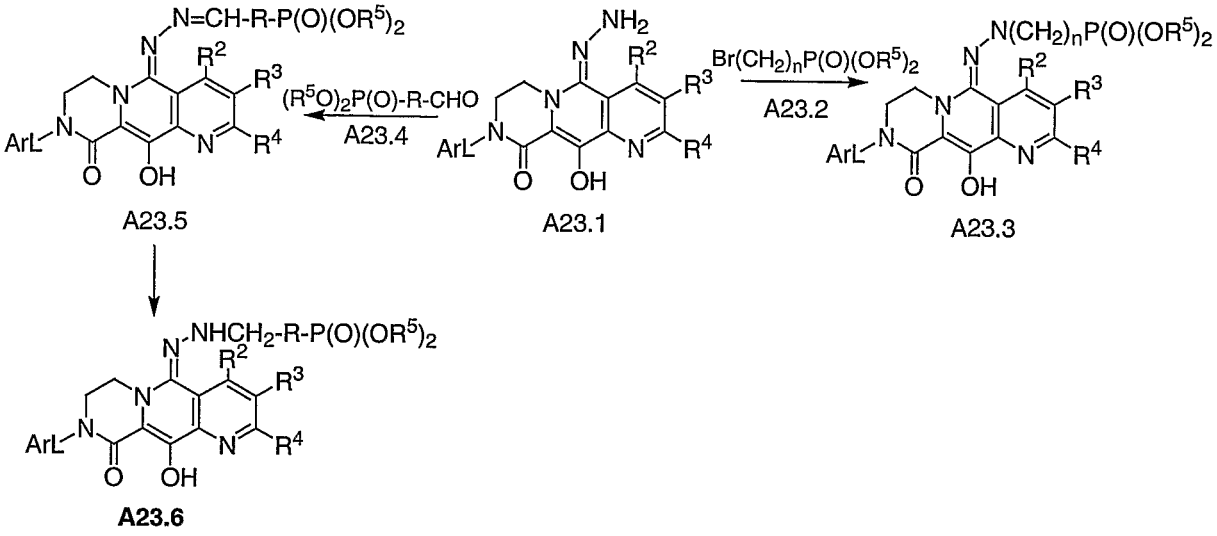


Example A22

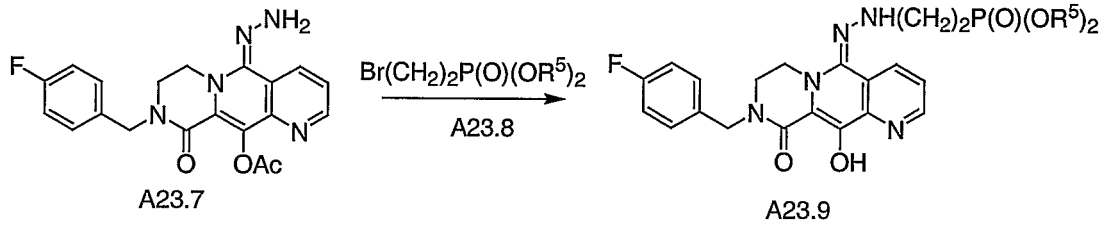


Scheme A23. Phosphonates IIIbb.

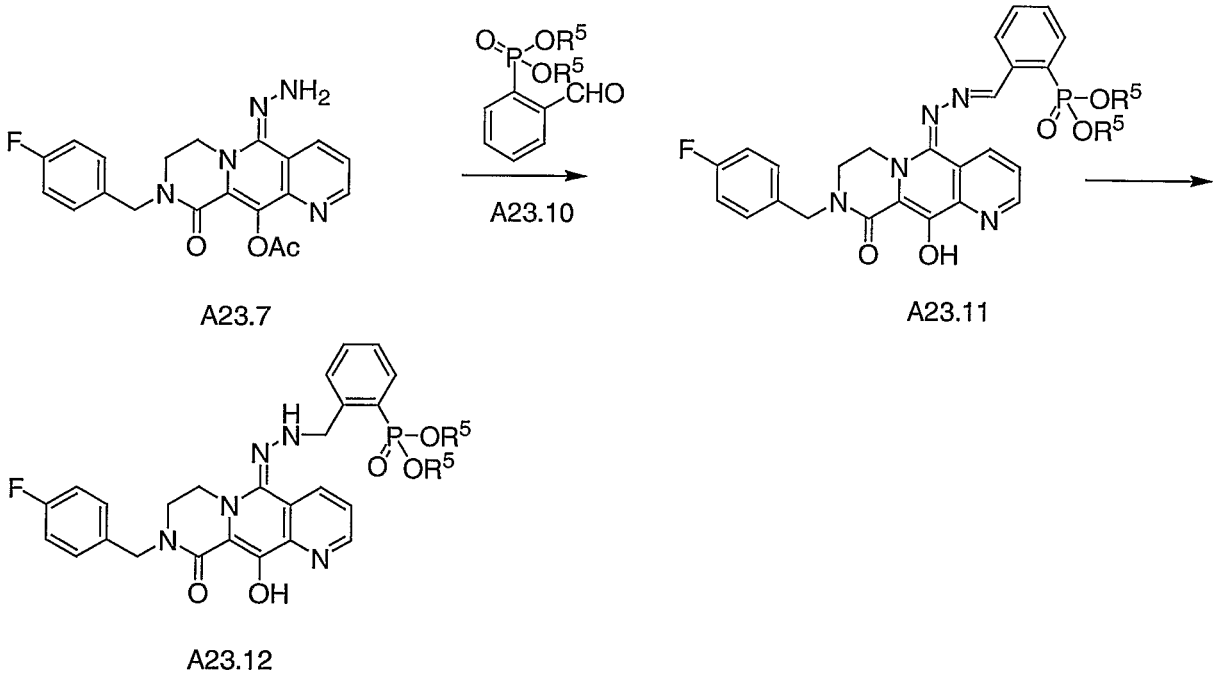
Method



Example A23-1

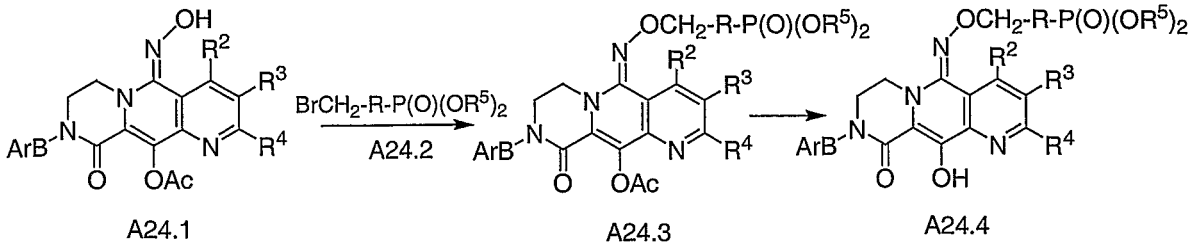


Example A23-2

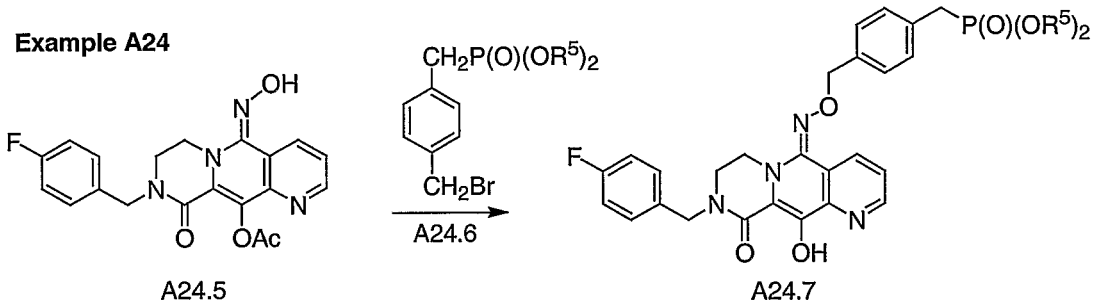


Scheme A24. Phosphonates IIIbb.

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°C 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**.

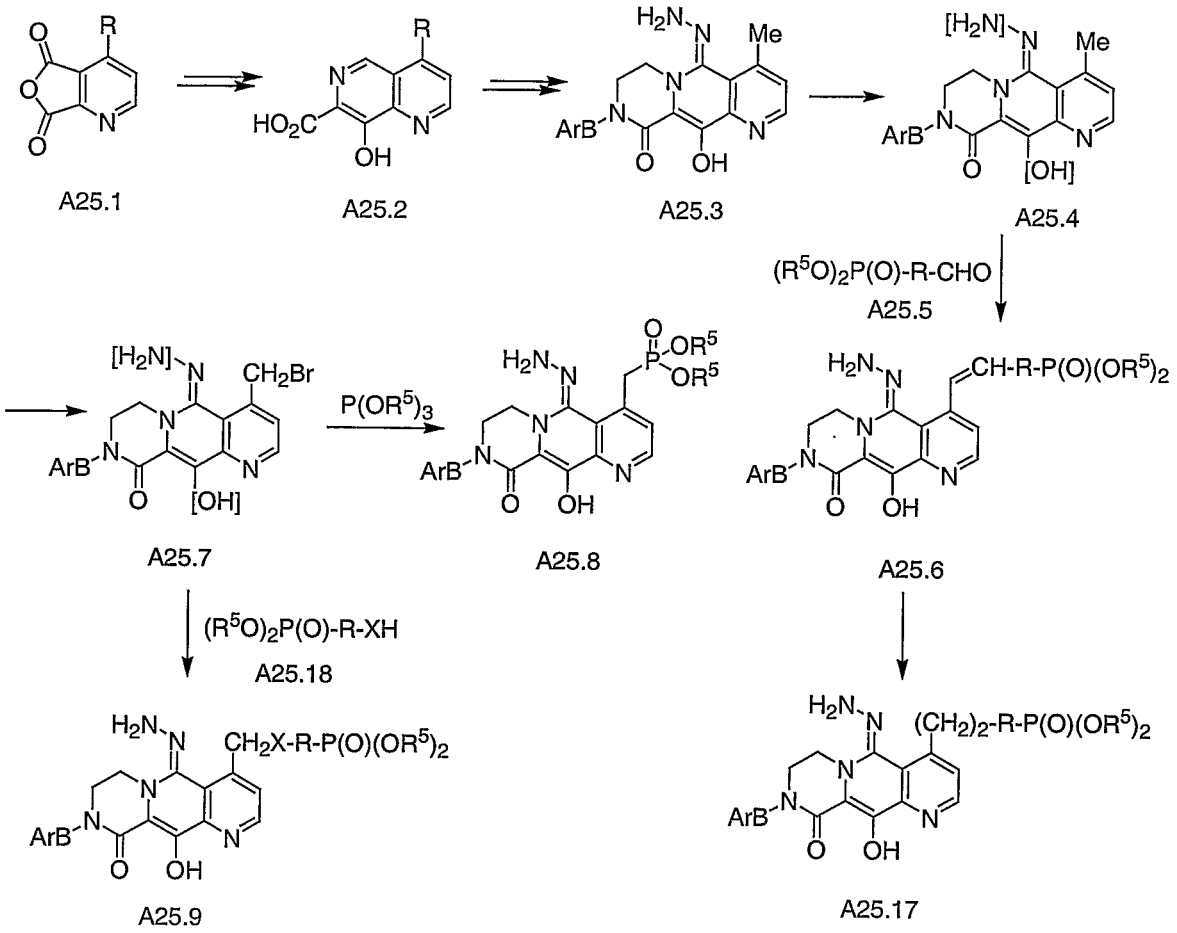
As a further example, the phthalimido-protected methyl-substituted tricycle **A25.11** is reacted in dioxan solution with a dialkyl formylphosphonate **A25.12** (Tet., 1994, 50, 10277) and lithium tetramethyl piperidide, to yield, after removal of the protecting groups, the unsaturated phosphonate **A25.13**.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

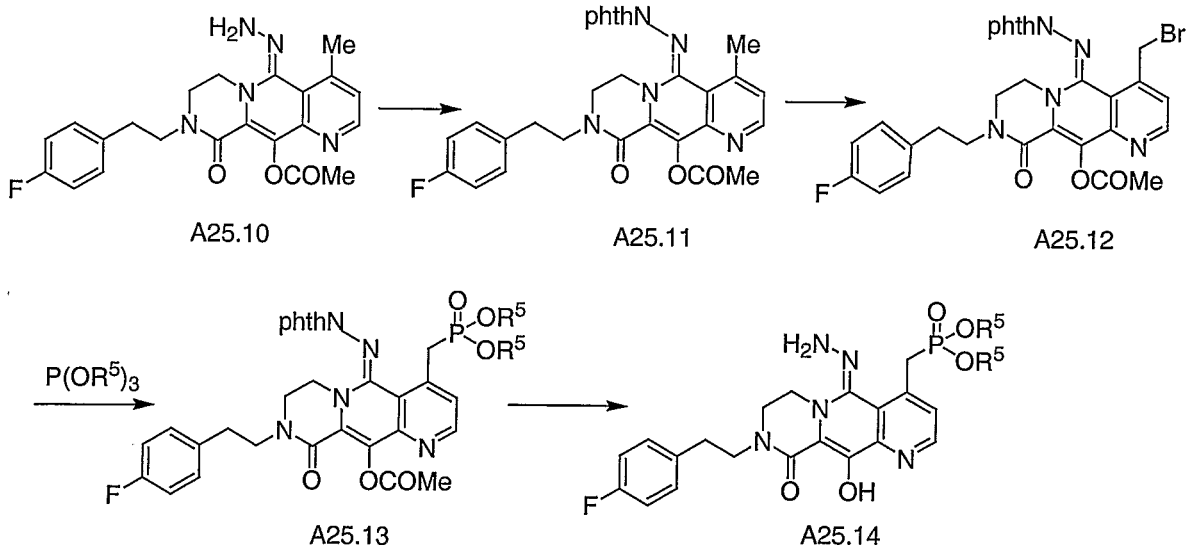
Using the above procedures, but employing, in place of the starting materials **A25.10**, **A25.11** or **A25.12**, different starting materials **A25.4** and **A25.7**, and/or different aldehydes **A25.5** or alcohols, thiols or amines **A25.18**, the corresponding products **A25.6**, **A25.8**, **A25.9**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

Scheme A25. Phosphonates IIIcc.

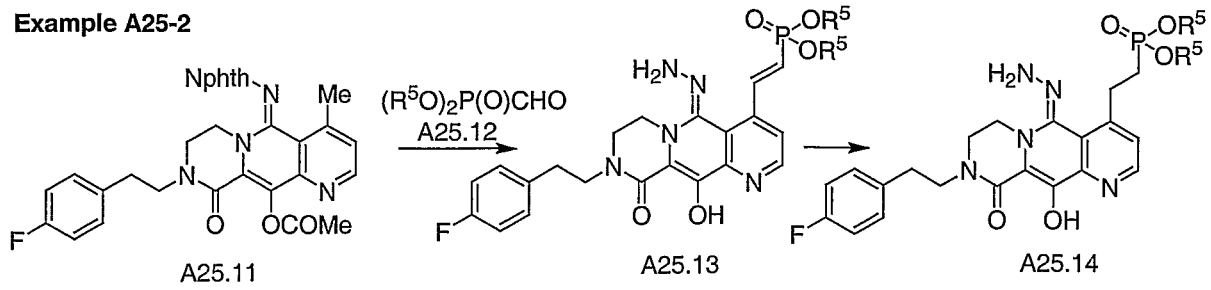
Method



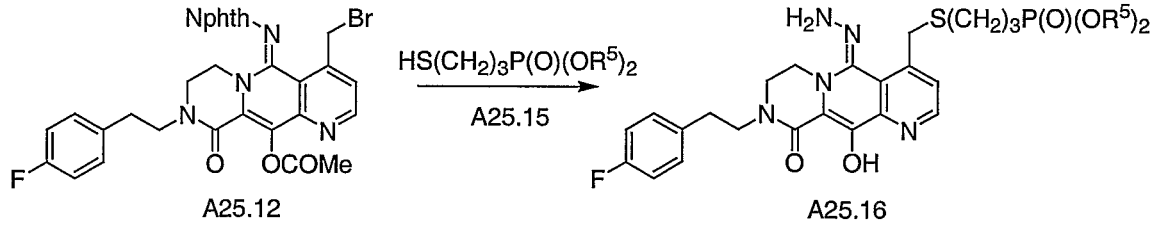
Example A25-1



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.

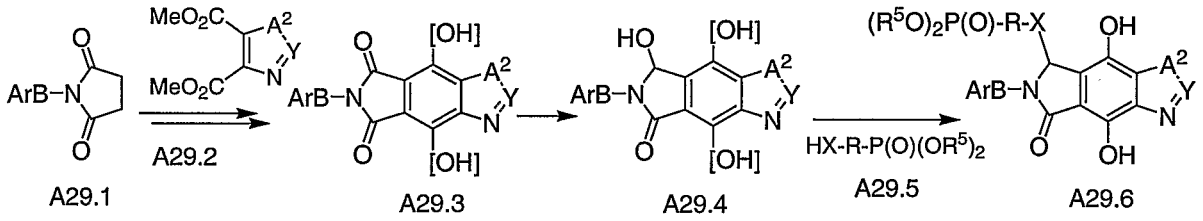
Scheme **A30** illustrates the preparation of phosphonate esters of structure **IVaa** in which the phosphonate is attached by means of a variable carbon linkage. In this procedure, dimethyl succinate **A30.1** is condensed, under base catalysis, for example using the procedure described on Scheme 1 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

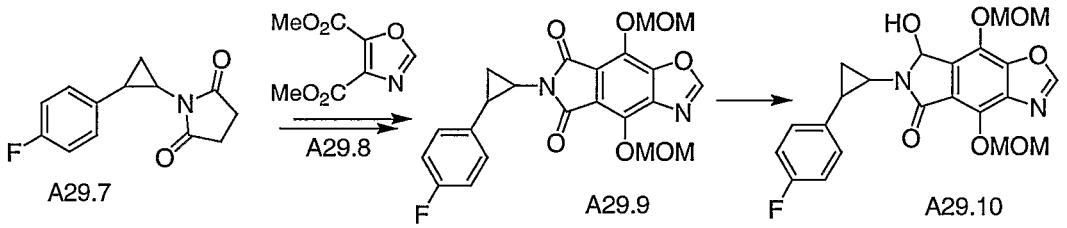
the amide **A30.16**. Cyclization is effected as described above to prepare 6-cyclohexylmethyl-4,9-bis-methoxymethoxy-1-methyl-1,5,6,8-tetrahydro-1,3,6-triaza-cyclopenta[b]naphthalen-7-one **A30.17**. The product is then reacted in dioxan solution with a dialkyl bromoethyl phosphonate **A30.18** (Aldrich)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

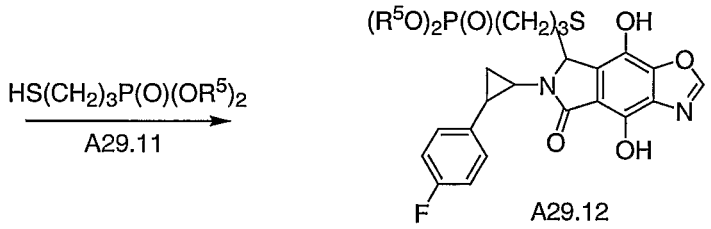
Using the above procedures, but employing, in place of the starting materials **A30.1** and **A30.11**, different starting materials **A30.1** and **A30.2**, and/or different phosphonates **A30.9**, the corresponding products **A30.10** are obtained.

Scheme A29. Phosphonates IVaa.
Method



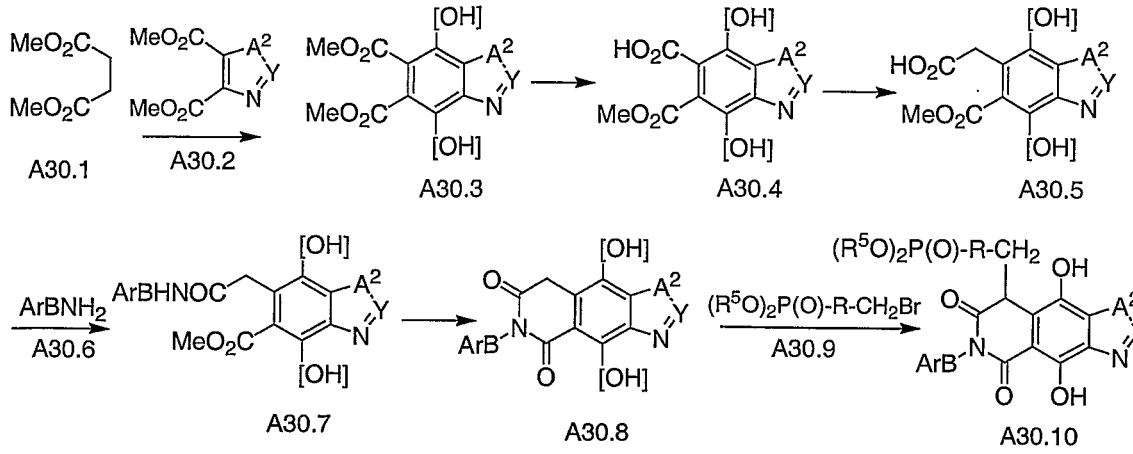
Example A29



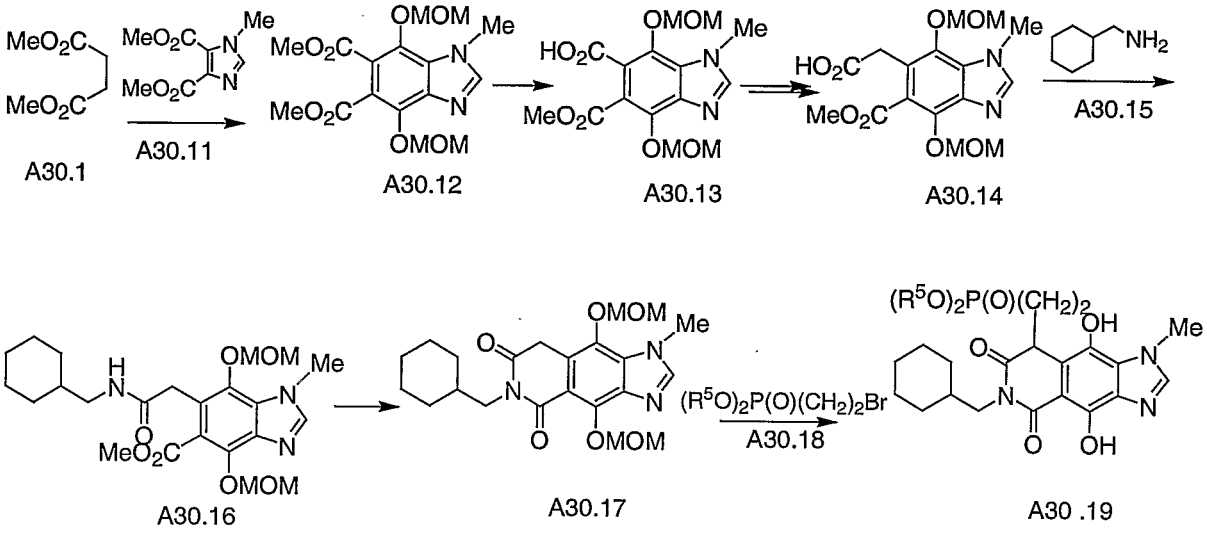


Scheme A30. Phosphonates IVaa.

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.

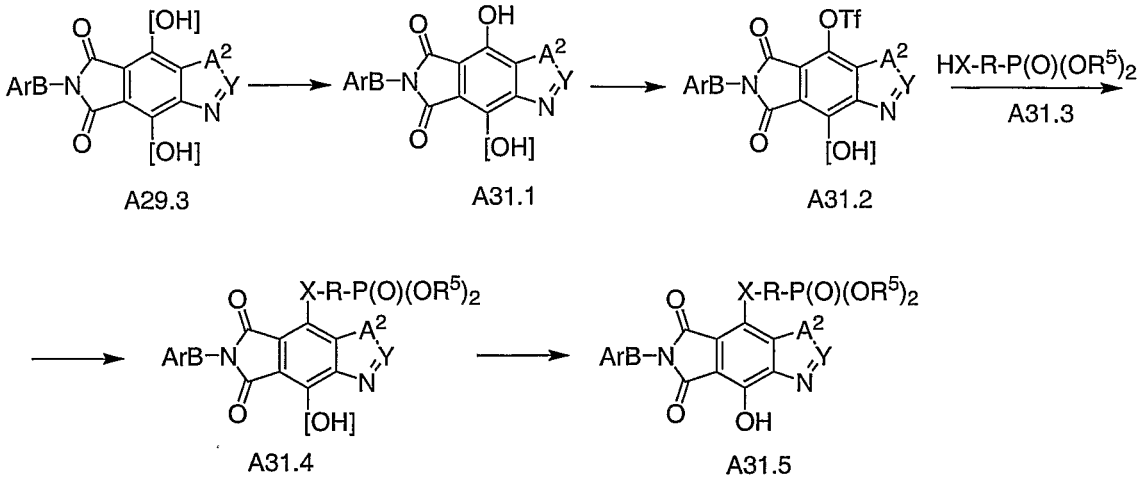
Scheme **A32** depicts the preparation of phosphonate esters of structure **Vbb** in which the phosphonate is attached by means of an ether linkage. In this procedure, dimethyl succinate **A32.1** is condensed under basic conditions, with a heterocyclic dicarboxylic ester **A32.2** to afford the bicyclic 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 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**.

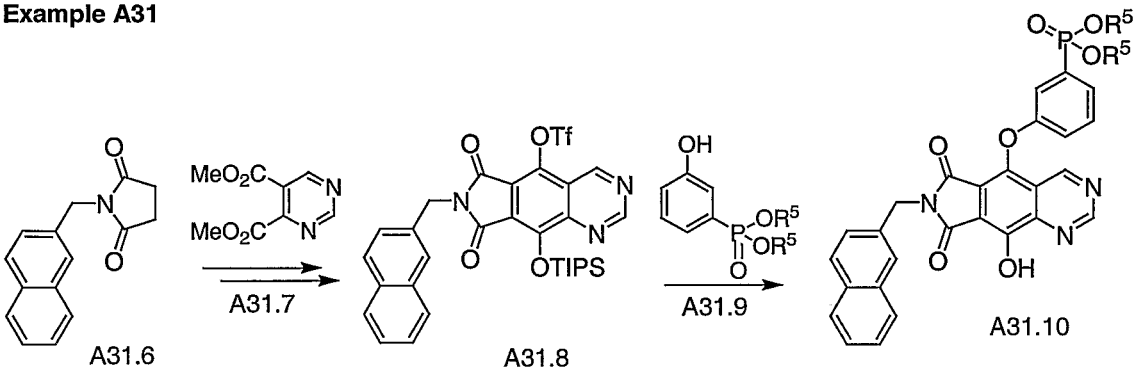
Using the above procedures, but employing, in place of the starting material **A32.10** different starting materials **A32.2** and/or different phosphonates **A32.8**, the corresponding products **A32.9** are obtained.

Scheme A31.Phosphonates IVbb.

Method

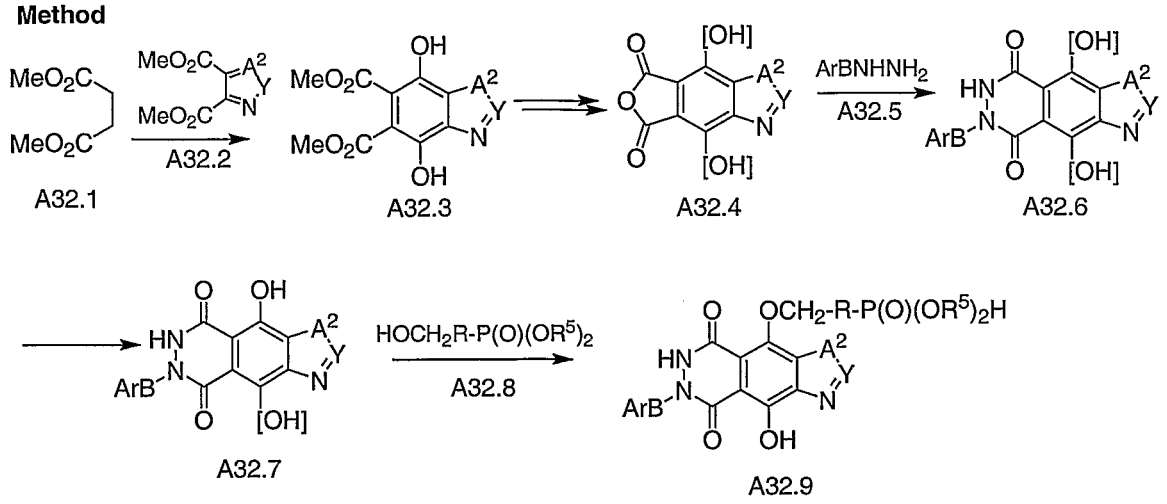


Example A31

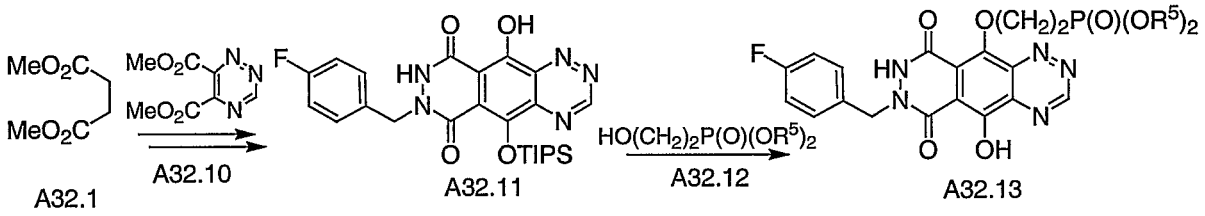


Scheme A32. Phosphonates IVbb.

Method



Example A32



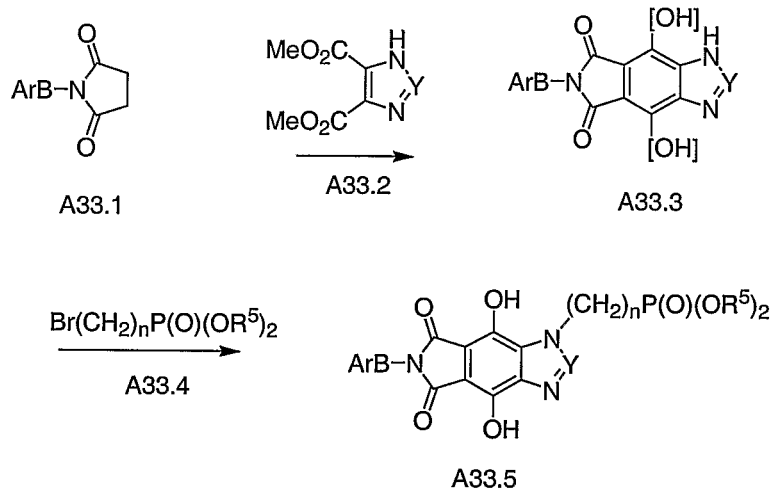
Preparation of the intermediate phosphonate esters IVcc.

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**.

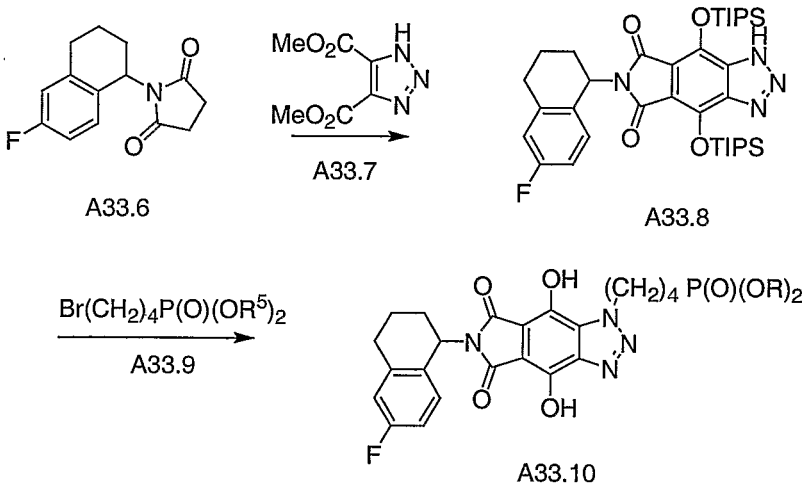
For example, 1-(6-fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-pyrrolidine-2,5-dione **A33.6**, prepared by the reaction of 2-amino-7-fluoro-1,2,3,4-tetrahydronaphthalene (US Patent No. 5,538,988) and succinic anhydride, is reacted with dimethyl 1,2,3-triazole-4,5-dicarboxylate **A33.7** (Interchim) to 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



Interconversions of the phosphonates R-link-P(O)(OR^5)$_2$, R-link-P(O)(OR^5)(OH) and R-link-P(O)(OH)$_2$.

Schemes **A1** - **A33** described the preparations of phosphonate esters of the general structure R-link-P(O)(OR^5)$_2$, in which the groups R^5 may be the same or different. The R^5 groups attached to a phosphonate esters **Iaa** - **IVcc**, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of

phosphonates are illustrated in Scheme **A34**. The group R in Scheme **A34** represents the substructure to which the substituent link-P(O)(OR^5)$_2$ is attached, either in the compounds **Iaa - IVcc** or in precursors thereto. The R^5 group may be changed, using the procedures described below, either in the precursor compounds, or in the esters **Iaa - IVcc**. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^5. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **A34.1** into the corresponding phosphonate monoester **A34.2** (Scheme **A34**, Reaction **1**) can be accomplished by a number of methods. For example, the ester **A34.1** in which R^5 is an aralkyl group such as benzyl, can be converted into the monoester compound **A34.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester **A34.1** in which R^5 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **A34.2** can be effected by treatment of the ester **A34.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **A34.1** in which one of the groups R^5 is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **A34.2** in which R^5 is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^5 are alkenyl, such as allyl, can be converted into the monoester **A34.2** in which R^5 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **A34.1** or a phosphonate monoester **A34.2** into the corresponding phosphonic acid **A34.3** (Scheme **A34**, Reactions **2** and **3**) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **A34.2** in which R^5 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **A34.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate

monoester **A34.2** in which R^5 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **A34.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **A34.1** in which R^5 is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **A34.1** in which R^5 is phenyl is described in J. Am. Chem. Soc., 78, 2336, 1956.

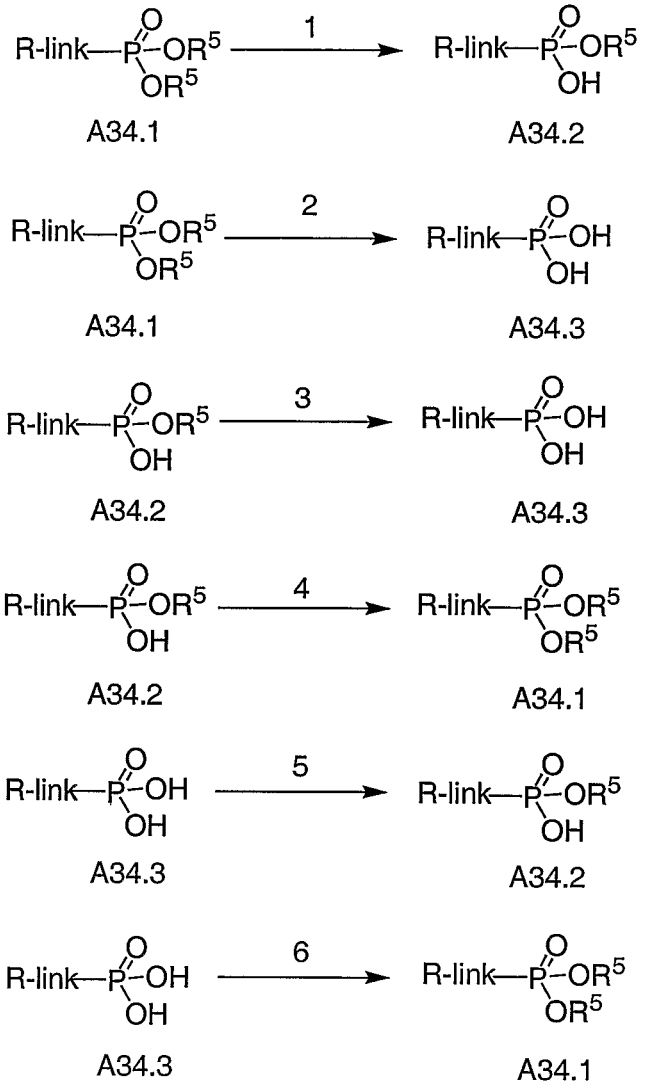
The conversion of a phosphonate monoester **A34.2** into a phosphonate diester **A34.1** (Scheme **A34**, Reaction **4**) in which the newly introduced R^5 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **A34.2** is reacted with a hydroxy compound R^5OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **A34.2** to the diester **A34.1** can be effected by the use of the Mitsonobu reaction, as described above (Scheme **A6**). The substrate is reacted with the hydroxy compound R^5OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **A34.2** can be transformed into the phosphonate diester **A34.1**, in which the introduced R^5 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^5Br, in which R^5 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **A34.2** is transformed into the chloro analog $RP(O)(OR^5)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^5)Cl$ is then reacted with

the hydroxy compound R^5OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **A34.1**.

A phosphonic acid R-link-$P(O)(OH)_2$ can be transformed into a phosphonate monoester $RP(O)(OR^5)(OH)$ (Scheme **A34**, Reaction **5**) by means of the methods described above of for the preparation of the phosphonate diester R-link-$P(O)(OR^5)_2$ **A34.1**, except that only one molar proportion of the component R^5OH or R^5Br is employed.

A phosphonic acid R-link-$P(O)(OH)_2$ **A34.3** can be transformed into a phosphonate diester R-link-$P(O)(OR^5)_2$ **A34.1** (Scheme **A34**, Reaction **6**) by a coupling reaction with the hydroxy compound R^5OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **A34.3** can be transformed into phosphonic esters **A34.1** in which R^5 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°C. Alternatively, phosphonic acids **A34.3** can be transformed into phosphonic esters **A34.1** in which R^5 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^5Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **A34.1**.

Scheme A34



Preparation of Carboalkoxy-Substituted Phosphonate Bisamidates, Monoamidates, Diesters and Monoesters.

A number of methods are available for the conversion of phosphonic acids into amidates and esters. In one group of methods, the phosphonic acid is either converted into an isolated activated intermediate such as a phosphoryl chloride, or the phosphonic acid is activated in situ for reaction with an amine or a hydroxy compound.

The conversion of phosphonic acids into phosphoryl chlorides is accomplished by reaction with thionyl chloride, for example as described in J. Gen. Chem. USSR, 1983, 53, 480, Zh. Obschei Khim., 1958, 28, 1063, or J. Org. Chem., 1994, 59, 6144, or by reaction with oxalyl chloride, as described in J. Am. Chem. Soc., 1994, 116, 3251, or J. Org. Chem., 1994, 59, 6144, or by reaction with phosphorus pentachloride, as described in J. Org.

Chem., 2001, 66, 329, or in J. Med. Chem., 1995, 38, 1372. The resultant phosphoryl chlorides are then reacted with amines or hydroxy compounds in the presence of a base to afford the amidate or ester products.

Phosphonic acids are converted into activated imidazolyl derivatives by reaction with carbonyl diimidazole, as described in J. Chem. Soc., Chem. Comm., 1991, 312, or Nucleosides Nucleotides 2000, 19, 1885. Activated sulfonyloxy derivatives are obtained by the reaction of phosphonic acids with trichloromethylsulfonyl chloride, as described in J. Med. Chem. 1995, 38, 4958, or with triisopropylbenzenesulfonyl chloride, as described in Tet. Lett., 1996, 7857, or Bioorg. Med. Chem. Lett., 1998, 8, 663. The activated sulfonyloxy derivatives are then reacted with amines or hydroxy compounds to afford amidates or esters.

Alternatively, the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a diimide coupling agent. The preparation of phosphonic amidates and esters by means of coupling reactions in the presence of dicyclohexyl carbodiimide is described, for example, in J. Chem. Soc., Chem. Comm., 1991, 312, or J. Med. Chem., 1980, 23, 1299 or Coll. Czech. Chem. Comm., 1987, 52, 2792. The use of ethyl dimethylaminopropyl carbodiimide for activation and coupling of phosphonic acids is described in Tet. Lett., 2001, 42, 8841, or Nucleosides Nucleotides, 2000, 19, 1885.

A number of additional coupling reagents have been described for the preparation of amidates and esters from phosphonic acids. The agents include Aldrithiol-2, and PYBOP and BOP, as described in J. Org. Chem., 1995, 60, 5214, and J. Med. Chem., 1997, 40, 3842, mesitylene-2-sulfonyl-3-nitro-1,2,4-triazole (MSNT), as described in J. Med. Chem., 1996, 39, 4958, diphenylphosphoryl azide, as described in J. Org. Chem., 1984, 49, 1158, 1-(2,4,6-triisopropylbenzenesulfonyl-3-nitro-1,2,4-triazole (TPSNT) as described in Bioorg. Med. Chem. Lett., 1998, 8, 1013, bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP), as described in Tet. Lett., 1996, 37, 3997, 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphinane, as described in Nucleosides Nucleotides 1995, 14, 871, and diphenyl chlorophosphate, as described in J. Med. Chem., 1988, 31, 1305.

Phosphonic acids are converted into amidates and esters by means of the Mitsonobu reaction, in which the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The procedure is described in Org. Lett., 2001, 3, 643, or J. Med. Chem., 1997, 40, 3842.

Phosphonic esters are also obtained by the reaction between phosphonic acids and halo compounds, in the presence of a suitable base. The method is described, for example, in Anal. Chem., 1987, 59, 1056, or J. Chem. Soc. Perkin Trans., I, 1993, 19, 2303, or J. Med. Chem., 1995, 38, 1372, or Tet. Lett., 2002, 43, 1161.

Schemes **1** - **5** illustrate the conversion of phosphonate esters and phosphonic acids into carboalkoxy-substituted phosphorobisamidates (Scheme **1**), phosphoroamidates (Scheme **2**), phosphonate monoesters (Scheme **3**) and phosphonate diesters, (Scheme **4**)

Scheme **1** illustrates various methods for the conversion of phosphonate diesters **1.1** into phosphorobisamidates **1.5**. The diester **1.1**, prepared as described previously, is hydrolyzed, either to the monoester **1.2** or to the phosphonic acid **1.6**. The methods employed for these transformations are described above. The monoester **1.2** is converted into the monoamidate **1.3** by reaction with an aminoester **1.9**, in which the group R^2 is H or alkyl, the group R^4 is an alkylene moiety such as, for example, $CHCH_3$, $CHPr^I$, $CH(CH_2Ph)$, $CH_2CH(CH_3)$ and the like, or a group present in natural or modified aminoacids, and the group R^5 is alkyl. The reactants are combined in the presence of a coupling agent such as a carbodiimide, for example dicyclohexyl carbodiimide, as described in J. Am. Chem. Soc., 1957, 79, 3575, optionally in the presence of an activating agent such as hydroxybenztriazole, to yield the amidate product **1.3**. The amidate-forming reaction is also effected in the presence of coupling agents such as BOP, as described in J. Org. Chem., 1995, 60, 5214, Aldrithiol, PYBOP and similar coupling agents used for the preparation of amides and esters. Alternatively, the reactants **1.2** and **1.9** are transformed into the monoamidate **1.3** by means of a Mitsonobu reaction. The preparation of amidates by means of the Mitsonobu reaction is described in J. Med. Chem., 1995, 38, 2742. Equimolar amounts of the reactants are combined in an inert solvent such as tetrahydrofuran in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The thus-obtained monoamidate ester **1.3** is then transformed into amidate phosphonic acid **1.4**. The conditions used for the hydrolysis reaction depend on the nature of the R^1 group, as described previously. The phosphonic acid amidate **1.4** is then reacted with an aminoester **1.9**, as described above, to yield the bisamidate product **1.5**, in which the amino substituents are the same or different.

An example of this procedure is shown in Scheme **1**, Example **1**. In this procedure, a dibenzyl phosphonate **1.14** is reacted with diazabicyclooctane (DABCO) in toluene at reflux, as described in J. Org. Chem., 1995, 60, 2946, to afford the monobenzyl

phosphonate **1.15**. The product is then reacted with equimolar amounts of ethyl alaninate **1.16** and dicyclohexyl carbodiimide in pyridine, to yield the amidate product **1.17**. The benzyl group is then removed, for example by hydrogenolysis over a palladium catalyst, to give the monoacid product **1.18**. This compound is then reacted in a Mitsonobu reaction with ethyl leucinate **1.19**, triphenyl phosphine and diethylazodicarboxylate, as described in J. Med. Chem., 1995, 38, 2742, to produce the bisamidate product **1.20**.

Using the above procedures, but employing, in place of ethyl leucinate **1.19** or ethyl alaninate **1.16**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

Alternatively, the phosphonic acid **1.6** is converted into the bisamidate **1.5** by use of the coupling reactions described above. The reaction is performed in one step, in which case the nitrogen-related substituents present in the product **1.5** are the same, or in two steps, in which case the nitrogen-related substituents can be different.

An example of the method is shown in Scheme **1**, Example **2**. In this procedure, a phosphonic acid **1.6** is reacted in pyridine solution with excess ethyl phenylalaninate **1.21** and dicyclohexylcarbodiimide, for example as described in J. Chem. Soc., Chem. Comm., 1991, 1063, to give the bisamidate product **1.22**.

Using the above procedures, but employing, in place of ethyl phenylalaninate, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

As a further alternative, the phosphonic acid **1.6** is converted into the mono or bis-activated derivative **1.7**, in which Lv is a leaving group such as chloro, imidazolyl, triisopropylbenzenesulfonyloxy etc. The conversion of phosphonic acids into chlorides **1.7** (Lv = Cl) is effected by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17. The conversion of phosphonic acids into monoimidazolides **1.7** (Lv = imidazolyl) is described in J. Med. Chem., 2002, 45, 1284 and in J. Chem. Soc. Chem. Comm., 1991, 312. Alternatively, the phosphonic acid is activated by reaction with triisopropylbenzenesulfonyl chloride, as described in Nucleosides and Nucleotides, 2000, 10, 1885. The activated product is then reacted with the aminoester **1.9**, in the presence of a base, to give the bisamidate **1.5**. The reaction is performed in one step, in which case the nitrogen substituents present in the product **1.5** are the same, or in two steps, via the intermediate **1.11**, in which case the nitrogen substituents can be different.

Examples of these methods are shown in Scheme **1**, Examples **3** and **5**. In the procedure illustrated in Scheme **1**, Example **3**, a phosphonic acid **1.6** is reacted with ten

molar equivalents of thionyl chloride, as described in Zh. Obschei Khim., 1958, 28, 1063, to give the dichloro compound **1.23**. The product is then reacted at reflux temperature in a polar aprotic solvent such as acetonitrile, and in the presence of a base such as triethylamine, with butyl serinate **1.24** to afford the bisamidate product **1.25**.

Using the above procedures, but employing, in place of butyl serinate **1.24**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

In the procedure illustrated in Scheme **1**, Example **5**, the phosphonic acid **1.6** is reacted, as described in J. Chem. Soc. Chem. Comm., 1991, 312, with carbonyl diimidazole to give the imidazolide **1.32**. The product is then reacted in acetonitrile solution at ambient temperature, with one molar equivalent of ethyl alaninate **1.33** to yield the monodisplacement product **1.34**. The latter compound is then reacted with carbonyl diimidazole to produce the activated intermediate **1.35**, and the product is then reacted, under the same conditions, with ethyl N-methylalaninate **1.33a** to give the bisamidate product **1.36**.

Using the above procedures, but employing, in place of ethyl alaninate **1.33** or ethyl N-methylalaninate **1.33a**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

The intermediate monoamidate **1.3** is also prepared from the monoester **1.2** by first converting the monoester into the activated derivative **1.8** in which Lv is a leaving group such as halo, imidazolyl etc, using the procedures described above. The product **1.8** is then reacted with an aminoester **1.9** in the presence of a base such as pyridine, to give an intermediate monoamidate product **1.3**. The latter compound is then converted, by removal of the R^1 group and coupling of the product with the aminoester **1.9**, as described above, into the bisamidate **1.5**.

An example of this procedure, in which the phosphonic acid is activated by conversion to the chloro derivative **1.26**, is shown in Scheme **1**, Example **4**. In this procedure, the phosphonic monobenzyl ester **1.15** is reacted, in dichloromethane, with thionyl chloride, as described in Tet. Let., 1994, 35, 4097, to afford the phosphoryl chloride **1.26**. The product is then reacted in acetonitrile solution at ambient temperature with one molar equivalent of ethyl 3-amino-2-methylpropionate **1.27** to yield the monoamidate product **1.28**. The latter compound is hydrogenated in ethylacetate over a 5% palladium on carbon catalyst to produce the monoacid product **1.29**. The product is subjected to a Mitsonobu coupling procedure, with equimolar amounts of butyl alaninate **1.30**, triphenyl

phosphine, diethylazodicarboxylate and triethylamine in tetrahydrofuran, to give the bisamidate product **1.31**.

Using the above procedures, but employing, in place of ethyl 3-amino-2-methylpropionate **1.27** or butyl alaninate **1.30**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

The activated phosphonic acid derivative **1.7** is also converted into the bisamidate **1.5** via the diamino compound **1.10**. The conversion of activated phosphonic acid derivatives such as phosphoryl chlorides into the corresponding amino analogs **1.10**, by reaction with ammonia, is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976. The diamino compound **1.10** is then reacted at elevated temperature with a haloester **1.12**, in a polar organic solvent such as dimethylformamide, in the presence of a base such as dimethylaminopyridine or potassium carbonate, to yield the bisamidate **1.5**.

An example of this procedure is shown in Scheme **1**, Example **6**. In this method, a dichlorophosphonate **1.23** is reacted with ammonia to afford the diamide **1.37**. The reaction is performed in aqueous, aqueous alcoholic or alcoholic solution, at reflux temperature. The resulting diamino compound is then reacted with two molar equivalents of ethyl 2-bromo-3-methylbutyrate **1.38**, in a polar organic solvent such as N-methylpyrrolidinone at ca. 150°C, 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 bisamidate product **1.39**.

Using the above procedures, but employing, in place of ethyl 2-bromo-3-methylbutyrate **1.38**, different haloesters **1.12** the corresponding products **1.5** are obtained.

The procedures shown in Scheme **1** are also applicable to the preparation of bisamidates in which the aminoester moiety incorporates different functional groups. Scheme **1**, Example **7** illustrates the preparation of bisamidates derived from tyrosine. In this procedure, the monoimidazolide **1.32** is reacted with propyl tyrosinate **1.40**, as described in Example **5**, to yield the monoamidate **1.41**. The product is reacted with carbonyl diimidazole to give the imidazolide **1.42**, and this material is reacted with a further molar equivalent of propyl tyrosinate to produce the bisamidate product **1.43**.

Using the above procedures, but employing, in place of propyl tyrosinate **1.40**, different aminoesters **1.9**, the corresponding products **1.5** are obtained. The aminoesters employed in the two stages of the above procedure can be the same or different, so that bisamidates with the same or different amino substituents are prepared.

Scheme **2** illustrates methods for the preparation of phosphonate monoamidates.

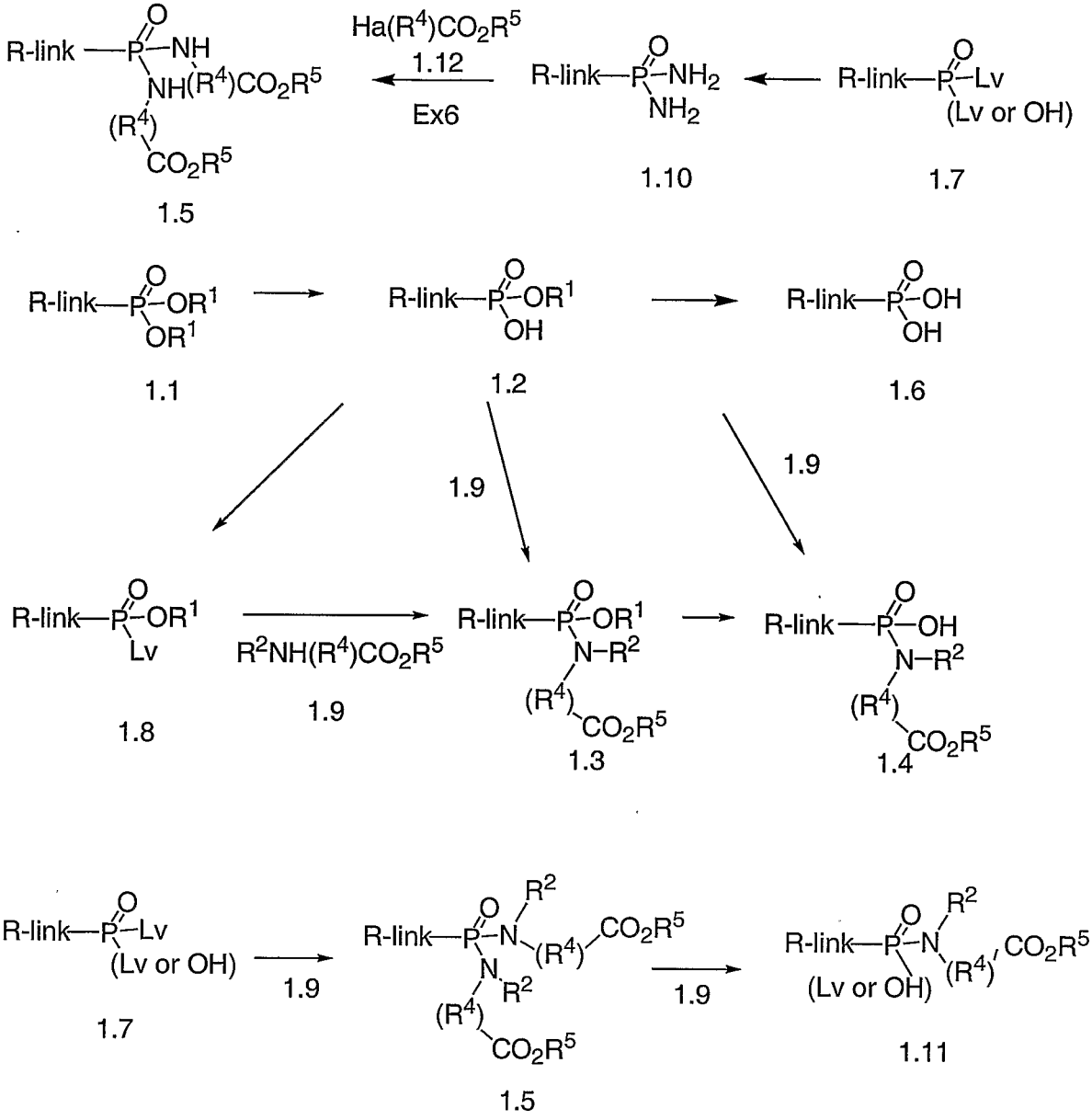
In one procedure, a phosphonate monoester **1.1** is converted, as described in Scheme **1**, into the activated derivative **1.8**. This compound is then reacted, as described above, with an aminoester **1.9**, in the presence of a base, to afford the monoamidate product **2.1**.

The procedure is illustrated in Scheme **2**, Example **1**. In this method, a monophenyl phosphonate **2.7** is reacted with, for example, thionyl chloride, as described in J. Gen. Chem. USSR., 1983, 32, 367, to give the chloro product **2.8**. The product is then reacted, as described in Scheme **1**, with ethyl alaninate **2.9**, to yield the amidate **2.10**.

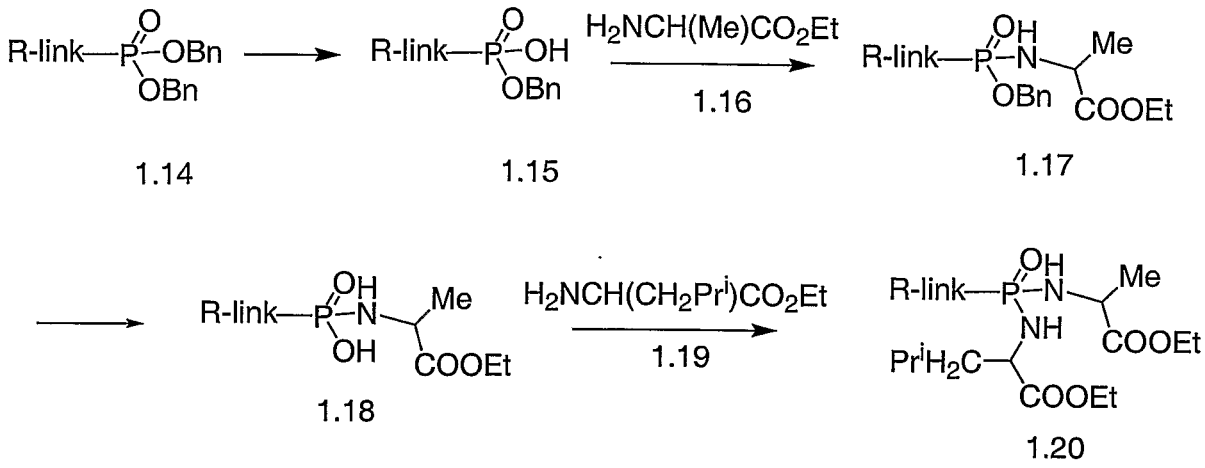
Using the above procedures, but employing, in place of ethyl alaninate **2.9**, different aminoesters **1.9**, the corresponding products **2.1** are obtained.

Alternatively, the phosphonate monoester **1.1** is coupled, as described in Scheme **1**, with an aminoester **1.9** to produce the amidate **2.1**. If necessary, the R^1 substituent is then altered, by initial cleavage to afford the phosphonic acid **2.2**. The procedures for this transformation depend on the nature of the R^1 group, and are described above. The phosphonic acid is then transformed into the ester amidate product **2.3**, by reaction with the hydroxy compound R^3OH, in which the group R^3 is aryl, heteroaryl, alkyl, cycloalkyl, haloalkyl etc, using the same coupling procedures (carbodiimide, Aldrithiol-2, PYBOP, Mitsonobu reaction etc) described in Scheme **1** for the coupling of amines and phosphonic acids.

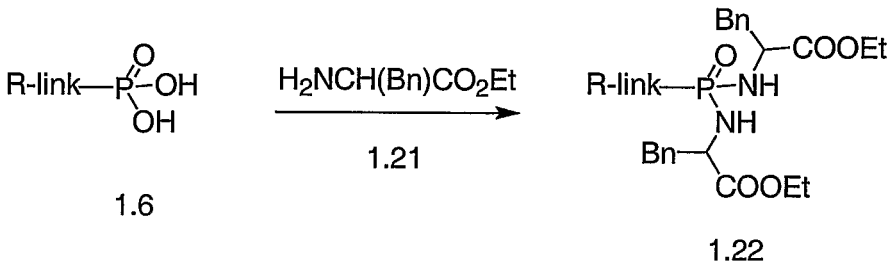
Scheme 1


R-link—P(=O)(NH)NH(R4)CO2R5 (R4)CO2R5
1.5
Ha(R4)CO2R5
1.12
Ex6
R-link—P(=O)(NH2)NH2
1.10
R-link—P(=O)Lv (Lv or OH)
1.7
R-link—P(=O)(OR1)OR1
1.1
R-link—P(=O)(OR1)OH
1.2
R-link—P(=O)(OH)OH
1.6
1.9
1.9
R-link—P(=O)(OR1)Lv
1.8
R2NH(R4)CO2R5
1.9
R-link—P(=O)(OR1)N(R2)(R4)CO2R5
1.3
R-link—P(=O)(OH)N(R2)(R4)CO2R5
1.4
R-link—P(=O)Lv (Lv or OH)
1.7
1.9
R-link—P(=O)N(R2)(R4)CO2R5 N(R2)(R4)CO2R5
1.5
1.9
R-link—P(=O)N(R2)(R4)CO2R5 (Lv or OH)
1.11

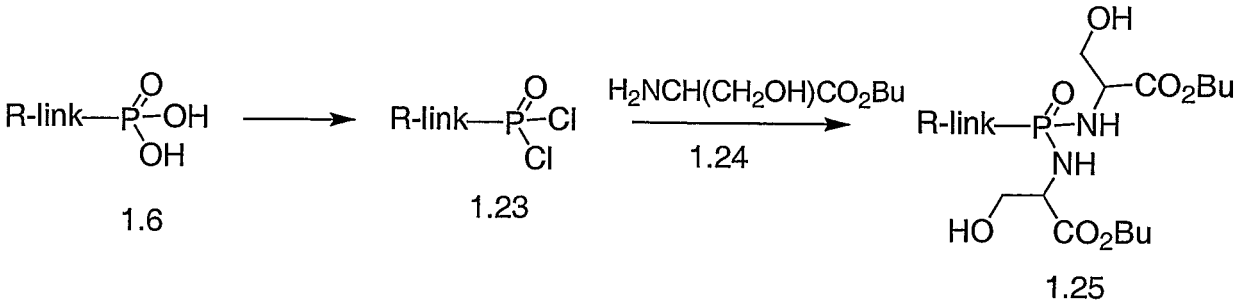
Scheme 1 Example 1



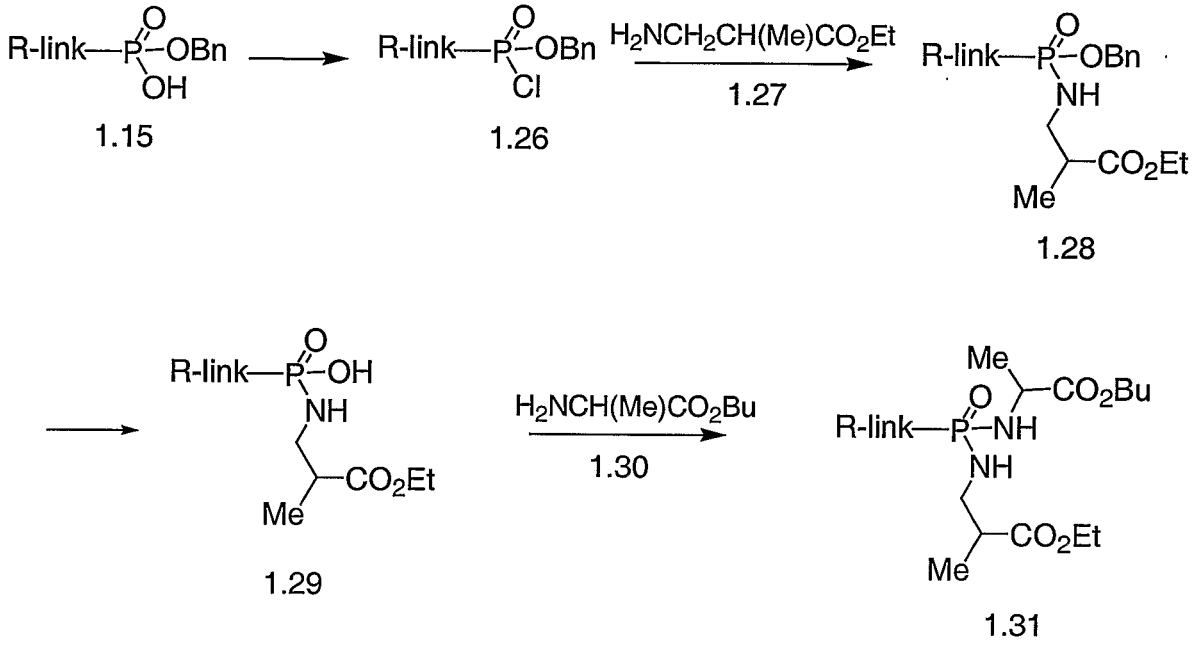
Scheme 1 Example 2



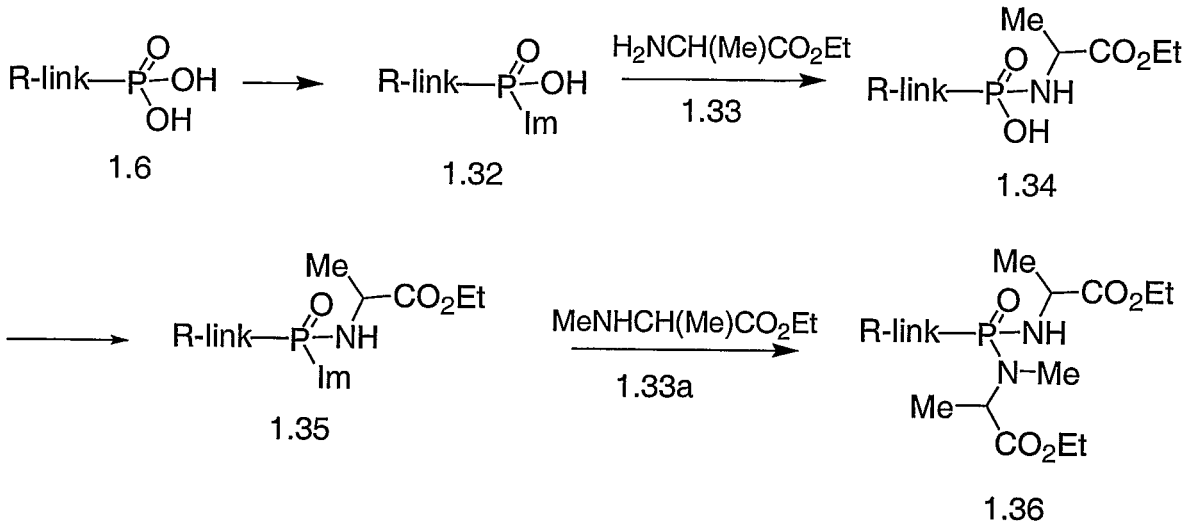
Scheme 1 Example 3



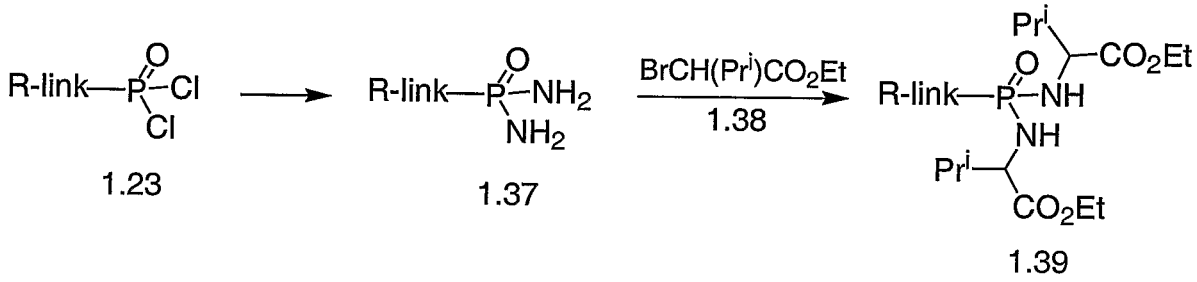
Scheme 1 Example 4



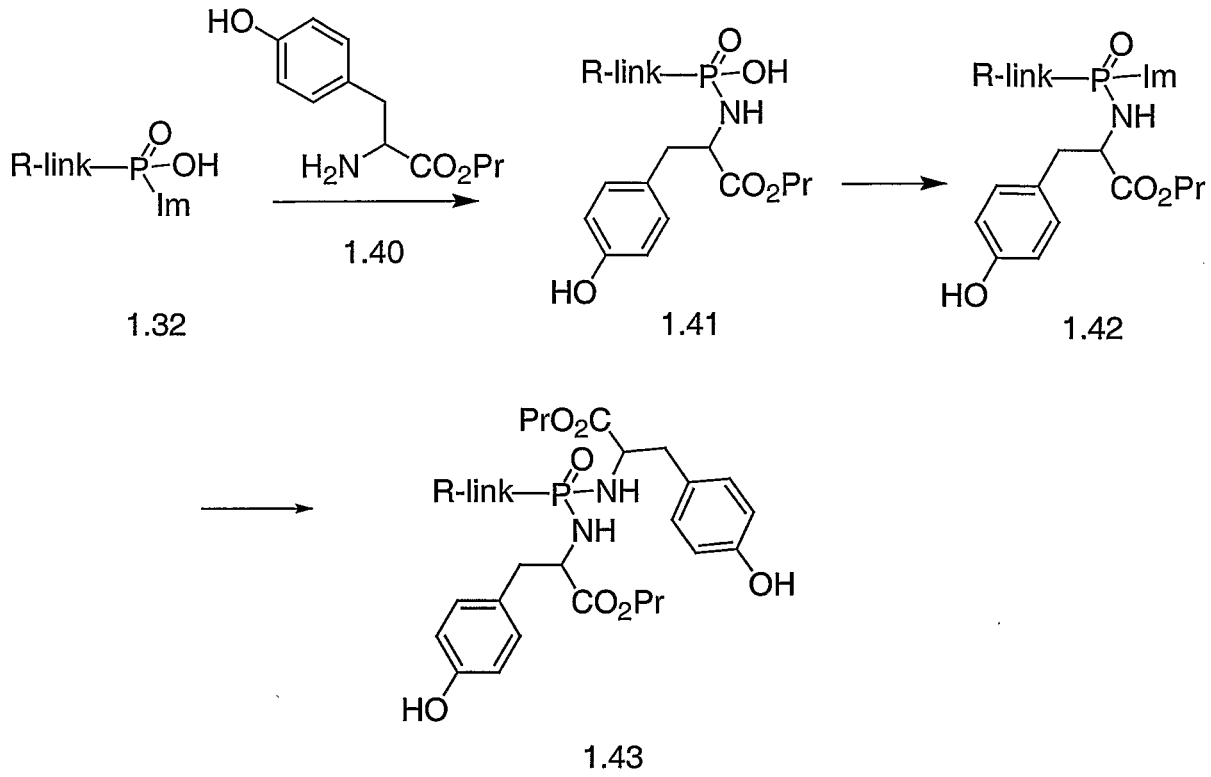
Scheme 1 Example 5



Scheme 1 Example 6



Scheme 1 Example 7



Examples of this method are shown in Scheme **2**, Examples and **2** and **3**. In the sequence shown in Example **2**, a monobenzyl phosphonate **2.11** is transformed by reaction with ethyl alaninate, using one of the methods described above, into the monoamidate **2.12**. The benzyl group is then removed by catalytic hydrogenation in ethylacetate solution over a 5% palladium on carbon catalyst, to afford the phosphonic acid amidate **2.13**. The product is then reacted in dichloromethane solution at ambient temperature with equimolar amounts of 1-(dimethylaminopropyl)-3-ethylcarbodiimide and trifluoroethanol **2.14**, for example as described in Tet. Lett., 2001, 42, 8841, to yield the amidate ester **2.15**.

In the sequence shown in Scheme **2**, Example **3**, the monoamidate **2.13** is coupled, in tetrahydrofuran solution at ambient temperature, with equimolar amounts of dicyclohexyl carbodiimide and 4-hydroxy-N-methylpiperidine **2.16**, to produce the amidate ester product **2.17**.

Using the above procedures, but employing, in place of the ethyl alaninate product **2.12** different monoacids **2.2**, and in place of trifluoroethanol **2.14** or 4-hydroxy-N-methylpiperidine **2.16**, different hydroxy compounds R^3OH, the corresponding products **2.3** are obtained.

Alternatively, the activated phosphonate ester **1.8** is reacted with ammonia to yield the amidate **2.4**. The product is then reacted, as described in Scheme **1**, with a haloester **2.5**, in the presence of a base, to produce the amidate product **2.6**. If appropriate, the nature of the R^1 group is changed, using the procedures described above, to give the product **2.3**. The method is illustrated in Scheme **2**, Example **4**. In this sequence, the monophenyl phosphoryl chloride **2.18** is reacted, as described in Scheme **1**, with ammonia, to yield the amino product **2.19**. This material is then reacted in N-methylpyrrolidinone solution at 170°C with butyl 2-bromo-3-phenylpropionate **2.20** and potassium carbonate, to afford the amidate product **2.21**.

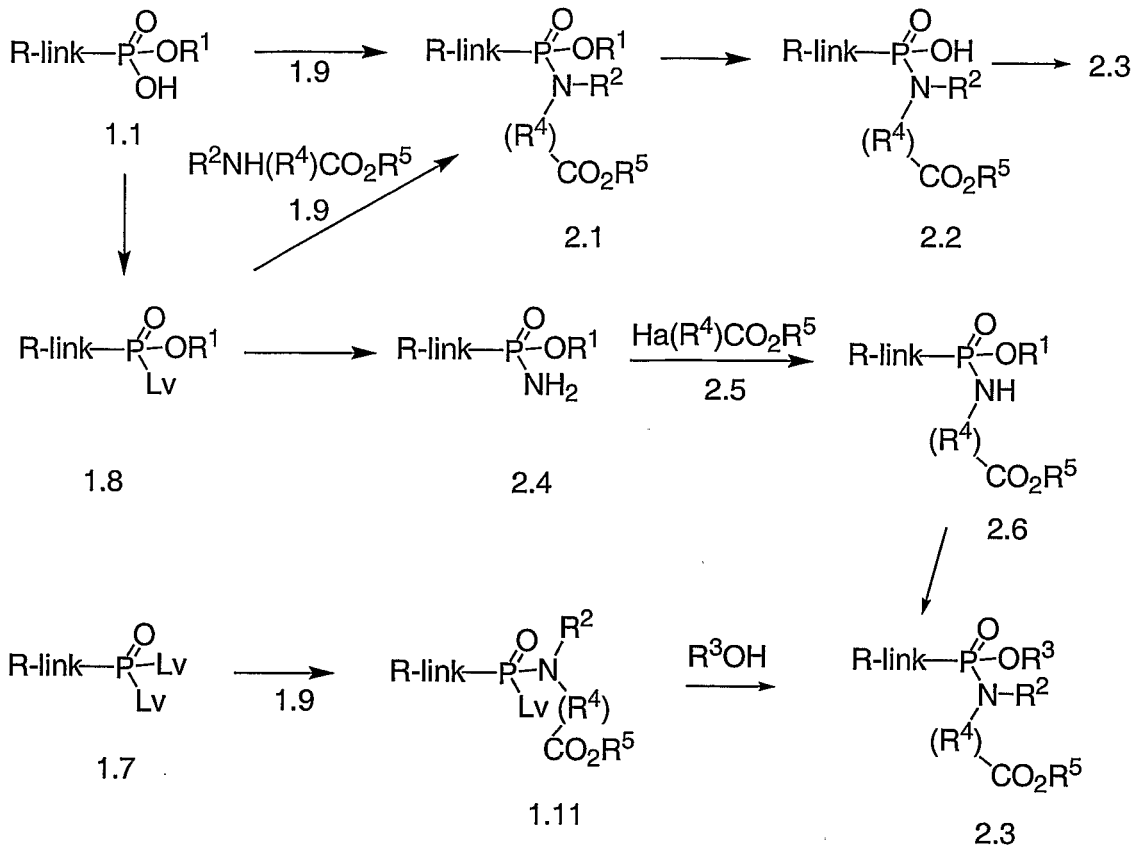
Using these procedures, but employing, in place of butyl 2-bromo-3-phenylpropionate **2.20**, different haloesters **2.5**, the corresponding products **2.6** are obtained.

The monoamidate products **2.3** are also prepared from the doubly activated phosphonate derivatives **1.7**. In this procedure, examples of which are described in Synlett., 1998, 1, 73, the intermediate **1.7** is reacted with a limited amount of the aminoester **1.9** to give the mono-displacement product **1.11**. The latter compound is then reacted with the hydroxy compound R^3OH in a polar organic solvent such as dimethylformamide, in the presence of a base such as diisopropylethylamine, to yield the monoamidate ester **2.3**.

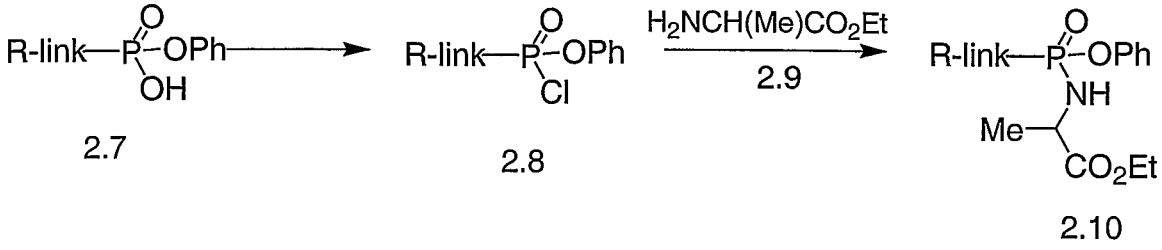
The method is illustrated in Scheme **2**, Example **5**. In this method, the phosphoryl dichloride **2.22** is reacted in dichloromethane solution with one molar equivalent of ethyl N-methyl tyrosinate **2.23** and dimethylaminopyridine, to generate the monoamidate **2.24**. The product is then reacted with phenol **2.25** in dimethylformamide containing potassium carbonate, to yield the ester amidate product **2.26**.

Using these procedures, but employing, in place of ethyl N-methyl tyrosinate **2.23** or phenol **2.25**, the aminoesters **1.9** and/or the hydroxy compounds R^3OH, the corresponding products **2.3** are obtained.

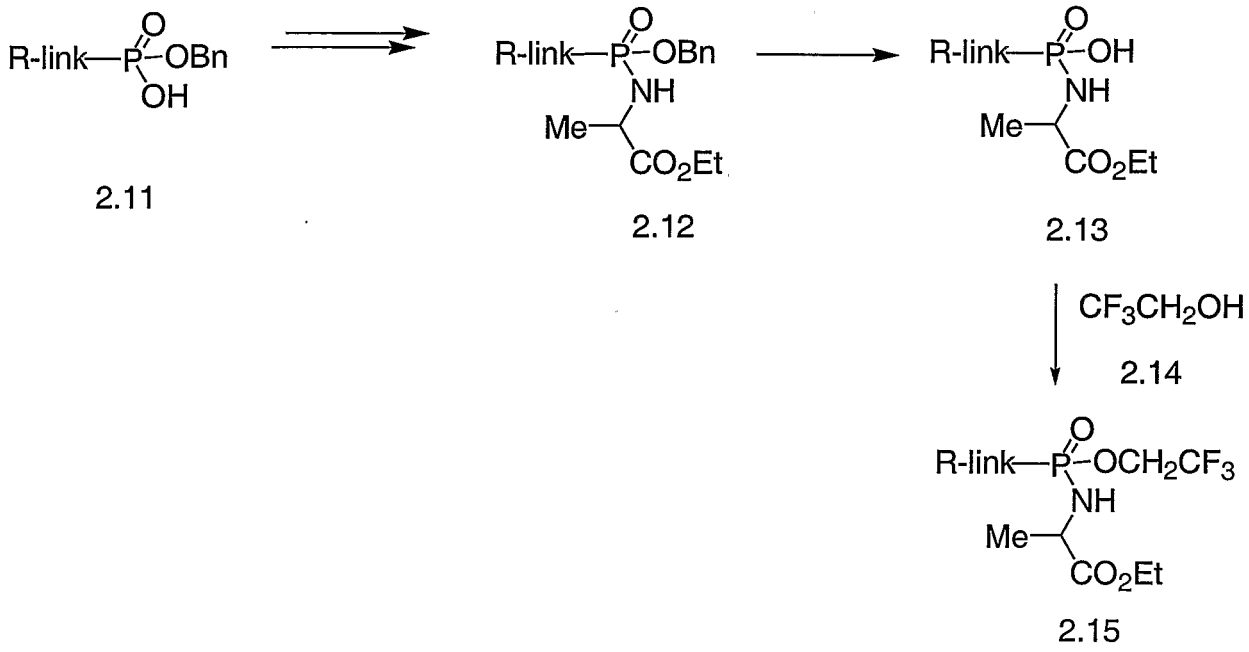
Scheme 2


R-link—P(=O)(OR1)OH
1.1
1.9
R-link—P(=O)(OR1)N(R2)(R4)CO2R5
2.1
R-link—P(=O)(OH)N(R2)(R4)CO2R5
2.2
2.3
R2NH(R4)CO2R5
1.9
R-link—P(=O)(OR1)Lv
1.8
R-link—P(=O)(OR1)NH2
2.4
Ha(R4)CO2R5
2.5
R-link—P(=O)(OR1)NH(R4)CO2R5
2.6
R-link—P(=O)(Lv)Lv
1.7
1.9
R-link—P(=O)(N(R2)Lv(R4)CO2R5)
1.11
R3OH
R-link—P(=O)(OR3)N(R2)(R4)CO2R5
2.3

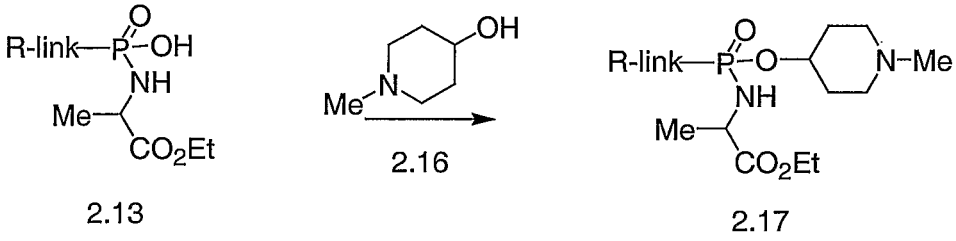
Scheme 2 Example 1



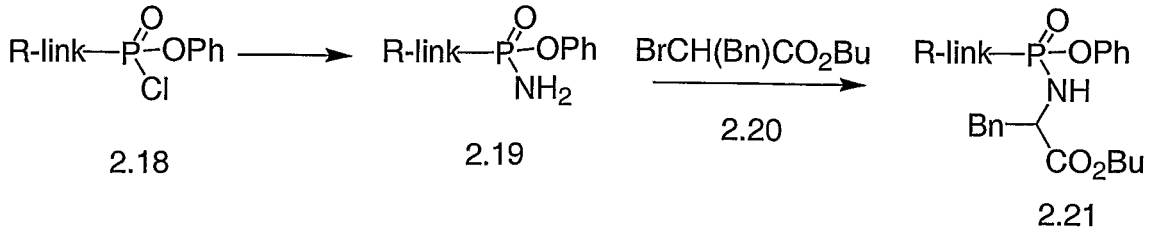
Scheme 2 Example 2



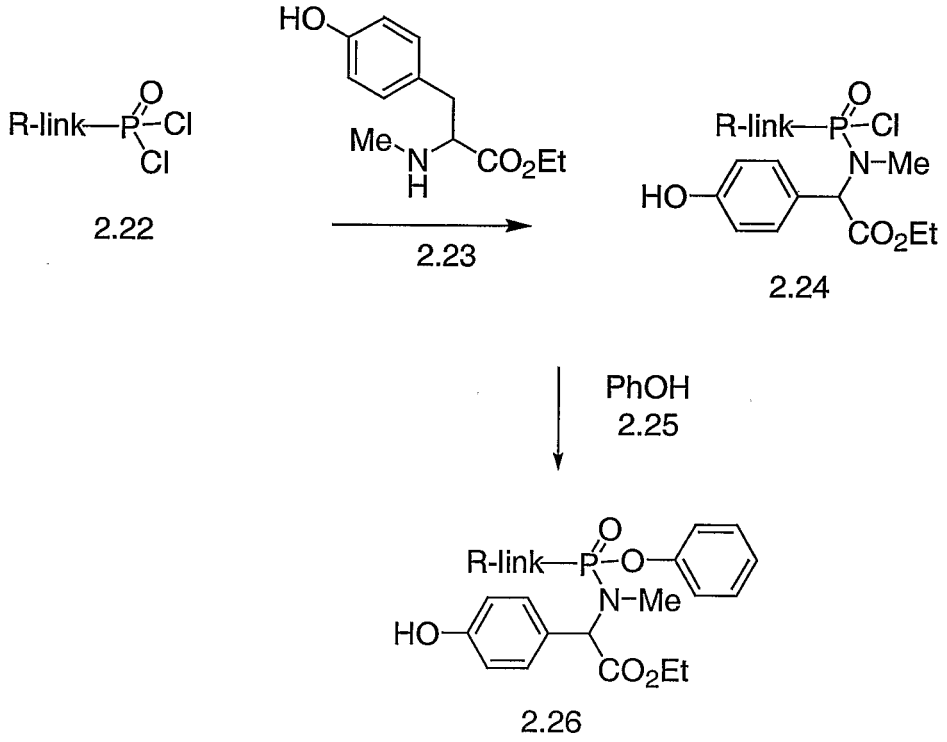
Scheme 2 Example 3



Scheme 2 Example 4



Scheme 2 Example 5



Scheme **3** illustrates methods for the preparation of carboalkoxy-substituted phosphonate diesters in which one of the ester groups incorporates a carboalkoxy substituent.

In one procedure, a phosphonate monoester **1.1**, prepared as described above, is coupled, using one of the methods described above, with a hydroxyester **3.1**, in which the groups R^4 and R^5 are as described in Scheme **1**. For example, equimolar amounts of the reactants are coupled in the presence of a carbodiimide such as dicyclohexyl carbodiimide, as described in Aust. J. Chem., 1963, 609, optionally in the presence of dimethylaminopyridine, as described in Tet., 1999, 55, 12997. The reaction is conducted in an inert solvent at ambient temperature.

The procedure is illustrated in Scheme **3**, Example **1**. In this method, a monophenyl phosphonate **3.9** is coupled, in dichloromethane solution in the presence of dicyclohexyl carbodiimide, with ethyl 3-hydroxy-2-methylpropionate **3.10** to yield the phosphonate mixed diester **3.11**.

Using this procedure, but employing, in place of ethyl 3-hydroxy-2-methylpropionate **3.10**, different hydroxyesters **3.1**, the corresponding products **3.2** are obtained.

The conversion of a phosphonate monoester **1.1** into a mixed diester **3.2** is also accomplished by means of a Mitsonobu coupling reaction with the hydroxyester **3.1**, as described in Org. Lett., 2001, 643. In this method, the reactants **1.1** and **3.1** are combined in a polar solvent such as tetrahydrofuran, in the presence of a triarylphosphine and a dialkyl azodicarboxylate, to give the mixed diester **3.2**. The R^1 substituent is varied by cleavage, using the methods described previously, to afford the monoacid product **3.3**. The product is then coupled, for example using methods described above, with the hydroxy compound R^3OH, to give the diester product **3.4**.

The procedure is illustrated in Scheme **3**, Example **2**. In this method, a monoallyl phosphonate **3.12** is coupled in tetrahydrofuran solution, in the presence of triphenylphosphine and diethylazodicarboxylate, with ethyl lactate **3.13** to give the mixed diester **3.14**. The product is reacted with tris(triphenylphosphine) rhodium chloride (Wilkinson catalyst) in acetonitrile, as described previously, to remove the allyl group and produce the monoacid product **3.15**. The latter compound is then coupled, in pyridine solution at ambient temperature, in the presence of dicyclohexyl carbodiimide, with one molar equivalent of 3-hydroxypyridine **3.16** to yield the mixed diester **3.17**.

Using the above procedures, but employing, in place of the ethyl lactate **3.13** or 3-hydroxypyridine, a different hydroxyester **3.1** and/or a different hydroxy compound R^3OH, the corresponding products **3.4** are obtained.

The mixed diesters **3.2** are also obtained from the monoesters **1.1** via the intermediacy of the activated monoesters **3.5**. In this procedure, the monoester **1.1** is converted into the activated compound **3.5** by reaction with, for example, phosphorus pentachloride, as described in J. Org. Chem., 2001, 66, 329, or with thionyl chloride or oxalyl chloride (Lv = Cl), or with triisopropylbenzenesulfonyl chloride in pyridine, as described in Nucleosides and Nucleotides, 2000, 19, 1885, or with carbonyl diimidazole, as

described in J. Med. Chem., 2002, 45, 1284. The resultant activated monoester is then reacted with the hydroxyester **3.1**, as described above, to yield the mixed diester **3.2**.

The procedure is illustrated in Scheme **3**, Example **3**. In this sequence, a monophenyl phosphonate **3.9** is reacted, in acetonitrile solution at 70°C, with ten equivalents of thionyl chloride, so as to produce the phosphoryl chloride **3.19**. The product is then reacted with ethyl 4-carbamoyl-2-hydroxybutyrate **3.20** in dichloromethane containing triethylamine, to give the mixed diester **3.21**.

Using the above procedures, but employing, in place of ethyl 4-carbamoyl-2-hydroxybutyrate **3.20**, different hydroxyesters **3.1**, the corresponding products **3.2** are obtained.

The mixed phosphonate diesters are also obtained by an alternative route for incorporation of the R^3O group into intermediates **3.3** in which the hydroxyester moiety is already incorporated. In this procedure, the monoacid intermediate **3.3** is converted into the activated derivative **3.6** in which Lv is a leaving group such as chloro, imidazole, and the like, as previously described. The activated intermediate is then reacted with the hydroxy compound R^3OH, in the presence of a base, to yield the mixed diester product **3.4**.

The method is illustrated in Scheme **3**, Example **4**. In this sequence, the phosphonate monoacid **3.22** is reacted with trichloromethanesulfonyl chloride in tetrahydrofuran containing collidine, as described in J. Med. Chem., 1995, 38, 4648, to produce the trichloromethanesulfonyloxy product **3.23**. This compound is reacted with 3-(morpholinomethyl)phenol **3.24** in dichloromethane containing triethylamine, to yield the mixed diester product **3.25**.

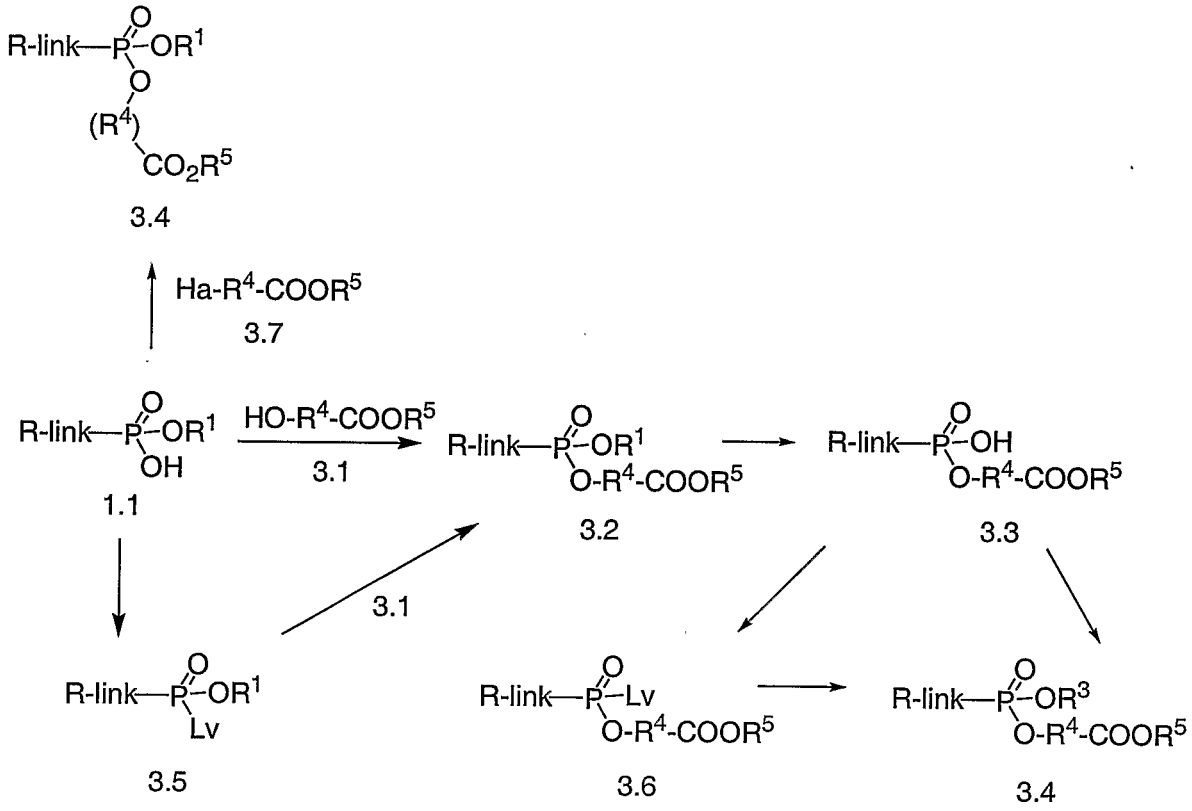
Using the above procedures, but employing, in place of with 3-(morpholinomethyl)phenol **3.24**, different carbinols R^3OH, the corresponding products **3.4** are obtained.

The phosphonate esters **3.4** are also obtained by means of alkylation reactions performed on the monoesters **1.1**. The reaction between the monoacid **1.1** and the haloester **3.7** is performed in a polar solvent in the presence of a base such as diisopropylethylamine, as described in Anal. Chem., 1987, 59, 1056, or triethylamine, as described in J. Med. Chem., 1995, 38, 1372, or in a non-polar solvent such as benzene, in the presence of 18-crown-6, as described in Syn. Comm., 1995, 25, 3565.

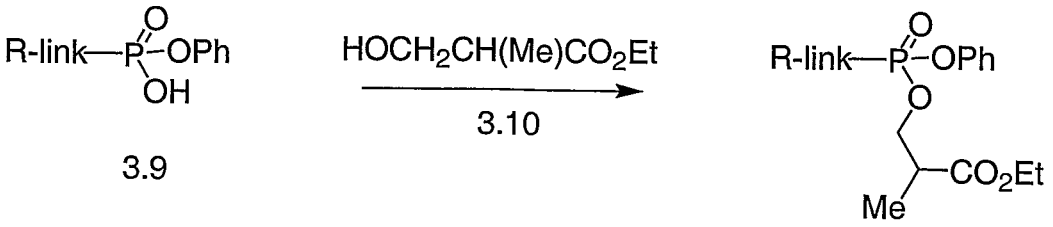
The method is illustrated in Scheme **3**, Example **5**. In this procedure, the monoacid **3.26** is reacted with ethyl 2-bromo-3-phenylpropionate **3.27** and diisopropylethylamine in dimethylformamide at 80°C to afford the mixed diester product **3.28**.

Using the above procedure, but employing, in place of ethyl 2-bromo-3-phenylpropionate **3.27**, different haloesters **3.7**, the corresponding products **3.4** are obtained.

Scheme 3



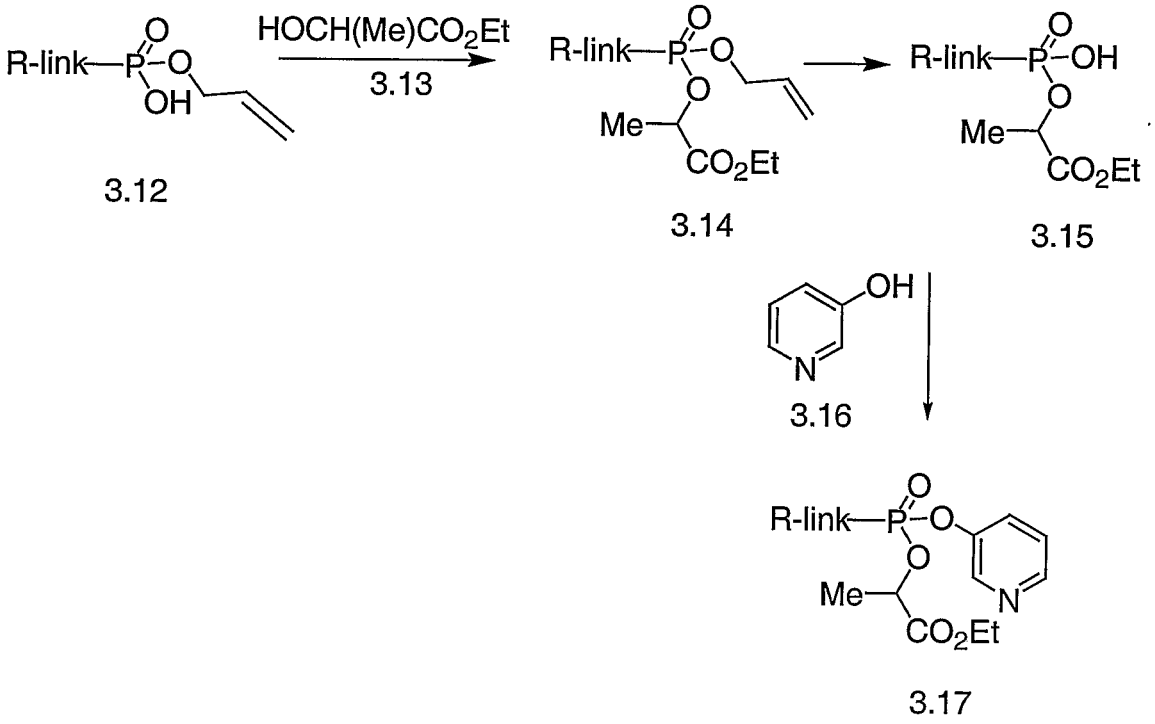
Scheme 3 Example 1



3.9

3.11

Scheme 3 Example 2



3.12

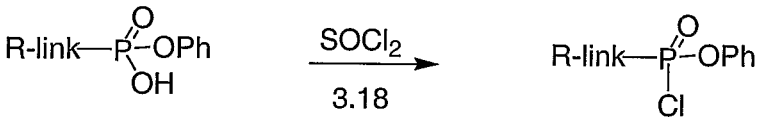
3.14

3.15

3.16

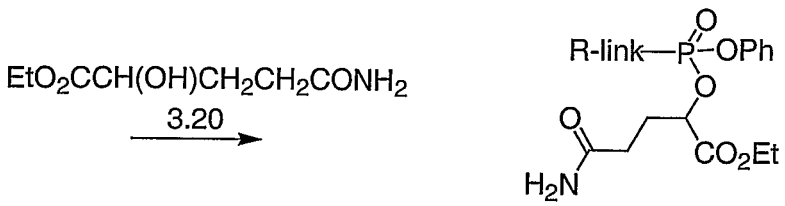
3.17

Scheme 3 Example 3



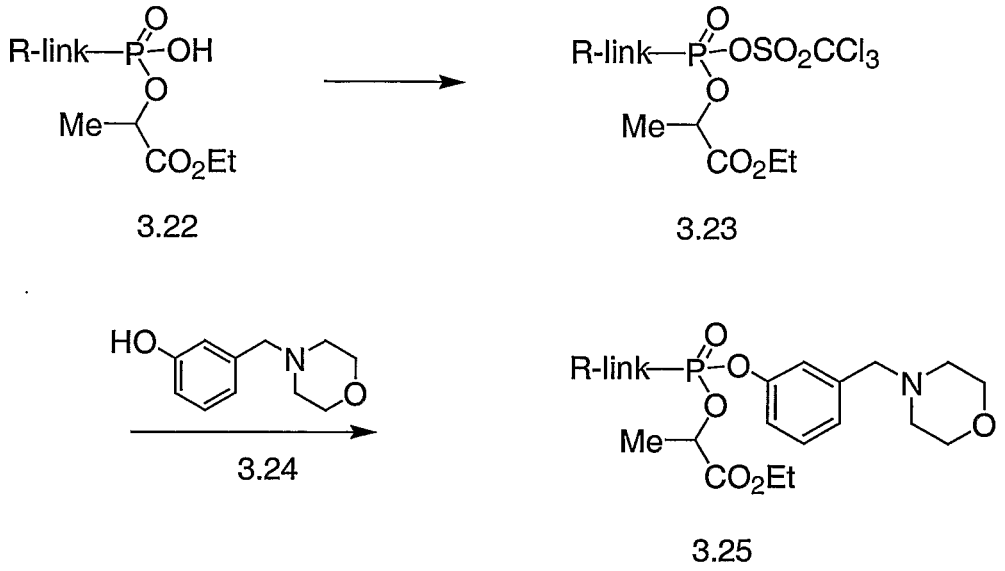
3.9

3.19

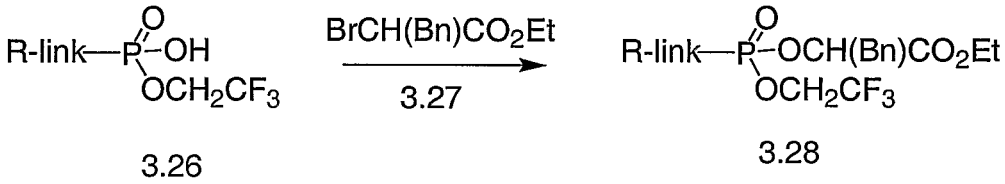


3.21

Scheme 3 Example 4



Scheme 3 Example 5



Scheme **4** illustrates methods for the preparation of phosphonate diesters in which both the ester substituents incorporate carboalkoxy groups.

The compounds are prepared directly or indirectly from the phosphonic acids **1.6**. In one alternative, the phosphonic acid is coupled with the hydroxyester **4.2**, using the conditions described previously in Schemes **1** - **3**, such as coupling reactions using dicyclohexyl carbodiimide or similar reagents, or under the conditions of the Mitsonobu reaction, to afford the diester product **4.3** in which the ester substituents are identical.

This method is illustrated in Scheme **4**, Example **1**. In this procedure, the phosphonic acid **1.6** is reacted with three molar equivalents of butyl lactate **4.5** in the presence of Aldrithiol-2 and triphenyl phosphine in pyridine at ca. 70°C, to afford the diester **4.6**.

Using the above procedure, but employing, in place of butyl lactate **4.5**, different hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

Alternatively, the diesters **4.3** are obtained by alkylation of the phosphonic acid **1.6** with a haloester **4.1**. The alkylation reaction is performed as described in Scheme **3** for the preparation of the esters **3.4**.

This method is illustrated in Scheme **4**, Example **2**. In this procedure, the phosphonic acid **1.6** is reacted with excess ethyl 3-bromo-2-methylpropionate **4.7** and diisopropylethylamine in dimethylformamide at ca. 80°C, as described in Anal. Chem., 1987, 59, 1056, to produce the diester **4.8**.

Using the above procedure, but employing, in place of ethyl 3-bromo-2-methylpropionate **4.7**, different haloesters **4.1**, the corresponding products **4.3** are obtained.

The diesters **4.3** are also obtained by displacement reactions of activated derivatives **1.7** of the phosphonic acid with the hydroxyesters **4.2**. The displacement reaction is performed in a polar solvent in the presence of a suitable base, as described in Scheme **3**. The displacement reaction is performed in the presence of an excess of the hydroxyester, to afford the diester product **4.3** in which the ester substituents are identical, or sequentially with limited amounts of different hydroxyesters, to prepare diesters **4.3** in which the ester substituents are different.

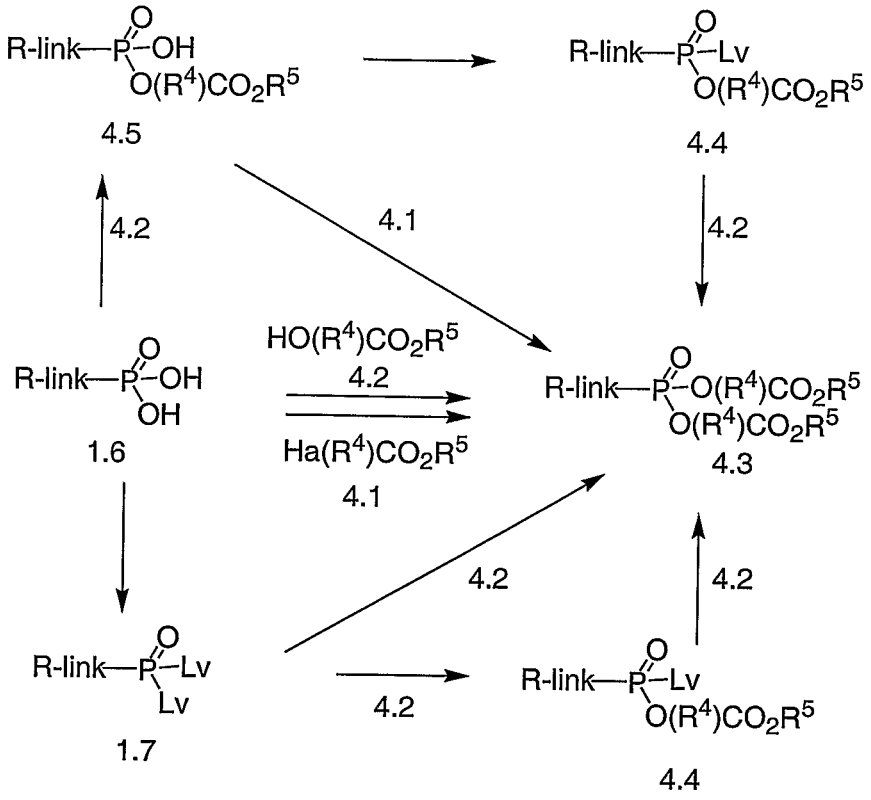
The methods are illustrated in Scheme **4**, Examples **3** and **4**. As shown in Example **3**, the phosphoryl dichloride **2.22** is reacted with three molar equivalents of ethyl 3-hydroxy-2-(hydroxymethyl)propionate **4.9** in tetrahydrofuran containing potassium carbonate, to obtain the diester product **4.10**.

Using the above procedure, but employing, in place of ethyl 3-hydroxy-2-(hydroxymethyl)propionate **4.9**, different hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

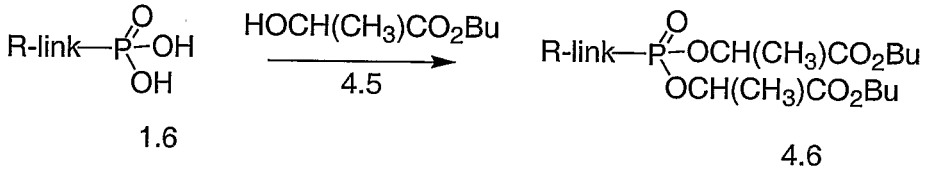
Scheme **4**, Example **4** depicts the displacement reaction between equimolar amounts of the phosphoryl dichloride **2.22** and ethyl 2-methyl-3-hydroxypropionate **4.11**, to yield the monoester product **4.12**. The reaction is conducted in acetonitrile at 70°C in the presence of diisopropylethylamine. The product **4.12** is then reacted, under the same conditions, with one molar equivalent of ethyl lactate **4.13**, to give the diester product **4.14**.

Using the above procedures, but employing, in place of ethyl 2-methyl-3-hydroxypropionate **4.11** and ethyl lactate **4.13**, sequential reactions with different hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

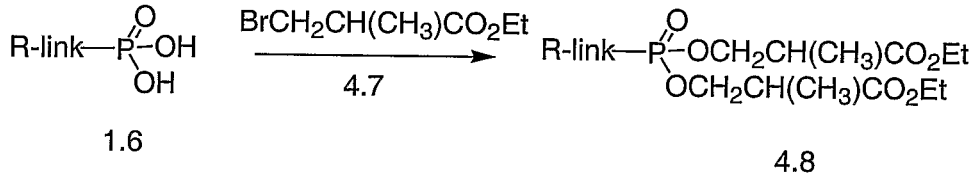
Scheme 4



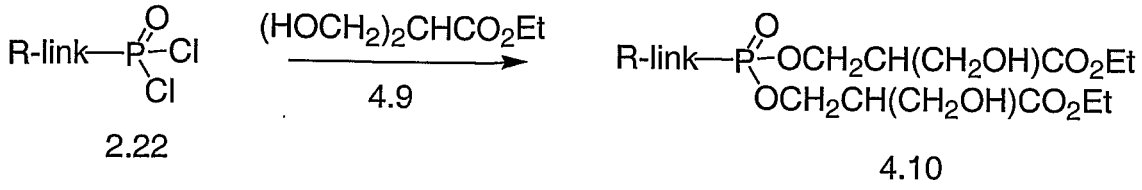
Scheme 4 Example 1



Scheme 4 Example 2

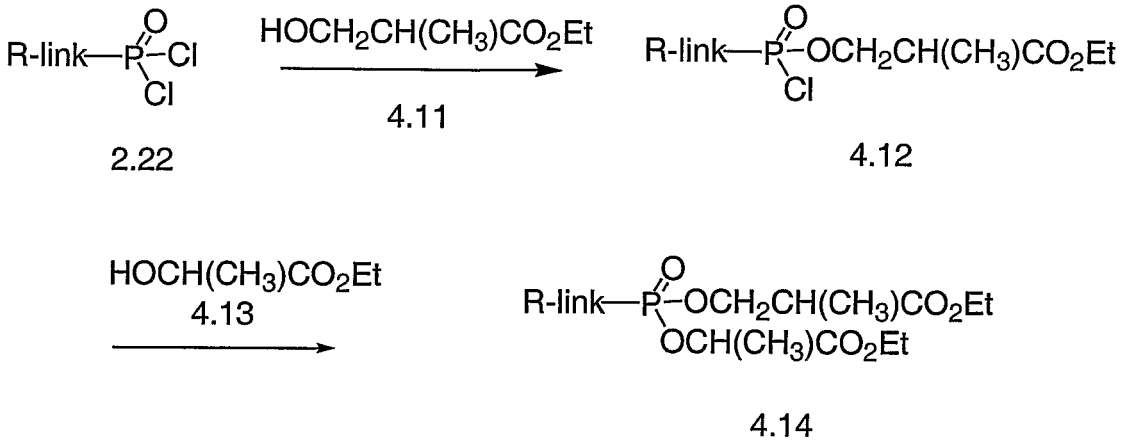


Scheme 4 Example 3



2.22 4.10

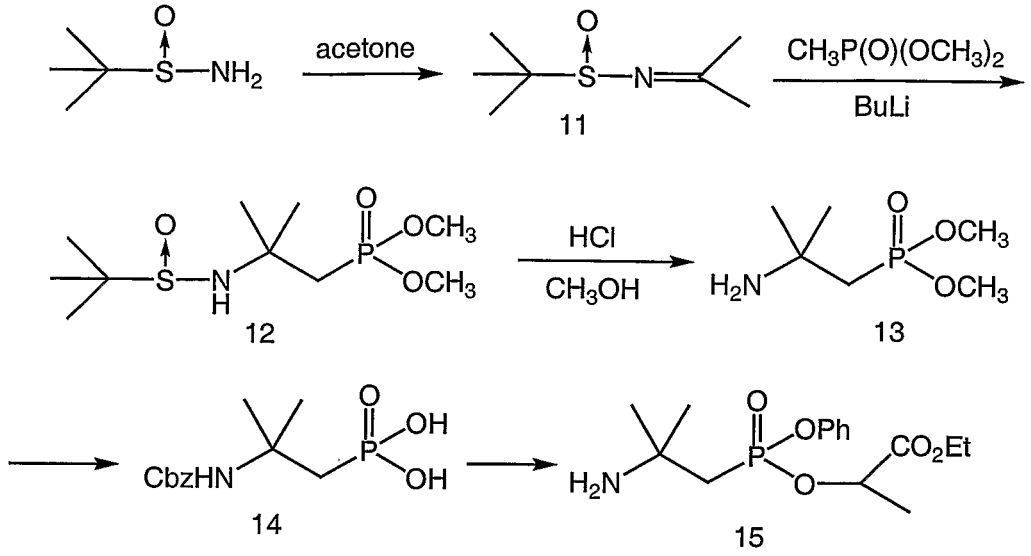
Scheme 4 Example 4



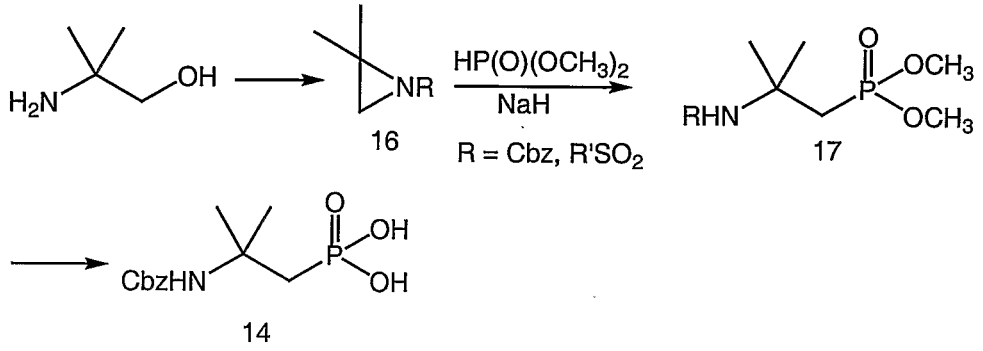
2.22 4.12 4.14

2,2-Dimethyl-2-aminoethylphosphonic acid intermediates can be prepared by the route in Scheme 5. Condensation of 2-methyl-2-propanesulfinamide with acetone give sulfinyl imine **11** (*J. Org. Chem.* **1999**, *64*, 12). Addition of dimethyl methylphosphonate lithium to **11** afford **12**. Acidic methanolysis of **12** provide amine **13**. Protection of amine with Cbz group and removal of methyl groups yield phosphonic acid **14**, which can be converted to desired **15** (Scheme 5a) using methods reported earlier on. An alternative synthesis of compound **14** is also shown in Scheme 5b. Commercially available 2-amino-2-methyl-1-propanol is converted to aziridines **16** according to literature methods (*J. Org. Chem.* **1992**, *57*, 5813; *Syn. Lett.* **1997**, *8*, 893). Aziridine opening with phosphite give **17** (*Tetrahedron Lett.* **1980**, *21*, 1623). Reprotection) of **17** affords **14**.

Scheme 5a



Scheme 5b



Biological Activity of HIV-Integrase Inhibitor Compounds

Representative compounds of the invention were tested for biological activity by methods including anti-HIV assay, measuring inhibition of HIV-integrase strand transfer catalysis, and cytotoxicity. See: Wolfe, etal *J. Virol.* (1996) 70:1424-1432; Hazuda, etal *Nucleic Acids Res.* (1994) 22:1121-22; Hazuda, etal *J. Virol.* (1997) 71:7005-7011; Hazuda, etal *Drug Design and Discovery* (1997) 15:17-24; and Hazuda, etal *Science* (2000) 287:646-650. The antiviral activity of a compound of the invention can be determined using pharmacological models which are well known in the art. While many of the compounds of the present invention demonstrate inhibition of integration of HIV reverse-transcribed DNA, there may be other mechanisms of action whereby HIV replication or proliferation is affected. The compounds of the invention may be active via inhibition of HIV-integrase or other enzymes associated with HIV infection, AIDS, or ARC. Furthermore, the compounds of the invention may have significant activity against other viral diseases. Thus, the specific

assays embodied in Examples x-y are not meant to limit the present invention to a specific mechanism of action.

Pharmaceutical Formulations and Routes of Administration

The compounds of the invention may be 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. Formulations optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986) and include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

Compounds of the invention and their physiologically acceptable salts (hereafter collectively referred to as the active ingredients) may be administered by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including ocular, buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural). The preferred route of administration may vary with for example the condition of the recipient.

While it is possible for the active ingredients to be administered alone it is preferably to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the present invention comprise at least one active ingredient, as above defined, together with one or more pharmaceutically 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 not deleterious to the recipient thereof.

The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. 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. 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 solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be 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 compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

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 PEG400) 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 dimethylsulfoxide 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 present 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, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus 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 can be used.

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 nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns (including

particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35 microns, etc), which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as pentamidine for treatment of pneumocystis pneumonia.

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 may be 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 injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be 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 an 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 present invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor. Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention can be 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 can be controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given invention compound. Controlled release formulations adapted for oral administration in which discrete units comprising one or more compounds of the invention can be prepared according to conventional methods. Controlled release formulations may be employed for the treatment or prophylaxis of various microbial infections particularly human bacterial, human parasitic protozoan or human viral infections caused by microbial species including Plasmodium, Pneumocystis, herpes viruses (CMV, HSV 1, HSV 2, VZV, and the like), retroviruses, adenoviruses and the like. The controlled release formulations can be used to treat HIV infections and related conditions such as tuberculosis, malaria, pneumocystis pneumonia, CMV retinitis, AIDS, AIDS-related complex (ARC) and progressive generalized lymphadeopathy (PGL), and AIDS-related neurological conditions such as multiple sclerosis, and tropical spastic paraparesis. Other human retroviral infections that may be treated with the controlled release formulations according to the invention include Human T-cell Lymphotropic virus (HTLV)-I and IV and HIV-2 infections. The invention accordingly provides pharmaceutical formulations for use in the treatment or prophylaxis of the above-mentioned human or veterinary conditions and microbial infections.

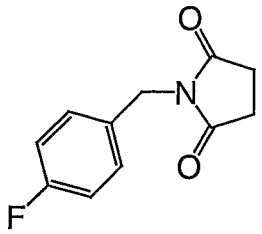
Combination Therapy

The compounds of the invention may be employed in combination with other therapeutic agents for the treatment or prophylaxis of the infections or conditions indicated above. Examples of such further therapeutic agents include agents that are effective for the treatment or prophylaxis of viral, parasitic or bacterial infections or associated conditions or for treatment of tumors or related conditions include 3'-azido-3'-deoxythymidine (zidovudine, AZT), 2'-deoxy-3'-thiacytidine (3TC), 2',3'-dideoxy-2',3'-didehydroadenosine (D4A), 2',3'-dideoxy-2',3'-didehydrothymidine (D4T), carbovir (carbocyclic 2',3'-dideoxy-2',3'-didehydroguanosine), 3'-azido-2',3'-dideoxyuridine, 5-fluorothymidine, (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU), 2-chlorodeoxyadenosine, 2-deoxycoformycin, 5-fluorouracil, 5-fluorouridine, 5-fluoro-2'-deoxyuridine, 5-trifluoromethyl-2'-deoxyuridine, 6-azauridine, 5-fluoroorotic acid, methotrexate, triacetyluridine, 1-(2'-deoxy-2'-fluoro-1-β-arabinosyl)-5-iodocytidine (FIAC), tetrahydro-imidazo(4,5, 1-jk)-(1,4)-benzodiazepin-

2(1H)-thione (TIBO), 2'-nor-cyclicGMP, 6-methoxypurine arabinoside (ara-M), 6-methoxypurine arabinoside 2'-O-valerate, cytosine arabinoside (ara-C), 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine (ddC), 2',3'-dideoxyadenosine (ddA) and 2',3'-dideoxyinosine (ddI), acyclic nucleosides such as acyclovir, penciclovir, famciclovir, ganciclovir, HPMPC, PMEA, PMEG, PMPA, PMPDAP, FPMPA, HPMPA, HPMPDAP, (2R, 5R)-9->tetrahydro-5-(phosphonomethoxy)-2-furanyladenine, (2R, 5R)-1->tetrahydro-5-(phosphonomethoxy)-2-furanylthymine, other antivirals including ribavirin (adenine arabinoside), 2-thio-6-azauridine, tubercidin, aurintricarboxylic acid, 3-deazaneoplanocin, neoplanocin, rimantidine, adamantine, and foscarnet (trisodium phosphonoformate), antibacterial agents including bactericidal fluoroquinolones (ciprofloxacin, pefloxacin and the like), aminoglycoside bactericidal antibiotics (streptomycin, gentamicin, amicacin and the like) β-lactamase inhibitors (cephalosporins, penicillins and the like), other antibacterials including tetracycline, isoniazid, rifampin, cefoperazone, claithromycin and azithromycin, antiparasite or antifungal agents including pentamidine (1,5-bis(4'-aminophenoxy)pentane), 9-deaza-inosine, sulfamethoxazole, sulfadiazine, quinapyramine, quinine, fluconazole, ketoconazole, itraconazole, Amphotericin B, 5-fluorocytosine, clotrimazole, hexadecylphosphocholine and nystatin, renal excretion inhibitors such as probenicid, nucleoside transport inhibitors such as dipyridamole, dilazep and nitrobenzylthioinosine, immunomodulators such as FK506, cyclosporin A, thymosin α-1, cytokines including TNF and TGF-β, interferons including IFN-α, IFN-β, and IFN-γ, interleukins including various interleukins, macrophage/granulocyte colony stimulating factors including GM-CSF, G-CSF, M-CSF, cytokine antagonists including anti-TNF antibodies, anti-interleukin antibodies, soluble interleukin receptors, protein kinase C inhibitors and the like.

EXAMPLES

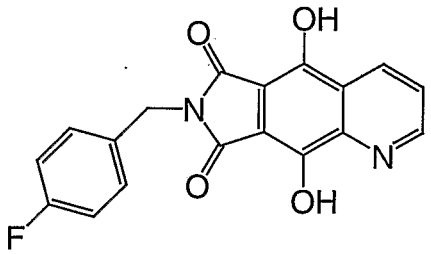
Example 1 N-4-fluorobenzyl-succinimide **1**



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**

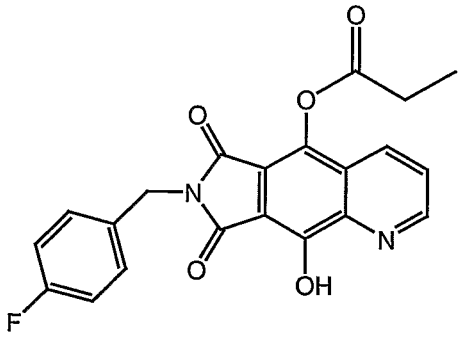


2

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.

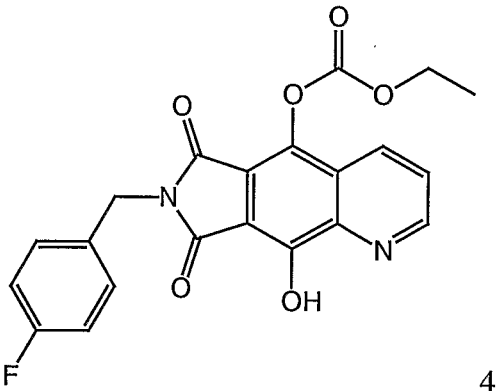
Example 3 5-O-Propanoate, 8-hydroxy-[6,7]-N-(4-fluorobenzyl)-succinimido-quinoline **3**



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**

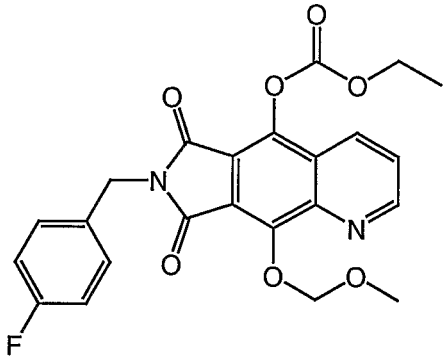


4

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)

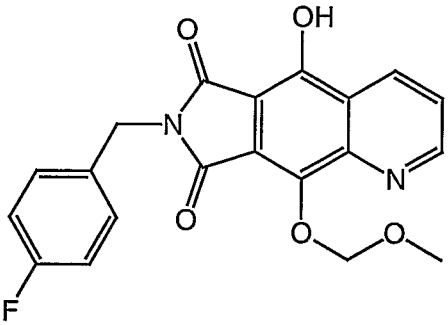
Example 5 Carbonic acid ethyl ester 7-(4-fluoro-benzyl)-9-methoxymethoxy-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **5**



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%). ^{1}H 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).

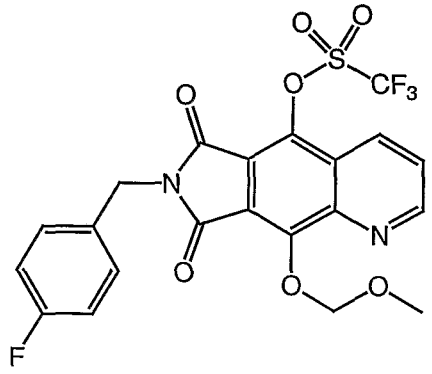
Example 6 7-(4-Fluoro-benzyl)-5-hydroxy-9-methoxymethoxy-pyrrolo[3,4-g]quinoline-6,8-dione **6**



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). ^{1}H 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**



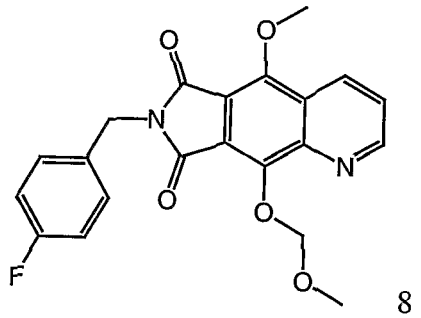
7

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%). ^{1}H 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).

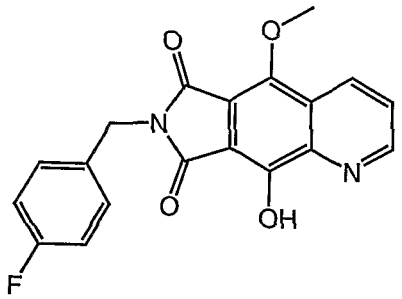
Example 8 7-(4-Fluoro-benzyl)-5-methoxy-9-methoxymethoxy-pyrrolo[3,4-g]quinoline-6,8-dione **8**



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).

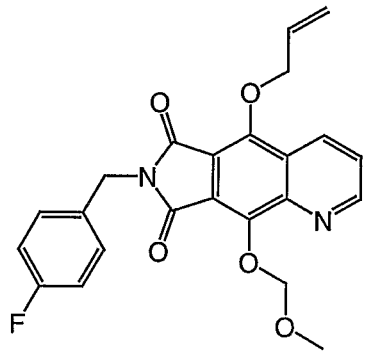
Example 9 7-(4-Fluoro-benzyl)-9-hydroxy-5-methoxy-pyrrolo[3,4-g]quinoline-6,8-dione **9**



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).

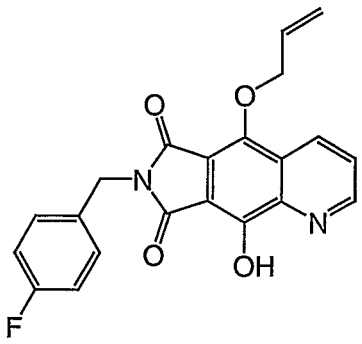
Example 10 5-Allyloxy-7-(4-fluoro-benzyl)-9-methoxymethoxy-pyrrolo[3,4-g]quinoline-6,8-dione **10**



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).

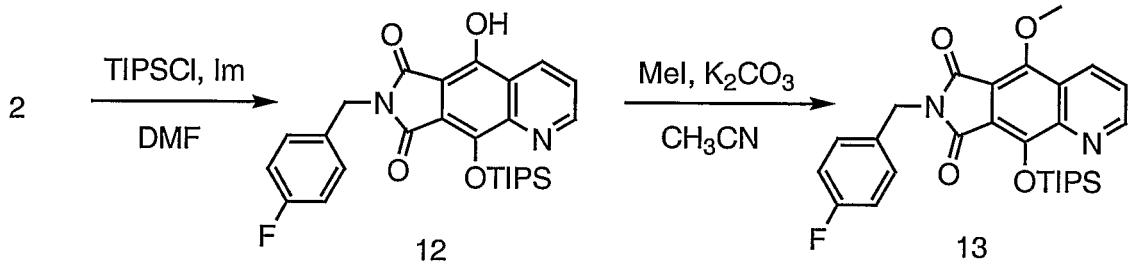
Example 11 5-Allyloxy-7-(4-fluoro-benzyl)-9-hydroxy-pyrrolo[3,4-g]quinoline-6,8-dione **11**



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).

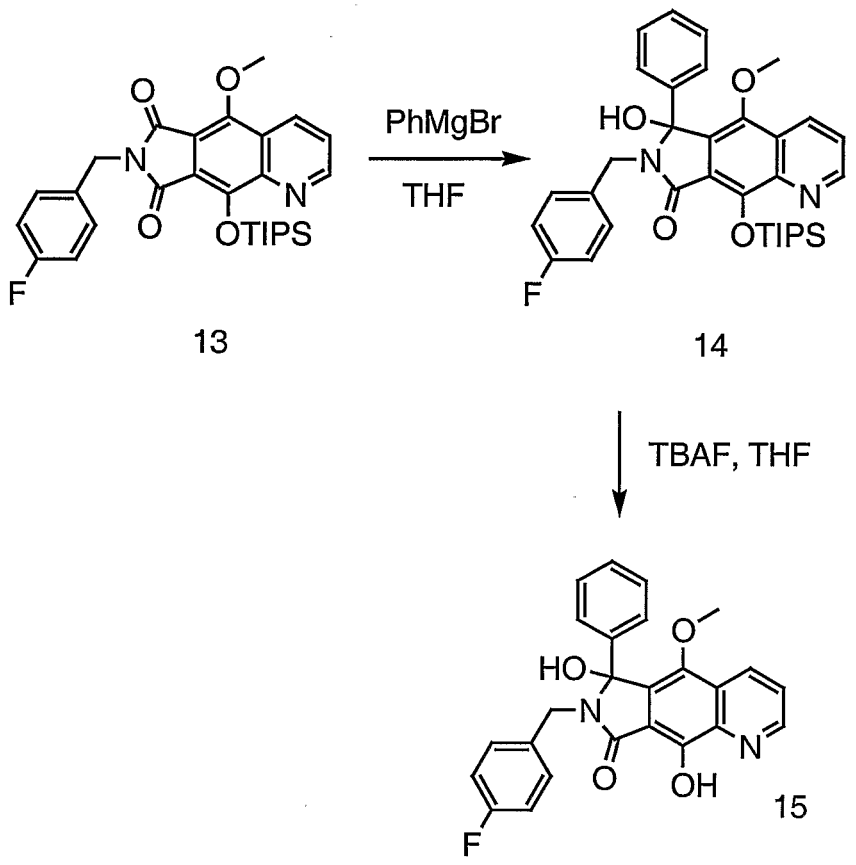
Example 12 7-(4-Fluoro-benzyl)-5-hydroxy-9-triisopropylsilanyloxy-pyrrolo[3,4-g]quinoline-6,8-dione **12**



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**

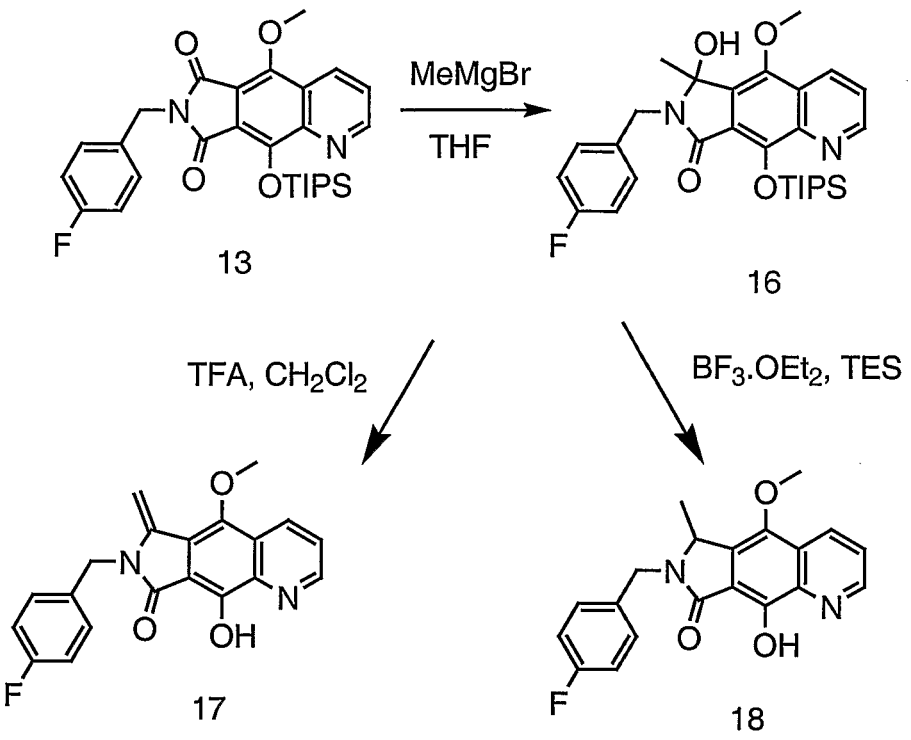
A mixture of **13** (36 mg, 0.071 mmol) in 0.35 mL of dry THF was cooled to 0°C. A 26 μL aliquot of a 3 M solution of phenyl magnesium bromide in ether (0.078 mmol) was added to the mixture and the reaction was allowed to warm up to room temperature. The reaction was worked up in 30 minutes when the 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.

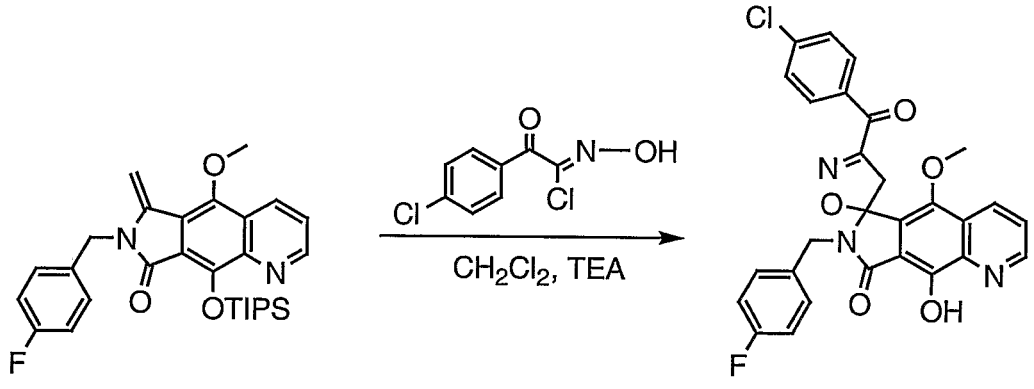
Example 17 7-(4-Fluoro-benzyl)-9-hydroxy-5-methoxy-6-methylene-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **17**

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].

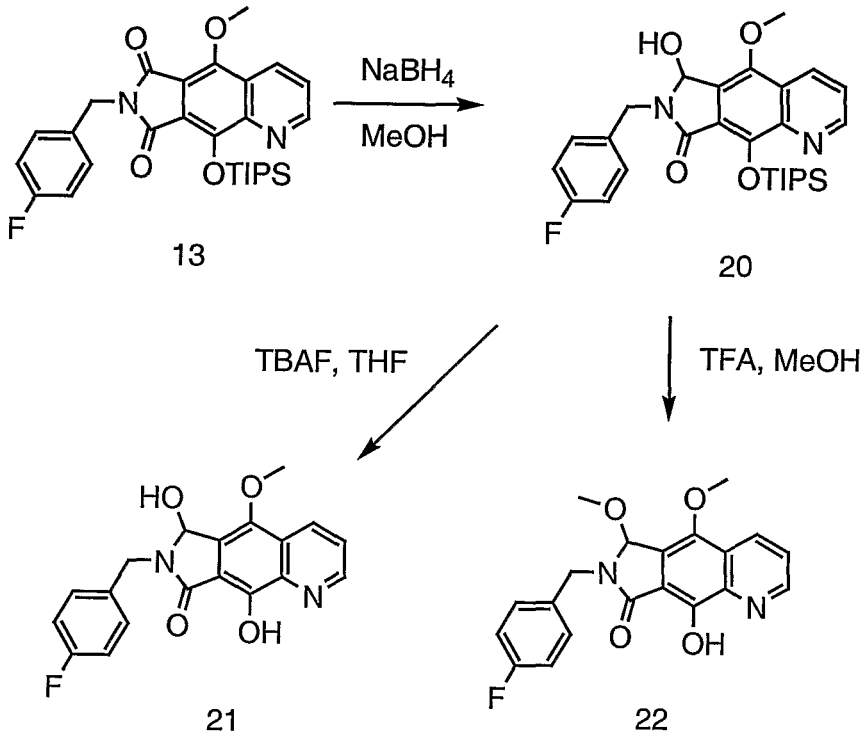


17a 19

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,

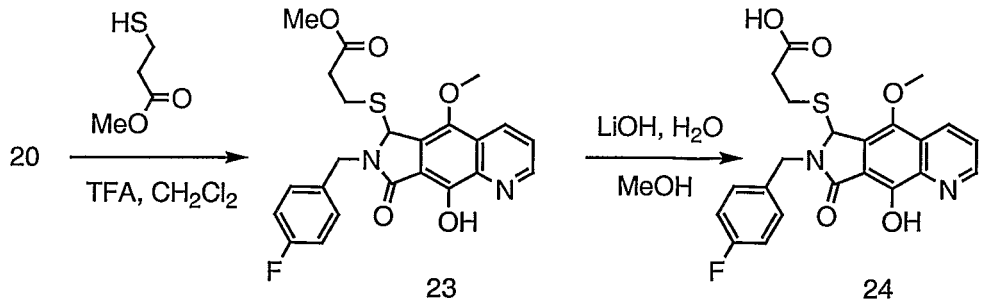
3H, *J*= 8 Hz), 3.72 (d, 1H, *J*= 11 Hz), 4.11 (s, 3H), 4.23 (d, 1H, *J*= 15 Hz), 4.85 (d, 1H, *J*= 15 Hz), 5.79 (d, 1H, *J*= 11 Hz), 6.97 (t, 2H, *J*= 9 Hz), 7.27 (dd, 2H, *J*= 6, 9 Hz), 7.43 (dd, 1H, *J*= 4, 8 Hz), 8.43 (dd, 1H, *J*= 2, 8 Hz), 8.81 (dd, 1H, *J*= 2, 4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 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^+].

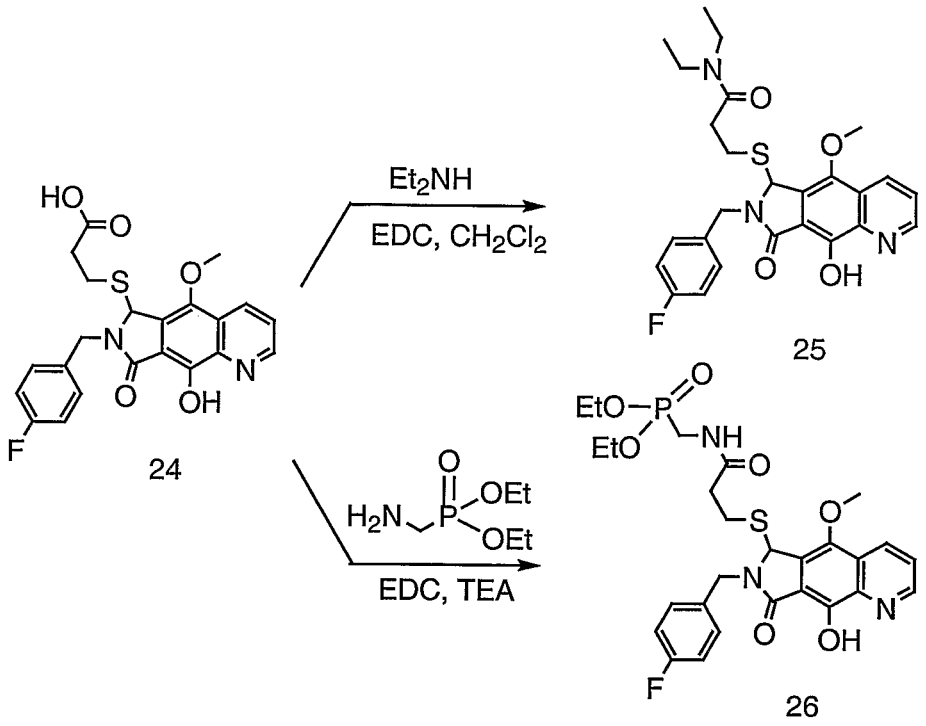


Example 23 3-[7-(4-Fluoro-benzyl)-9-hydroxy-5-methoxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-6-ylsulfanyl]-propionic acid methyl ester **23**

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 [$2M-2H]^-$.



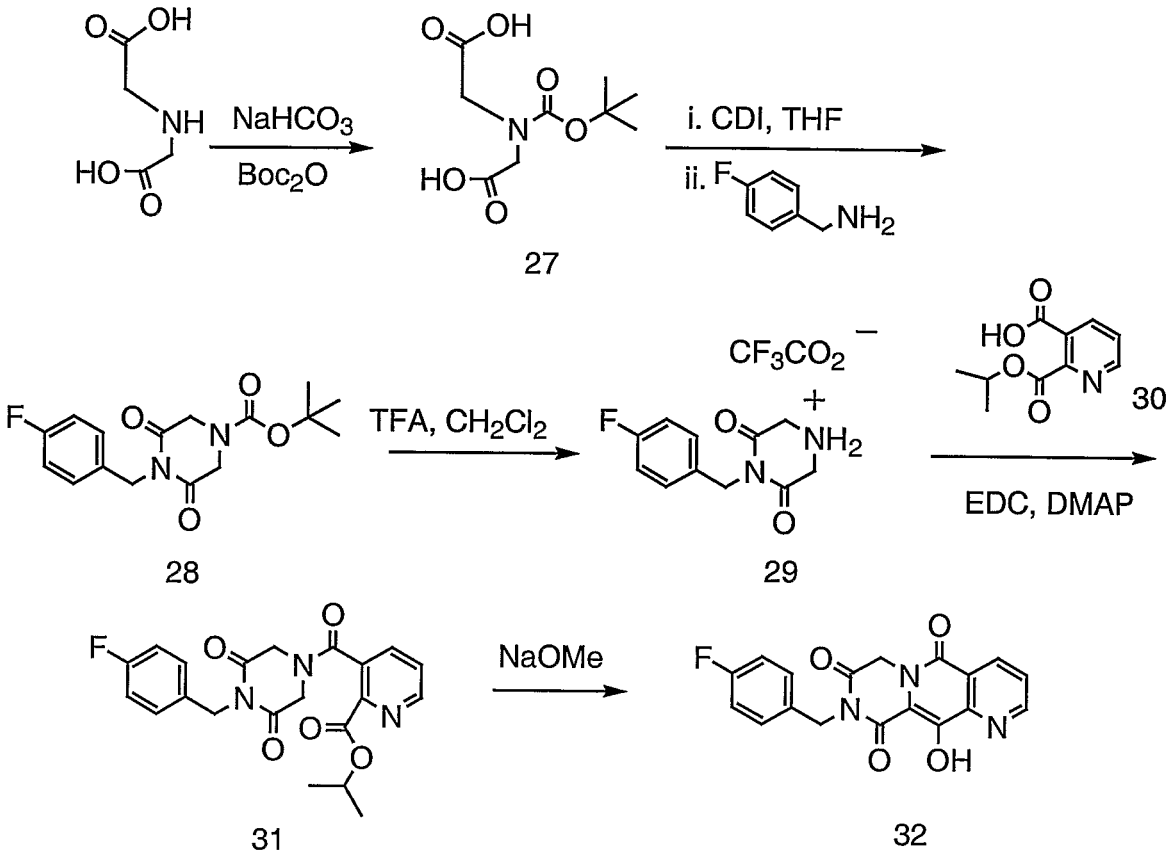
Example 25 N,N-Diethyl-3-[7-(4-fluoro-benzyl)-9-hydroxy-5-methoxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-6-ylsulfanyl]-propionamide **25**

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. ^1H 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. ^1H 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. ^1H 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. ^1H 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^+].

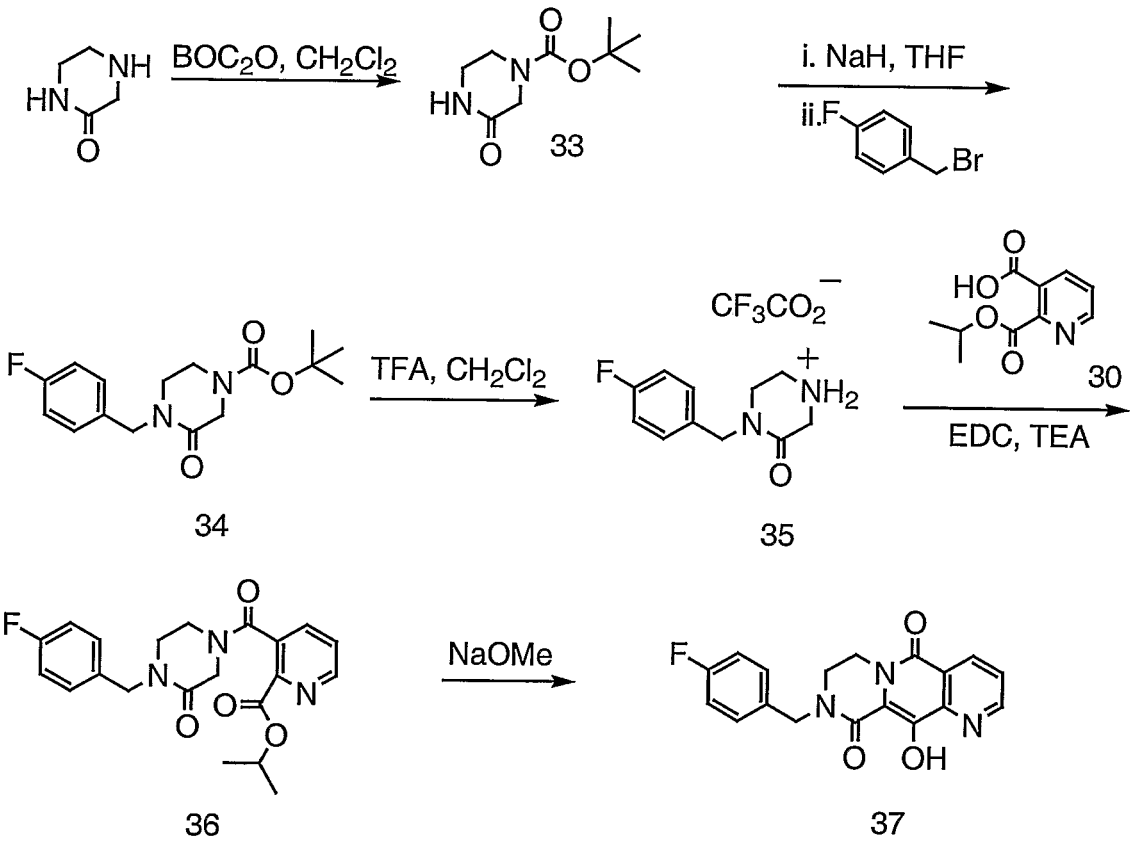
Example 31 3-[4-(4-Fluoro-benzyl)-3,5-dioxo-piperazine-1-carbonyl]-pyridine-2-carboxylic acid isopropyl ester **31**

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**

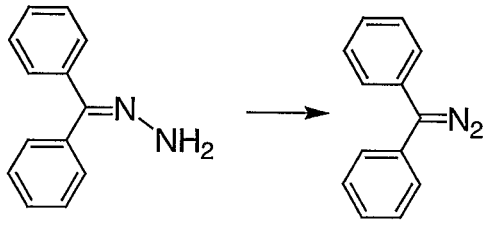
A solution of **34** (1.4 g, 4.5 mmol) in 6 mL of a 1:1 solution of CH_2Cl_2: TFA was stirred at ambient temperature for 2 hours when all of the starting materials were consumed as judged by TLC. The reaction mixtures were dried *in vacuo* to yield 1.5 g of **35** as a thick oil which was used in the 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].

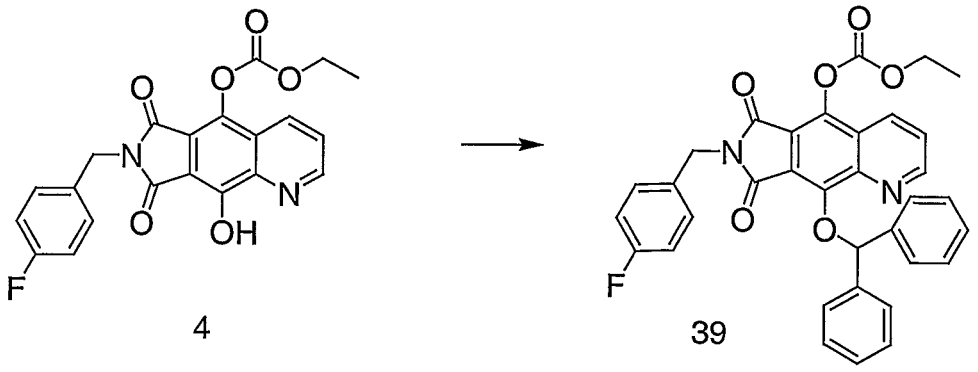
Example 37 7-(4-Fluoro-benzyl)-9-hydroxy-6,7-dihydro-5H-1,7,10a-triaza-anthracene-8,10-dione **37**

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. ^1H 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 room temperature 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 %).

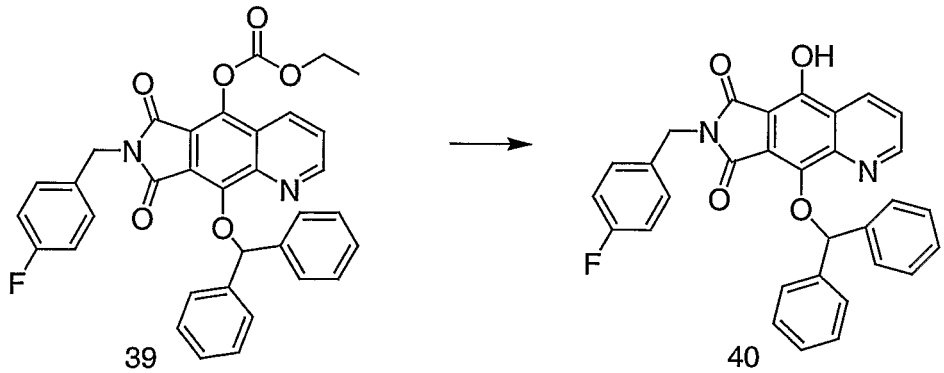


4 39

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).

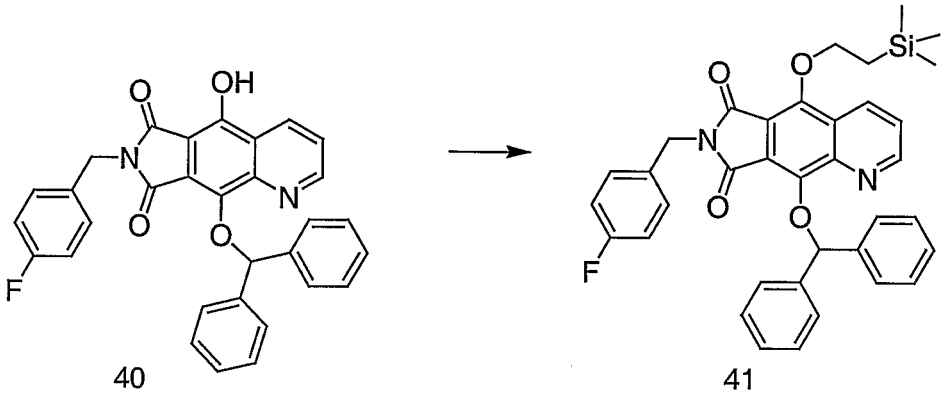
The reaction was repeated, where mono-carbonate **4** (2 g, 0.4878 mmol) was dissolved in 9 mL of dichloroethane. To this was added diphenyldiazomethane (0.189 g, 0.9756 mmol) and stirred at 70°C for two hours. After starting material consumed, concentrated off some solvent, and chromatographed (25% 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)



39 40

Example 40

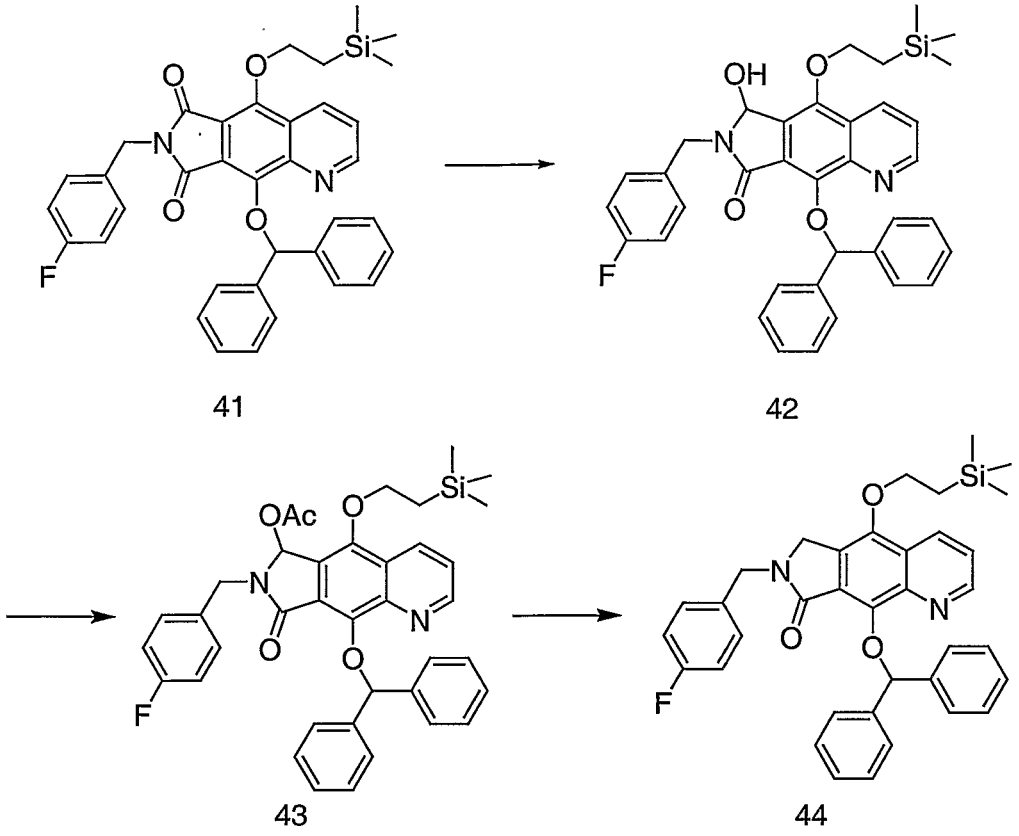
A solution of K_2CO_3 (24.2 g, 175.2 mmol) in water (120 mL) and 4-dimethylaminopyridine (4.24 g, 35.0 mmol) was added to the ethyl carbonate **39** (10.1 g, 17.5 mmol) in THF (180 mL). The mixture is stirred at room temperature under nitrogen atmosphere overnight. Most of THF is removed under reduced 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).



Example 42

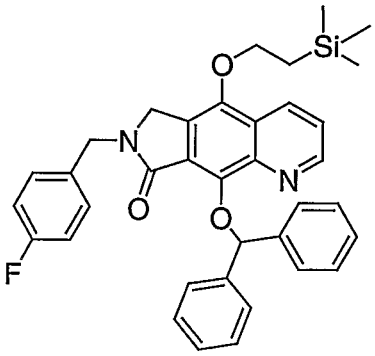
Compound **41** (3.3 g, 5.46 mmol) was dissolved in the mixture of THF (40 mL), isopropanol (20 mL) and water (10 mL) and chilled to 0°C in an ice-bath. To this was added lithium borohydride (373.0 mg, 16.4 mmol) slowly. The mixture was stirred at 0°C for 1 hour and at room temperature for 1 hour under 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 to give crude product **43** (3.5 g).

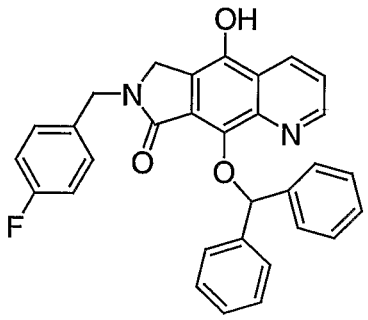
Example 44

Crude product **43** was dissolved in anhydrous dichloromethane (60mL) under nitrogen. To this solution was added 2,6-lutidine (3.2 mL, 23.7 mmol), triethylsiliane (10 mL), then trimethylsilyl triflate (1.5 mL, 8.2 mmol) slowly. The mixture was stirred at room temperature for 3 hours. TLC indicated the completion of the reaction. It was quenched with 1N HCl (30 mL) and extracted with CH_2Cl_2 twice (2x50 mL). The organic layer was washed with saturatedNaHCO$_3$, 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**). ^{1}H 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).



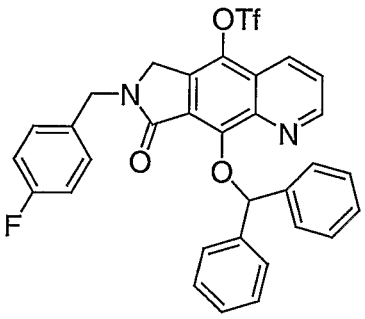
Mol. Wt.: 590.76

44



Mol. Wt.: 490.52

45



Mol. Wt.: 622.59

46

Example 45

To 9-benzhydryloxy-7-(4-fluoro-benzyl)-5-(2-trimethylsilanyl-ethoxy)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **44** (300.8 mg, 0.509 mmol) in anhydrous THF (20 mL), was added tetrabutylammonium fluoride hydrate (500 mg, 1.02 mmol). The reaction mixture turned to red and was stirred at room temperature under nitrogen for 1 hour. The reaction

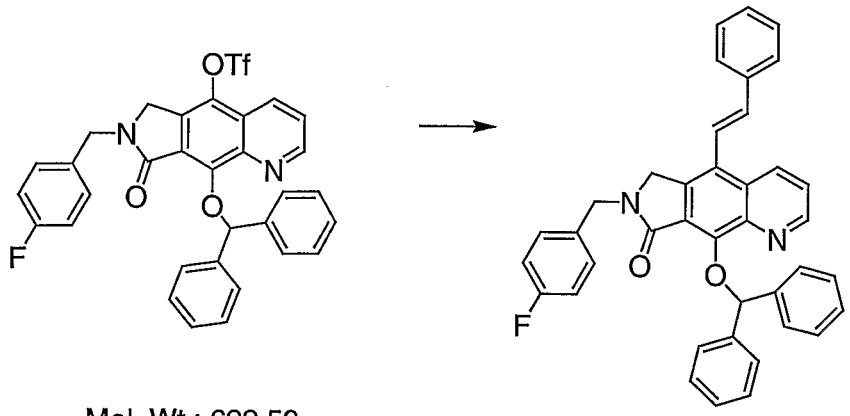
was monitored by TLC (EtOAc/Hexane = 3/7). After completion of the reaction, it was diluted with EtOAc (50 mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated to give a crude product **45** (280 mg).

The reaction was repeated whereby, to a solution of lactam **44** (0.026g, 0.044 mmol) in THF (0.441 mL) was added triethylamine (0.025 mL, 0.176 mmol) and tetrabutylammonium fluoride in 1M THF (0.066 mL). The reaction mixture was stirred at room temperature under an inert atmosphere for 30 minutes, monitored to completion by MS. The mixture was diluted with dichloromethane, washed with saturated NH_4Cl, dried ($MgSO_4$), and concentrated *in vacuo*. The crude material **45** was taken forward immediately with no further purification or characterization: MS: 491 (M+1).

Alternatively, to a solution of 9-benzhydryloxy-7-(4-fluoro-benzyl)-5-(2-trimethylsilanyl-ethoxy)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **44** (30 mg, 0.051 mmol) dissolved in THF (1 mL) was added tetrabutylammonium fluoride hydrate (1M in THF, 150 μL). The reaction mixture turned to red and was stirred at room temperature for 1/2 hours under an inert atmosphere, which generated 9-benzhydryloxy-7-(4-fluoro-benzyl)-5-hydroxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **45**. TLC was used to monitor the reaction.

Example 46

Crude compound **45** was dissolved in dichloromethane (20 mL). To this was added cesium carbonate (200 mg, 0.611 mmol) and *N*-phenyltrifluoromethane sulfonimide (220 mg, 0.611 mmol). The mixture was stirred at room temperature under nitrogen for 16 hours. The reaction was monitored by TLC (EtOAc/Hexane = 3/7). After completion of the reaction, it was diluted with EtOAc (50 mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated. The residue was chromatographed on a silica gel column, eluting with EtOAc/Hexane to afford the clean product **46** (135 mg, 42.6% in 2 steps). ^1H NMR ($CDCl_3$): δ 9.1 (d, 1H), 8.3 (d, 1H), 8.0 (s, 1H), 7.7 (d, 4H), 7.6 (dd, 1H), 7.2-7.4 (m, 8H), 7.1 (t, 2H), 4.8 (s, 2H), 4.4 (s, 2H). MS: 623 (M+1), 645(M+23).



Mol. Wt.: 622.59

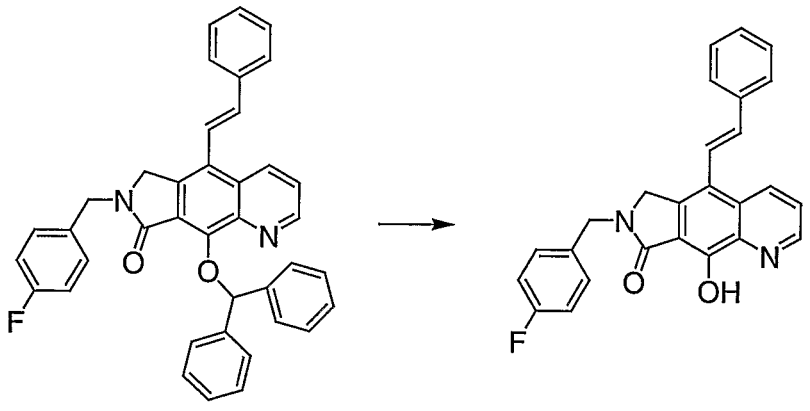
46

Mol. Wt.: 576.66

47

Example 47

To the triflate **46** (66.6 mg, 0.107 mmol) in toluene (2.8 mL)/ethanol (1.2 mL)/water (0.8 mL) was added potassium carbonate (37 mg, 0.268 mmol), trans-phenylvinylboronic acid (24.5 mg, 0.160 mmol) and tetrakis(triphenylphosphine)-palladium (0) (18.5 mg, 0.016 mmol). The mixture in the flask was flushed with argon three times and heated to 120°C under argon for 3 hours. The mixture was cooled to room temperature, diluted with EtOAc and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed on a silica gel column, eluting with EtOAc/Hexane to afford the product **47** (51.4 mg, 83%). ^1H NMR ($CDCl_3$): δ 9.0 (d, 1H), 8.4 (d, 1H), 8.1 (s, 1H), 7.7 (d, 4H), 7.2-7.5 (m, 14H), 7.1 (d, 1H), 7.0 (dd, 2H), 6.8 (d, 1H), 4.8 (s, 2H), 4.4(s, 2H). MS: 577 (M+1), 599(M+23).



Mol. Wt.: 576.66

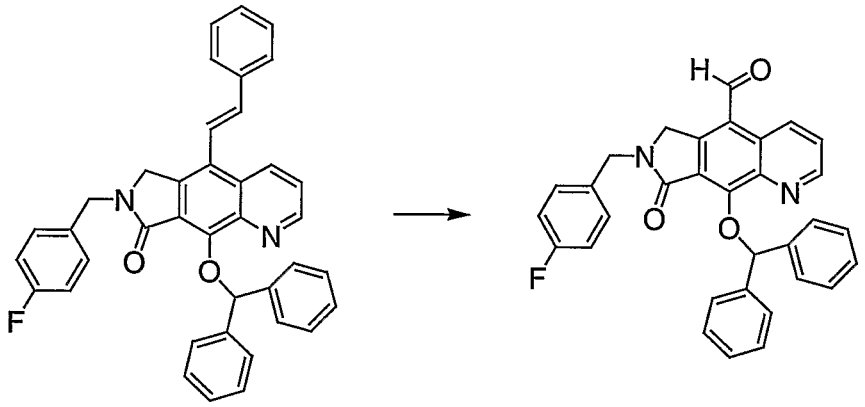
47

Mol. Wt.: 410.44

48

Example 48

The compound **47** (12 mg, 0.02 mmol) was dissolved in dichloromethane (1 mL) at room temperature under nitrogen. Triethylsilane (200 μL) was added followed by TFA (100 μL) slowly. The mixture became smoke and dark. It was stirred at room temperature for 30 min. The solvent was removed under reduced pressure. The crude product was triturated in diethylether/hexane to afford a yellow solid **48** (9 mg, 90%). ^{1}H NMR ($CDCl_3$): δ 9.0 (d, 1H), 8.6 (d, 1H), 7.5 (m, 3H), 7.2-7.4 (m, 6H), 7.1 (m, 2H), 6.8 (d, 1H), 4.8 (s, 2H), 4.5(s, 2H). MS: 411 (M+1).

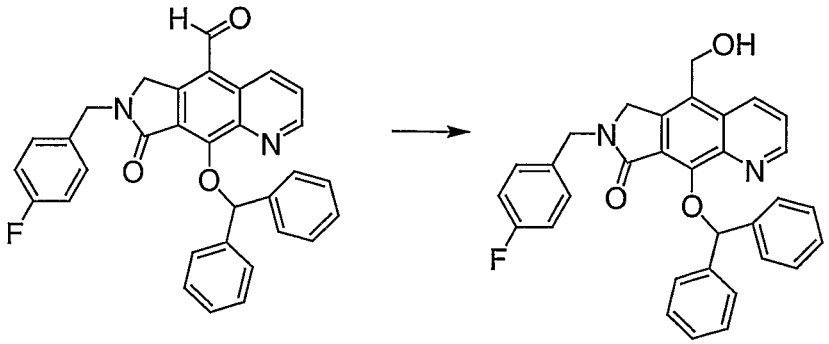


Mol. Wt.: 576.66
47

Mol. Wt.: 502.54
49

Example 49

Compound **47** (405 mg, 0.7 mmol) in dichloromethane (150 mL) was chilled to -78°C. Ozone (O_3) was passed slowly into the solution over 30 min. TLC indicated the completion of the reaction. Nitrogen was bubbled into the mixture for 10 min to expel excess O_3. Dimethyl sulfate (10 mL) was then added the mixture at -78°C and the mixture was warmed to room temperature slowly with stirring. After 16 hours, the mixture was evaporated to dryness and the residue was purified by chromatography on a silica gel column, eluting with methanol/dichloromethane to give product of **49** (166.5 mg) and its hydrate form (122 mg), total yield of 80.8%. ^{1}H NMR ($CDCl_3$): δ 10.7 (s, 1H, CHO), 9.1 (m, 2H), 8.4 (s, 1H), 7.7 (d, 4H), 7.6 (dd, 2H), 7.2-7.4 (m, 8H), 7.0 (t, 2H), 4.8 (s, 2H), 4.6 (s, 2H). MS: 503 (M+1), 525(M+23).

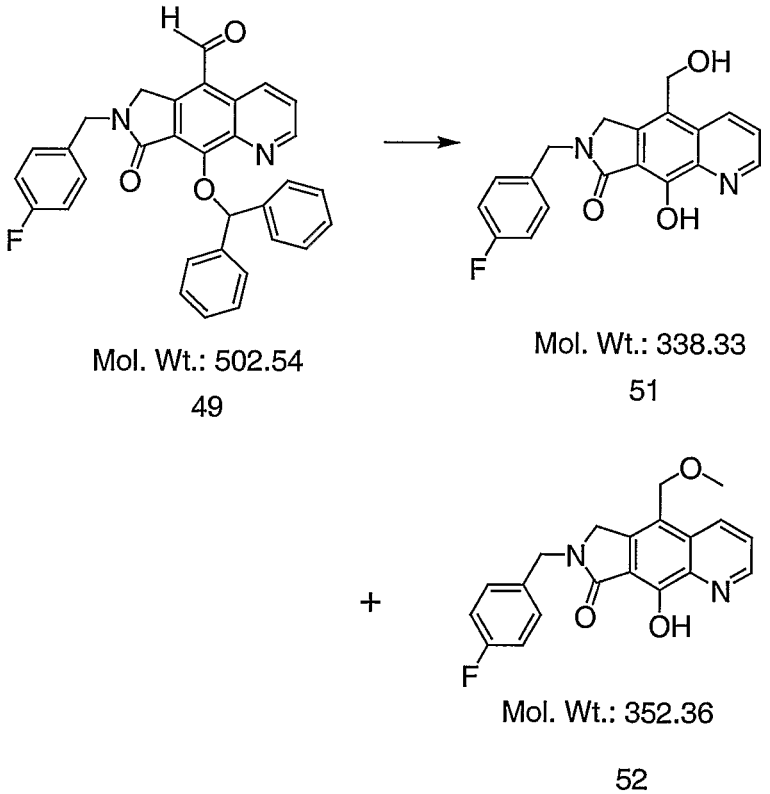


Mol. Wt.: 502.54
49

Mol. Wt.: 504.55
50

Example 50

The aldehyde **49** (23 g, 0.046 mmol) was dissolved in anhydrous THF (1 mL) and MeOH (0.1 mL) at room temperature. To this was added sodium borohydride (5.2 mg, 0.14 mmol) slowly. The mixture was stirred at room temperature for 30 min under nitrogen. TLC indicated the completion of the reaction. The mixture was diluted with water (5 mL). The insoluble material was collected by filtration and washed with hexane and air-dried to give product **50** (13.5 mg, 59%). ^{1}H NMR (CD_3OD): δ 9.3 (d, 1H), 9.1 (d, 1H), 8.1 (dd, 1H), 8.0 (s, 1H), 7.5 (d, 4H), 7.4 (dd, 2H), 7.3 (m, 6H), 7.1 (t, 2H), 5.0 (s, 2H), 4.9 (s, 2H), 4.7 (s, 2H). MS: 505 (M+1), 527(M+23).



Mol. Wt.: 502.54
49

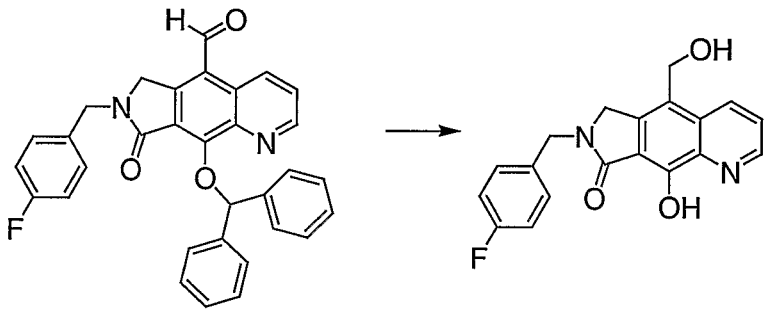
Mol. Wt.: 338.33
51

Mol. Wt.: 352.36
52

Example 51

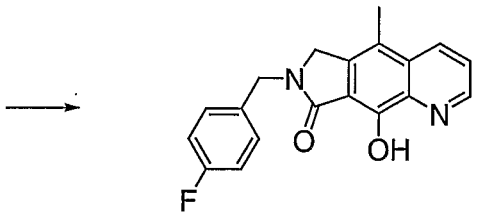
The aldehyde **49** (121 mg, 0.24 mmol) was dissolved in anhydrous THF (5 mL) and MeOH (0.5 mL) at room temperature. To this was added sodium borohydride (27 mg, 0.72 mmol) slowly. The mixture was stirred at room temperature for 30 min under nitrogen. It was diluted with 1N HCl (10 mL), and stirred for 10 min. The phases were separated and the aqueous phase was lyophilized to give a yellow solid, which was washed with water and ether. The solid was dried to give 50 mg of product **51.** ^{1}H NMR (DMSO-d_6): δ 9.0 (d, 1H), 8.8 (d, 1H), 7.5 (m, 1H), 7.4 (m, 2H), 7.2 (m, 2H), 5.0 (s, 1H, PhOH), 4.8 (s, 2H), 4.7 (s, 2H), 4.5 (s, 2H). MS: 339 (M+1).

The organic phase was concentrated. The residue was dissolved in DMF (2 mL) 1and purified by Prep-HPLC to give 10 mg of product **52**. HPLC condition: mobile phase A (1%AcOH in water), mobile phase B (1% AcOH in AcCN); gradient: 20% to 50%B in 30 min; flow rate: 20 mL/min; column: Phenomenex, Luna 5μ, C18 (2), 150mm x 21.2 mm. ^{1}H NMR (DMSO-d_6): δ 9.5 (d, 1H), 89.0 (d, 1H), 7.7 (m, 1H), 7.3 (m, 2H), 7.2 (m, 2H), 4.7 (s, 2H), 4.6 (s, 2H), 4.5 (s, 2H), 3.5 (s, 3H, under water peak). MS: 353 (M+1).



Mol. Wt.: 502.54
49

Mol. Wt.: 338.33
51



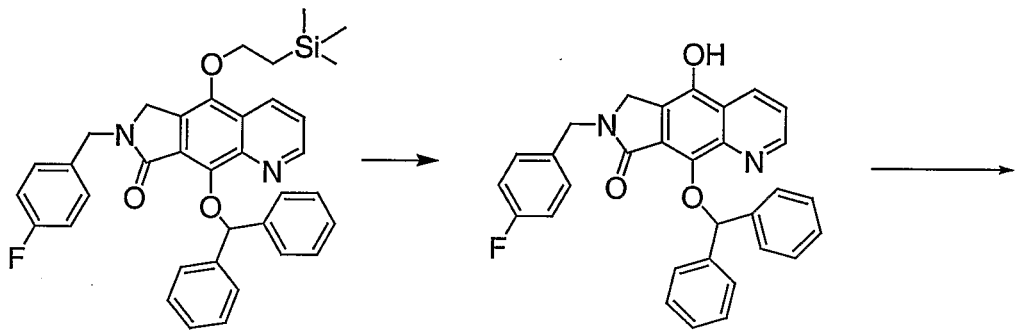
Mol. Wt.: 322.33
53

Example 52

The aldehyde **49** (118 mg, 0.23 mmol) was dissolved in anhydrous THF (5 mL) and MeOH (0.5 mL) at room temperature. To this was added sodium borohydride (27 mg, 0.72

mmol) slowly. The mixture was stirred at room temperature for 30 min under nitrogen. It was diluted with 1N HCl (10 mL), and stirred for 10 min. The phases were separated and the aqueous phase was lyophilized to give a yellow solid as product **51**.

The alcohol **51**(crude from reduction) was suspended in dichloromethane (10 mL) at room temperature under nitrogen. Triethylsilane (3 mL) was added followed by TFA (1 mL) slowly. The mixture became homogeneous and was stirred at room temperature overnight under nitrogen. The solvent was removed under reduced pressure. The crude product was dissolved in 2 mL of DMF then purified by prep-HPLC to gave a clean product of **53** (22.4 mg, 30%). HPLC condition: mobile phase A (1%TFA in water), mobile phase B (1% TFA in AcCN); gradient: 5% to 100%B in 20 min; flow rate: 20 mL/min; column: Phenomenex, Luna 5μ, C18 (2), 150mm x 21.2 mm. ^{1}H NMR (CD_3OD): δ 9.0 (d, 1H), 8.9 (d, 1H), 7.9 (dd, 1H), 7.4 (d, 4H), 7.1 (t, 2H), 4.8 (s, 2H), 4.9 (s, 2H), 4.5 (s, 2H), 2.5 (s, 3H). MS: 323 (M+1).

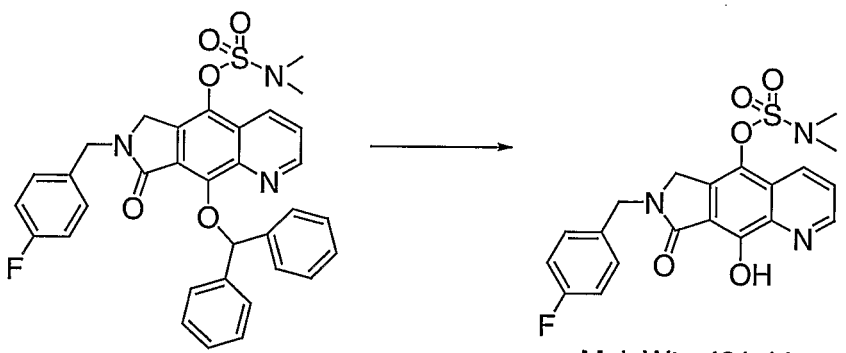


Mol. Wt.: 590.76

44

Mol. Wt.: 490.52

45



Mol. Wt.: 597.66

54

Mol. Wt.: 431.44

55

Example 53

To the compound **44** (350.0 mg, 0.592 mmol) in anhydrous THF (20 mL), was added tetrabutylammonium fluoride (1M in THF, 651 μl, 0.651 mmol) and triethylamine

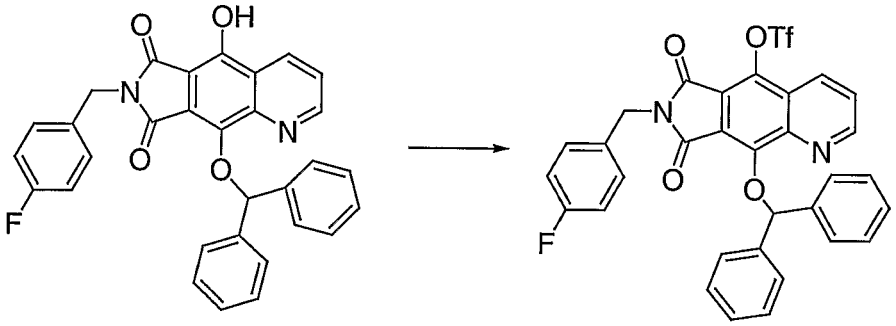
(330 µl, 2.37 mmol). The reaction mixture turned to red and was stirred at room temperature under nitrogen for 1 hour. The reaction forming **45** was monitored by TLC (EtOAc/Hexane = 3/7).

Example 54

Triethylamine (330 µL, 2.37 mmol) was added to the reaction mixture followed by a catalytic amount of DMAP, and N, N-dimethylsulfamoyl chloride (160 µL, 1.5 mmol). The mixture was stirred at room temperature under nitrogen for 16 hours. After completion of the reaction, it was diluted with dichloromethane (50 mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated. The residue was chromatographed on a silica gel column, eluting with EtOAc/Hexane to afford the product **54** (205.4 mg, 58% in 2 steps). ^1H NMR ($CDCl_3$): δ 9.0 (d, 1H), 8.4 (d, 1H), 8.0 (s, 1H), 7.7 (d, 4H), 7.5 (dd, 1H), 7.1-7.3 (m, 8H), 7.0 (t, 2H), 4.8 (s, 2H), 4.4 (s, 2H), 3.0 (s, 3H). MS: 598 (M+1).

Example 55

The compound **54** ((205.4 mg, 0.344 mmol) was dissolved in dichloromethane (6 mL) at room temperature under nitrogen. Triethylsilane (2 mL) was added followed by TFA (1 mL) slowly. The mixture became smoky and dark and was stirred at room temperature for 30 min. The solvent was removed under reduced pressure. The crude product was triturated in diethylether/hexane to afford a yellow solid **55**, 169 mg, 93%. ^1H NMR (CD_3OD): δ 9.0 (d, 1H), 8.6 (d, 1H), 7.8 (dd, 1H), 7.4 (m, 2H), 7.1 (m, 2H), 4.8 (s, 2H), 4.6 (s, 2H), 3.1 (s, 6H). MS: 432 (M+1).



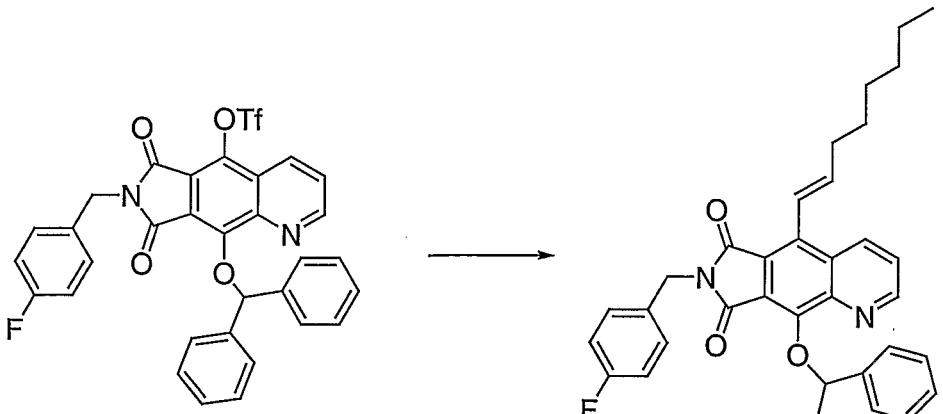
Mol. Wt.: 504.51 Mol. Wt.: 636.57

40 56

Example 56

The phenol **40** (1.0 g, 1.984 mmol) and DIEA (1.04 mL, 6.0 mmol) in dichloromethane (20 mL) was chilled to –78°C. To this was added trifluoromethanesulfonic anhydride (0.78 mL, 3.0 mmol) slowly under the nitrogen. The reaction was completed in 1 hour. It was quenched with 1.5 mL of methanol and stirred for 5 min more. Warmed to room temperature, it was washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and concentrated to afford the forming product **56** (1.2g, 95%).

The reaction was repeated, where monophenol **40** (0.1807 g, 0.358 mmol) was dissolved in 4 mL dry dichloromethane. To this was added diisopropylethylamine (0.182 mL, 1.074 mmol.) After cooling to –78°C, triflic anhydride was added (0.14 mL, 0.537 mmol) and was stirred at this temperature for twenty 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 (0.2518 g, 0.396 mmol, 100%) which was stored crude as a solution in 10 mL dry benzene. ^1H NMR ($CDCl_3$) δ 9.2 (dd, 1H), 8.46 (d, 1H), 8.068 (s, 1H), 7.75 (dd, 1H), 7.6 (d, 4H), 7.47 (dd, 1H), 7.27 (m, 7H), 7.19, dd, 2H), 4.87 (s, 2H.) MS: 637 (M+1)

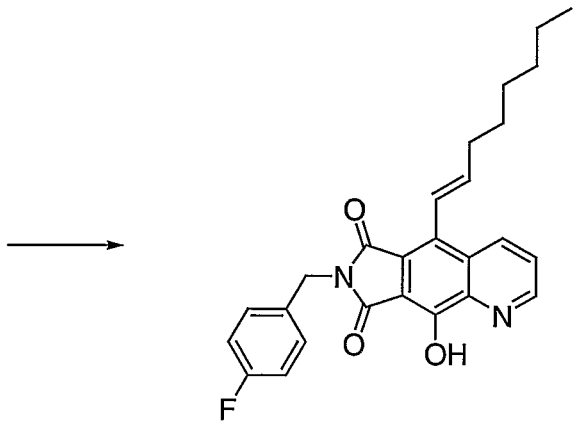


Mol. Wt.: 636.57

56

Mol. Wt.: 598.71

57



Mol. Wt.: 432.49

58

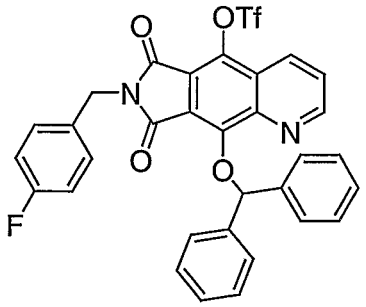
Example 57

To the triflate **56** (78.0 mg, 0.122 mmol) in toluene (2.8 mL)/ethanol (1.2 mL)/water (0.8 mL) was added potassium carbonate (42 mg, 0.306 mmol), 1-octeneboronic acid (29.0 mg, 0.184 mmol) and tetrakis (triphenylphosphine)-palladium (0) (21.0 mg, 0.018 mmol). The mixture in the flask was flushed with argon three times. It was heated to 120°C under argon for 3 hours. Cooling to room temperature, it was diluted with EtOAc and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed on a silica gel column, eluting with EtOAc/Hexane to afford the product **57** (11.4 mg, 15.6%).

Example 58

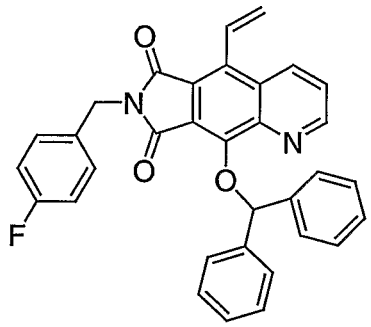
The compound **57** (6 mg, 0.01 mmol) was dissolved in dichloromethane (1 mL) at room temperature under nitrogen. Triethylsilane (200 μL) was added followed by TFA

(100 μL) slowly. The mixture became smoky and dark and was stirred at room temperature for 30 min. The solvent was removed under reduced pressure. The crude product was triturated in diethylether/hexane to afford a yellow solid TFA salt of **58**, 3 mg, 57%. ^{1}H NMR (CD_3OD): δ 9.0 (d, 1H), 8.8 (d, 1H), 7.8 (dd, 1H), 7.4 (dd, 2H), 7.1 (d, 1H), 7.0 (dd, 2H), 6.2 (m, 1H), 4.8 (s, 2H), 2.4 (m, 2H), 1.6 (m, 2H), 1.3-1.5 (m, 6H), 0.9 (t, 3H). MS: 433 (M+1).



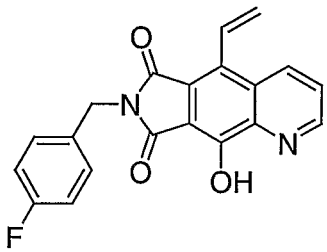
Mol. Wt.: 636.57

56



Mol. Wt.: 514.55

59



Mol. Wt.: 348.33

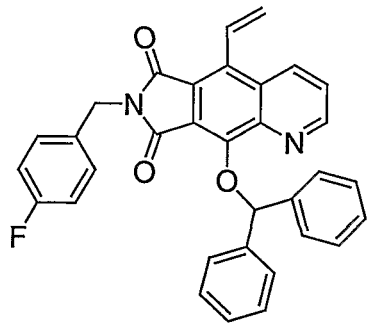
60

Example 59

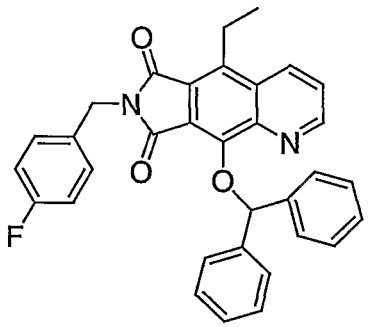
To the triflate **56** (100 mg, 0.157 mmol) in toluene (2.8 mL)/ethanol (1.2 mL)/water (0.8 mL) was added potassium carbonate (54 mg, 0.392 mmol), vinylboronic acid (17 mg, 0.235 mmol) and tetrakis (triphenylphosphine)-palladium (0) (27.0 mg, 0.023 mmol). The mixture in the flask was flushed with argon three times. It was heated to 120°C under argon for 3 hours. Cooling to room temperature, it was diluted with EtOAc and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed on a silica gel column, eluting with EtOAc/Hexane to afford the product **59** (32.3mg, 40%).

Example 60

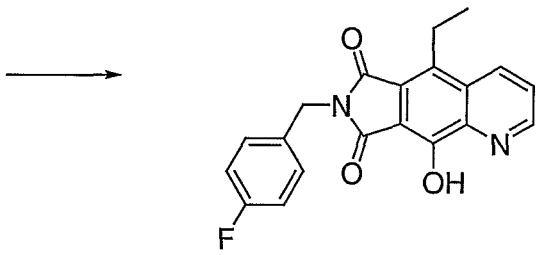
The compound **59** (11 mg, 0.01 mmol) was dissolved in dichloromethane (1 mL) at room temperature under nitrogen. Triethylsilane (200 μL) was added followed by TFA (100 μL) slowly. The mixture became smoky and dark and was stirred at room temperature for 30 min. The solvent was removed under reduced pressure. The crude product was triturated in diethylether/hexane to afford a yellow solid TFA salt of **60**, 2.3 mg, 31.4%. ^{1}H NMR ($CDCl_3$): δ 9.0 (d, 1H), 8.8 (d, 1H), 7.7 (dd, 1H), 7.5 (m, 2H), 7.0 (m, 2H), 6.0 (d, 1H), 5.6 (d, 1H), 5.3 (s, 1H, OH), 4.8 (s, 2H). MS: 349 (M+1).



Mol. Wt.: 514.55
59



Mol. Wt.: 516.56
61



Mol. Wt.: 350.34
62

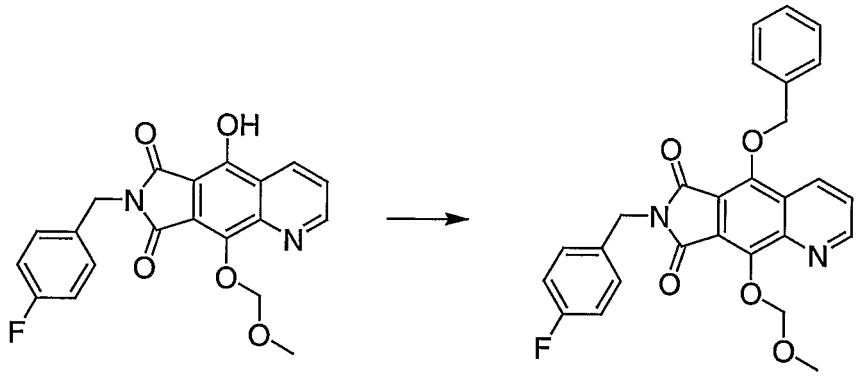
Example 61

The compound **59** (157 g, 0.11 mmol) was dissolved in anhydrous THF (5 mL) and MeOH (0.5 mL) at room temperature. To this was added sodium borohydride (13 mg, 0.33 mmol) slowly. The mixture was stirred at room temperature for 1 hour under nitrogen. It was diluted with EtOAc (50 mL), and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel prep-TLC, eluting with EtOAc/Hexane (3/7) to afford the product **61** (12.5mg, 22%).

Example 62

The compound **61** (11 mg, 0.01 mmol) was dissolved in dichloromethane (1 mL) at room temperature under nitrogen. Triethylsilane (200 μL) was added followed by TFA

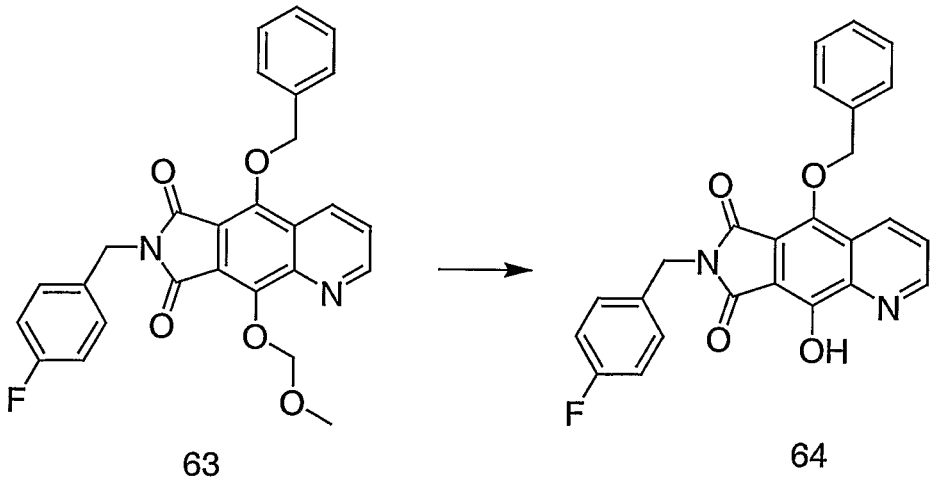
(100 μL) slowly. The mixture became smoky and dark and was stirred at room temperature for 30 min. The solvent was removed under reduced pressure. The crude product was triturated in diethylether/hexane to afford a yellow solid TFA salt of **62**, 8 mg, 75%. ^{1}H NMR ($CDCl_3$): δ 9.0 (d, 1H), 8.5 (d, 1H), 7.7 (dd, 1H), 7.5 (dd, 2H), 7.0 (m, 2H), 4.8 (s, 2H), 3.5 (q, 2H), 1.3 (t, 3H). MS: 451 (M+1).



6 63

Example 63

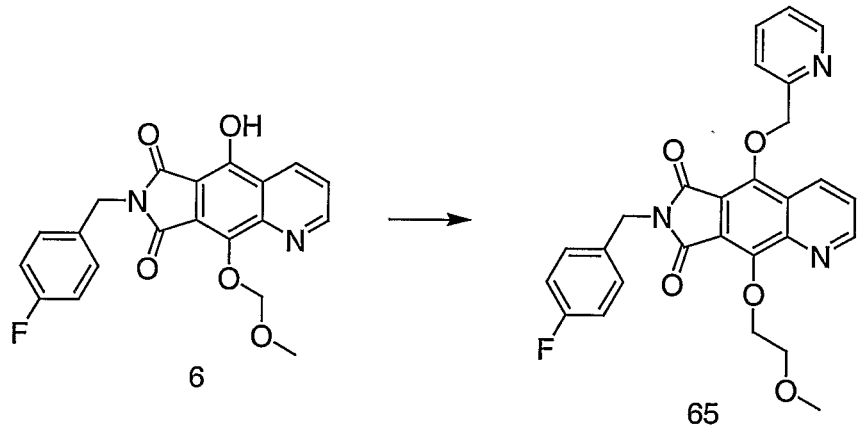
Mono-phenol **6** (0.02 g, 0.052 mmol) was added to 1.5 mL dry dimethylformamide. To this was added benzyl bromide (0.0124 ml, 0.104 mmol) and K_2CO_3 (0.0215 g, 0.156 mmol) and stirred at 50°C. After 1.5 hrs reaction completed by TLC. Diluted with 100 mL ethylacetate, washed with saturated NH_4Cl solution and brine. The organic phase was dried ($MgSO_4$), concentrated, and chromatographed (25% ethylacetate/hexanes) to give product **63** (0.013 g, 0.0275 mmol, 53%.). ^{1}H NMR ($CDCl_3$) δ 9.03 (dd, 1H), 8.6 (d, 1H), 7.54 (m, 6H), 7.4 (m, 2H), 7.05 (dd, 2H), 5.8 (s, 2H), 5.6 (s, 2H), 4.9 (s, 2H), 3.7 (s, 3H). MS: 473 (M+1)



63 64

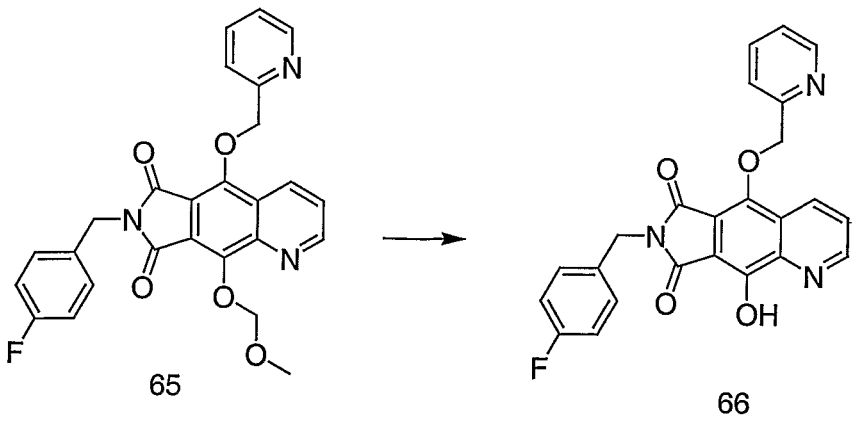
Example 64

Benzyl ether (0.013 g, 0.0275 mmol) was dissolved in 1 mL dry dichloromethane. To this was added trifluoroacetic acid (0.0213 mL, 0.275 mmol) and stirred 2.5 hrs. Concentrated off volatiles, azeotroped with toluene (2x), concentrated to give crude product. Triturated with 1:1 diethylether/hexanes to give product **64** (0.0078 g, 0.0182 mmol, 66%). ^{1}H NMR ($CDCl_3$) δ 8.96 (dd, 1H), 8.6 (d, 1H), 7.6 (dd, 1H), 7.5 (m, 5H), 7.37 (m, 2H), 7.05 (dd, 2H), 5.6 (s, 2H), 4.88 (s, 2H). MS: 429 (M+1), 427 (M-1)



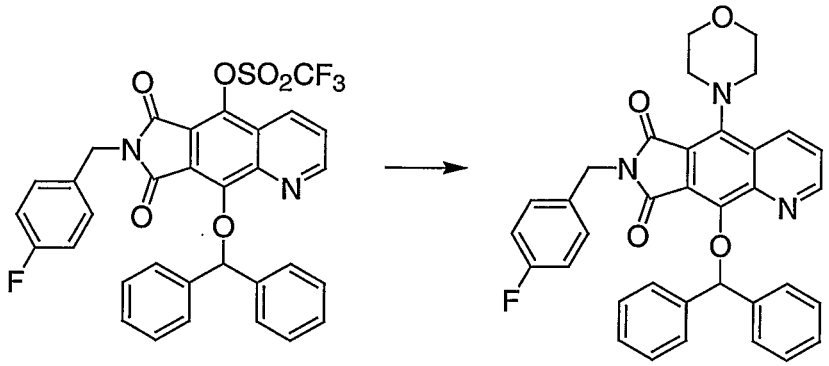
Example 65

Monophenol **6** (0.04 g, 0.1047 mmol) was dissolved in 2 mL of dry dimethylformamide. To this was added 2-bromomethyl pyridine HBr salt (0.0529 g, 0.209 mmol) and K_2CO_3 (0.144 g, 1.047 mmol.) Stirred at 50°C for twelve hours. Diluted with ethylacetate, washed with brine (saturated NaCl) and 1M HCl, dried ($MgSO_4$,), and concentrated. The crude product was chromatographed (20 to 50 % ethylacetate/hexanes) to give product **65**: (0.0032 g, 0.0067 mmol, 6.5%.) ^{1}H NMR ($CDCl_3$) δ 9.03 (d, 1H), 8.72 (d, 1H), 8.6 (d, 1H), 7.8 (dd, 1H), 7.7 (dd, 1H), 7.57 (dd, 1H), 7.48 (dd, 2H), 7.0 (dd, 2H), 5.8 (s, 2H), 5.65 (s, 2H), 4.86 (s, 2H), 3.72 (s, 3H.) MS: 488 (M+1)



Example 66

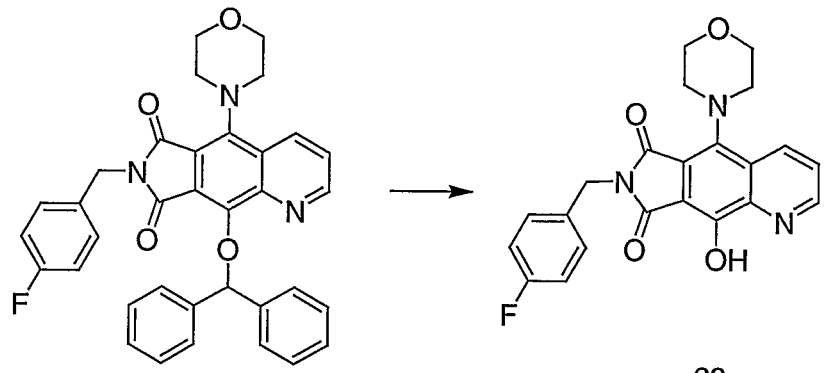
Pyridyl ether **65** (0.0032 g, 0.0067 mmol) was dissolved in 1 mL dry dichloromethane. To this was added trifluoroacetic acid (0.0052 mL, 0.0676 mmol) and stirred 12 hrs. Concentrated off volatiles, azeotroped with toluene (2x), concentrated to give crude product. Triturated with 1:1 diethylether/hexanes to give product **66** (0.0012 g, 0.0028 mmol, 42%.) ^{1}H NMR ($CDCl_3$) δ 8.96 (d, 1H), 8.73 (d, 1H), 8.6 (d, 1H), 7.8 (dd, 1H), 7.7 (d, 1H), 7.63 (dd, 1H), 7.5 (dd, 2H), 7.3 (m, 1H), 7.04 (dd, 2H), 5.67 (s, 2H), 4.87 (s, 2H.) MS: 430 (M+1), 428 (M-1)



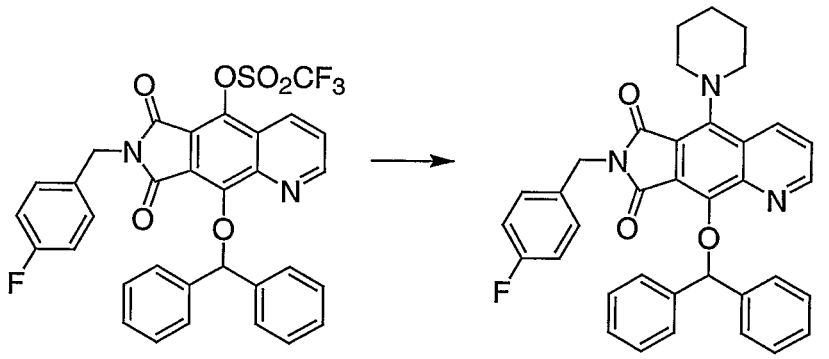
46 67

Example 67

Triflate **46** in benzene was concentrated to give (0.0225 g, 0.0353 mmol) and dissolved in 3 mL of dichloroethane. To this was added triethylamine (0.0073 mL, 0.0529 mmol) and morpholine (0.0092 ml, 0.118 mmol) and reaction stirred at 65°C. After 15 hrs, reaction still incomplete by TLC, added another 0.118 mL of morpholine. After 21 hrs reaction time concentrated off volatiles and chromatographed (10 to 25% ethylacetate/hexanes) to give product **67** (0.0061 g, 0.01, 30%). ^{1}H NMR ($CDCl_3$) δ 9.09 (dd, 1H), 8.89 (d, 1H), 8.03 (s, 1H), 7.65 (m, 5H), 7.49 (dd, 1H), 7.27 (m, 7H), 7.06 (dd, 2H), 4.85 (s, 2H), 3.92 (dd, 4H), 3.92 (br m, 4H). MS: 574 (M+1)



67 68



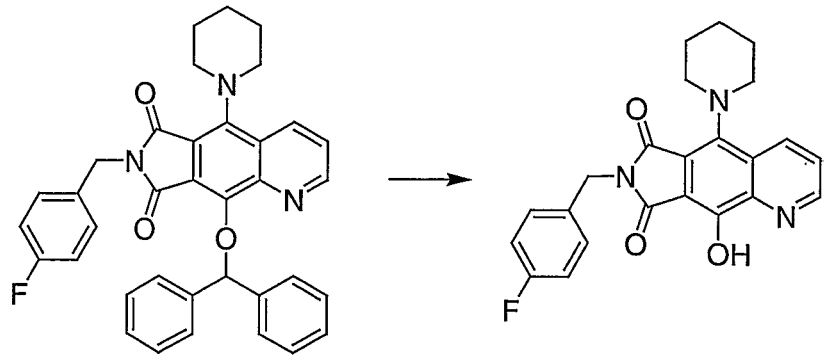
46 69

Example 68

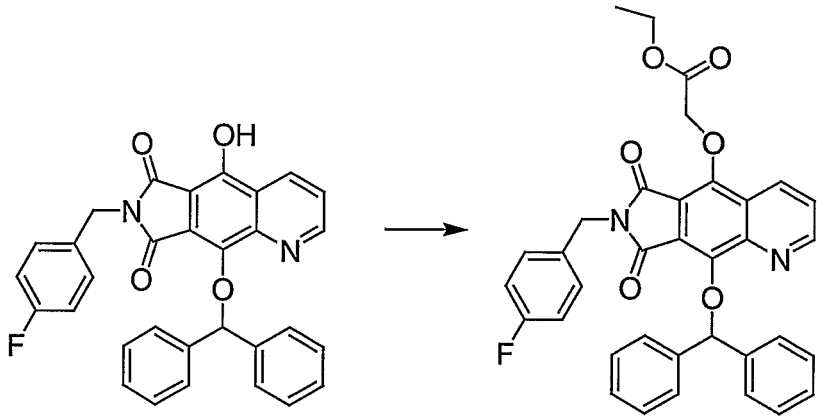
Tertiary amine **67** was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene, solidified with hexane and concentrated to give crude. Triturated with 1:1 diethylether/hexanes to give product **68** (0.002 g, 0.0049 mmol, 49%). ^{1}H NMR ($CDCl_3$) δ 8.98 (m, 2H), 7.7 (dd, 1H), 7.53 (dd, 2H), 7.05 (dd, 2H), 4.86 (s, 2H), 3.96 (dd, 4H), 3.35 (br m, 4H). MS: 408 (M+1), 406 (M-1)

Example 69

Triflate **46** in benzene was concentrated to give (0.045 g, 0.0706 mmol) and dissolved in 3 mL of dichloroethane. To this was added triethylamine (0.0147 mL, 0.1059 mmol) and morpholine (0.0209 ml, 0.2118 mmol) and reaction stirred at 70°C. After 15 hrs of stirring, concentrated off volatiles and chromatographed (8 to 10% ethylacetate/hexanes) to give product **69** (0.0085 g, 0.01488, 44%.) ^{1}H NMR ($CDCl_3$) δ 9.068 (dd, 1H), 8.79 (d, 1H), 7.8 (s, 1H), 7.6 (d, 4H), 7.57 (dd, 1H), 7.46 (dd, 2H), 7.27 (m, 6H), 7.06 (dd, 2H), 4.84 (s, 2H), 3.24 (br s, 4H), 1.73 (br s, 6H.) MS: 572 (M+1)



69 70



45 71

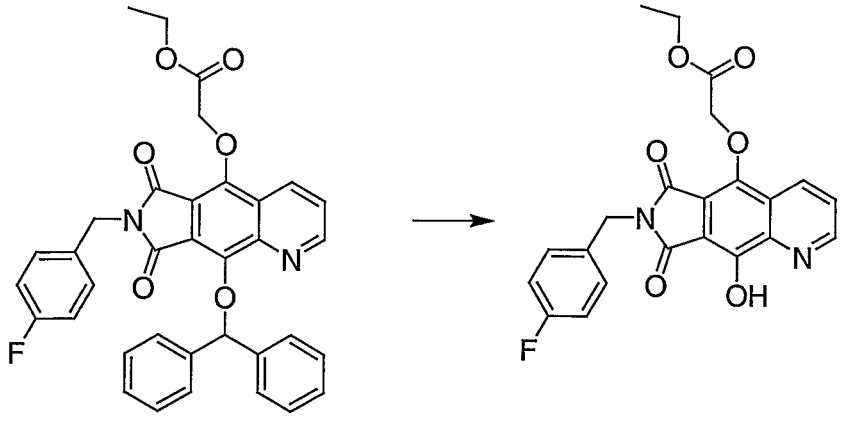
Example 70

Tertiary amine **69** was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene, solidified with hexane and concentrated to give crude. Triturated with 1:1 diethylether/hexanes to give product **70** (0.0043 g, 0.0106 mmol, 72%.) ^{1}H NMR ($CDCl_3$) δ 8.96 (dd, 1H), 8.85 (d, 1H), 7.66 (dd, 1H), 7.5 (m, 2H), 7.04 (dd, 2H), 4.85 (s, 2H), 3.29 (br s, 4H), 1.77 (br s, 6H.) MS: 406 (M+1), 404 (M-1)

Example 71

Monophenol **45** (0.03 g, 0.0595 mmol) was dissolved in 2 mL dry dimethylformamide. To this was added ethyl bromoacetate (0.0131 mL, 0.119 mmol) and freshly ground K_2CO_3 (0.025 g, 0.178 mmol.) Stirred at 50°C, for two hours until starting material consumed. Concentrated off some solvent, diluted with ethylacetate, washed with saturated NH_4Cl solution, concentrated organics to give crude product. Chromatographed (10 to 25% ethylacetate/hexanes) to give product **71** (0.0321 g, 0.054 mmol, 91%.) ^{1}H

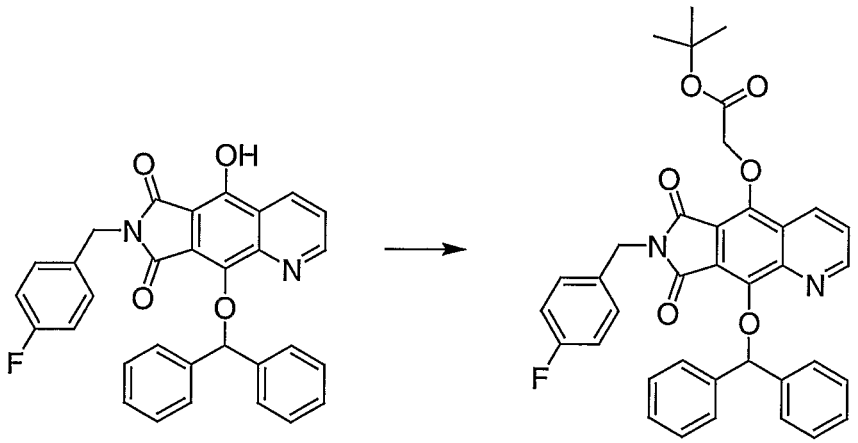
NMR ($CDCl_3$) δ 9.1 (dd, 1H), 8.96 (d, 1H), 7.9 (s,1H), 7.62 (d, 4H), 7.445 (m, 2H), 7.27 (m, 7 H), 7.059 (dd, 2H), 5.21 (s, 2H), 4.83 (s, 2H), 4.22 (q, 2H), 1.23 (t, 3H). MS: 591 (M+1).



71 72

Example 72

Ethyl ester **71** was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated with 1:1 diethylether/hexanes to give product **72** (0.0209 g, 0.049 mmol, 91%.) ^{1}H NMR ($CDCl_3$) δ 9.0 (m, 2H), 7.7 (dd, 1H), 7.5 (dd, 2H), 7.04 (dd, 2H), 5.33 (s, 2H), 4.84 (s, 2H), 4.24 (q, 2H), 1.28 (t, 3H.) MS: 425 (M+1), 423 (M-1)

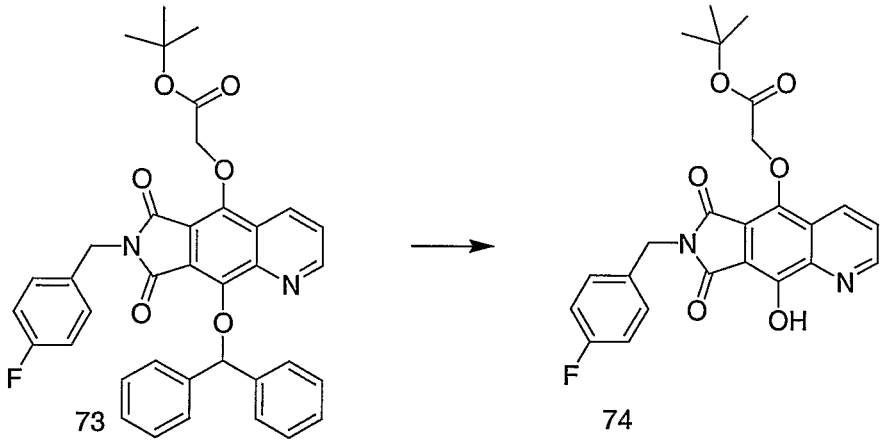


45 73

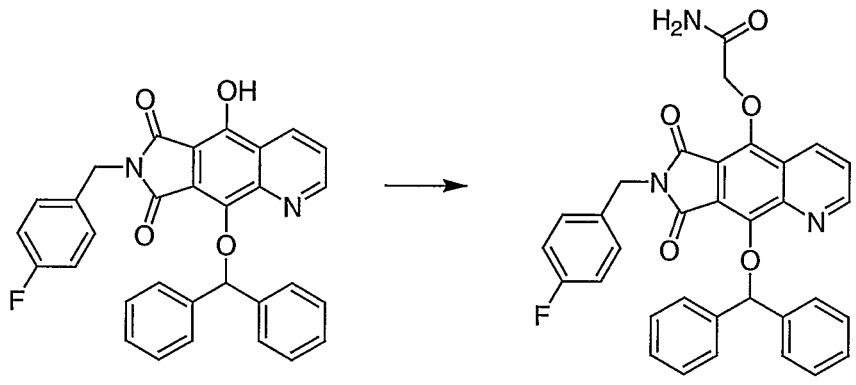
Example 73

Monophenol **45** (0.03 g, 0.0595 mmol) was dissolved in 2 mL dry dimethylformamide. To this was added t-butyl bromoacetate (0.0175 mL, 0.119 mmol) and

freshly ground K_2CO_3 (0.025 g, 0.178 mmol.) Stirred at 50°C, for one hour until starting material consumed. Concentrated off some solvent, diluted with ethylacetate, washed with saturated NH_4Cl solution, concentrated organics to give crude product. Chromatographed (10 to 15% ethylacetate/hexanes) to give product **73** (0.0309 g, 0.05 mmol, 84%.) ^{1}H NMR ($CDCl_3$) δ 9.09 (dd, 1H), 8.97 (d, 1H), 7.92 (s,1H), 7.62 (d, 4H), 7.44 (m, 2H), 7.27 (m,7 H), 7.05 (dd, 2H), 5.12 (s, 2H), 4.83 (s, 2H), 1.38 (s, 9H.) MS: 619 (M+1)



73 74



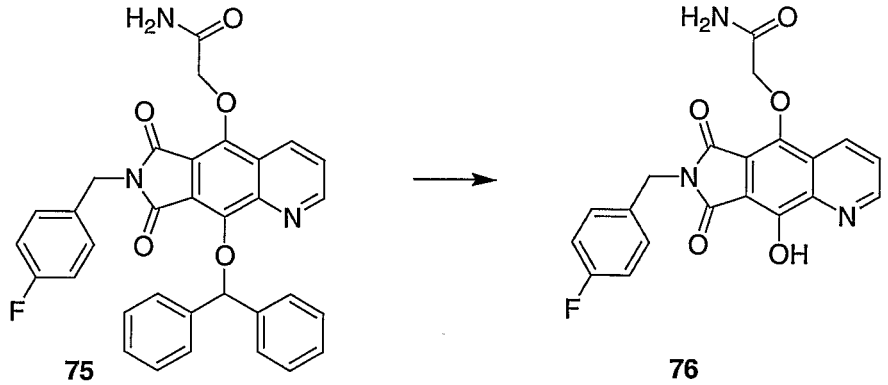
45 75

Example 74

Tertiary Butyl ester **73** was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated with 1:1 diethylether/hexanes to give product **74** (0.0189 g, 0.042 mmol, 84%.) ^{1}H NMR ($CDCl_3$) δ 9.05 (m, 2H), 7.72 (dd, 1H), 7.5 (dd, 2H), 7.04 (dd, 2H), 5.22 (s, 2H), 4.84 (s, 2H), 1.44 (s, 9H.) MS: 453 (M+1), 451 (M-1)

Example 75

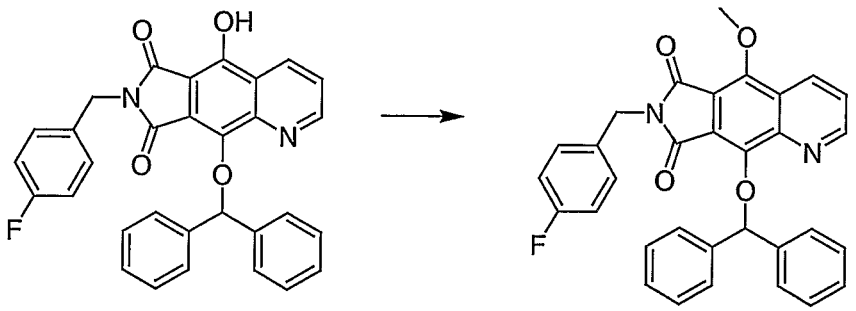
Monophenol **45** (0.04 g, 0.079 mmol) was dissolved in 1 mL dry dimethylformamide. To this was added 2-bromoacetamide (0.022 g, 0.158 mmol) and freshly ground K_2CO_3 (0.0345 g, 0.25 mmol.) Stirred at 60 °C, for three hours until starting material nearly consumed. Concentrated off some solvent, diluted with ethylacetate, washed with saturated $NaHCO_3$ solution, concentrated organics to give crude product. Chromatographed (10 to 50% ethylacetate/hexanes) to give product **75** (0.0204 g, 0.0355 mmol, 46%.) ^{1}H NMR ($CDCl_3$) δ 9.15 (dd, 1H), 8.53 (d, 1H), 7.96 (s, 1H), 7.6 (m, 4H), 7.45 (dd, 2H), 7.27 (m, 7H), 7.06 (dd, 2H), 5.73 (br s, 1H), 4.84 (s, 2H), 4.77 (s, 2H.) MS: 562 (M+1)



75 **76**

Example 76

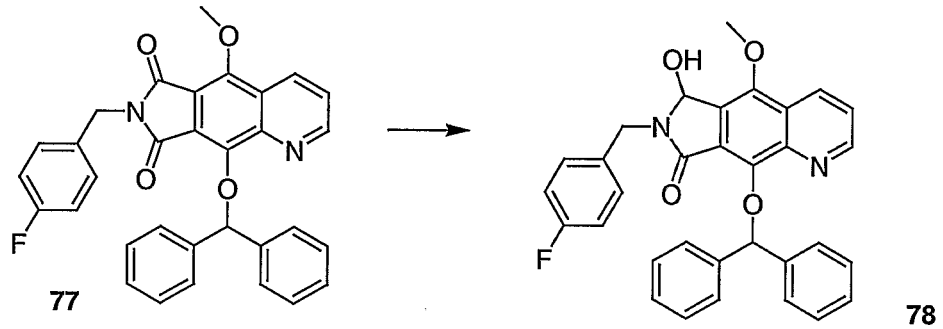
Amide **75** was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated with 1:1 diethylether/hexanes to give product **76** (0.0095 g, 0.024 mmol, 67%.) ^{1}H NMR (CD_3SOCD_3) δ 9.08 (dd, 1H), 8.93 (d, 1H), 7.87 (dd, 1H), 7.73 (br s, 1H), 7.41 (dd, 2H), 7.19 (dd, 2H), 4.86 (s, 2H), 4.75 (s, 2H.) MS: 396 (M+1), 394 (M-1)



45 **77**

Example 77

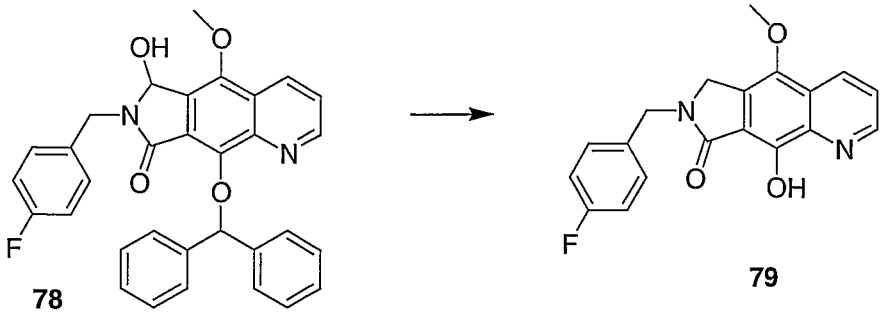
Monophenol **45** (2.9 g, 5.75 mmol) was dissolved in 20 mL dry dimethylformamide. To this was added methyl iodide (3.58 mL, 57.5 mmol) and freshly ground K_2CO_3 (3.17 g, 23 mmol.) Stirred at 40° C for one hour, until starting material consumed. Diluted with dichloromethane, washed with saturated NH_4Cl solution, 2.5 % LiCl solution, concentrated organics to give crude product. Chromatographed (15 to 55% ethylacetate/hexanes to give product **77** (2.54 g, 4.9 mmol, 85%.) ^{1}H NMR ($CDCl_3$) δ 9.1 (dd, 1H), 8.64 (dd, 1H), 7.91 (s, 1H), 7.62 (m, 5H), 7.46 (dd, 2H), 7.27 (m, 7H), 7.05 (dd, 2H), 4.84 (s, 2H), 4.28 (s, 3H.) MS: 519 (M+1)



77 78

Example 78

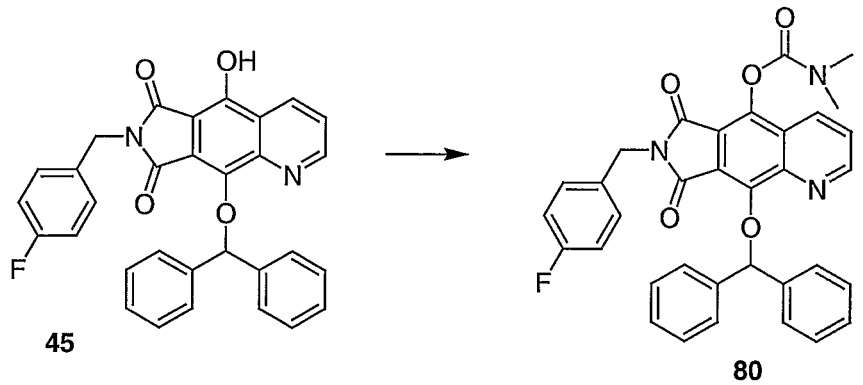
Methyl ether **77** was dissolved in 115 mL of dry tetrahydrofuran and 25 mL of dry methanol. To this was added three equivalents of a 0.5 M solution of NaBH4 (29.4 mL, 14.7 mmol) in 2-methoxyethyl ether. After 15 hrs at room temperature, concentrated off some solvent, diluted with dichloromethane, washed with 1M HCl solution with NaCl added, concentrated, chromatographed (15-66% ethylacetate/hexanes) to give oil. Triturated with hexane to give product **78** (1.3 g, 2.5 mmol, 68%.) ^{1}H NMR (CD_3SOCD_3) δ 9.08 (dd, 1H), 8.5 (d, 1H), 7.89 (s, 1H), 7.75 (d, 2H), 7.69 (dd, 1H), 7.63 (d, 2H), 7.42 (dd, 2H), 7.27(m, 7H), 6.9(d, 1H), 5.92 (dd, 1H), 4.97 (d J=15 Hz, 1H), 4.45 (d J=15Hz, 1H), 4.04 (s, 3H.) MS: 521 (M+1)



78 79

Example 79

Aminal **78** was dissolved in 15 mL of dichloromethane. To this was added 2 mL of triethylsilane and 1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated with 1:1 diethylether/hexanes to give reduced product. Dissolved in 30 mL of dichloromethane and cooled to 0 °C. To this was added 4 mL of triethylsilane and trimethylsilyltriflate (1.36 mL, 7.5 mmol.) Stirred vigorously for three minutes, then concentrated off volatiles, diluted with dichloromethane, washed quickly with saturated $NaHCO_3$ solution, concentrated organics to give crude product **79**. Triturated with 1:1 diethylether/hexanes to give product (0.806 g, 2.38 mmol, 95% for two steps.) ^1H NMR ($CDCl_3$) δ 8.96 (dd, 1H), 8.50 (d, 1H), 7.56 (dd, 1H), 7.37 (dd, 2H), 7.09 (dd, 2H), 4.78 (s, 2H), 4.51 (s, 2H), 3.98 (s, 3H). MS: 339 (M+1), 337 (M-1).

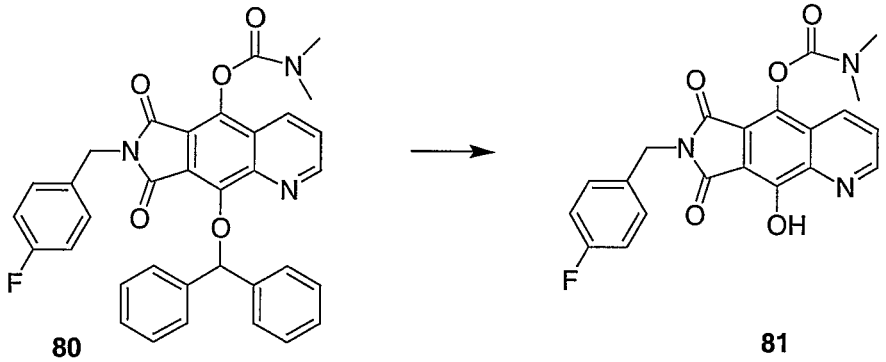


45 80

Example 80

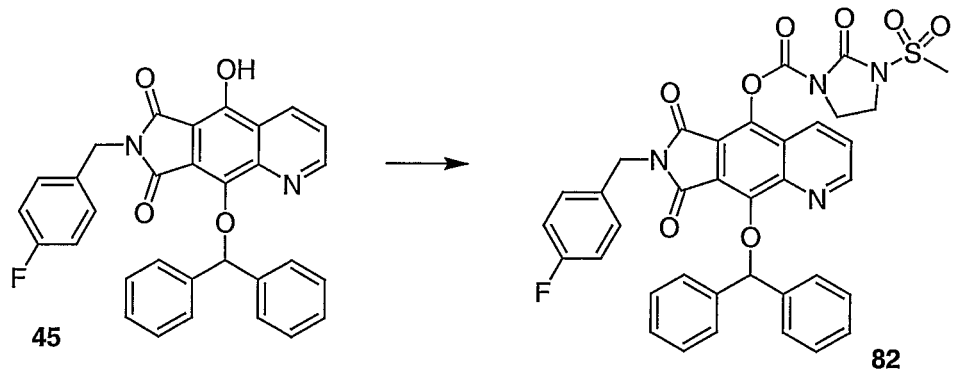
Monophenol **45** (0.02 g, 0.0396 mmol) was dissolved in 1 mL dry dichloromethane. To this was added at 0 °C triethylamine (0.0165 mL, 0.1188 mmol) and dimethylcarbamoyl chloride (0.0054 mL, 0.0594 mmol). Catalytic amount of DMAP was also added. Stirred at room temperature overnight. Dilute with dichloromethane, washed with saturated $NaHCO_3$

solution and saturated NH_4Cl solution, concentrated to give crude. Triturated with 1:1 diethylether/hexanes and chromatographed (10% methanol/ 45 % ethylacetate / 45% hexanes) to give product **80** (0.012 g, 0.0198 mmol, 50%.) ^1H NMR ($CDCl_3$) δ 9.12 (s, 1H), 8.4 (d, 1H), 7.97 (s, 1H), 7.62 (d, 4H), 7.43 (dd, 2H), 7.27 (m, 7H), 7.05 (dd, 2H), 4.81 (s, 2H), 3.26 (s, 3H), 3.09 (s, 3H.) MS: 576 (M+1)



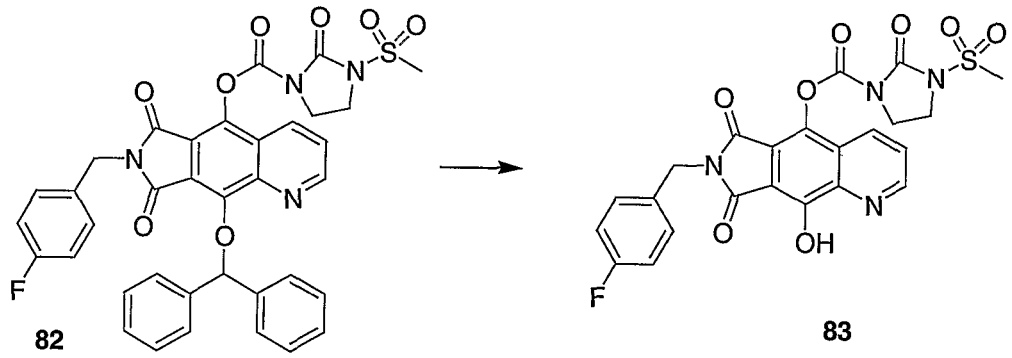
Example 81

Carbamate **80** (0.012 g, 0.0198 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated with 1:1 diethylether/hexanes to give product **81** (0.0054g, 0.013mmol, 67%.) ^1H NMR ($CDCl_3$) δ 8.98 (s, 1H), 8.49 (d, 1H), 7.7 (dd, 1H), 7.46 (dd, 2H), 7.03 (dd, 2H), 4.83 (s, 2H), 3.31 (s, 3H), 3.12 (s, 3H). MS: 410 (M+1), 408 (M-1).



Example 82

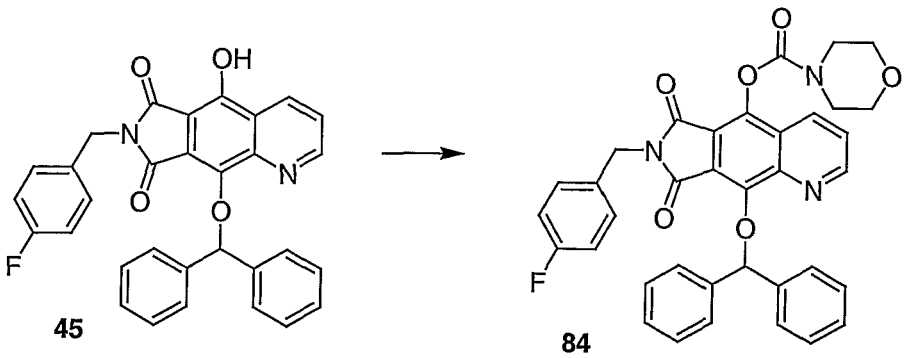
Monophenol **45** (0.035 g, 0.0694 mmol) was dissolved in 1 mL dry dichloroethane. To this was added triethylamine (0.038 mL, 0.277 mmol) and 3-chlorocarbonyl-1-methanesulfonyl-2-imidazolidinone (0.0314 g, 0.1388 mmol Stirred at room temperature for five minutes. Dilute with dichloromethane, washed with saturated $NaHCO_3$ solution and saturated NH_4Cl solution, dried ($MgSO_4$), concentrated to give crude. Chromatographed (10% methanol/ 45 % ethylacetate / 45% hexanes) to give product **82** (0.036 g, 0.0518 mmol, 75%.) ^1H NMR ($CDCl_3$) 9.16 (dd, 1H), 8.49 (dd, 1H), 8.00 (s, 1H), 7.66 (dd, 1H), 7.61 (d, 4H), 7.40 (dd, 2H), 7.27 (m, 6H), 7.05 (dd, 2H), 4.81 (s, 2H), 4.2 (dd, 2H), 4.08 (dd, 2H), 3.92 (s, 3H). MS: 695 (M+1).



82 **83**

Example 83

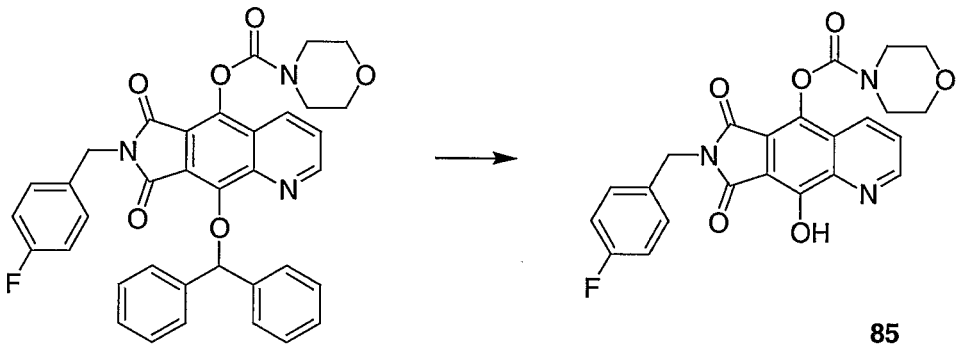
Carbamate **82** (0.036 g, 0.0518 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated with 1:1 diethylether/hexanes to give product **83** (0.025 g, 0.047 mmol, 91%.) ^1H NMR ($CDCl_3$) δ 9.04 (d, 1H), 8.58 (d, 1H), 7.75 (dd, 1H), 7.43 (dd, 2H), 7.04 (dd, 2H), 4.82 (s, 2H), 4.22 (dd, 2H), 4.10 (dd, 2H). MS: 529 (M+1), 527 (M-1).



45 **84**

Example 84

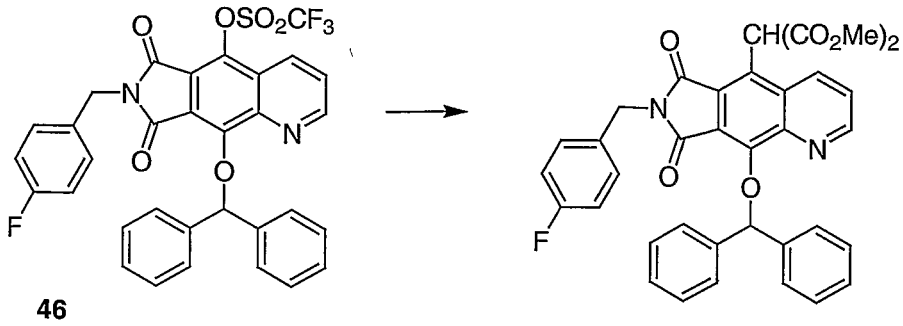
Monophenol **45** (0.045 g, 0.089 mmol) was dissolved in 1 mL dry dichloroethane. To this was added triethylamine (0.049 mL, 0.356 mmol) and 4-morpholine carbonyl chloride (0.0207 mL, 0.178 mmol.) Stirred at room temperature for 1.5 hours. Dilute with dichloromethane, washed with saturated $NaHCO_3$, concentrated to give crude. Chromatographed (15% to 60% ethylacetate/hexanes) to give product **84** (0.039 g, 0.063 mmol, 71%.) ^1H NMR ($CDCl_3$) 9.13 (dd, 1H), 8.40 (d, 1H), 7.98 (s, 1H), 7.62 (dd, 4H), 7.4 (dd, 2H), 7.27 (m, 7H), 7.05 (dd, 2H), 4.81 (s, 2H), 3.84 (br s, 6H), 3.62 (br s, 2H.) MS: 618 (M+1)



84 **85**

Example 85

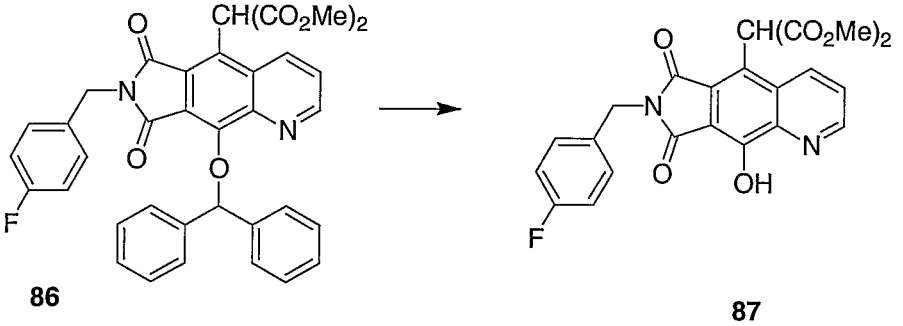
Carbamate **84** (0.039 g, 0.063 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated with 1:1 diethylether/hexanes to give product **85** (0.014 g, 0.032 mmol, 51%.) ^1H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.48 (d, 1H), 7.72 (dd, 1H), 7.49 (dd, 2H), 7.04 (dd, 2H), 4.83 (s, 2H), 3.88 (br s, 6H), 3.66 (br s, 2H.) MS: 452 (M+1), 450 (M-1)



46 86

Example 86

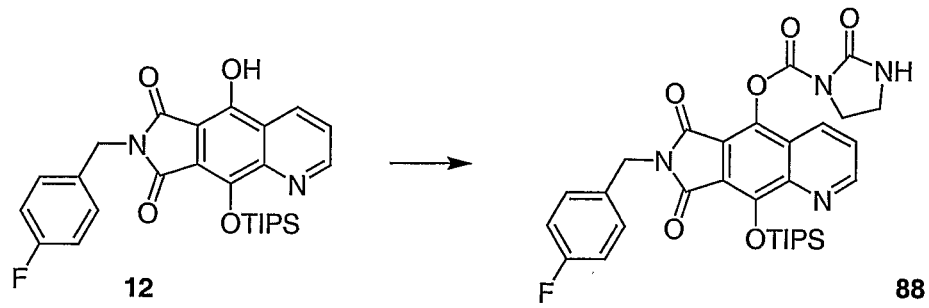
Triflate **46** in benzene concentrated to give (0.048 g, 0.075 mmol) and dissolved in 1 mL dry tetrahydrofuran. To this was added freshly ground K_2CO_3 (0.069 , 0.5 mmol) and dimethylmalonate (0.017 mL, 0.15 mmol) and stirred at 50° C. After 15 hours, starting material consumed, concentrated to give oil. Chromatographed (5% to 30% ethylacetate/hexanes) to give product **86** (0.012 g, 0.0195 mmol, 26%.) ^{1}H NMR ($CDCl_3$) δ 9.09 (d, 1H), 8.51 (d, 1H), 8.12 (s, 1H), 7.65 (d, 4H), 7.57 (dd, 1H), 7.48 (dd, 2H), 7.27 (m, 6H), 7.07 (dd, 2H), 4.85 (s, 2H), 3.72 (6H.) MS: 619 (M+1)



86 87

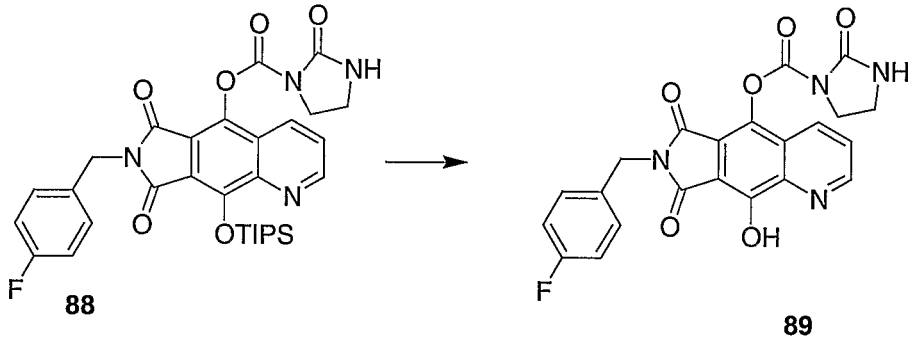
Example 87

Di-ester **86** (0.008 g, 0.0129 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **87** (0.0022 g, 0.0049 mmol, 38%.) ^{1}H NMR ($CDCl_3$) δ 8.95 (d, 1H), 8.60 (d, 1H), 7.70 (dd, 1H), 7.55 (dd, 2H), 7.05 (dd, 2H), 4.87 (s, 2H), 3.76 (s, 6H.) MS: 453 (M+1), 451 (M-1)



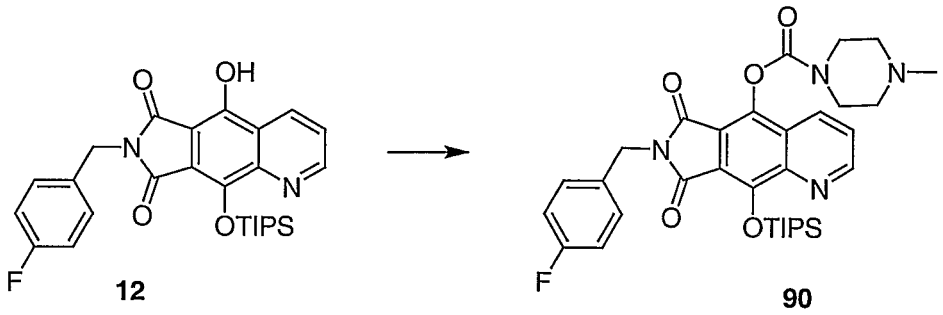
Example 88

Mono-phenol **12** (0.03 g, 0.06 mmol) was dissolved in 1 mL of dichloroethane. To this was added triethylamine (0.033 mL, 0.24 mmol) and 2-oxo-1-imidazolidinecarbonyl chloride (0.0178 g, 0.12 mmol.) Catalytic amount of DMAP added, and stirred at room temperature for three hours. Diluted with dichloromethane, washed with saturated NH_4Cl solution, concentrated to give crude. Chromatographed (10% ethylacetate/hexane to 10% methanol/45% ethylacetate/45% hexanes) to give product **88** (0.0247 g, 0.0395 mmol, 68%.) ^1H NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.53 (d, 1H), 7.63 (dd, 1H), 7.43 (dd, 2H), 7.03 (dd, 2H), 4.81 (s, 2H), 4.25 (dd, 2H), 3.69 (dd, 2H), 1.55 (m, 3H), 1.14 (d, 18H.) MS: 607 (M+1)



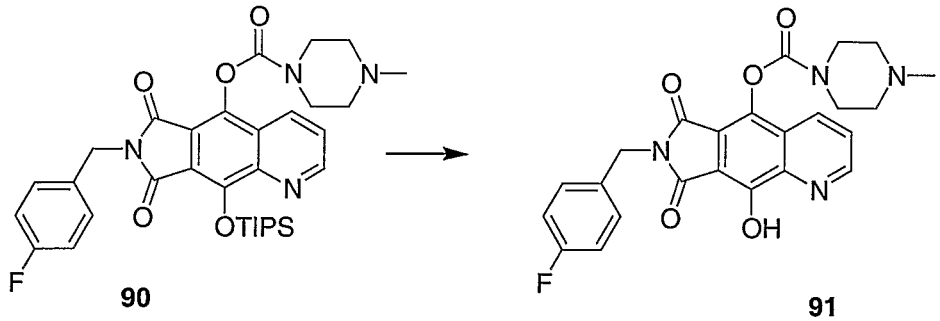
Example 89

Urea **88** (0.024 g, 0.0395 mmol) was dissolved in 1 mL of dry dichloromethane. To this was added ten equivalents (0.03 mL, 0.395 mmol) of trifluoroacetic acid. Stirred at room temperature, for fifteen hours. Concentrated off volatiles, azeotroped with toluene (2x), concentrated to give crude. Crude product triturated with 1:1 diethylether/hexanes to give product **89** (0.0119 g, 0.026 mmol, 67%.) ^1H NMR ($CDCl_3$) δ 9.00 (d, 1H), 8.58 (d, 1H), 7.73 (dd, 1H), 7.47 (dd, 2H), 7.03 (dd, 2H), 4.83 (s, 2H), 4.28 (dd, 2H), 3.70 (dd, 2H.) MS: 451 (M+1), 449 (M-1)



Example 90

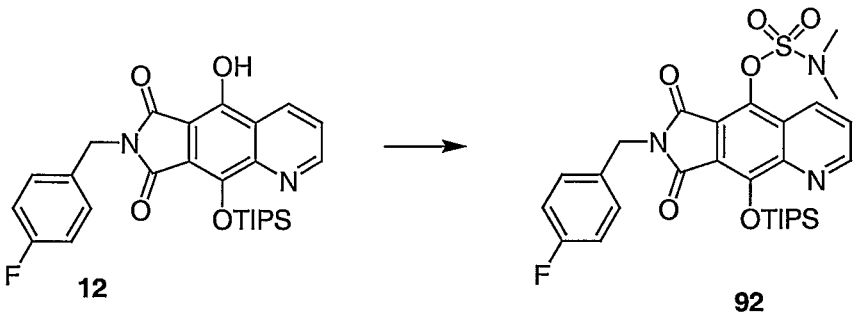
Mono-phenol **12** (0.04 g, 0.08 mmol) was dissolved in 1.5 mL dry tetrahydrofuran. To this was added triethylamine (0.0445 mL, 0.32 mmol) and bispentafluorophenyl carbonate (0.063 g, 0.16 mmol) and catalytic dimethylaminopyridine. Stirred at room temperature. After three hours, added methyl piperazine (0.04 mL, 0.36 mmol.) After two hours TLC indicated product formed however TIPSCl was removed. Diluted with dichloromethane, washed with saturated NH_4Cl solution, concentrated organics to give crude. Dissolved in 1.5 mL dichloroethane, added triethylamine (0.11 mL, 0.8 mmol) and TIPSCl (0.085 mL, 0.4 mmol) and stirred at 50° C. Stirred for four hours until starting material was consumed. Diluted with dichloromethane, washed with saturated brine, concentrated organics to give crude. Chromatographed (50% ethylacetate/hexanes to 20% methanol/60% ethylacetate/20%hexanes) to give product **90** (0.027 g, 0.0435 mmol, 54% for two steps.) ^1H NMR ($CDCl_3$) δ 9.05 (d, 1H), 8.60 (d, 1H), 7.61 (dd, 1H), 7.41 (dd, 2H), 7.03 (dd, 2H), 4.81 (s, 2H), 3.71 (br m, 8H), 2.43 (s, 3H), 1.60 (m, 3H), 1.15 (d, 18H.) MS: 621 (M+1)



Example 91

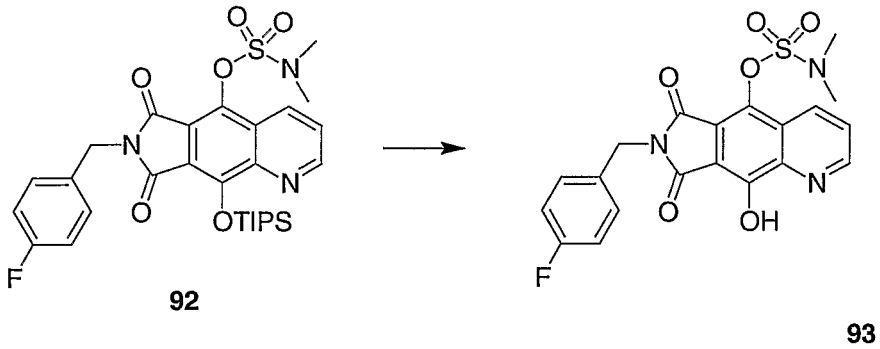
Mono-carbamate **90** (0.027 g, 0.0435 mmol) was dissolved in 1 mL of dichloromethane. To this was added trifluoroacetic acid (0.067 mL, 0.87 mmol) and stirred at room temperature. After twenty hours, concentrated off volatiles, azeotroped with

toluene (2x), concentrated to give crude. Triturate with 1:1 diethylether/hexanes to give product **91** (0.0177 g, 0.038 mmol, 87%.) ^{1}H NMR (CD_3SOCD_3) δ 9.09 (s, 1H), 8.71 (d, 1H), 7.67 (dd, 1H), 7.42 (dd, 2H), 7.07 (dd, 2H), 4.81 (s, 2H), 3.45 (br m, 8H), 2.90 (s, 3H.) MS: 465 (M+1), 463 (M-1)



Example 92

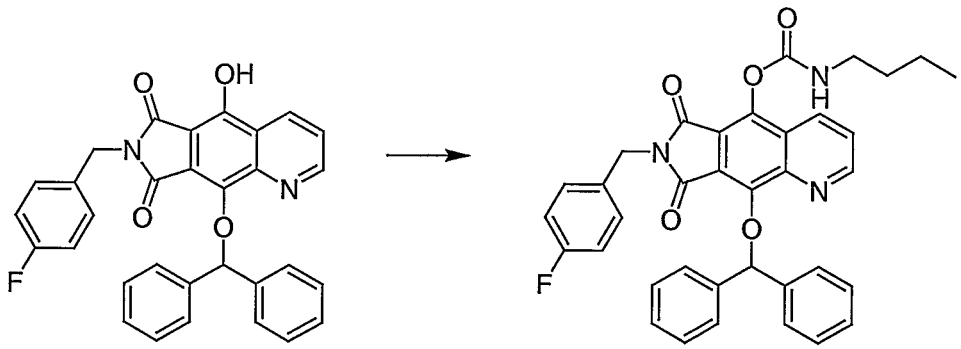
Mono-phenol **12** (0.04 g, 0.08 mmol) was dissolved in 1.5 mL dichloromethane. To this was added triethylamine (0.044 mL, 0.32 mmol), dimethylsulfamoyl chloride (0.017 mL, 0.16 mmol) and catalytic dimethylaminopyridine. Stirred at room temperature for 30 minutes. Diluted with dichloromethane, washed with saturated NH4Cl solution, concentrated organics to give crude. Chromatographed (25% ethylacetate/hexanes) to give product **92** (0.017 g, 0.02828 mmol, 35%.) ^{1}H NMR ($CDCl_3$) δ 8.95 (d, 1H), 8.79 (d, 1H), 7.66 (dd, 1H), 7.45 (dd, 2H), 7.03 (dd, 2H), 4.84 (s, 2H), 3.24 (s, 6H), 1.55 (m, 3H), 1.14 (d, 18H.) MS: 602 (M+1)



Example 93

Mono-carbamate **92** (0.017 g, 0.02828 mmol) was dissolved in 1 mL of dichloromethane. To this was added trifluoroacetic acid (0.044 mL, 0.5657 mmol) and stirred at room temperature. After twenty hours, concentrated off volatiles, azeotroped with

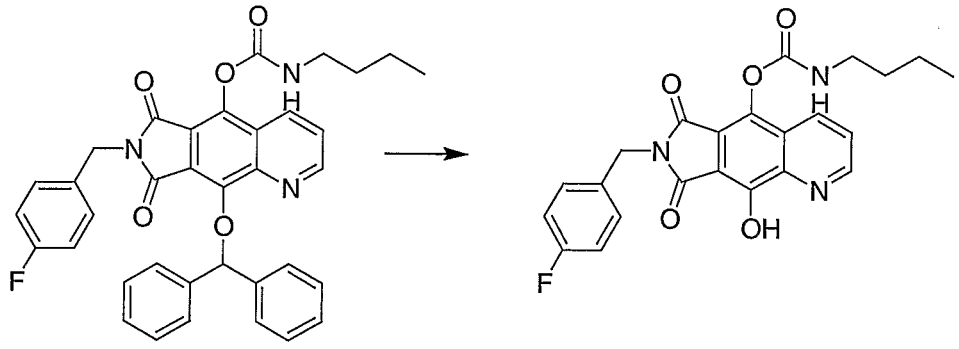
toluene (2x), concentrated to give crude. Triturate with 1:1 diethylether/hexanes to give product **93** (0.0081 g, 0.018 mmol, 64%.) ^{1}H NMR ($CDCl_3$) δ 9.00 (d, 1H), (8.84 (d, 1H), 7.76 (dd, 1H), 7.49 (dd, 2H), 7.03 (dd, 2H), 4.86 (s, 2H), 3.24 (s, 6H.) MS: 446 (M+1), 444 (M-1)



45 **94**

Example 94

Mono-phenol **45** (0.04 g, 0.08 mmol) was dissolved in 1.5 mL tetrahydrofuran. To this was added diisopropylethylamine (0.052 mL, 0.3 mmol), bis-pentafluorophenyl carbonate (0.047 g, 0.119 mmol) and catalytic dimethylaminopyridine. Stirred at room temperature. After 75 minutes, cooled to 0 °C, n-butylamine (0.079 mL, 0.08 mmol) added. Stirred for 1.5 hours, then diluted with dichloromethane, washed with saturated brine, 1 M HCl, concentrated organics to give crude. Chromatographed (25% ethylacetate/hexanes to give product **94** (0.0028 g, 0.0048 mmol, 6 %.) ^{1}H NMR ($CDCl_3$) δ 9.12 (d, 1H), 8.41 (d, 1H), 7.98 (s, 1H), 7.61 (d, 4H), 7.43 (dd, 2H), 7.27 (m, 7H), 7.043 (dd, 2H), 5.37 (m, 1H), 4.82 (s, 2H), 3.35 (q, 2H), 1.67 (m, 2H), 1.49 (m, 2H), 1.01 (t, 3H.) MS: 604 (M+1)



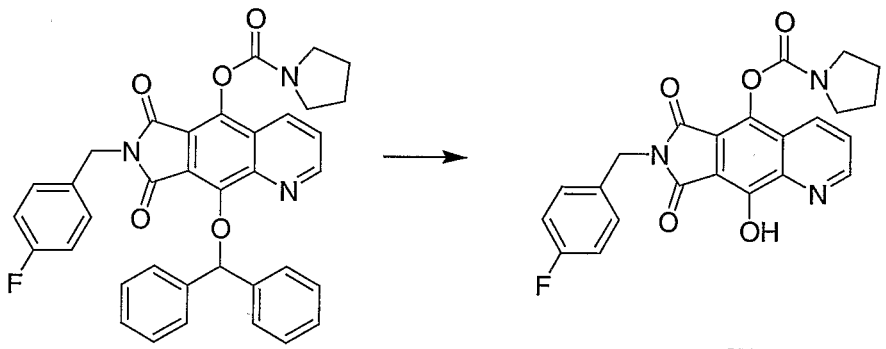
94 **95**

Example 95

Carbamate **94** (0.006 g, 0.0099 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude which was triturated twice with 1:1 diethylether/hexanes to give product **95** (0.0014 g, 0.003 mmol, 32%.) ^{1}H NMR ($CDCl_3$) δ 8.98 (s, 1H), 8.49 (d, 1H), 7.68 (dd, 1H), 7.47 (dd, 2H), 7.03 (dd, 2H), 5.40 (m, 1H), 4.83 (s, 2H), 3.38 (q, 2H), 3.15 (m, 2H), 1.49 (m, 2H), 1.03 (t, 3H.) MS: 438 (M+1), 436 (M-1)

Example 96

Monophenol **45** (0.05 g, 0.099 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added triethylamine (0.03 mL, 0.2 mmol) and pyrrolidine carbonyl chloride (0.0214 mL, 0.2 mmol.) Stirred at 30 °C for fifteen hours. Diluted with dichloromethane, washed with 1 M HCl solution, concentrated organics to give crude. Chromatographed (20% to 50% ethylacetate/hexanes) to give product **96** (0.033 g, 0.0555 mmol, 57%.) ^{1}H NMR ($CDCl_3$) δ 9.11 (dd, 1H), 8.45 (d, 1H), 7.97 (s, 1H), 7.62 (d, 5H), 7.40 (dd, 2H), 7.27 (m, 6H), 7.05 (dd, 2H), 4.81 (s, 2H), 3.75 (dd, 2H), 3.54 (dd, 2H), 2.05 (m, 4H.) MS: 602 (M+1)

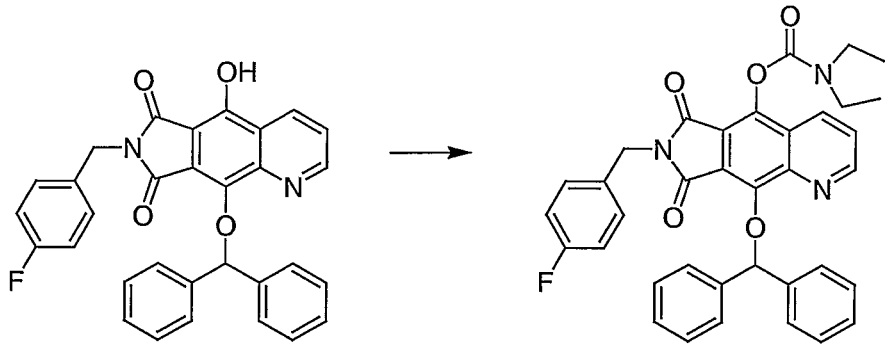


96 **97**

Example 97

Carbamate **96** (0.033 g, 0.055 mmol) was dissolved in 0.5 mL of dichloromethane. Triethylsilane (0.2 mL) and of trifluoroacetic acid (0.1 mL) were added. The mixture was stirred at room temperature and was complete after ten minutes by TLC. The mixture was concentrated in vacuo and azeotroped with toluene to give a crude residue which was triturated twice with 1:1 diethylether/hexanes to give product **97** (0.0123 g, 0.028 mmol, 51%). ^{1}H NMR ($CDCl_3$) δ 8.98 (d, 1H), 8.51 (d, 1H), 7.70 (dd, 1H), 7.46 (dd, 2H), 7.03

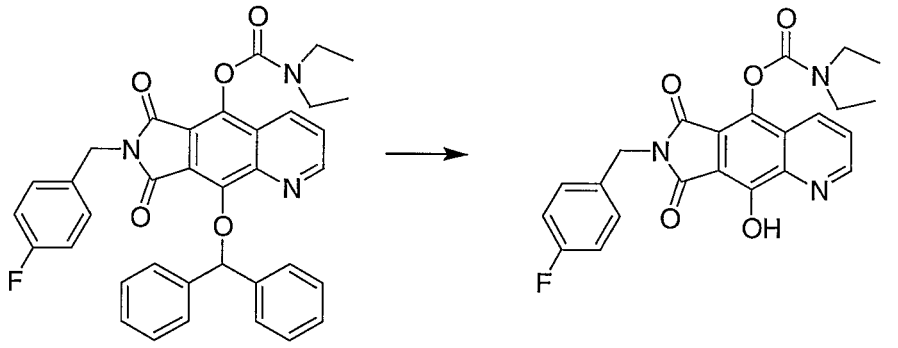
(dd, 2H), 4.82 (s, 2H), 3.81 (dd, 2H), 3.57 (dd, 2H), 2.09 (m, 4H.) MS: 436 (M+1), 434 (M-1)



45 98

Example 98

Monophenol **45** (0.03 g, 0.06 mmol) was dissolved in 1.5 mL of dichloromethane. Triethylamine (0.033 mL, 0.238 mmol) and diethylcarbamoyl chloride (0.015 mL, 0.119 mmol) were added. The mixture was stirred at 60 °C for five hours. The mixture was diluted with dichloromethane, washed with 1 M HCl solution, and concentrated to give crude product. The crude product was chromatographed (20% to 50% ethylacetate/hexanes) to give product **98** (0.0237 g, 0.040 mmol, 66%.) ^{1}H NMR ($CDCl_3$) δ 9.12 (s, 1H), 8.34 (d, 1H), 7.97 (s, 1H), 7.63 (d, 4H), 7.40 (dd, 2H), 7.27 (m, 7H), 7.01 (dd, 2H), 4.81 (s, 2H), 3.61 (dd, 2H), 3.50 (q, 2H), 1.41 (t, 3H), 1.37 (t, 3H.) MS: 604 (M+1)

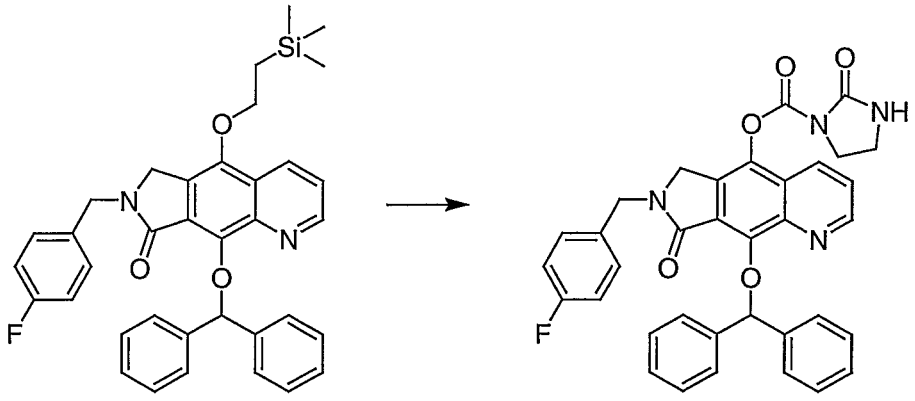


98 99

Example 99

Carbamate **98** (0.023 g, 0.04 mmol) was dissolved in 0.5 mL of dichloromethane. Triethylsilane (0.2 mL) and trifluoroacetic acid (0.1 mL) were added. The mixture was stirred at room temperature and after ten minutes was complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1

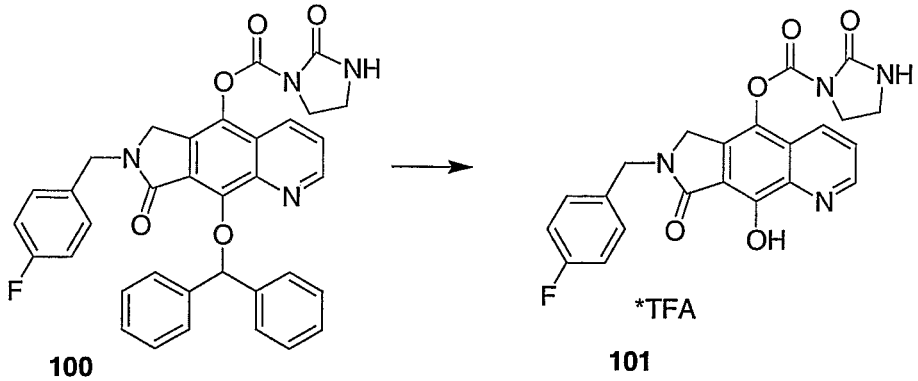
diethylether/hexanes to give product **99** (0.01 g, 0.024 mmol, 60%.) ^{1}H NMR ($CDCl_3$) δ 8.98 (d, 1H), 8.45 (d, 1H), 7.70 (dd, 1H), 7.48 (dd, 2H), 7.03 (dd, 2H), 4.82 (s, 2H), 3.67 (q, 2H), 3.48 (q, 2H), 1.46 (t, 3H), 1.32 (t, 3H.) MS: 438 (M+1), 436 (M-1)



44 **100**

Example 100

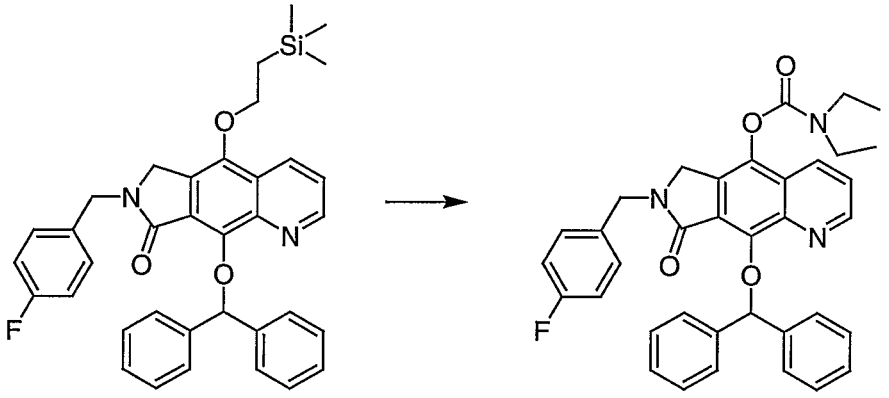
Trimethylsilyl ether **44** (0.022 g, 0.0373 mmol) was dissolved in 0.5 mL dry tetrahydrofuran. To this was added triethylamine (0.031 mL, 0.2238 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.0559 mL, 0.0559 mmol.) Stirred at room temperature 10 minutes until starting material consumed. Then added catalytic amount of dimethylaminopyridine and 2-oxo-1-imidazolidinecarbonyl chloride (0.022 g, 0.1492 mmol.) Stirred at room temperature for three hours, then diluted with dichloromethane, washed with 1M HCl solution, saturated $NaHCO_3$, saturated brine, concentrated to give crude. Chromatographed (50% ethylacetate/hexanes to 1:1:1 methanol, ethylacetate, hexanes) to give product **100** (0.0197 g, 0.031 mmol, 88%.) ^{1}H NMR ($CDCl_3$) δ 9.04 (dd, 1H), 8.31 (d, 1H), 8.02 (s, 1H), 7.73 (d, 4H), 7.53 (dd, 1H), 7.27 (m, 6H), 7.04 (dd, 2H), 5.00 (s, 1H) 4.80 (s, 2H), 4.10 (dd, 2H), 3.64 (dd, 2H.) MS: 603 (M+1)



100 **101**

Example 101

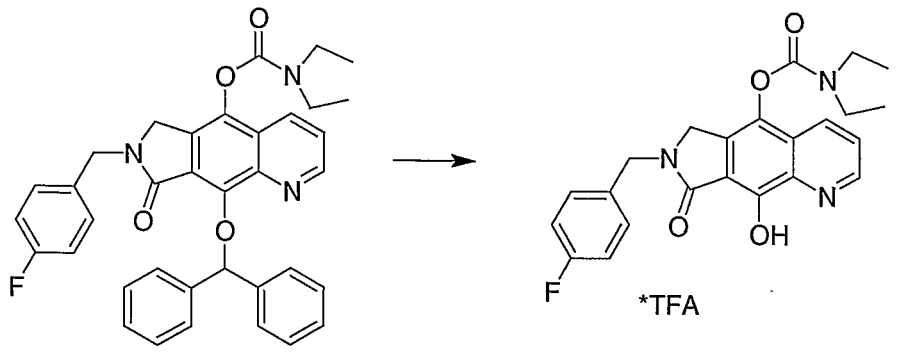
Carbamate **100** (0.019 g, 0.031 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **101** (0.006 g, 0.011 mmol, 35%.) ^{1}H NMR (CD_3SOCD_3) δ 8.98 (s, 1H), 8.48 (d, 1H), 7.77 (dd, 1H), 7.72 (s, 1H), 7.36 (dd, 2H), 7.22 (dd, 2H), 4.70 (s, 2H), 4.37 (s, 2H), 4.03 (dd, 2H), 3.41 (dd, 2H.) ^{19} F NMR: -74.6 MS: 437 (M+1), 435 (M-1)



44 **102**

Example 102

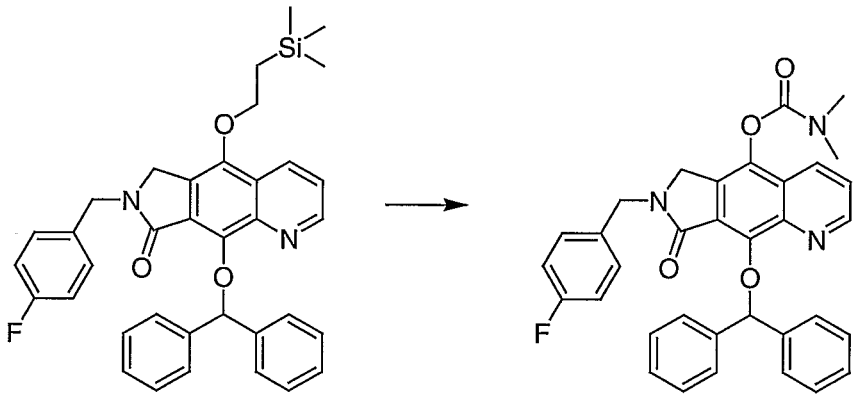
Trimethylsilylethyl ether **44** (0.03 g, 0.0508 mmol) was dissolved in 0.5 mL dry tetrahydrofuran. Triethylamine (0.042 mL, 0.3048 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.1016 mL, 0.1016 mmol) were added and stirred at room temperature for 10 minutes until starting material was consumed. A catalytic amount of dimethylaminopyridine was added, followed by diethylcarbamoyl chloride (0.026 mL, 0.2032 mmol). The mixture was stirred at room temperature for four hours, then diluted with dichloromethane, washed with 1M HCl solution, saturated $NaHCO_3$, saturated brine, and concentrated to the crude product. Chromatographed (25% to 50% ethylacetate/hexanes) to give product **102** (0.014 g, 0.024 mmol, 47%.) ^{1}H NMR ($CDCl_3$) δ 9.04 (s, 1H), 8.11 (d, 1H), 8.03 (s, 1H), 7.76 (d, 4H), 7.51 (dd, 1H), 7.27 (m, 8H), 7.08 (dd, 2H), 4.80 (s, 2H), 4.21 (s, 2H), 3.53 (q, 2H), 3.40 (q, 2H), 1.33 (t, 3H), 1.23 (t, 3H.) MS: 590 (M+1)



102 103

Example 103

Carbamate **102** (0.01 g, 0.0169 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **103** (0.0073 g, 0.014 mmol, 80%.) ^{1}H NMR ($CDCl_3$) δ 9.01 (s, 1H), 8.23 (d, 1H), 7.60 (dd, 1H), 7.33 (dd, 2H), 7.09 (dd, 2H), 4.77 (s, 2H), 4.37 (s, 2H), 3.56 (q, 2H), 3.43 (q, 2H), 1.37 (t, 3H), 1.26 (t, 3H.) ^{19} F NMR: -76.2 MS: 424 (M+1), 422 (M-1)

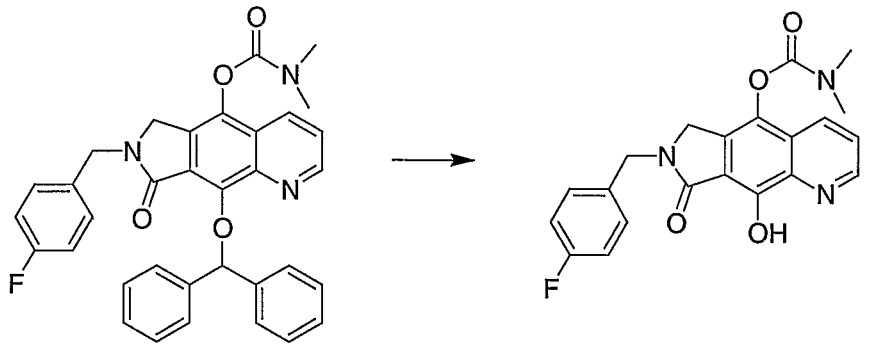


44 104

Example104

Trimethylsilylethyl ether **44** (0.03 g, 0.0508 mmol) was dissolved in 0.5 mL dry tetrahydrofuran. To this was added triethylamine (0.042 mL, 0.3048 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.1016 mL, 0.1016 mmol.) Stirred at room temperature 10 minutes until starting material consumed. Then added catalytic amount of dimethylaminopyridine and dimethylcarbamoyl chloride (0.0187 mL, 0.2032 mmol.) Stirred at room temperature for six hours, then diluted with

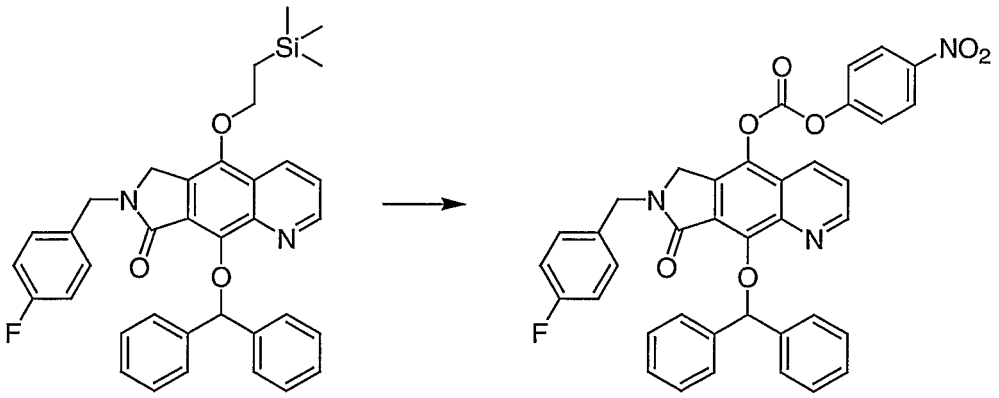
dichloromethane, washed with 1M HCl solution, saturated $NaHCO_3$, saturated brine, concentrated to give crude. Chromatographed (20% to 50% ethylacetate/hexanes) to give product **104** (0.014 g, 0.024 mmol, 48%.) ^{1}H NMR ($CDCl_3$) δ 9.04 (d, 1H), 8.14 (d, 1H), 8.03 (s, 1H), 7.75 (d, 4H), 7.51 (dd, 1H), 7.27 (m, 8H), 7.16 (dd, 2H), 4.80 (s, 2H0, 4.23 (s, 2H), 3.19 (s, 3H), 3.02 (s, 3H.) MS: 562 (M+1)



104 **105**

Example 105

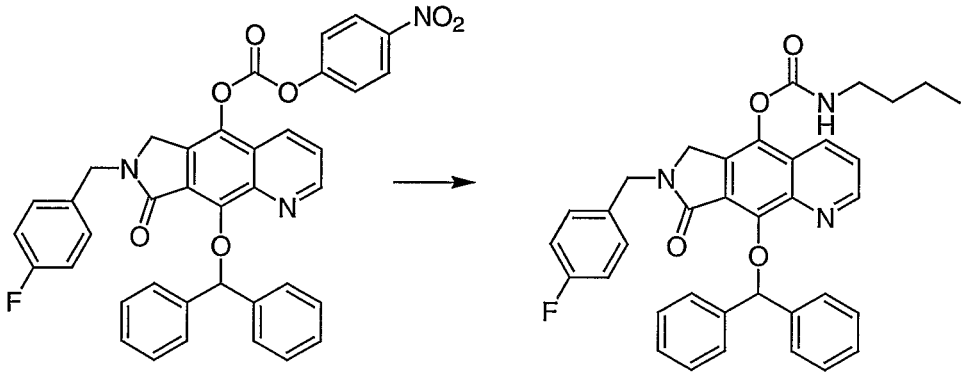
Carbamate **104** (0.012 g, 0.021 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **105** (0.0068 g, 0.017 mmol, 82%.) ^{1}H NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.25 (d, 1H), 7.59 (dd, 1H), 7.36 (dd, 2H), 7.09 (dd, 2H), 4.77 (s, 2H), 4.38 (s, 2H), 3.24 (s, 3H), 3.06 (s, 3H.) MS: 396 (M+1), 394 (M-1)



44 **106**

Example 106

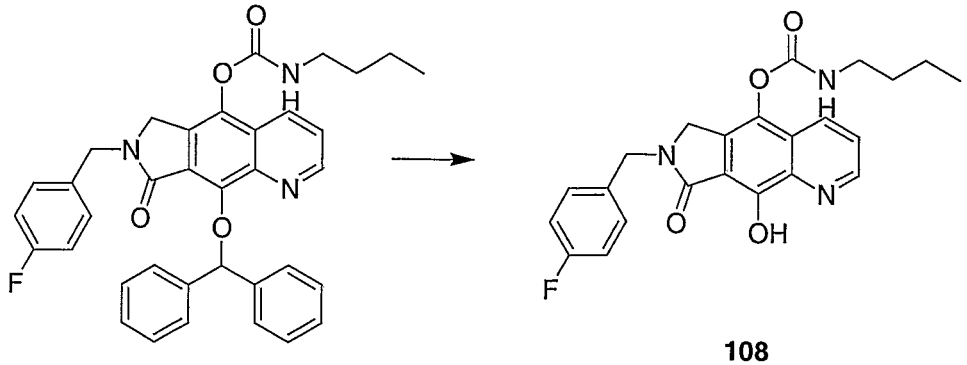
Trimethylsilylethyl ether **44** (0.03 g, 0.0508 mmol) was dissolved in 0.5 mL dry tetrahydrofuran. To this was added triethylamine (0.0282 mL, 0.2032 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.076 mL, 0.076 mmol.) Stirred at room temperature 10 minutes until starting material consumed. After fifteen minutes, diluted with dichloromethane, washed with washed with 1M HCl solution, saturated $NaHCO_3$, saturated brine, concentrated to give crude. Diluted in 1 mL dichloromethane. To this was added triethylamine (0.028 mL, 0.2032 mmol), para-nitrochloroformate (0.02 g, 0.1016 mmol) and catalytic dimethylaminopyridine. Stirred at room temperature for 30 minutes, then diluted with dichloromethane, washed with saturated NH_4Cl solution, concentrated organics to give crude. Chromatographed (50% ethylacetate/hexanes) to give product **106** (0.009 g, 0.0137 mmol, 27%) ^{1}H NMR ($CDCl_3$) δ 9.10 (s, 1H), 8.16 (d, 2H), 8.10 (s, 1H), 7.71 (d, 4H), 7.53 (dd, 1H), 7.27 (m, 9H), 7.09 (dd, 2H), 6.93 (d, 2H), 4.79 (s, 2H), 4.23 (s, 2H.) MS: 656 (M+1)



106 **107**

Example 107

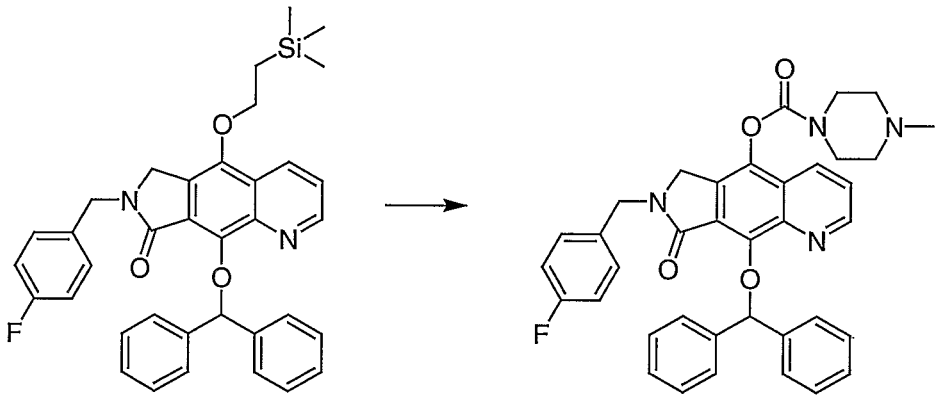
Carbonate **106** (0.009 g, 0.0137 mmol) was dissolved in 0.5mL dichloromethane. To this was added triethylamine (0.0282 mL, 0.2032 mmol) and n-butylamine (0.01 mL, 0.1016 mmol) and stirred at room temperature. After 15 minutes, starting material consumed. Diluted with dichloromethane, washed with 1M HCl solution, saturated brine, concentrated to give crude. Chromatographed (30% ethylacetate/hexanes) to give product **107** (0.0075 g, 0.012 mmol, 88%.) ^{1}H NMR ($CDCl_3$) δ 9.02 (s, 1H), 8.15 (d, 1H), 8.04 (s,1H), 7.75 (d, 4H), 7.50 (dd, 1H), 7.27 (m, 6H), 7.08 (dd, 2H), 5.18 (s, 1H), 4.80 (s, 2H), 4.21 (s, 2H), 3.31 (q, 2H), 1.59 (m, 2H), 1.41 (m, 2H), 0.99 (t, 3H.) MS: 590 (M+1)



107 108

Example 108

Carbamate **107** (0.007 g, 0.012 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **108** (0.0028 g, 0.0066 mmol, 56%.) ^{1}H NMR ($CDCl_3$) δ 8.98 (s, 1H), 8.27 (d, 1H), 7.59 (dd, 1H), 7.31 (dd, 2H), 7.06 (dd, 2H), 5.19 (s, 1H), 4.77 (s, 2H), 4.37 (s, 2H), 3.32 (q, 2H), 1.65 (m, 2H), 1.44 (m, 2H), 1.01 (t, 3H) MS: 424 (M+1), 422 (M-1)

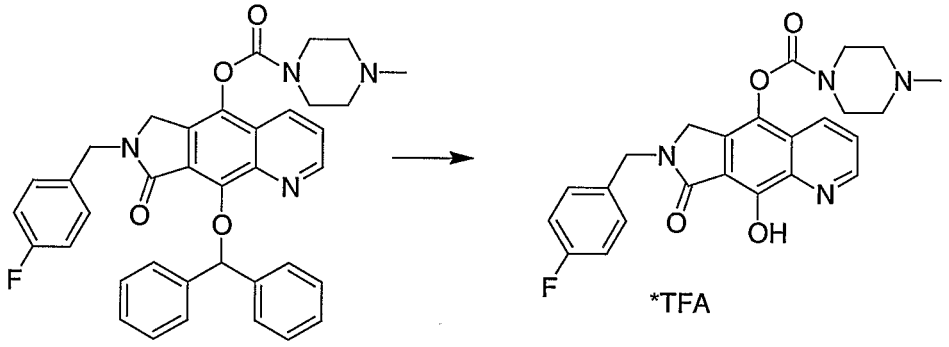


44 109

Example 109

Trimethylsilylethyl ether **44** (0.01 g, 0.0169 mmol) was dissolved in 0.5 mL dry tetrahydrofuran. To this was added triethylamine (0.014 mL, 0.0339 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.0339 mL, 0.0339 mmol.) Stirred at room temperature 10 minutes until starting material consumed. Diluted with dichloromethane, washed with washed with 1M HCl solution, saturated $NaHCO_3$, saturated brine, concentrated to give crude. Dissolved in 0.5 mL dichloromethane, added catalytic

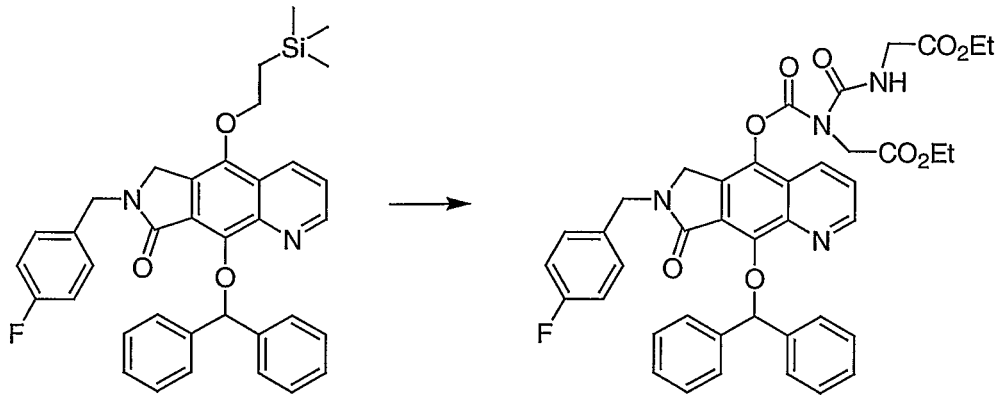
dimethylaminopyridine, triethylamine (0.042 mL, 0.1017 mmol) and cooled to 0 °C. To this was added a 1M solution of triphosgene in dichloromethane (0.1017 mL, 0.1017 mmol) and stirred 30 minutes. Methyl piperazine (0.0168 mL, 0.1521 mmol) was then added and stirred at room temperature for fifteen minutes. Diluted with dichloromethane, washed with brine, concentrated volatiles to give crude. Chromatographed (50% ethylacetate/hexanes to 10% methanol/ethylacetate) to give product **109** (0.0055 g, 0.009 mmol, 53%.) ^{1}H NMR ($CDCl_3$) δ 9.04 (d, 1H), 8.10 (d, 1H), 8.03 (s, 1H), 7.75 (d, 4H), 7.52 (dd, 1H), 7.27 (m, 8H), 7.05 (dd, 2H), 4.80 (s, 2H), 4.22 (s, 2H), 3.77 (br s, 2H), 3.58 (br s, 2H), 2.48 (br s, 4H), 2.37 (s, 3H.) MS: 617 (M+1)



109 **110**

Example 110

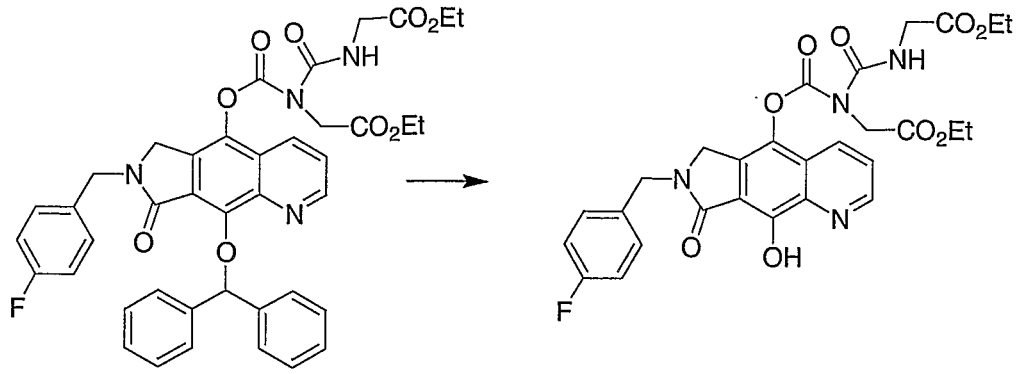
Carbamate **109** (0.007 g, 0.01136 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **110** (0.004 g, 0.007 mmol, 63%.) ^{1}H NMR ($CDCl_3$) δ 9.00 (s, 1H), 8.11 (d, 1H), 7.59 (dd, 1H), 7.35 (dd, 2H), 7.08 (dd, 2H), 4.78 (s, 2H), 4.35 (s, 2H), 3.50 (br m, 8H), 2.93 (s, 3H.), ^{19}F NMR: -76.2 MS: 451 (M+1), 449 (M-1)



44 111

Example 111

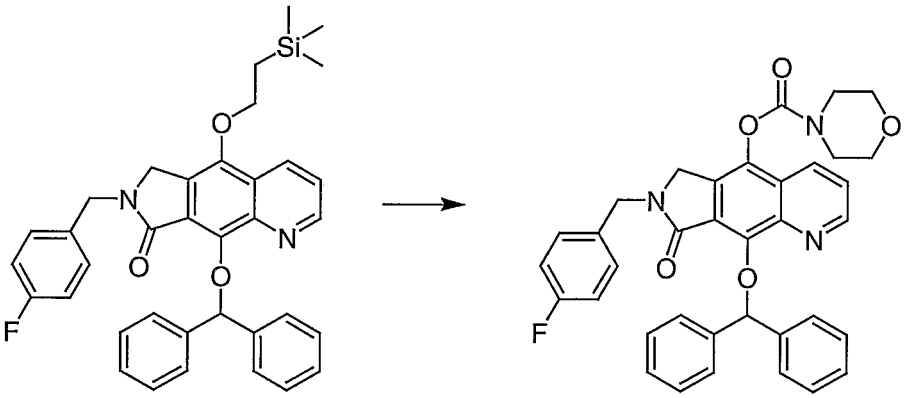
Trimethylsilylethyl ether **44** (0.02 g, 0.0339 mmol) was dissolved in 0.5 mL dry tetrahydrofuran. Triethylamine (0.0188 mL, 0.135 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.0678 mL, 0.0678 mmol) were added. The mixture was stirred at room temperature for 10 minutes until starting material consumed. The mixture was diluted with dichloromethane, washed with 1M HCl solution, saturated $NaHCO_3$, saturated brine, and concentrated to give crude. The crude residue was dissolved in 0.5 mL dichloromethane, and catalytic dimethylaminopyridine, triethylamine (0.0188 mL, 0.135 mmol) and ethyl isocyanatoacetate (Aldrich, St. Louis, MO, 0.011 mL, 0.1017 mmol) were added and stirred at room temperature (Satchell and Satchell, Chem. Soc. Rev. (1975) 4:231-250; R.G. Arnold etal., Chem. Soc. (1957) 57:47-76). After four hours, starting material was consumed. The mixture was diluted with dichloromethane, washed with 1M HCl, brine, and concentrated in vacuo to give crude product. The crude product was chromatographed on silica gel (10% to 50% ethylacetate/hexanes) to give product **111** (0.0118 g, 0.156 mmol, 46%) ^1H NMR ($CDCl_3$) δ 9.07 (d, 1H), 8.73 (s, 1H), 8.17 (d, 1H), 8.08 (s, 1H), 7.76 (d, 4H), 7.57 (dd, 1H), 7.27 (m, 8H), 7.08 (dd, 2H), 4.81 (s, 2H), 4.74 (s, 2H), 4.20 (m, 4H), 4.07 (d, 4H), 1.27 (m, 6H). MS: 749 (M+1), 747 (M-1).



111 112

Example 112

Carbamate **111** (0.011 g, 0.0177 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **112** (0.0056 g, 0.0095 mmol, 54%.) ^{1}H NMR ($CDCl_3$) δ 8.99 (s, 1H), 8.76 (s, 1H), 8.27 (d, 1H), 7.63 (dd, 1H), 7.35 (dd, 2H), 7.09 (dd, 2H), 4.79 (d, 4H), 4.33 (d, 2H), 4.23 (m, 4H), 4.09 (d, 2H), 1.30 (m, 6H.) MS: 583 (M+1), 581 (M-1)

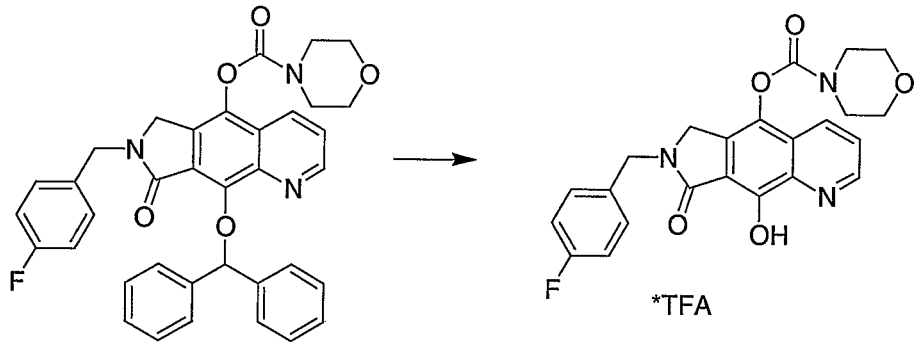


44 113

Example 113

Trimethylsilylethyl ether **44** (0.02 g, 0.0339 mmol) was dissolved in 0.5 mL dry tetrahydrofuran. To this was added triethylamine (0.019 mL, 0.14 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.0678 mL, 0.0678 mmol.) Stirred at room temperature 10 minutes until starting material consumed. Diluted with dichloromethane, washed with washed with 1M HCl solution, saturated $NaHCO_3$, saturated brine, concentrated to give crude. Dissolved in 0.5 mL dichloromethane, added catalytic

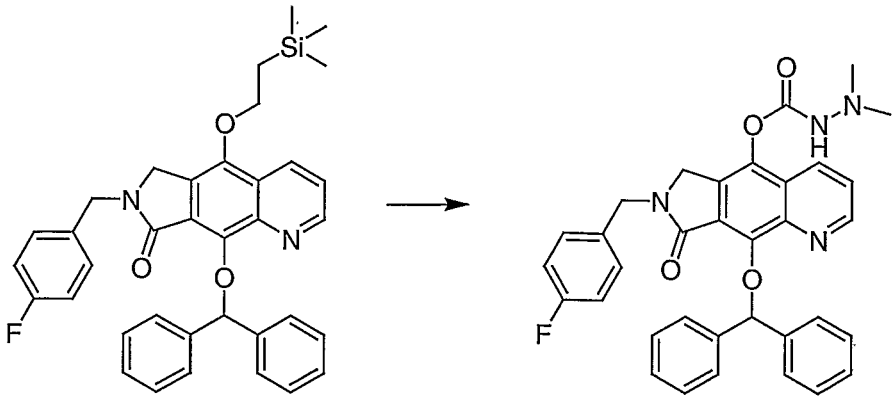
dimethylaminopyridine, triethylamine (0.019 mL, 0.14 mmol) and cooled to 0 °C. To this was added a 1M solution of triphosgene in dichloromethane (0.0678 mL, 0.0678 mmol) and stirred 60 minutes. Morpholine (0.009 mL, 0.1016 mmol) was then added and stirred at room temperature for 30 minutes. Diluted with dichloromethane, washed with 1M HCl, brine, concentrated volatiles to give crude. Chromatographed (40% ethylacetate/hexanes to 60% ethylacetate/hexanes) to give product **113** (0.0176 g, 0.028 mmol, 86%.) ^{1}H NMR ($CDCl_3$) δ 9.05 (d, 1H), 8.09 (d, 1H), 8.04 (s, 1H), 7.75 (d, 4H), 7.53 (dd, 1H), 7.27 (m, 8H), 7.06 (dd, 2H), 4.81 (s, 1H), 4.23 (s, 2H), 3.78 (br s, 6H), 3.56 (br s, 2H.) MS: 604 (M+1), 602 (M-1)



113 **114**

Example 114

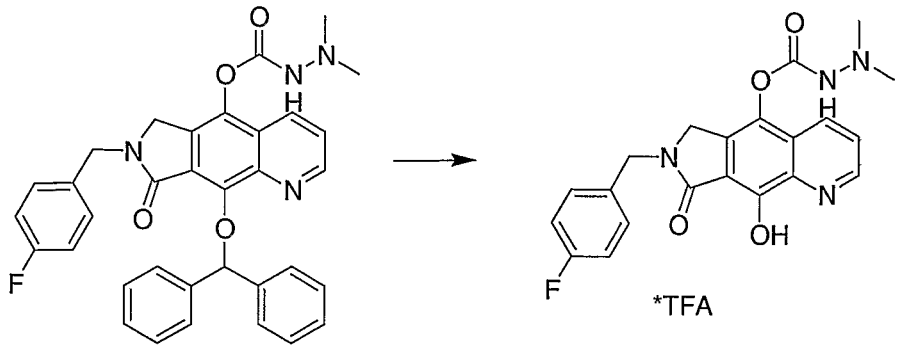
Carbamate **113** (0.017 g, 0.028 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **114** (0.0085 g, 0.015 mmol, 55%.) ^{1}H NMR ($CDCl_3$) δ 9.02 (s, 1H), 8.24 (d, 1H), 7.62 (dd, 1H), 7.33 (dd, 2H), 7.07 (dd, 2H), 4.78 (s, 2H), 4.39 (s, 2H), 3.82 (br s, 6H), 3.60 (br s, 2H.) ^{19} F NMR: -76.2 MS: 438 (M+1), 436 (M-1)



44 115

Example 115

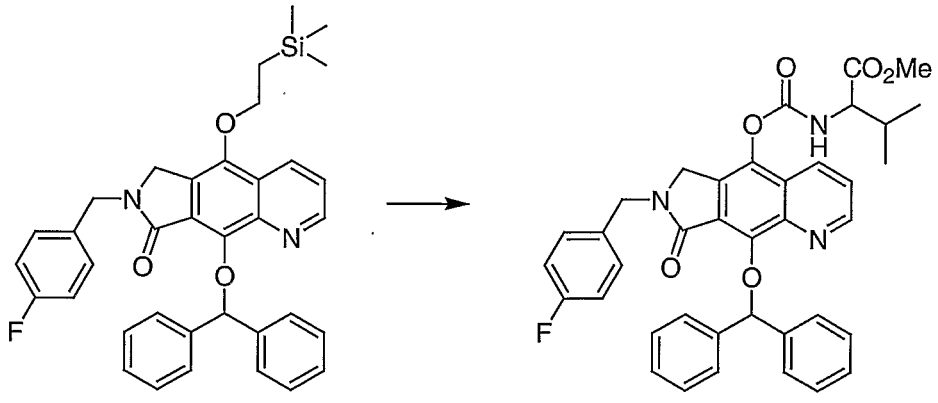
Trimethylsilylethyl ether **44** (0.02 g, 0.0339 mmol) was dissolved in 0.5 mL dry tetrahydrofuran. To this was added diisopropylethylamine (0.024 mL, 0.135 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.0678 mL, 0.0678 mmol.) Stirred at room temperature 10 minutes until starting material consumed. Diluted with dichloromethane, washed with washed with 1M HCl solution, saturated $NaHCO_3$, saturated brine, concentrated to give crude. Dissolved in 0.5 mL dichloromethane, added catalytic dimethylaminopyridine, diisopropylethylamine (0.024 mL, 0.135 mmol) and cooled to 0 °C. To this was added a 1M solution of triphosgene (bis[trichloromethyl] carbonate) in dichloromethane (0.0678 mL, 0.0678 mmol) and stirred 45 minutes. Dimethylhydrazine (0.01 mL, 0.135 mmol) was then added and stirred at room temperature for 20 minutes. Diluted with dichloromethane, washed with saturated NH_4Cl solution, concentrated volatiles to give crude. Chromatographed (10% ethylacetate/hexanes to 60% ethylacetate/hexanes) and purified by preparatory TLC plate (60% ethylacetate/hexanes) to give product **115** (0.004 g, 0.0069 mmol, 20%.) ^1H NMR ($CDCl_3$) δ 9.05 (d, 1H), 8.11 (d, 1H), 8.04 (s, 1H), 7.75 (d, 4H), 7.5 (dd, 1H), 7.27 (m, 8H), 7.07 (dd, 2H), 6.14 (s, 1H), 4.80 (s, 2H), 4.23 (s, 2H), 2.70 (6H.) MS: 577 (M+1)



115 116

Example 116

Carbamate **115** (0.009 g, 0.0156 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **116** (0.003 g, 0.0057 mmol, 37%.) ^{1}H NMR ($CDCl_3$) δ 8.96 (s, 1H), 8.24 (d, 1H), 7.56 (dd, 1H), 7.33 (dd, 2H), 7.06 (dd, 2H), 4.76 (s, 2H), 4.39 (s, 2H), 2.74 (s, 3H.) ^{19} F NMR: -76.1 MS: 411 (M+1), 409 (M-1)

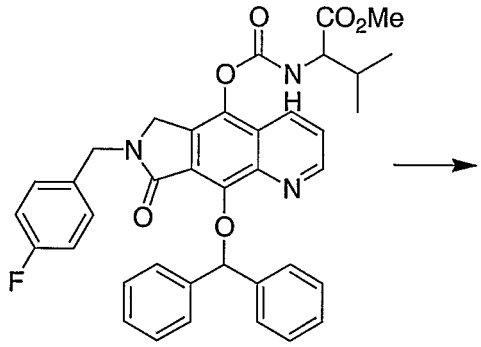


44 117

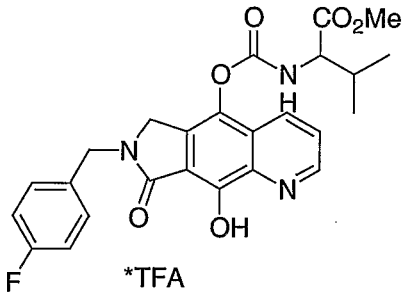
Example 117

Trimethylsilylethyl ether **44** (0.02 g, 0.0339 mmol) was dissolved in 0.5 mL dry tetrahydrofuran. To this was added triethylamine (0.0188 mL, 0.135 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.0678 mL, 0.0678 mmol.) Stirred at room temperature 10 minutes until starting material consumed. Diluted with dichloromethane, washed with washed with 1M HCl solution, saturated, saturated brine, concentrated to give crude. Dissolved in 0.5 mL dichloromethane, added catalytic

dimethylaminopyridine, triethylamine (0.0188 mL, 0.135 mmol) and methyl (s)-(-)-2-isocyanato-3-methyl butyrate (0.0048 mL, 0.0339 mmol) and stirred at room temperature. After 4.5 hours, starting material consumed. Diluted with dichloromethane, washed with saturated NH_4Cl solution, concentrated organics to give crude. Chromatographed (10% to 50% ethylacetate/hexanes) to give product **117** (0.0085 g, 0.013 mmol, 39%.) ^{1}H NMR ($CDCl_3$) δ 9.03 (s, 1H), 8.17 (d, 1H), 8.05 (s, 1H), 7.75 (4H), 7.52 (dd, 1H), 7.27 (m, 8H), 7.07 (dd, 2H), 5.70 (d, 1H), 4.80 (s, 2H), 4.21 (s, 2H), 3.79 (s, 3H), 2.28 (dsp, 1H), 1.03 (d, 3H), 0.98 (d, 3H.) MS: 649 (M+1)



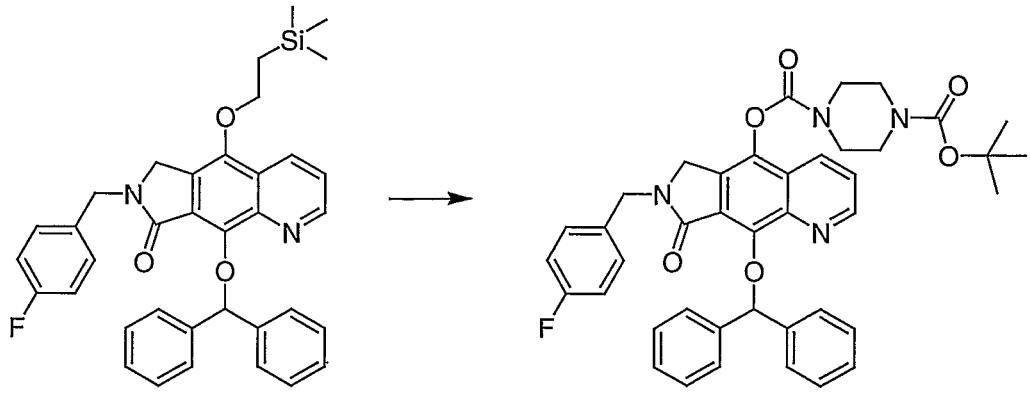
117



118

Example 118

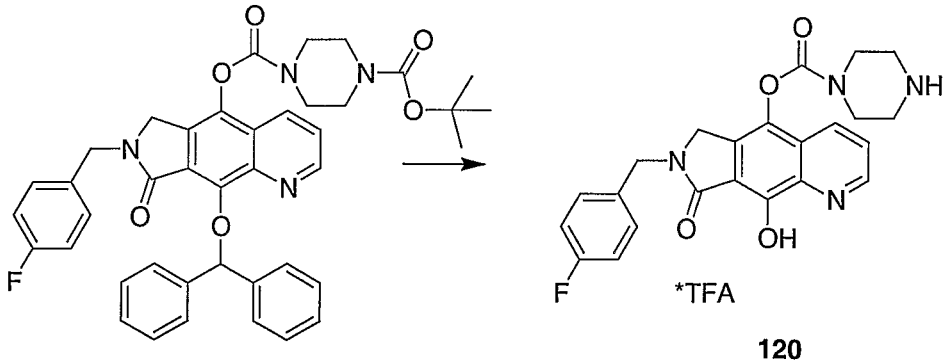
Carbamate **117** (0.004 g, 0.006 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **118** (0.0027 g, 0.0046 mmol, 76%.) ^{1}H NMR ($CDCl_3$) δ 9.00 (s, 1H), 8.31 (d, 1H), 7.60 (dd, 1H), 7.33 (dd, 2H), 7.09 (dd, 2H), 5.76 (d, 1H), 4.77 (s, 2H), 4.36 (s, 2H), 3.81 (s, 3H), 2.28 (dsp, 1H), 1.06 (d, 3H), 1.00 (d, 3H.) ^{19}F NMR: -76.2 MS: 482 (M+1), 480 (M-1)



44 119

Example 119

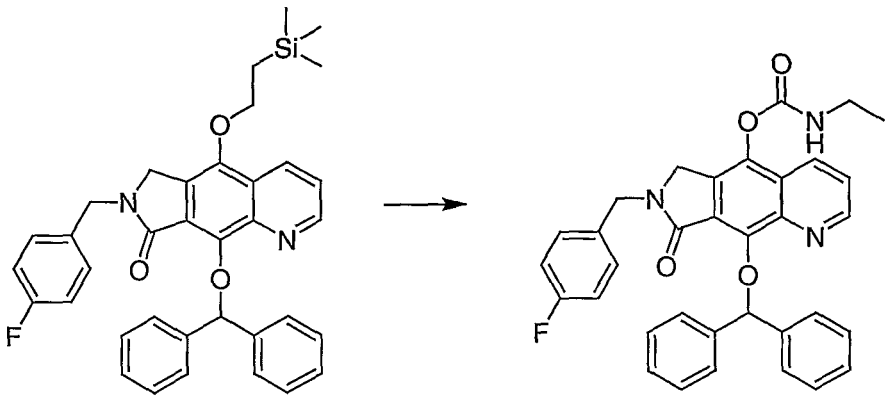
Trimethylsilylethyl ether **44** (0.2 g, 0.339 mmol) was dissolved in 3 mL dry tetrahydrofuran. To this was added triethylamine (0.139 mL, 1 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.0678 mL, 0.0678 mmol.) Stirred at room temperature 10 minutes until starting material consumed. Diluted with dichloromethane, washed with washed with 1M HCl solution, saturated brine, concentrated to give crude. Dissolved in 3 mL dichloromethane, added catalytic dimethylaminopyridine, triethylamine (0.754 mL, 5.4 mmol) and cooled to 0 °C. To this was added a 1M solution of triphosgene in dichloromethane (0.1356 mL, 0.1356 mmol) and stirred 50 minutes. BOC-piperazine (0.37 g, 2 mmol) was then added and stirred at room temperature for 30 minutes. Diluted with dichloromethane, washed with 1M HCl, brine, concentrated volatiles to give crude. Chromatographed (10% to 30% acetone/toluene) to give product **119** (0.1158 g, 0.166 mmol, 49%.) ^{1}H NMR ($CDCl_3$) δ 9.04 (d, 1H), 8.09 (d, 1H), 8.04 (s, 1H), 7.75 (d, 4H), 7.50 (dd, 1H), 7.27 (m, 8H), 7.05 (dd, 2H), 4.80 (s, 2H), 4.22 (s, 2H), 3.73 (br s, 2H), 3.53 (br s, 4H), 1.51 (s, 9H.) MS: 688 (M+1)



119 120

Example 120

Carbamate **119** (0.057 g, 0.082 mmol) was dissolved in 1 mL of dichloromethane. To this was added 0.4 mL of triethylsilane and 0.2 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Then dissolved in 1 mL dichloromethane, 1 ml trifluoroacetic acid. Stirred at room temperature for one hour. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **120** (0.0317 g, 0.059 mmol, 72%.) ^{1}H NMR (CD_3SOCD_3) δ 8.97 (br m, 2H), 8.40 (d, 1H), 7.75 (dd, 1H), 7.35 (dd, 2H), 7.23 (dd, 2H), 4.71 (s, 2H), 4.38 (s, 2H), 3.91 (br s, 2H), 3.24 (br s, 4H.) ^{19} F NMR: -74.5 MS: 437 (M+1), 435 (M-1)

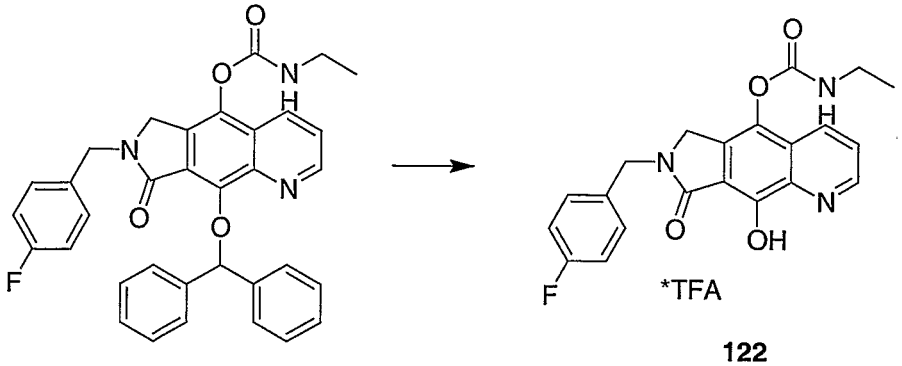


44 **121**

Example 121

Trimethylsilylethyl ether **44** (0.035 g, 0.0596 mmol) was dissolved in 0.8 mL dry tetrahydrofuran. To this was added triethylamine (0.05 mL, 0.358 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.119 mL, 0.119 mmol.) Stirred at room temperature 10 minutes until starting material consumed. Diluted with dichloromethane, washed with washed with 1M HCl solution, saturated brine, concentrated to give crude. Dissolved in 0.8 mL dichloromethane, added triethylamine (0.05 mL, 0.358 mmol) and ethyl isocyanate (0.0046 mL, 0.0595 mmol) and stirred at room temperature. After 6 hours, starting material consumed. Diluted with dichloromethane, washed with saturated brine, concentrated organics to give crude. Chromatographed (10% to 50% ethylacetate/hexanes) to give product **121** (0.0112 g, 0.023 mmol, 39%.) ^{1}H NMR ($CDCl_3$)

δ 9.05 (s, 1H), 8.17 (d, 1H), 8.04 (s, 1H), 7.76 (d, 4H), 7.50 (dd, 1H), 7.27 (m, 8H), 7.05 (dd, 2H), 4.80 (s, 2H), 4.23 (s, 2H), 3.33 (q, 2H), 1.27 (t, 3H.) MS: 562 (M+1)



121 122

Example 122

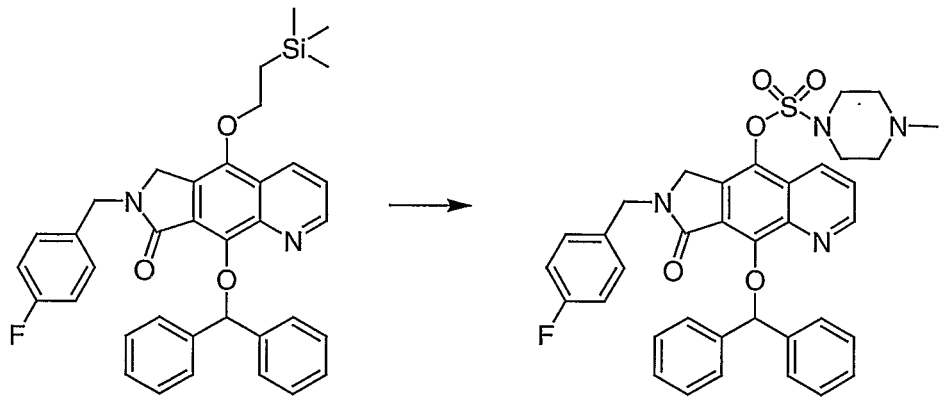
Carbamate **121** (0.0112 g, 0.023 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **122** (0.0033 g, 0.0076 mmol, 33%.) ^{1}H NMR ($CDCl_3$) δ 9.06 (s, 1H), 8.37 (d, 1H), 7.64 (dd, 1H), 7.33 (dd, 2H), 7.06 (dd, 2H), 5.24 (s, 1H), 4.77 (s, 2H), 4.39 (s, 2H), 3.38 (q, 2H), 1.30 (t, 3H.) ^{19} F NMR: -76.2 MS: 397 (M+1), 395 (M-1)



123

Example 123

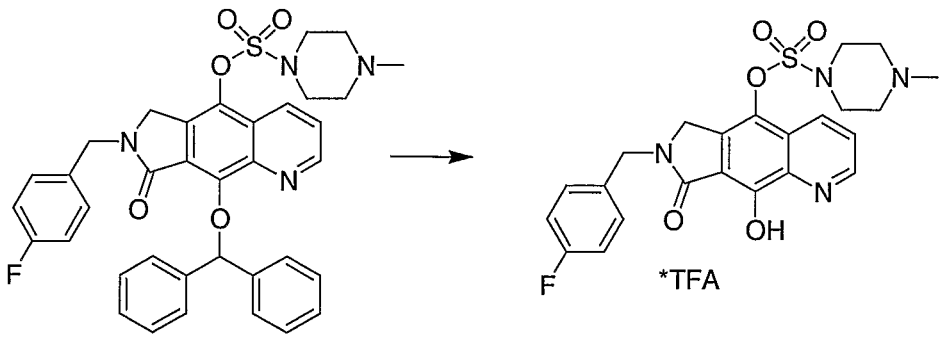
N-Methyl piperazine (0.33 mL, 3 mmol) was added slowly and with caution to a mixture of sulfuryl chloride (0.72 mL, 9 mmol) in 6 mL of acetonitrile. The solution was heated to reflux for 15 hours. After starting material consumed, solution concentrated to oil, azeotroped with toluene (2x), concentrated to give crude product which was triturated with diethylether to give the product **123** as a pale brown solid (0.5 g, 71%.) ^{1}H NMR (CD_3SOCD_3) δ 3.90 (br s, 2H), 3.59 (br s, 2H.), 3.38 (br. S, 4H), 2.67 (s, 3H); MS: 200 (M+1).



44 124

Example 124

Trimethylsilylethyl ether **44** (0.03 g, 0.0508 mmol) was dissolved in 0.5 mL dry tetrahydrofuran. Triethylamine (0.021 mL, 0.1525 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.1016 mL, 0.1016 mmol.) were added. The mixture was stirred at room temperature 10 minutes until starting material was consumed, then diluted with dichloromethane, washed with washed with 1M HCl solution, saturated brine, and concentrated. The crude product was dissolved in 0.5 mL dichloromethane. Catalytic dimethylaminopyridine, triethylamine (0.035 mL, 0.254 mmol) and methyl piperazine sulfamoyl chloride HCl salt 123 (0.024 g, 0.1016 mmol) were added and stirred at room temperature. After 15 hours, starting material was consumed. The mixture was diluted with dichloromethane, washed with saturated brine, and concentrated organics to give crude product which was chromatographed (1% to 10% methanol/dichloromethane) to give product **124** (0.016 g, 0.0246 mmol, 48%.) ^{1}H NMR ($CDCl_3$) δ 9.07 (s, 1H), 8.38 (d, 1H), 8.08 (s, 1H), 7.75 (d, 4H), 7.55 (dd, 1H), 7.27 (m, 8H), 7.08 (dd, 2H), 4.81 (s, 2H), 4.46 (s, 2H), 3.51 (br s, 4H), 2.54 (br s, 4H), 3.35 (s, 3H.) MS: 653 (M+1)



124 125

Example 125

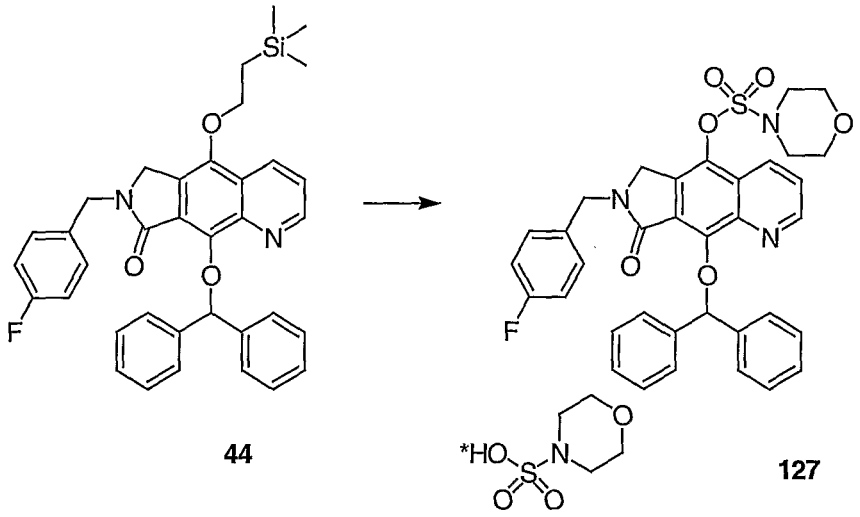
Sulfamate **124** (0.016 g, 0.0246 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **125** (0.008 g, 0.0133 mmol, 54%.) ^{1}H NMR ($CDCl_3$) δ 9.02 (s, 1H), 8.37 (d, 1H), 7.67 (dd, 1H), 7.33 (dd, 2H), 7.06 (dd, 2H), 4.80 (s, 2H), 4.57 (s, 2H), 3.95 (br s, 4H), 3.29 (br s, 4H), 2.89 (s, 3H.) ^{19} F NMR: -76.2 MS: 487 (M+1), 485 (M-1)



126

Example 126

Morpholine (0.436 mL, 5 mmol) was added slowly and with caution to a mixture of sulfuryl chloride (1.205 mL, 15 mmol) in 5 mL acetonitrile. Heated to reflux and stirred for 24 hours. After starting material consumed, solution concentrated to oil, azeotroped with toluene (2x), concentrated to give crude product **126** stored as a 2M solution in dichloromethane (0.999 g, 5 mmol, 100%.) ^{1}H NMR (CD_3SOCD_3) δ 3.80 (br s, 4H), 3.28 (br s, 4H.) MS: 186 (M+1)

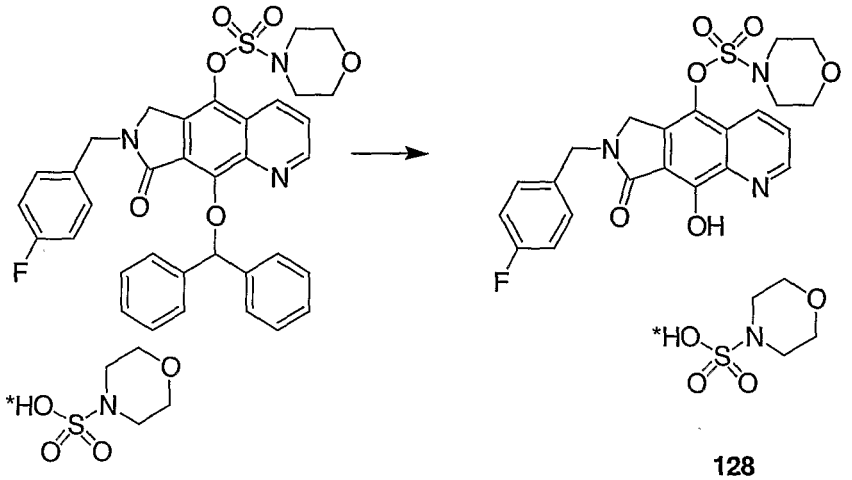


44 **127**

Example 127

Trimethylsilylethyl ether **44** (0.027 g, 0.0457 mmol) was dissolved in 0.5 mL dry tetrahydrofuran. To this was added triethylamine (0.025 mL, 0.1828 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.0915 mL, 0.0915 mmol.)

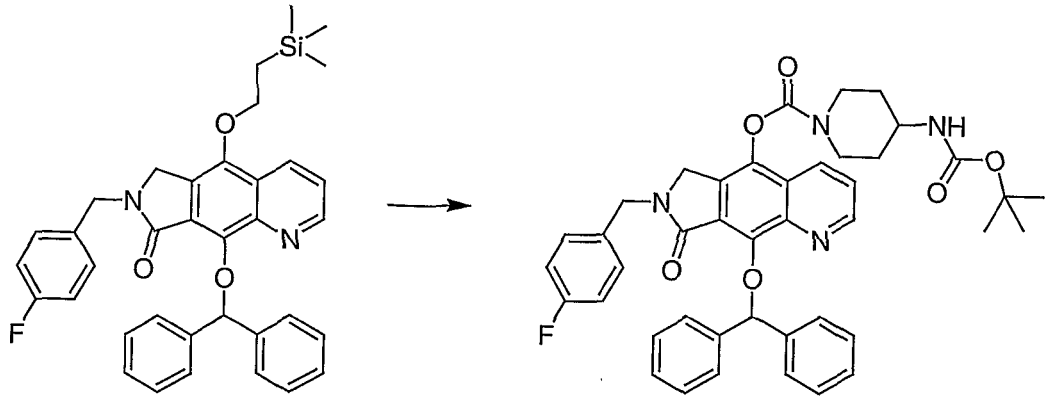
Stirred at room temperature 10 minutes until starting material consumed. Diluted with dichloromethane, washed with washed with 1M HCl solution, saturated brine, concentrated to give crude. Dissolved in 0.5 mL dichloromethane, added catalytic dimethylaminopyridine, triethylamine (0.025 mL, 0.1828 mmol) and 2 M morpholine sulfamoyl chloride solution **126** in dichloromethane (0.05 g, 0.10 mmol) and stirred at room temperature. After 1.5 hours, starting material consumed. Diluted with dichloromethane, washed with saturated brine, concentrated organics to give crude. Chromatographed (10% to 40% ethylacetate/hexanes) to give product **127** (0.0199 g, 0.031 mmol, 68%.) ^{1}H NMR ($CDCl_3$) δ 9.07 (s, 1H), 8.35 (d, 1H), 8.09 (s, 1H), 7.75 (d, 4H), 7.56 (dd, 1H), 7.27 (m, 8H), 7.05 (dd, 2H), 4.82 (s, 2H), 4.46 (s, 2H), 3.81 (m, 4H), 3.75 (m, 4H), 3.48 (m, 4H), 3.27 (m, 4H.) MS: 790 (M+1)



127 **128**

Example 128

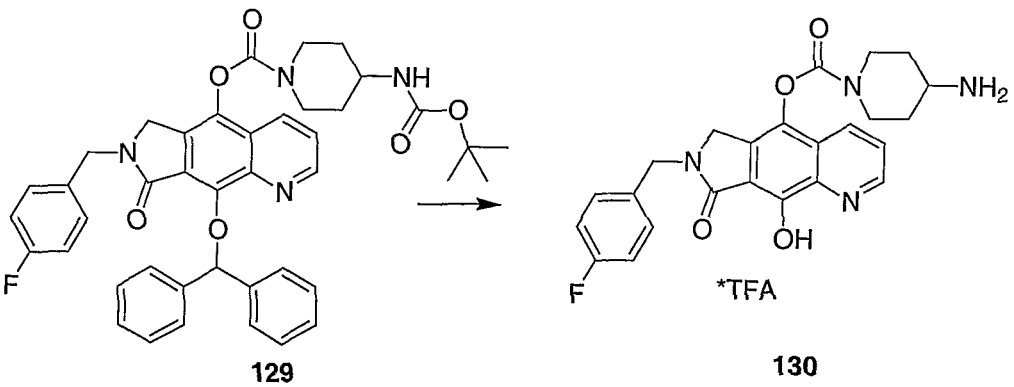
Sulfamate **127** (0.095 g, 0.012 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **128** (0.0054 g, 0.0086 mmol, 71%.) ^{1}H NMR ($CDCl_3$) δ 9.00 (s, 1H), 8.45 (d, 1H), 7.65 (dd, 1H), 7.33 (dd, 2H), 7.10 (dd, 2H), 4.79 (s, 2H), 4.59 (s, 2H), 3.86 (m, 4H), 3.76 (m, 4H), 3.59 (m, 4H), 3.28 (m, 4H.) MS: 624 (M+1), 622 (M-1)



44 129

Example 129

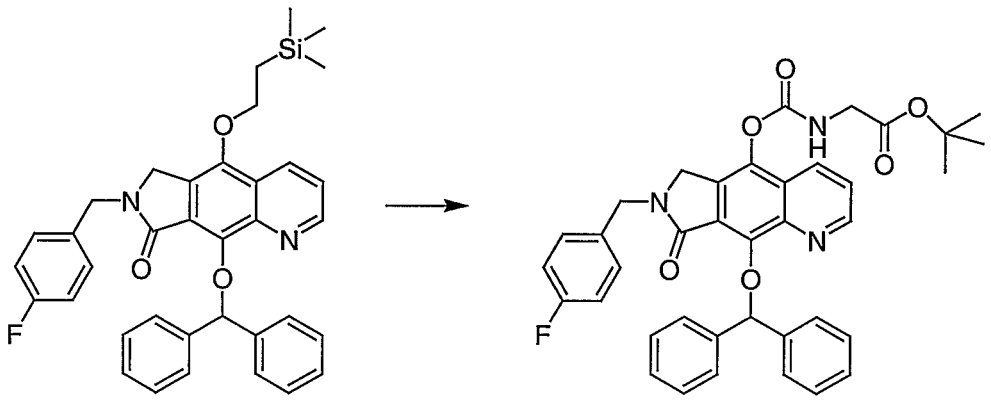
Trimethylsilylethyl ether **44** (0.1 g, 0.169 mmol) was dissolved in 2 mL dry tetrahydrofuran. To this was added triethylamine (0.094 mL, 0.676 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.339 mL, 0.339 mmol.) Stirred at room temperature 10 minutes until starting material consumed. Diluted with dichloromethane, washed with washed with 1M HCl solution, saturated brine, concentrated to give crude. Dissolved in 1.5 mL dichloromethane, added catalytic dimethylaminopyridine, triethylamine (0.139 mL, 1 mmol) and cooled to 0 °C. To this was added triphosgene (0.1 g, 0.339 mmol) and stirred 40 minutes. BOC-aminopiperidine (0.135 g, 0.678 mmol) was then added and stirred at room temperature for 10 minutes. Diluted with dichloromethane, washed with 1M HCl, brine, concentrated volatiles to give crude. Chromatographed (10% to 50% ethylacetate/hexanes) to give product **129** (0.072 g, 0.097 mmol, 59%.) ^{1}H NMR ($CDCl_3$) δ 9.04 (dd, 1H), 8.07 (d, 1H), 8.04 (s, 1H), 7.74 (d, 4H), 7.50 (dd, 1H), 7.27 (m, 8H), 7.06 (dd, 2H), 4.80 (s, 2H), 4.48 (br s, 1H), 4.28 (m, 1H), 4.21 (s, 3H), 3.71 (br s, 2H), 3.21 (dd, 2H), 3.03 (dd, 2H), 1.48 (s, 9H.) MS: 717 M+1)



129 130

Example 130

Carbamate **129** (0.07 g, 0.097mmol) was dissolved in 2 mL of dichloromethane. To this was added 0.5 mL of triethylsilane and 0.2 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Then dissolved in 1.5 mL dichloromethane, 1.5 ml trifluoroacetic acid. Stirred at room temperature for one hour. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **130** (0.0329 g, 0.058 mmol, 60%.) ^{1}H NMR (CD_3SOCD_3) δ 8.98 (s, 1H), 8.22 (d, 1H), 7.95 (s, 2H), 7.74 (dd, 1H), 7.35 (dd, 2H), 7.19 (dd, 2H), 4.70 (s, 2H), 4.35 (s, 3H), 4.00 (br s, 1H), 3.44 (br s, 7H.) ^{19}F NMR: -74.1 MS: 451 (M+1), 449 (M-1)

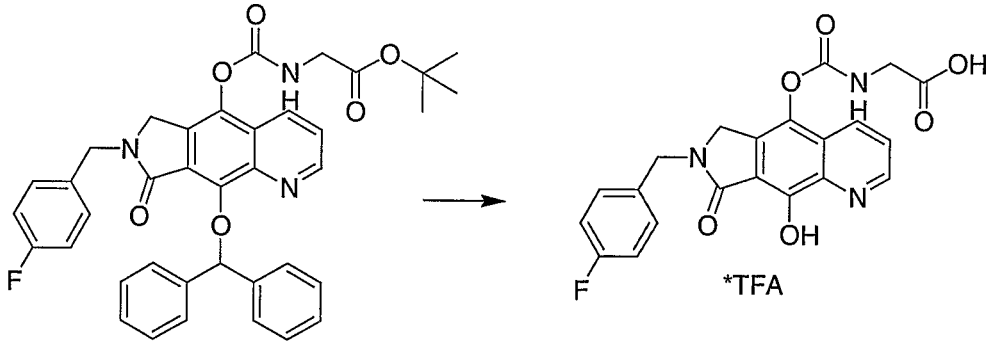


44 **131**

Example 131

Triphosgene (0.06 g, 0.2032 mmol) was added to 0.5 mL dichloromethane and cooled to 0 °C. To this was slowly added glycine tertiary-butyl ester HCl salt (0.034 g, 0.2032 mmol) and triethylamine (0.14 mL, 1 mmol) and stirred at 0 °C. Stirred thirty minutes until starting material consumed. Simultaneously, in a separate flask trimethylsilylethyl ether compound **44** was dissolved in 0.5 mL tetrahydrofuran. To this was added triethylamine (0.028 mL, 0.2032 mmol) and 1M tetrabutylammonium fluoride in tetrahydrofuran (0.1016 mL, 0.1016 mmol) and stirred at room temperature. After 20 minutes, diluted with dichloromethane, washed with 1M HCl solution and brine, concentrated to give crude. At 0 °C, crude dissolved in 0.5mL dichloromethane and added to the glycine isocyanate prepared *in situ* above. Stirred at 0 °C for 5minutes, then stirred for one hour at room temperature. Diluted with dichloromethane, washed with 1M HCl

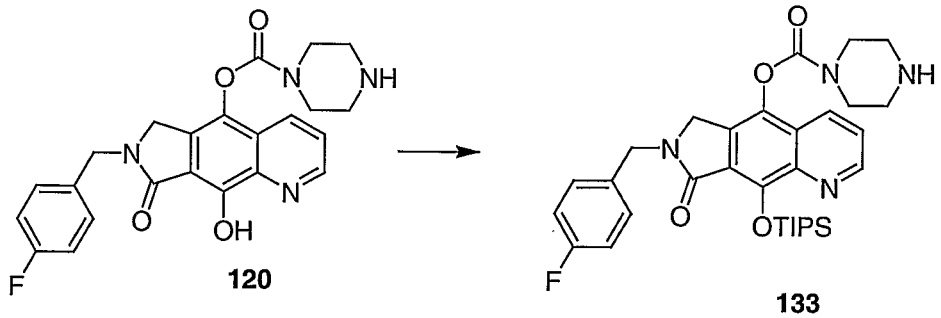
solution, brine, concentrated to give crude. Chromatographed (10% to 40% ethylacetate/hexanes) to give product **131** (0.017g, 0.026mmol, 52%.) ^{1}H NMR ($CDCl_3$) δ 9.03 (d, 1H), 8.20 (dd, 1H), 8.05 (s, 1H), 7.75 (d, 4H), 7.51 (dd, 1H), 7.27 (m, 8H), 7.04 (dd, 2H), 5.66 (s, 1H), 4.79 (s, 2H), 4.23 (s, 2H), 3.93 (d, 2H), 1.5 (s, 9H.) MS: 648 (M+1)



131 **132**

Example 132

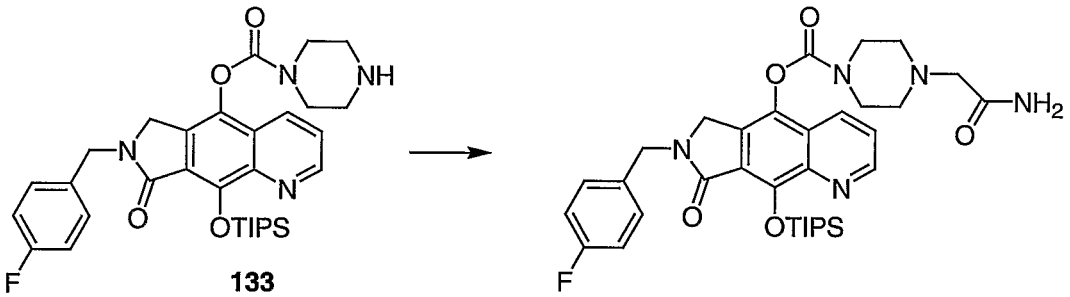
Carbamate **131** (0.017 g, 0.026 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Then dissolved in 0.5 mL dichloromethane, 0.2 mL triethylsilane, 0.2 ml trifluoroacetic acid. Stirred at room temperature for three hours. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated with 1:1 diethylether/hexanes to give product **132** (0.0088 gm, 0.021 mmol, 80%.) ^{1}H NMR (CD_3SOCD_3) δ 8.97 (s, 1H), 8.40 (s, 1H), 8.30 (d, 1H), 7.74 (dd, 1H), 7.37 (m, 2H), 7.23 (m, 2H), 4.69 (s, 2H0, 4.32 (s, 2H), 3.76 (d, 2H.) ^{19} F NMR: -74.3 MS: 426 (M+1), 424 (M-1)



120 **133**

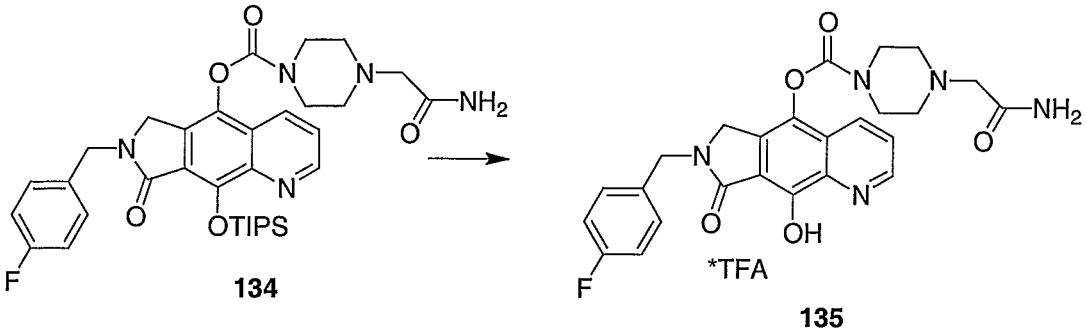
Example 133

Carbamate **120** (0.019 g, 0.0435 mmol) was dissolved in 0.5 mL of dichloroethane. To this was added triethylamine (0.072 mL, 0.52 mmol) and triisopropylsilyl chloride (0.058 mL, 0.26 mmol) and stirred at 50 °C. After 19 hours, starting material consumed, diluted with dichloromethane, washed with 1M HCl solution, brine and concentrated to give crude. Chromatographed to give product **133** (0.012 g, 0.0203 mmol, 47%.) ^{1}H NMR ($CDCl_3$) δ 8.86 (s, 1H), 8.06 (d, 1H), 7.54 (dd, 1H), 7.33 (dd, 2H), 7.08 (dd, 2H), 4.78 (s, 2H), 4.21 (s, 4H), 4.01 (br s, 2H), 3.35 (br s, 4H), 11.58 (m, 1H), 1.16 (d, 18H.) MS: 593 (M+1)



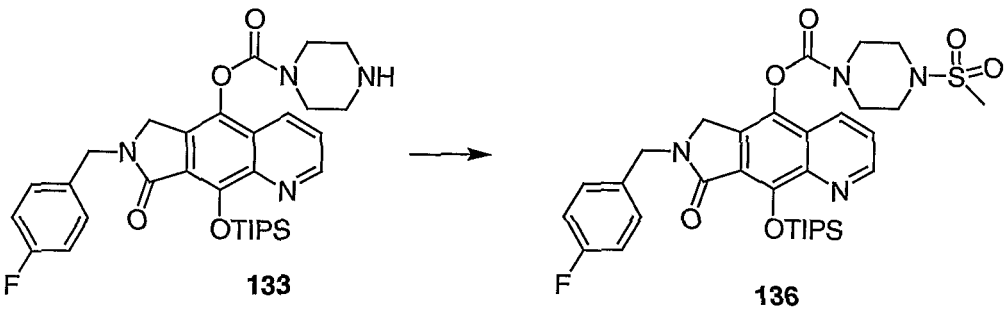
Example 134

Piperazine carbamate **133** (0.012 g, 0.0203 mmol) was dissolved 0.5 mL of acetonitrile and 0.2 mL dichloromethane. To this was added Cs_2CO_3 (0.0325 g, 0.1 mmol) and 2-bromoacetamide (0.009 g, 0.0608 mmol.) Stirred at room temperature for 3.5 days, until starting material was consumed. Diluted with dichloromethane, washed with saturated NH_4Cl solution, concentrated to give product **134** (0.0037 g, 0.0057, 28%.) ^{1}H NMR ($CDCl_3$) δ 8.87 (dd, 1H), 8.11 (d, 1H), 7.73 (s, 1H), 7.53 (dd, 1H), 7.34 (dd, 2H), 7.07 (dd, 2H), 4.78 (s, 2H), 4.23 (s, 2H), 3.84 (br s, 2H), 3.64 (br s, 2H), 3.14 (s, 2H), 2.62 (br s, 4H), 1.58 (m, 3H), 1.17 (d, 18H.) MS: 650 (M+1)



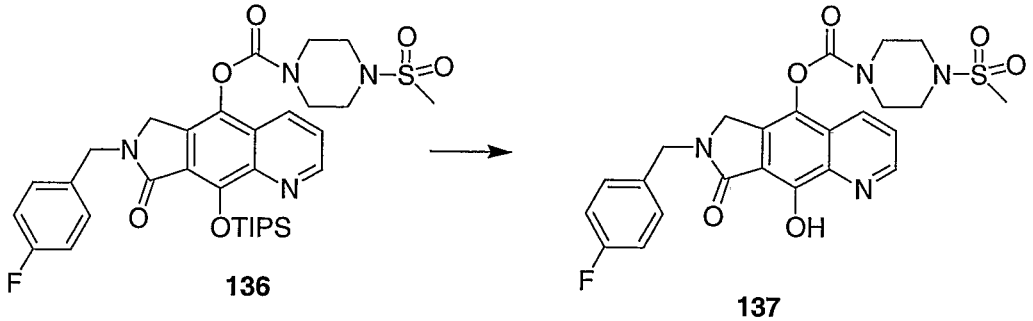
Example 135

Mono-carbamate **134** (0.0037 g, 0.0057 mmol) was dissolved in 0.2 mL of dichloromethane. To this was added trifluoroacetic acid (0.009 mL, 0.114 mmol) and stirred at room temperature. After twenty hours, concentrated off volatiles, azeotroped with toluene (2x), concentrated to give crude. Triturate with 1:1 diethylether/hexanes to give product **135** (0.0015 g, 0.0024 mmol, 43%.) ^{1}H NMR (CD_3OD) δ 8.96 (s, 1H), 8.38 (s, 1H), 7.75 (m, 2H), 7.39 (dd, 2H), 7.11 (dd, 2H), 4.87 (s, 2H), 4.42 (s, 2H), 4.0 (br m, 8H), 3.3 (s, 2H.) ^{19}F : -77.73 MS: 494 (M+1), 492 (M-1)



Example 136

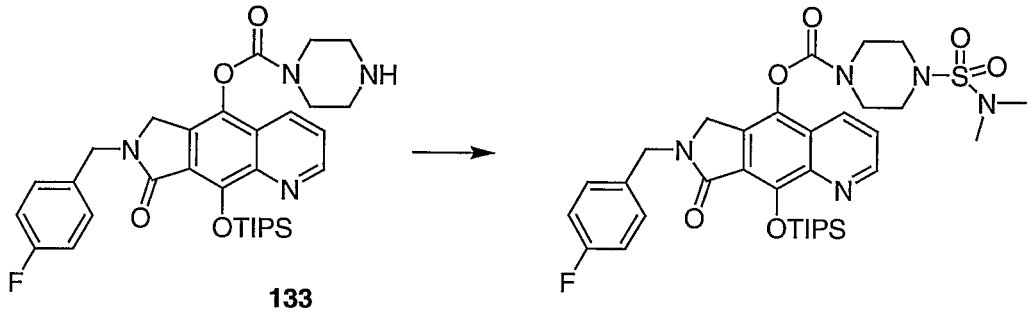
Piperazine carbamate **133** (0.033 g, 0.056 mmol) was dissolved in 0.5 mL dichloromethane. To this was added catalytic dimethylaminopyridine, triethylamine (0.031 mL, 0.225 mmol) and methanesulfonyl chloride (0.0087 mL, 0.112 mmol) at 0 °C. After five minutes, continued stirring at room temperature. After one hour starting material consumed. Diluted with dichloromethane, washed with saturated NH_4Cl solution, dried (Na_2SO_4) concentrated to give crude. Chromatographed (10% to 60% ethylacetate/hexanes) to give product **136** (0.013 g, 0.019 mmol, 35%.) ^{1}H NMR ($CDCl_3$) δ 8.88 (dd, 1H), 8.08 (d, 1H), 7.53 (dd, 1H), 7.33 (dd, 2H), 7.05 (dd, 2H), 4.79 (s, 2H), 4.23 (s, 2H), 3.93 (br s, 2H), 3.72 (br s, 2H), 3.37 (br s, 4H), 2.88 (s, 3H), 1.58 (m, 3H), 1.17 (d, 18H.) MS: 671 (M+1)



136 137

Example 137

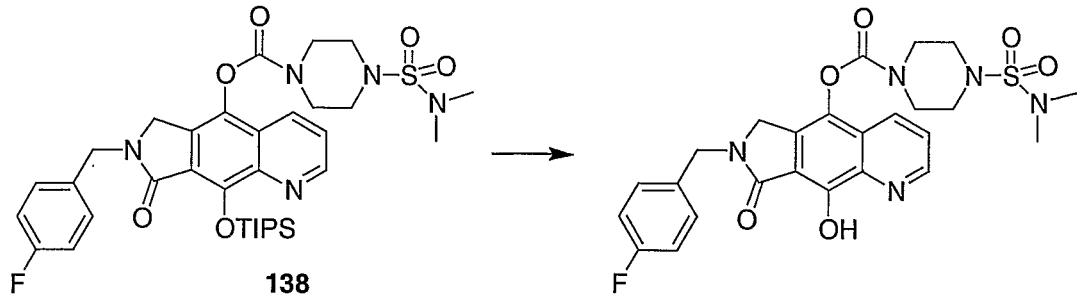
Mono-carbamate **136** (0.013 g, 0.019 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added trifluoroacetic acid (0.056 mL, 0.72 mmol) and stirred at room temperature. After twenty hours, concentrated off volatiles, azeotroped with toluene (2x), concentrated to give crude. Triturate with 1:1 diethylether/hexanes to give product **137** (0.0066 g, 0.013 mmol, 68%.) ^{1}H NMR ($CDCl_3$) δ 9.01 (s, 1H), 8.17 (s, 1H), 7.61 (s, 1H), 7.27 (dd, 2H), 7.07 (dd, 2H), 4.79 (s, 2H), 4.37 (s, 2H), 3.93 (br s, 2H), 3.72 (br s, 2H), 3.39 (br s, 4H), 2.89 (s, 3H.) MS: 515 (M+1), 513 (M-1)



133 138

Example 138

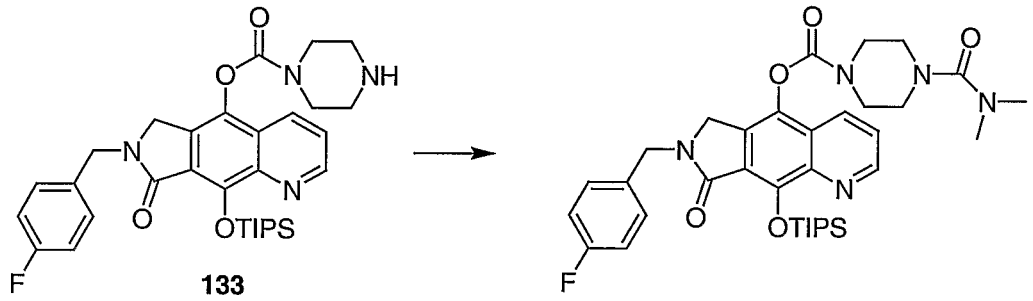
Piperazine carbamate **133** (0.033 g, 0.056 mmol) was dissolved in 0.5 mL dichloromethane. To this was added catalytic dimethylaminopyridine, triethylamine (0.031 mL, 0.225 mmol) and methanesulfonyl chloride (0.0087 mL, 0.112 mmol) at 0 °C. After five minutes, continued stirring at room temperature. After one hour starting material consumed. Diluted with dichloromethane, washed with saturated NH_4Cl solution, dried (Na_2SO_4) concentrated to give crude. Chromatographed (10% to 50% ethylacetate/hexanes) to give product **138** (0.012 g, 0.017 mmol, 31%.) ^{1}H NMR ($CDCl_3$) δ 8.87 (dd, 1H), 8.09 (d, 1H), 7.53 (dd, 1H), 7.31 (dd, 2H), 7.07 (dd, 2H), 4.79 (s, 2H), 4.23 (s, 2H), 3.87 (br s, 2H), 3.66 (br s, 2H), 3.35 (br s, 4H), 2.89 (s, 6H), 1.56 (m, 3H), 1.17 (d, 18H.) MS: 700 (M+1)



138 139

Example 139

Mono-carbamate **138** (0.012 g, 0.017 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added trifluoroacetic acid (0.056 mL, 0.72 mmol) and stirred at room temperature. After twenty hours, concentrated off volatiles, azeotroped with toluene (2x), concentrated to give crude. Triturate with 1:1 diethylether/hexanes to give product **139** (0.0039 g, 0.007 mmol, 42%.) ^{1}H NMR ($CDCl_3$) δ 9.00 (s, 1H), 8.18 (d, 1H), 7.60 (s, 1H), 7.27 (dd, 2H), 7.07 (dd, 2H), 4.78 (s, 2H), 4.36 (s, 2H), 3.88 (br s, 2H), 3.67 (br s, 2H), 3.35 (br s, 4H), 2.89 (s, 6H.) MS: 544 (M+1), 542 (M-1)

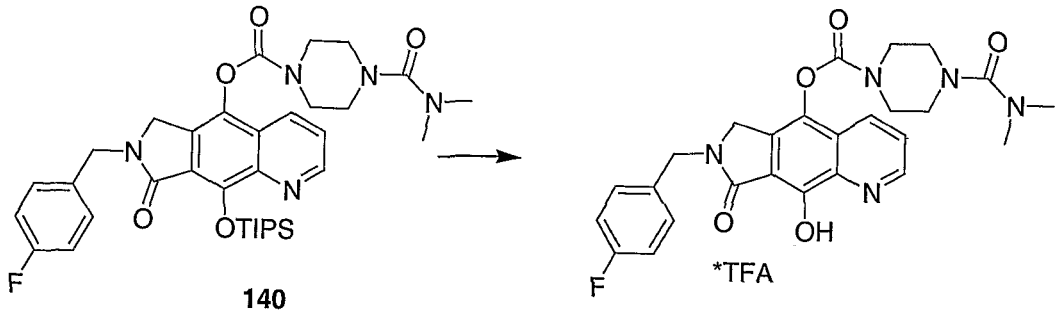


133 140

Example 140

Piperazine carbamate **133** (0.033 g, 0.056 mmol) was dissolved in 0.5 mL dichloromethane. To this was added catalytic dimethylaminopyridine, triethylamine (0.031 mL, 0.225 mmol) and methanesulfonyl chloride (0.0087 mL, 0.112 mmol) at 0 °C. After five minutes, continued stirring at room temperature. After one hour starting material consumed. Diluted with dichloromethane, washed with saturated NH_4Cl solution, dried (Na_2SO_4) concentrated to give crude. Chromatographed (50% to 100% ethylacetate/hexanes) to give product **140** (0.012 g, 0.018 mmol, 32%.) ^{1}H NMR ($CDCl_3$) δ 8.85 (dd, 1H), 8.11 (d, 1H), 7.52 (dd, 1H), 7.31 (dd, 2H), 7.07 (dd, 2H), 4.79 (s, 2H), 4.23

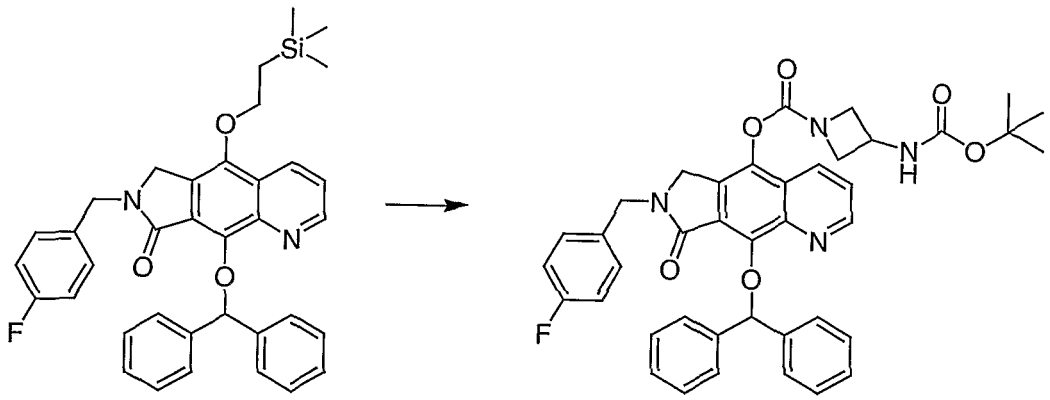
(s, 2H), 3.82 (br s, 2H), 3.60 (br s, 2H), 3.34 (br s, 4H), 2.91 (s, 6H), 1.56 (m, 3H), 1.17 (d, 18H.) MS: 664 (M+1)



140 141

Example 141

Mono-carbamate **140** (0.012 gm, 0.018 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added trifluoroacetic acid (0.056 mL, 0.72 mmol) and stirred at room temperature. After twenty hours, concentrated off volatiles, azeotroped with toluene (2x), concentrated to give crude. Triturate with 1:1 diethylether/hexanes to give product **141** (0.0051 g, 0.0083 mmol, 46%.) ^{1}H NMR ($CDCl_3$) δ 9.00 (s, 1H), 8.21 (s, 1H), 7.60 (s, 1H), 7.27 (dd, 2H), 7.07 (dd, 2H), 4.76 (s, 2H), 4.37 (s, 2H), 3.83 (br s, 2H), 3.61 (br s, 2H), 3.35 (br s, 4H), 2.92 (s, 6H.) ^{19}F: -76.3 MS: 508 (M+1), 506 (M-1)

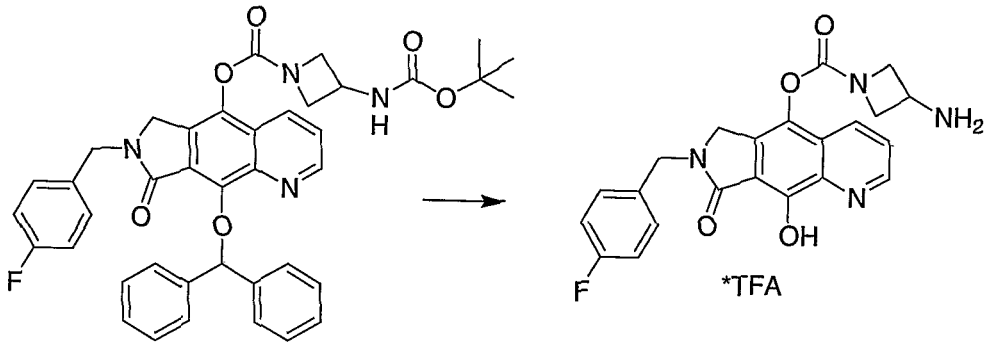


44 142

Example 142

Trimethylsilylethyl ether **44** (0.03 g, 0.0508 mmol) was dissolved in 0.5 mL dry tetrahydrofuran. To this was added triethylamine (0.028 mL, 0.2032 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.1016 mL, 0.1016 mmol.) Stirred at room temperature 10 minutes until starting material consumed. Diluted with dichloromethane, washed with washed with 1M HCl solution, saturated brine, dried

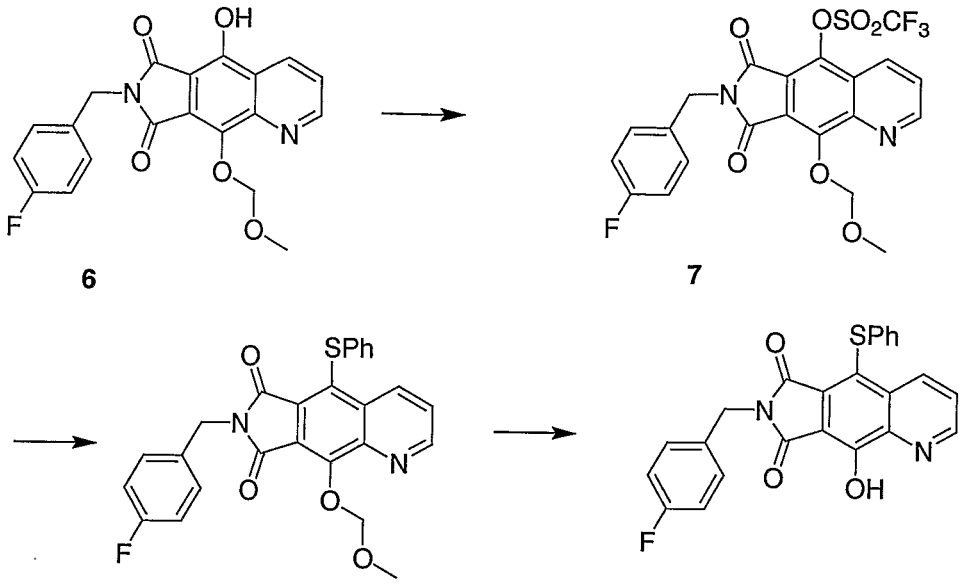
(Na_2SO_4,) concentrated to give crude. Dissolved in 0.5 mL dichloromethane, added catalytic dimethylaminopyridine, triethylamine (0.08 mL, 0.6 mmol) and cooled to 0 °C. To this was added triphosgene (0.03 g, 0.1016 mmol) and stirred 30 minutes. Azetid-3-yl carbamic acid t-butyl ester (0.035 g, 0.2032 mmol) and triethylamine (0.08 mL, 0.6 mmol) was then added and stirred at room temperature for 50 minutes. Diluted with dichloromethane, washed with 1M HCl, brine, dried (Na_2SO_4,) concentrated volatiles to give crude. Chromatographed (10% to 50% ethylacetate/hexanes) to give product **142** (0.024 g, 0.035 mmol, 69%.) ^{1}H NMR ($CDCl_3$) δ 9.04 (dd, 1H), 8.17 (d, 1H), 8.03 (s, 1H), 7.74 (d, 4H), 7.51 (dd, 1H), 7.27 (m, 8H), 7.08 (dd, 2H), 5.00 (m, 1H), 4.80 (s, 2H), 4.52 (m, 2H), 4.23 (s, 2H), 3.91 (m, 2H), 1.48 (s, 9H.) MS: 689 (M+1)



142 143

Example 143

Carbamate **142** (0.024 g, 0.035 mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.4 mL of triethylsilane and 0.2 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Then dissolved in 0.75 mL dichloromethane, 0.75 ml trifluoroacetic acid. Stirred at room temperature for one hour. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethylether/hexanes to give product **143** (0.0128 g, 0.024 mmol, 68%.) ^{1}H NMR (CD_3SOCD_3) δ 9.00 (s, 1H), 8.38 (br s, 3H), 7.75 (s, 1H), 7.36 (br s, 2H), 7.22 (br s, 2H), 4.72 (s, 2H), 4.32 (br m, 5H), 3.14 (br s, 2H.) ^{19}F NMR: -74.0 MS: 423 (M+1), 421 (M-1)



6 7

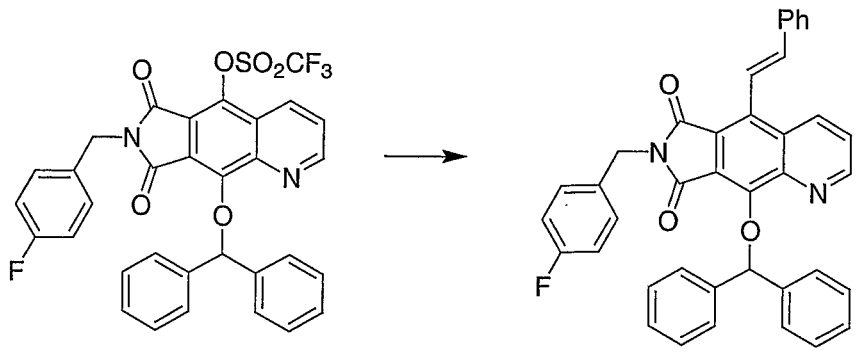
144 145

Example 144

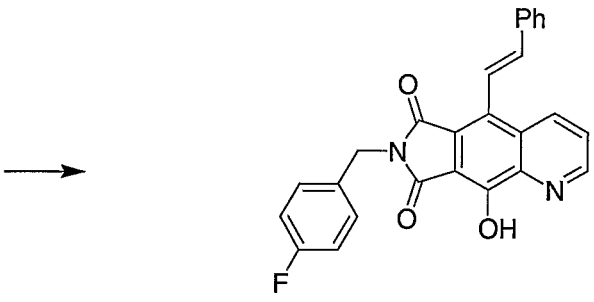
To crude triflate **7** (0.025 g, 0.048 mmol) in 1 mL of dichloroethane was added triethylamine (0.014 mL, 0.096 mmol) and benzenethiol (0.008 ml, 0.072 mmol) and the solution stirred at room temperature. After 15 hrs, the mixture was concentrated and chromatographed on silica gel eluting with EtOAc/hexanes to give compound **144** (0.01 g, 44%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 9.2 (m, 2H), 7.6 (dd, 1H),7.06 (m, 5H), 7.0 (t, 2 H), 5.97 (s, 2H), 4.85 (s, 2H), 3.72 (s, 3H); MS: 474 (M+1)

Example 145

MOM ether **144** (0.009 g, 0.019 mmol) in 1 mL of dichloromethane was treated with TFA (0.015 mL, 0.19 mmol) at room temperature for 15 hrs. The volatiles were removed in vacuo and the residue was triturated with diethylether to afford 7-(4-fluoro-benzyl)-9-hydroxy-5-phenylsulfanyl-pyrrolo[3,4-g]quinoline-6,8-dione **145** as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 9.31 (d, 2H), 7.81 (m, 1H), 7.46 (dd, 2H),7.17 (m, 5H), 7.04 (t, 2 H), 5.97 (s, 2H), 4.88 (s, 2H); MS: 430 (M+1).



56 146



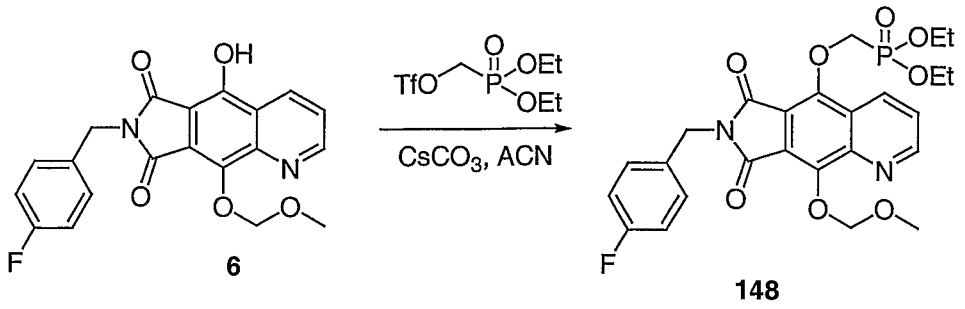
147

Example 146

To the triflate 5 (0.045 g, 0.07 mmol) in toluene (0.7 mL)/ethanol (0.3 mL)/water (0.2 mL) were added potassium carbonate (0.037 g, 0.175 mmol), trans-phenylvinylbronic acid (0.016 g, 0.105 mmol) and tetrakis (triphenylphosphine)-palladium (0) (0.012 g, 0.011 mmol). The mixture in the flask was flushed with argon three times. It was heated to 120°C under argon for 3 hours. Cooling to room temperature, it was diluted with EtOAc and washed with 1N HCl, saturated NaHCO3 and brine. The organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed on a silica gel column, eluting with EtOAc/Hexane to afford the product **146** (0.031g, 75%). MS: 613 (M+Na).

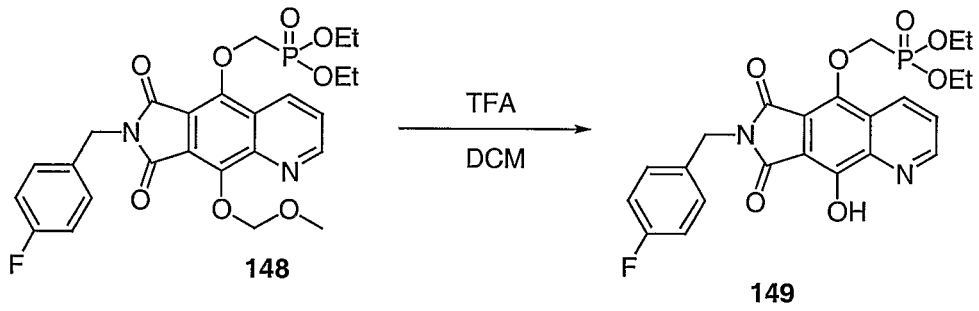
Example 147

Compound **146** (8 mg, 0.013 mmol) was dissolved in dichloromethane (1 mL) at room temperature under nitrogen. Triethylsilane (0.034 mL) was added followed by TFA (0.02 mL) slowly. The mixture was stirred at room temperature for 30 min. The solvent was removed at reduced pressure. The crude product was triturated in diethylether/hexane to afford a yellow solid **7**-(4-fluoro-benzyl)-9-hydroxy-5-styryl-pyrrolo[3,4-g]quinoline-6,8-dione **147** (0.005 g, 88%. ^1H NMR ($CDCl_3$): δ 8.99 (d, 1H), 8.88 (d, 1H), 8.05 (d, 1H), 7.67 (m, 3H), 7.36-7.52 (m, 5H), 7.01 (m, 3H), 4.87 (s, 2H); MS: 425 (M+1).



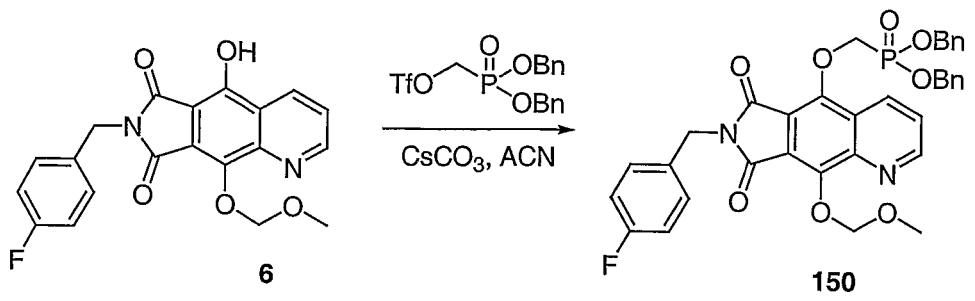
Example 148

To a solution of trifluoromethanesulfonic acid diethoxyphosphorylmethyl ester (D.P. Phillion, etal, *Tetra. Lett.*, 27 (1986) 1477-1480, 0.040 g, 0.104 mmol) dissolved in acetonitrile (0.75 mL) was added the phenol **6** (0.044 g, 0.146 mmol) and $CsCO_3$ (0.102 g, 0.314 mmol). The reaction mixture was stirred at room temperature for 3 hours under an inert atmosphere then filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (3/1 – ethylacetate/hexane) to afford the product **148** (0.014 g, 25%) as a solid: ^{1}H NMR ($CDCl_3$) δ 9.1 (d, 1H), 8.9 (d, 1H), 7.6 (dd, 1H), 7.5 (dd, 2H), 7.0 (t, 2H), 5.8 (s, 2H), 5.0 (d, 2H), 4.8 (s, 2H), 4.2 (m, 4H), 3.7 (s, 3H), 1.3 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 19.0; MS: 533 (M+1).



Example 149

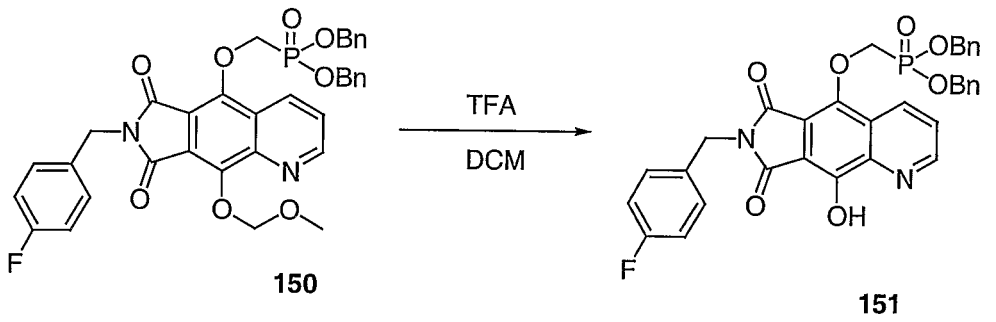
A solution of the phosphonate **148** (0.014 g, 0.026 mmol) in dichloromethane (0.96 mL) was treated with trifluoroacetic acid (0.020 mL, 0.260 mmol). The reaction mixture was stirred at room temperature under an inert atmosphere for 3 hours. The volatiles were removed in vacuo with toluene. The solid was triturated in diethylether/hexane to afford the product **149** (0.011g, 86%) as a TFA salt: ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.9 (d, 1H), 7.7 (dd, 1H), 7.5 (dd, 2H), 7.0 (t, 2H), 5.0 (d, 2H), 4.9 (s, 2H), 4.2 (m, 4H), 1.3 (s, 6H); ^{31}P NMR ($CDCl_3$) δ 19.2; MS: 489 (M+1), 487 (M-1).



6 150

Example 150

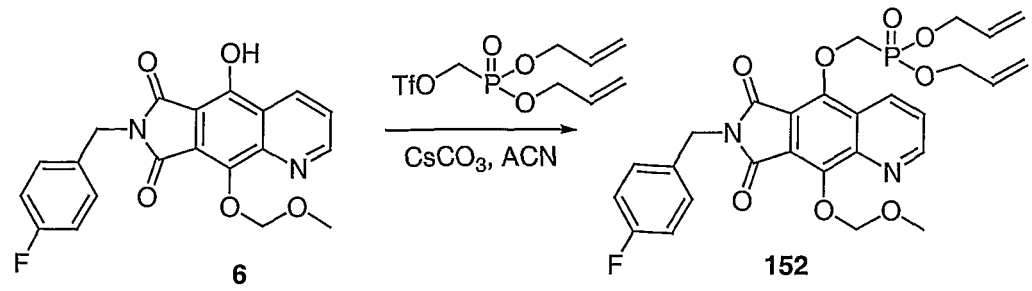
Dibenzyl hydroxymethyl phosphonate triflate was prepared from dibenzyl hydroxymethyl phosphonate (M. Krecmerova, et al, *Czech. Chem. Commun.*, 55, 1990, 2521-2536) by the method of: Y. Xu, etal, *J. Org. Chem.*, 61 (1996) 7697-7701. To a solution of dibenzyl hydroxymethyl phosphonate triflate (, 0.050 g, 0.131 mmol) dissolved in acetonitrile (1.87 mL) was added the phenol **6** (0.078 g, 0.183 mmol) and $CsCO_3$ (0.102 g, 0.314 mmol). The reaction mixture was stirred at room temperature for 3 hours under an inert atmosphere then filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (1/1 – ethylacetate/hexane) to afford the product **150** (0.030 g, 35%) as a solid: ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.65 (d, 1H), 7.5 (dd, 2H), 7.4 (dd, 1H), 7.3 (m, 10H), 7.0 (t, 2H), 5.8 (s, 2H), 5.1 (m, 4H), 4.9 (d, 2H), 4.8 (s, 2H), 3.7 (s, 3H); ^{31}P NMR ($CDCl_3$) δ 20.1; MS: 657 (M+1).



150 151

Example 151

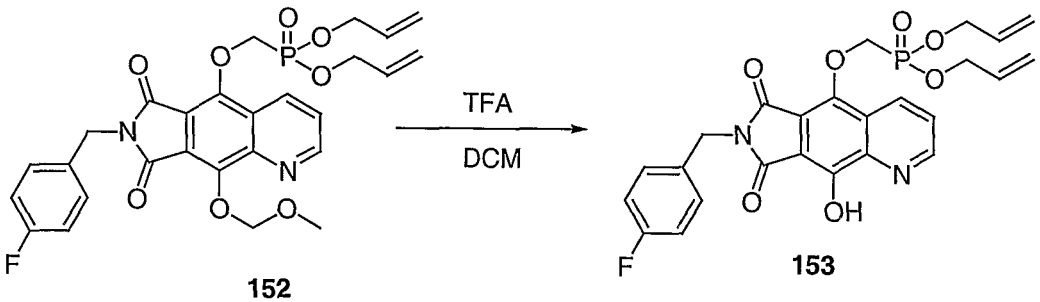
A solution of the phosphonate **150** (0.029 g, 0.044 mmol) in dichloromethane (1.6 mL) was treated with trifluoroacetic acid (0.034 mL, 0.44 mmol). The reaction mixture was stirred at room temperature under an inert atmosphere for 3 hours. The volatiles were removed *in vacuo* with toluene. The solid was triturated in diethylether/hexane to afford the product **151** (0.024 g, 89%) as a TFA salt: ^{1}H NMR ($CDCl_3$) δ 8.9 (d, 1H), 8.6 (d, 1H), 7.5 (dd, 2H), 7.45 (dd, 1H), 7.3-7.2 (m, 10H), 7.0 (t, 2H), 5.1-5.0 (m, 4H), 5.0 (d, 2H), 4.8 (s, 2H); ^{31}P NMR ($CDCl_3$) δ 20.3; MS: 613 (M+1), 611 (M-1).



6 152

Example 152

To a solution of diallyl hydroxymethyl phosphonate triflate (prepared by a method similar to: D.P. Phillion, etal, *Tetra. Lett.*, 27 (1986) 1477-1480 and Y. Xu, etal, *J. Org. Chem.*, 61 (1996) 7697-7701, 0.153 g, 0.471 mmol) dissolved in acetonitrile (6.7 mL) was added 7-(4-fluoro-benzyl)-5-hydroxy-9-methoxymethoxy-pyrrolo[3,4-g]quinoline-6,8-dione **6** (0.060 g, 0.157 mmol) and $CsCO_3$ (0.154 g, 0.471 mmol). The reaction mixture was stirred at room temperature for 2 hours under an inert atmosphere then filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (3/1 – ethylacetate/hexane) to afford [7-(4-fluoro-benzyl)-9-methoxymethoxy-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yloxymethyl]-phosphonic acid diallyl ester **152** (0.051 g, 59%) as a solid: ^{1}H NMR ($CDCl_3$) δ 9.05 (d, 1H), 8.85 (d, 1H), 7.6 (dd, 1H), 7.45 (dd, 2H), 7.0 (t, 2H), 5.9 (m, 2H), 5.8 (s, 2H), 5.3 (d, 2H), 5.2 (d, 2H), 5.0 (d, 2H), 4.8 (s, 2H), 4.6 (m, 4H), 3.7 (s, 3H); ^{31}P NMR ($CDCl_3$) δ 19.9; MS: 557 (M+1).

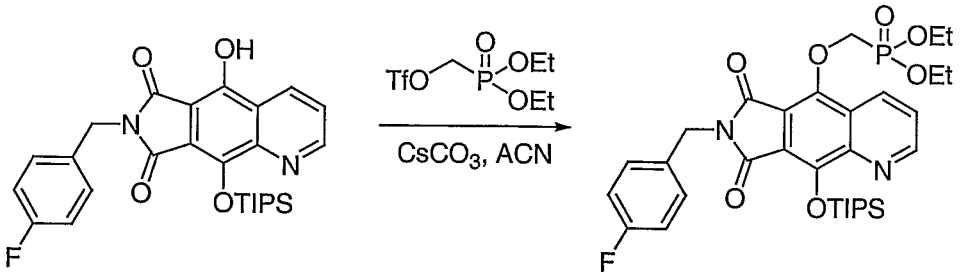


152 153

Example 153

A solution of the phosphonate **152** (0.0065 g, 0.0117 mmol) in dichloromethane (0.425 mL) was treated with trifluoroacetic acid (0.009 mL, 0.117 mmol). The reaction mixture was stirred at room temperature under an inert atmosphere for 1 hour. The volatiles were removed in vacuo with toluene. The solid was triturated in diethylether/hexane to afford the product **153** (0.006 g, 100%) as a TFA salt: ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.9

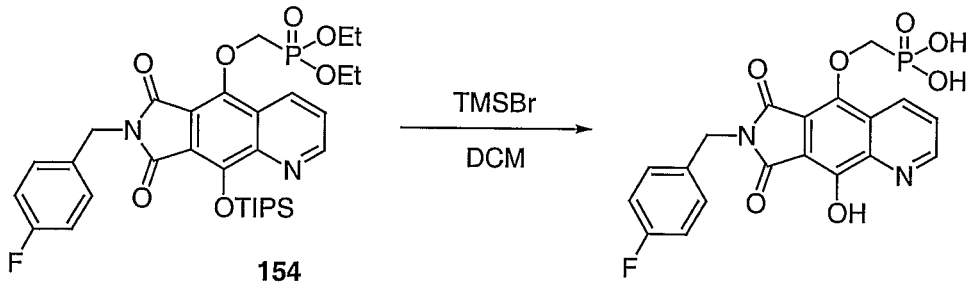
(d, 1H), 7.7 (dd, 2H), 7.5 (dd, 1H), 7.0 (t, 2H), 5.9 (m, 2H), 5.3 (d, 2H), 5.2 (d, 2H), 5.0 (d, 2H), 4.85 (s, 2H), 4.6 (m, 4H); ^{31}P NMR ($CDCl_3$) δ 20.0; MS: 513 (M+1), 511 (M-1).



12 154

Example 154

Diethyl hydroxymethyl phosphonate triflate was prepared from diethyl hydroxymethyl phosphonate (Aldrich, St. Louis, MO,) by the method of: D.P. Phillion, et al, *Tetra. Lett.*, 27, 1986, 1477-1480. To a solution of diethyl hydroxymethyl phosphonate triflate (0.61 g, 0.202 mmol) dissolved in acetonitrile (2.9 mL) was added the phenol **12** (0.100 g, 0.202 mmol) and $CsCO_3$ (0.198 g, 0.607 mmol). The reaction mixture was stirred at room temperature for 3 hours under an inert atmosphere then filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (1/1 – ethylacetate/hexane) to afford the product **154** (0.130 g, 100%) as a solid: ^{1}H NMR ($CDCl_3$) δ 8.95 (d, 1H), 8.9 (d, 1H), 7.6 (dd, 1H), 7.5 (dd, 2H), 7.0 (t, 2H), 4.9 (d, 2H), 4.8 (s, 2H), 4.2 (m, 4H), 1.5 (m, 3H), 1.3 (t, 6H), 1.2 (d, 18H); ^{31}P NMR ($CDCl_3$) δ 19.5; MS: 645 (M+1).

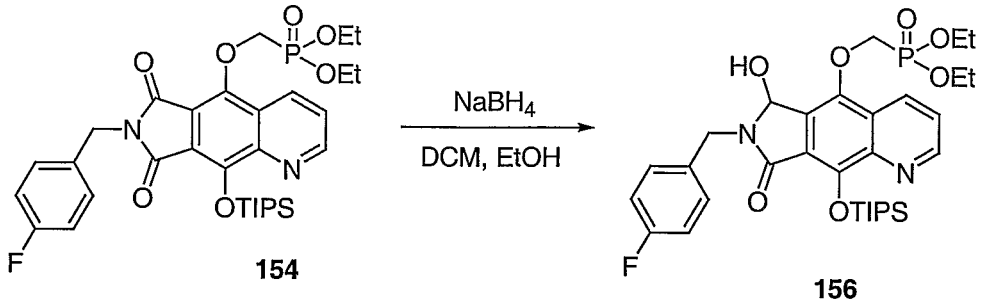


154 155

Example 155

A solution of the phosphonate **154** (0.020 g, 0.031 mmol) in dichloromethane (0.311 mL) was treated with trimethylsilane bromide (0.0246 mL, 0.186 mmol). The reaction mixture was stirred at room temperature overnight under an inert atmosphere. The volatiles were removed in vacuo with methanol. The solid was washed with dichloromethane to afford the diacid **155** (0.010 g, 77%): ^{1}H NMR (CD_3OD) δ 9.5 (d, 1H), 9.2 (d, 1H), 8.2 (dd,

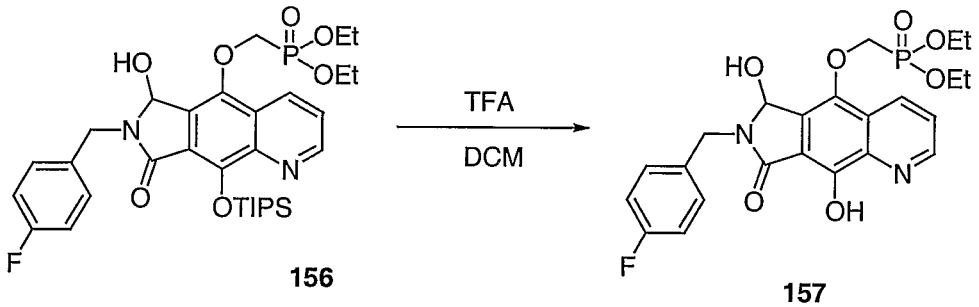
1H), 7.5 (dd, 2H), 7.1 (t, 2H), 5.0 (d, 2H), 4.9 (s, 2H); ^{31}P NMR (CD_3OD) δ 16.2; MS: 433 (M+1), 431 (M-1).



154 156

Example 156

To a solution of the phosphonate **154** (0.038 g, 0.059 mmol) dissolved in dichloromethane (0.297 mL) and ethanol (0.297 mL) was added sodium borohydride (0.475 mL, 0.237 mmol). The reaction mixture stirred at room temperature overnight under an inert atmosphere and then was concentrated in vacuo. The residue was dissolved in ethylacetate and washed with saturated NH_4Cl and brine. The organic phase was dried ($MgSO_4$) then concentrated in vacuo. The residue was purified by silica gel chromatography (1/99 – methanol/dichloromethane) to afford the product **156** (0.022 g, 59%): ^{1}H NMR ($CDCl_3$) δ 8.9 (d, 1H), 8.4 (d, 1H), 7.5 (dd, 1H), 7.4 (dd, 2H), 7.0 (t, 2H), 6.0 (s, 1H), 5.8 (bs, 1H), 5.2 (d, 1H), 4.6-4.4 (m, 2H), 4.4 (d, 1H), 4.3-4.2 (m, 4H), 1.6 (m, 3H), 1.4 (m, 6H), 1.15 (d, 18H); ^{31}P NMR ($CDCl_3$) δ 20.95; MS: 647 (M+1).

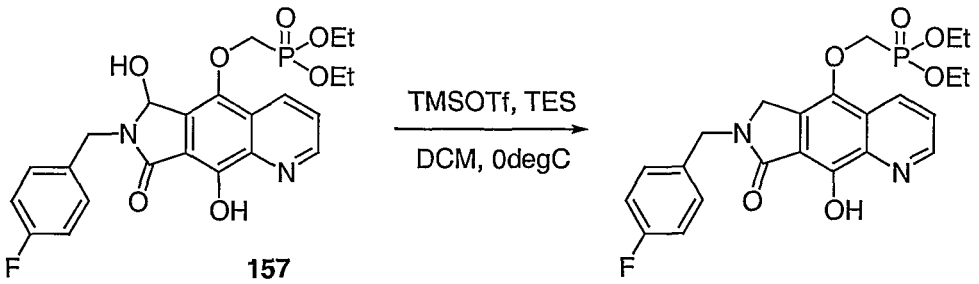


156 157

Example 157

A solution of the phosphonate **156** (0.025 g, 0.039 mmol) in dichloromethane (1.41 mL) was treated with trifluoroacetic acid (0.030 mL, 0.390 mmol). The reaction mixture was stirred at room temperature under an inert atmosphere overnight. The volatiles were removed in vacuo, azeotroping to dryness with toluene. The solid was triturated in diethylether/hexane to afford the product **157** (0.021 g, 100%) as a TFA salt: ^{1}H NMR

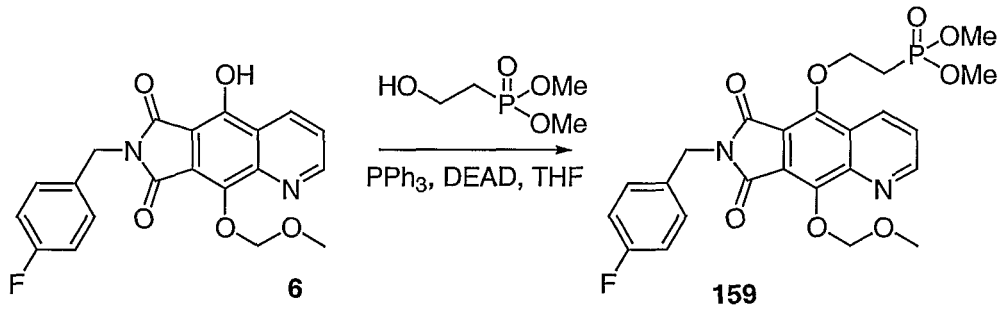
($CDCl_3$) δ 9.0 (d, 1H), 8.6 (d, 1H), 7.6 (dd, 1H), 7.4 (dd, 2H), 7.0 (t, 2H), 6.2 (bs, 1H), 6.0 (s, 1H), 5.1 (d, 1H), 4.7-4.5 (m, 2H), 4.5 (d, 1H), 4.25 (m, 4H), 1.4 (m, 6H); ^{31}P NMR ($CDCl_3$) δ 20.1; MS: 491 (M+1), 489 (M-1).



157 158

Example 158

A solution of phosphonate **157** (0.0185 g, 0.0378 mmol) in dichloromethane (0.455 mL) was cooled to 0° C. Triethylsilane (0.0603 mL, 0.378 mmol) and then trimethylsilane triflate (0.0205 mL, 0.113 mmol) were added. The reaction stirred for 15 minutes under an inert atmosphere. The mixture was partitioned between dichloromethane and water. The organic phase was washed with saturated $NaHCO_3$ then dried ($MgSO_4$) and concentrated in vacuo. The solid was triturated in diethylether/hexane to afford the product **158** (0.015 g, 84%): ^1H NMR ($CDCl_3$) δ 9.0 (dd, 1H), 8.6 (dd, 1H), 7.6 (dd, 1H), 7.35 (dd, 2H), 7.15 (t, 2H), 4.8 (s, 2H), 4.5 (s, 2H), 4.3 (d, 2H), 4.2 (m, 4H), 1.3 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 18.7; MS: 475 (M+1).

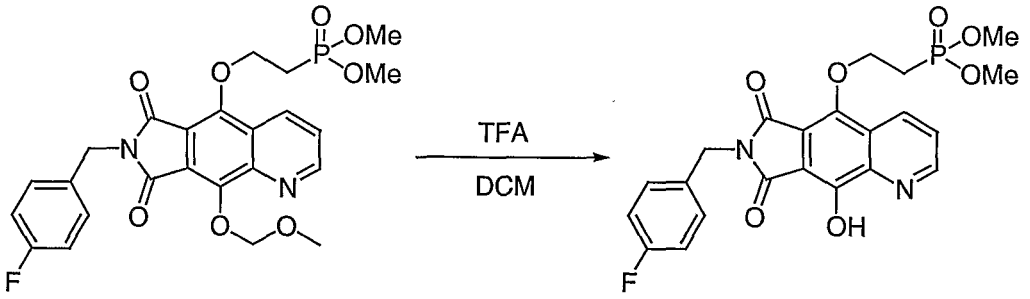


6 159

Example 159

To a solution of phenol **6** (0.063 g, 0.165 mmol) dissolved in THF (0.86 mL) was added dimethyl hydroxyethyl phosphonate (0.076 g, 0.495 mmol), triphenylphosphine (0.108 g, 0.412 mmol), and diethyl azodicarboxylate (0.039 mL, 0.247 mmol). The reaction mixture stirred at room temperature under an inert atmosphere overnight. The residue was purified directly by silica gel chromatography (5/95 – methanol/ethylacetate) to afford the

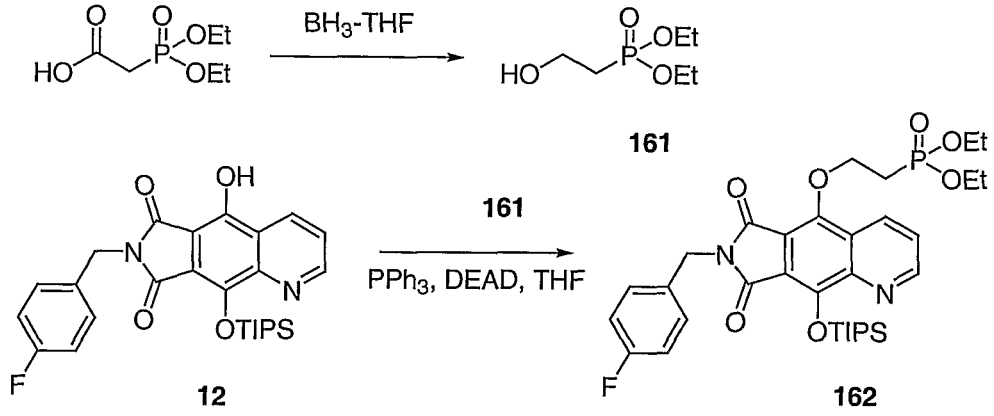
product **159** (0.022 g, 26%): ^{1}H NMR ($CDCl_3$) δ 9.05 (d, 1H), 8.9 (d, 1H), 7.6 (dd, 1H), 7.5 (dd, 2H), 7.0 (t, 2H), 5.8 (s, 2H), 4.8 (d, 2H), 4.75 (m, 2H), 3.8 (d, 6H), 3.7 (s, 3H), 2.5 (m, 2H); ^{31}P NMR ($CDCl_3$) δ 30.2; MS: 519 (M+1).



159 **160**

Example 160

A solution of the phosphonate **159** (0.012 g, 0.024 mmol) in dichloromethane (0.863 mL) was treated with trifluoroacetic acid (0.018 mL, 0.240 mmol). The reaction mixture was stirred at room temperature under an inert atmosphere overnight. The volatiles were removed in vacuo with toluene. The solid was triturated in diethylether/hexane to afford the product **160** (0.0095 g, 84%) as a TFA salt: ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.9 (d, 1H), 7.7 (dd, 1H), 7.5 (dd, 2H), 7.0 (t, 2H), 4.85 (d, 2H), 4.8 (m, 2H), 3.8 (d, 6H), 2.5 (m, 2H); ^{31}P NMR ($CDCl_3$) δ 30.3; MS: 475 (M+1), 473 (M-1).



12 **161** **162**

Example 161

A solution of diethyl phosphonacetic acid (0.700 g, 3.57 mmol) dissolved in THF was cooled to 0° C. Borane-THF complex (7.14 mL) in 1M THF was added dropwise. The reaction mixture was stirred for 3 hours under an inert atmosphere then concentrated in vacuo. The residue was directly purified by silica gel chromatography (5/95 – methanol/ethylacetate) to afford the product, diethyl hydroxyethyl phosphonate, **161** (0.583

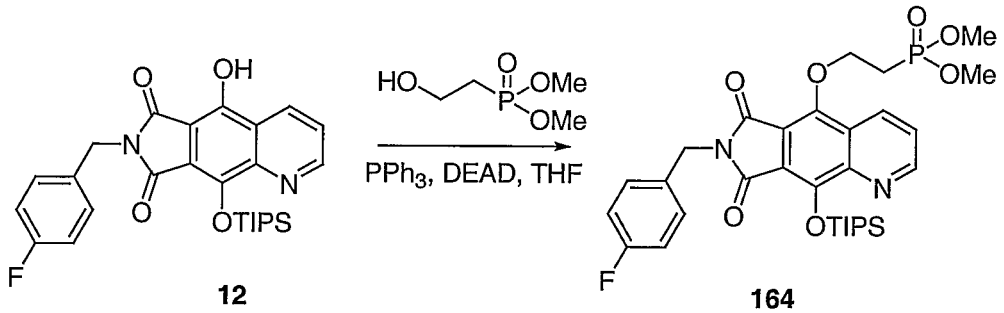
g, 90%) as an oil: ^{1}H NMR ($CDCl_3$) δ 4.1 (m, 4H), 3.9 (m, 2H), 2.1 (m, 2H), 1.3 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 30.4; MS: 183 (M+1).

Example 162

To a solution of phenol **12** (0.023 g, 0.046 mmol) dissolved in THF (0.24 mL) was added diethyl hydroxyethyl phosphonate **161** (0.025 g, 0.137 mmol), triphenylphosphine (0.030 g, 0.114 mmol), and diethyl azodicarboxylate (0.011 mL, 0.069 mmol). The reaction mixture stirred at room temperature under an inert atmosphere overnight. The residue was purified directly by silica gel chromatography (75/25 – ethylacetate/hexane). The residue was purified again by silica gel chromatography (80/20 toluene/acetone) to afford the product **162** (0.032 g, 48%): ^{1}H NMR ($CDCl_3$) δ 8.9 (d, 1H), 8.8 (d, 1H), 7.6 (dd, 1H), 7.45 (dd, 2H), 7.0 (t, 2H), 4.8 (s, 2H), 4.7 (m, 2H), 4.15 (m, 4H), 2.5 (m, 2H), 1.5 (m, 3H), 1.3 (t, 6H), 1.2 (d, 18H); ^{31}P NMR ($CDCl_3$) δ 27.6; MS: 659 (M+1).

Example 163

A solution of the phosphonate **162** (0.012 g, 0.018 mmol) in dichloromethane (0.663 mL) was treated with trifluoroacetic acid (0.014 mL, 0.180 mmol). The reaction mixture was stirred at room temperature under an inert atmosphere overnight. The volatiles were removed in vacuo with toluene. The solid was triturated in diethylether/hexane to afford the product **163** (0.008 g, 89%) as a TFA salt: ^{1}H NMR ($CDCl_3$) δ 9.0 (dd, 1H), 8.9 (dd, 1H), 7.7 (dd, 1H), 7.5 (dd, 2H), 7.0 (t, 2H), 4.8 (s, 2H), 4.75 (m, 2H), 4.15 (m, 4H), 2.45 (m, 2H), 1.3 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 27.5; MS: 503 (M+1), 501 (M-1).

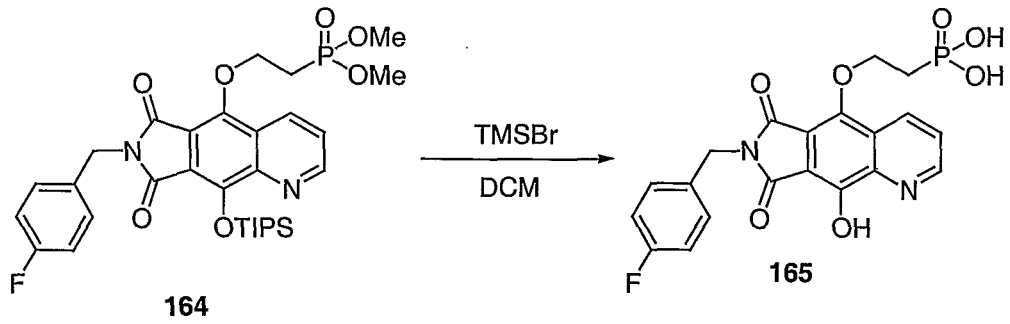


12 **164**

Example 164

To a solution of phenol **12** (0.097 g, 0.196 mmol) dissolved in THF (1.02 mL) was added (2-hydroxyethyl)-phosphonic acid dimethyl ester (0.091 g, 0.589 mmol), triphenylphosphine (0.129 g, 0.491 mmol), and diethyl azodicarboxylate (0.046 mL, 0.295 mmol). The reaction mixture stirred at room temperature under an inert atmosphere

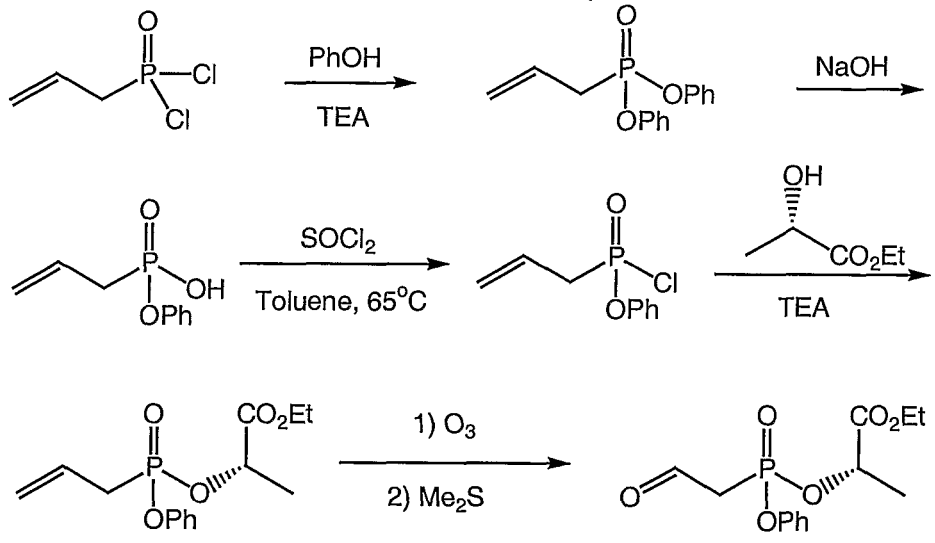
overnight. The residue was purified directly by silica gel chromatography (85/15 – ethylacetate/hexane) to afford a mixture of product **164** and triphenylphosphine oxide (0.160 g): ^{1}H NMR ($CDCl_3$) δ 8.95 (d, 1H), 8.75 (d, 1H), 7.7-7.4 (m, 12H), 7.0 (t, 2H), 4.8 (s, 2H), 4.7 (m, 2H), 3.8 (d, 6H), 2.5 (m, 2H), 1.5 (m, 3H), 1.2 (d, 18H); ^{31}P NMR ($CDCl_3$) δ 30.5 (triphenylphosphine oxide), 29.3; MS: 631 (M+1).



164 **165**

Example 165

A solution of the phosphonate **164** (0.025 g, 0.040 mmol) in dichloromethane (0.397 mL) was treated with trimethylsilane bromide (0.0314 mL, 0.24 mmol). The reaction mixture was stirred at room temperature under an inert atmosphere overnight. The volatiles were removed in vacuo with methanol. The solid was washed with dichloromethane to afford the diacid **165** (0.0094 g, 53%): ^{1}H NMR (CD_3OD) δ 9.4 (dd, 1H), 9.1 (dd, 1H), 8.05 (dd, 1H), 7.5 (dd, 2H), 7.1 (t, 2H), 4.9 (s, 2H), 4.8 (m, 2H), 2.45 (m, 2H); ^{31}P NMR (CD_3OD) δ 24.7; MS: 447 (M+1), 445 (M-1).



166

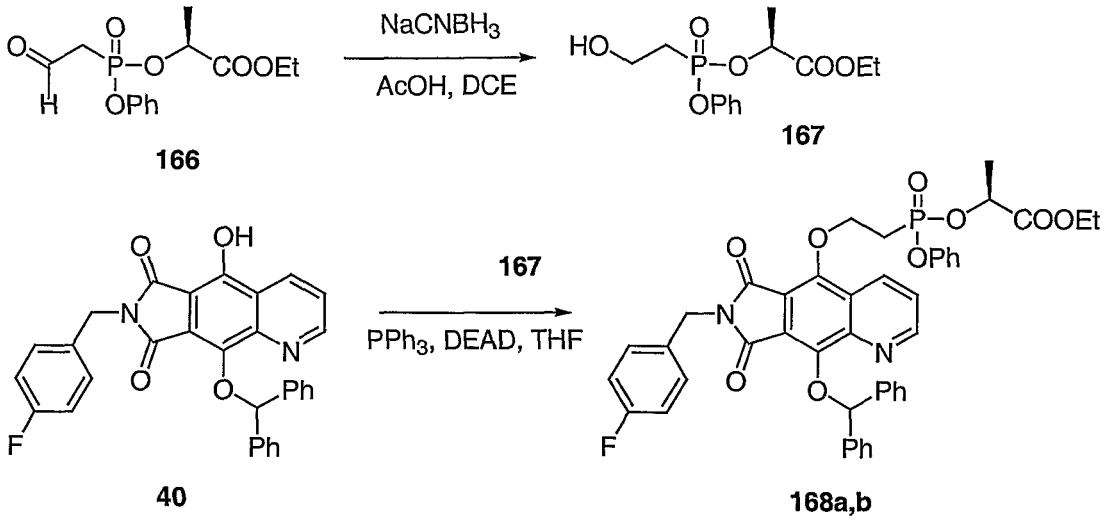
Example 166

To a solution of allylphosphonic dichloride (4 g, 25.4 mmol) and phenol (5.2 g, 55.3 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added triethylamine (TEA, 8.4 mL, 60 mmol). After stirring at room temperature for 1.5 h, the mixture was diluted with hexane-ethylacetate and washed with HCl (0.3 N) and water. The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (eluted with 2:1 hexane-ethyl acetate) to afford crude product diphenol allylphosphonate (7.8 g, containing the excessive phenol) as an oil which was used directly without any further purification. The crude material was dissolved in CH_3CN (60 mL), and NaOH (4.4N, 15 mL) was added at 0 °C. The resulting mixture was stirred at room temperature for 3 h, then neutralized with acetic acid to pH = 8 and concentrated under reduced pressure to remove most of the acetonitrile. The residue was dissolved in water (50 mL) and washed with CH_2Cl_2 (three 25 mL portions). The aqueous phase was acidified with concentrated HCl at 0 °C and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, evaporated and co-evaporated with toluene under reduced pressure to yield desired monophenol allylphosphonate (4.75 g. 95%) as an oil.

To a solution of monophenol allylphosphonate (4.75 g, 24 mmol) in toluene (30 mL) was added $SOCl_2$ (5 mL, 68 mmol) and DMF (0.05 mL). After stirring at 65 °C for 4 h , the reaction was complete as shown by ^{31}P NMR. The reaction mixture was evaporated and co-evaporated with toluene under reduced pressure to give the mono chloride (5.5 g) as an oil. To a solution of the mono chloride in CH_2Cl_2 (25 mL) at 0 °C was added ethyl (*S*)-lactate (3.3 mL, 28.8 mmol), followed by TEA. The mixture was stirred at 0 °C for 5 min, then at room temperature for 1 h, and concentrated under reduced pressure. The residue was partitioned between ethylacetate and HCl (0.2N), the organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the allyl monolactate (5.75 g, 80%) as an oil (2:1 mixture of two isomers): ^1H NMR ($CDCl_3$) δ 7.1-7.4 (m, 5H), 5.9 (m, 1H), 5.3 (m, 2H), 5.0 (m, 1H), 4.2 (m, 2H), 2.9 (m, 2H), 1.6; 1.4 (d, 3H), 1.25 (m, 3H); ^{31}P NMR ($CDCl_3$) δ 25.4, 23.9.

A solution of the allyl monolactate (2.5 g, 8.38 mmol) in CH_2Cl_2 (30 mL) was bubbled with ozone air at –78 °C until the solution became blue, then bubbled with nitrogen until the blue color disappeared. Methyl sulfide (3 mL) was added at –78 °C. The mixture was warmed up to room temperature, stirred for 16 h and concentrated under reduced

pressure to give desired aldehyde **166** (3.2 g, as a 1:1 mixture of DMSO): ^{1}H NMR ($CDCl_3$) δ 9.8 (m, 1H), 7.1-7.4 (m, 5H), 5.0 (m, 1H), 4.2 (m, 2H), 3.4 (m, 2H), 1.6; 1.4 (d, 3H), 1.25 (m, 3H). ^{31}P NMR ($CDCl_3$) δ 17.7, 15.4.



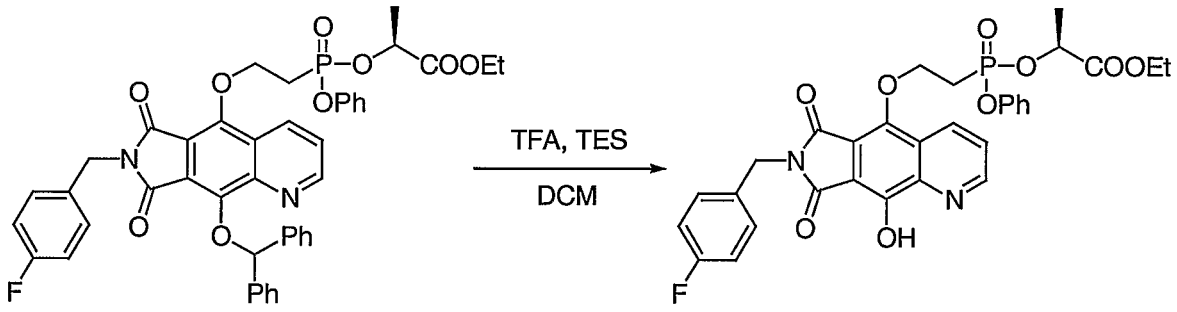
Example 167

To a solution of 2-[(2-oxo-ethyl)-phenoxy-phosphinoyloxy]-propionic acid ethyl ester; aldehyde **166** (0.082 g, 0.218 mmol) in a 1:1 mixture of DMSO and 1,2-dichloroethane was added acetic acid (0.050 mL, 0.870 mmol) then sodium cyanoborohydride (0.027 g, 0.435 mmol). The reaction mixture stirred at room temperature for three hours under an inert atmosphere. Saturated $NaHCO_3$ was added to the reaction mixture and was stirred for five more minutes. The mixture was concentrated in vacuo to remove most of the dichloroethane. Brine was added and then the crude product was extracted into ethylacetate. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (5/95 – methanol/dichloromethane) to afford the product **167** (0.047 g, 73%), an oil as a mixture of two diastereomers: ^{1}H NMR ($CDCl_3$) δ 7.1-7.4 (m, 5H), 5.1 (m, 1H), 4.25 (m, 2H), 4.1 (m, 2H), 2.3 (m, 4H), 1.6 & 1.4 (d, 3H), 1.25 (m, 3H); ^{31}P NMR ($CDCl_3$) δ 29.0, 26.8.

Example 168

To a solution of phenol **40** (0.033 g,0.065 mmol) dissolved in THF (0.34 mL) was added ethyl-lactate phosphonate alcohol **167** (0.029 g, 0.097 mmol), triphenylphosphine (0.043 g, 0.162 mmol), and diethyl azodicarboxylate (0.015 mL, 0.097 mmol). The reaction mixture stirred at room temperature under an inert atmosphere overnight. The residue was purified directly by silica gel chromatography (50/50 – ethylacetate/hexane) to afford the

product **168** (0.027 g, 53%). Separation of the diastereomers by chromatography allowed for characterization of **168a** (0.016g): ^{1}H NMR ($CDCl_3$) δ 9.1 (dd, 1H), 8.8 (dd, 1H), 7.9 (s, 1H), 7.6 (m, 4H), 7.55 (m, 1H), 7.4 (dd, 2H), 7.1-7.4 (m, 11H), 7.0 (t, 2H), 5.0 (m, 1H), 4.9 (s, 2H), 4.8 (m, 2H), 4.1 (q, 3H), 2.75 (m, 2H), 1.4 (d, 3H), 1.2 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 26.05; MS: 790 (M+1) - and **168b** (0.011g): ^{1}H NMR ($CDCl_3$) δ 9.1 (dd, 1H), 8.8 (dd, 1H), 7.95 (s, 1H), 7.6 (m, 4H), 7.55 (m, 1H), 7.40 (dd, 2H), 7.1-7.4 (m, 11H), 7.05 (t, 2H), 5.05 (m, 1H), 4.85 (s, 2H), 4.8 (m, 2H), 4.15 (q, 3H), 2.7 (m, 2H), 1.55 (d, 3H), 1.2 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 24.37; MS: 790 (M+1)



168a,b **169a,b**

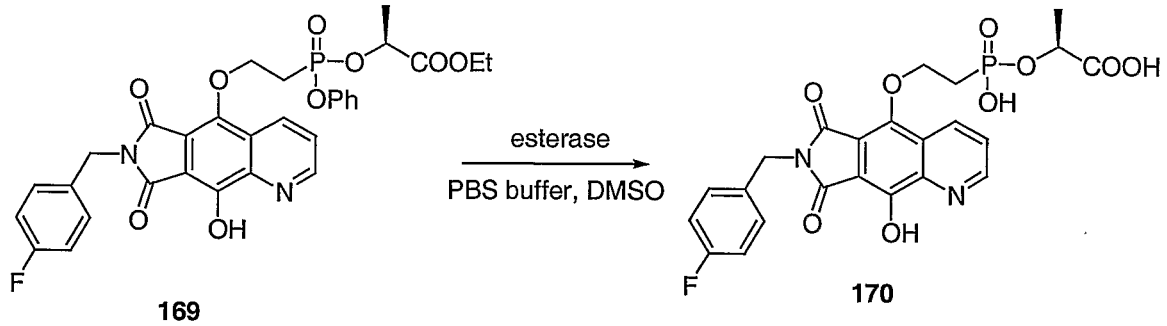
Example 169a

A solution of the phosphonate **168a** (0.013 g, 0.0165 mmol) in dichloromethane (0.5 mL) was treated with trifluoroacetic acid (0.1 mL) and triethylsilane (0.2 mL). The reaction mixture was stirred at room temperature under an inert atmosphere for 20 minutes. The volatiles were removed in vacuo with toluene. The solid was triturated in diethylether/hexane to afford the product **169a** (0.008 g, 80%) as a TFA salt: ^{1}H NMR ($CDCl_3$) δ 8.95 (dd, 1H), 8.9 (dd, 1H), 7.6 (m, 1H), 7.5 (dd, 2H), 7.1-7.4 (m, 5H), 7.0 (t, 2H), 5.0 (m, 1H), 5.0 (m, 2H), 4.85 (s, 2H), 4.15 (q, 3H), 2.8 (m, 2H), 1.4 (d, 3H), 1.25 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 26.13; MS: 623 (M+1), 621 (M-1).

Example 169b

A solution of the phosphonate **168b** (0.011 g, 0.014 mmol) in dichloromethane (0.5 mL) was treated with trifluoroacetic acid (0.1 mL) and triethylsilane (0.2 mL). The reaction mixture was stirred at room temperature under an inert atmosphere for 20 minutes. The volatiles were removed in vacuo with toluene. The solid was triturated in diethylether/hexane to afford the product **169b** (0.005 g, 60%) as a TFA salt: ^{1}H NMR ($CDCl_3$) δ 8.95 (dd, 1H), 8.9 (dd, 1H), 7.65 (m, 1H), 7.5 (dd, 2H), 7.1-7.4 (m, 5H), 7.0 (t,

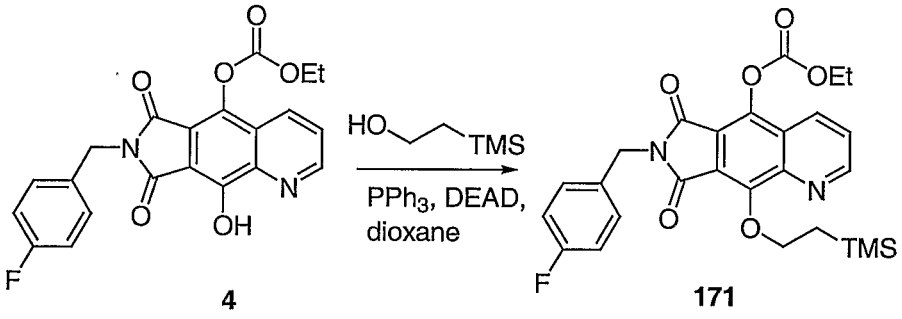
2H), 5.1 (m, 2H), 4.9 (m, 1H), 4.85 (s, 2H), 4.15(q, 3H), 2.7 (m, 2H), 1.55 (d, 3H), 1.2 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 24.44; MS: 623 (M+1), 621 (M-1).



169 170

Example 170

A solution of ethyl-lactate phosphonate **169** (0.021g, 0.034 mmol) in DMSO (0.675 mL) and phosphate buffer saline (3.38 ml) was heated to 40° C. The reaction mixture was treated with esterase-from porcine liver (0.200 mL) and stirred overnight. Another equivalent of esterase was added the following day and the mixture stirred another day. The mixture was concentrated and purified by reversed phase HPLC to afford the product **170** (0.008 g, 46%) as a solid: ^{1}H NMR (CD_3OD) δ 8.95 (dd, 1H), 8.9 (dd, 1H), 7.75 (m, 1H), 7.45 (dd, 2H), 7.05 (t, 2H), 4.9 (s, 2H), 4.85 (m, 3H), 2.5 (m, 2H), 1.5 (d, 3H); ^{31}P NMR (CD_3OD) δ 26.26; MS: 519 (M+1), 517 (M-1).

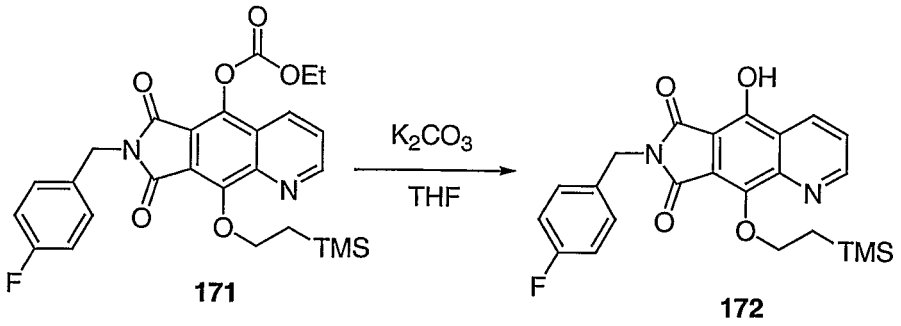


4 171

Example 171

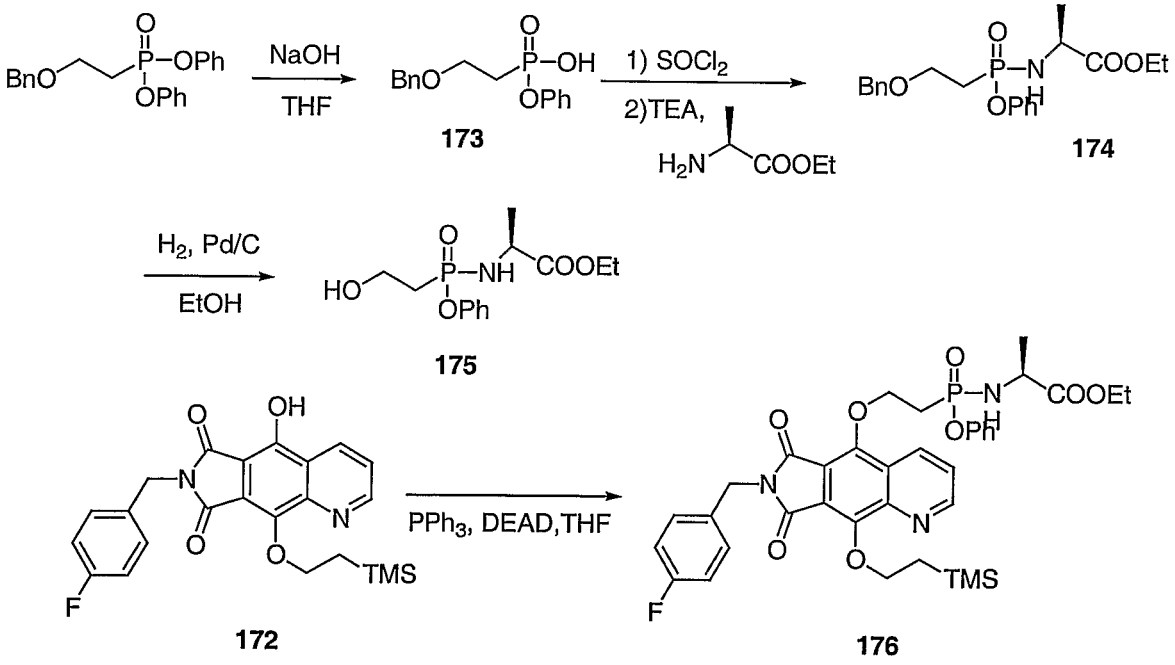
To a solution of phenol **4** (1.14 g, 2.79 mmol) dissolved in dioxane (27.9 mL) was added 2-(trimethylsilyl)-ethanol (0.600 mL, 4.18 mmol), triphenylphosphine (1.46 g, 5.57 mmol), and diethyl azodicarboxylate (0.88 mL, 5.57 mmol). The reaction mixture stirred at room temperature under an inert atmosphere overnight. The residue was purified directly by silica gel chromatography (30/70 – ethylacetate/hexane) to afford the product **171** (0.240 g, 67%): ^{1}H NMR ($CDCl_3$) δ 9.1 (dd, 1H), 8.5 (dd, 1H), 7.65 (dd, 1H), 7.45 (dd, 2H), 7.0 (t,

2H), 4.9 (m, 2H), 4.8 (s, 2H), 4.45 (q, 2H), 1.5 (t, 3H), 1.4 (m, 2H), 0.1 (s, 9H); MS: 510 (M+1).



Example 172

To the ethyl carbonate **171** (0.716 g, 1.4 mmol) in THF (70.2 mL) was added a solution (45 mL) of K_2CO_3 (1.94 g, 14 mmol) in water and 4-dimethylaminopyridine (0.035 g, 0.281 mmol). The yellow solution was stirred at room temperature under an inert atmosphere overnight. Most of THF was removed in vacuo and the remaining solution was diluted with dichloromethane, washed with 1N HCl and brine, then dried ($MgSO_4$) and concentrated. The crude product was triturated in diethylether/hexane to afford the yellow solid product **172** (0.428 g, 70%): ^{1}H NMR ($CDCl_3$) δ 9.1 (dd, 1H), 8.65 (dd, 1H), 7.6 (dd, 1H), 7.5 (dd, 2H), 7.0 (t, 2H), 4.85 (s, 2H), 4.85 (m, 2H), 1.35 (m, 2H), 0.1 (s, 9H); MS: 438 (M+1).



Example 173

To a solution of (2-benzyloxy-ethyl)-phosphonic acid dibenzyl ester (0.200 g, 0.543 mmol) in THF was added a solution of NaOH (1.36 mL, 1M) in water. The reaction mixture was stirred at room temperature for 3 hours. Most of THF was removed in vacuo and the residue was dissolved in water. The aqueous solution was washed with ethylacetate three times then acidified with 1N HCl (to pH=1) then extracted with ethylacetate. The organic phase was dried ($MgSO_4$), concentrated and co-evaporated with toluene in vacuo to afford the mono-acid, (2-benzyloxy-ethyl)-phosphonic acid monobenzyl ester, **173** (0.160 g. 100%) as an oil with no further purification: ^1H NMR ($CDCl_3$) δ 9.25 (bs, 1H), 7.4-7.1 (m, 10H), 4.5 (s, 2H), 3.8 (m, 2H), 2.25 (m, 2H); ^{31}P NMR ($CDCl_3$) δ 28.63.

Example 174

To a solution of the mono-acid **173** (0.160 g, 0.576 mmol) dissolved in acetonitrile (3.84 mL) was added thionyl chloride (0.42 mL, 5.76 mmol). The reaction mixture was heated to 70 °C and stirred for 3 hours at which point the reaction was completed as shown by ^{31}P NMR ($CDCl_3$) δ 36.7. The reaction mixture was concentrated as such to afford the intermediate mono-chloridate as an oil which was immediately dissolved in dichloromethane (2.88 mL) and treated with triethylamine (0.321 mL, 2.30 mmol). The reaction mixture was cooled to 0 °C and L-alanine ethyl ester (0.265 g, 1.73 mmol) was added. The mixture was stirred overnight at room temperature under an inert atmosphere and then was concentrated in vacuo. The residue was partitioned between ethylacetate and saturated NH_4Cl, and the organic phase was washed with brine, dried ($MgSO_4$) then concentrated in vacuo. The residue was purified by chromatography on silica gel washed with methanol prior to use (1/1 – ethylacetate/hexane) to afford the amidate **174** (0.095 g, 45%) as an oil with a 1:1.2 mixture of diastereomers: ^1H NMR ($CDCl_3$) δ 7.1-7.4 (m, 10H), 4.6 (s, 2H), 4.1 (q, 2H), 3.8 (m, 2H), 3.65 (m, 1H), 2.3 (m, 2H), 1.3 & 1.2 (d, 3H), 1.25 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 29.51, 28.70.

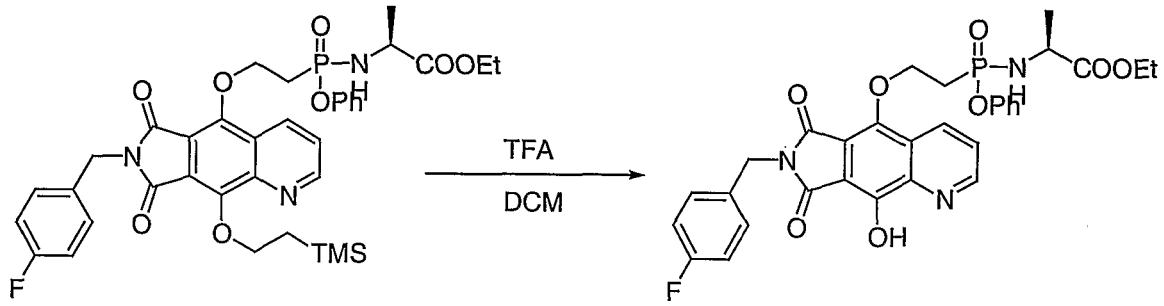
Example 175

To a solution of the amidate **174** (0.095 g, 0.243 mmol) dissolved in ethanol (4.9 mL) was added palladium (on carbon). The reaction was purged under a vacuum then submitted to hydrogen gas (via balloon attached to the reaction vessel). After several purges between gas and vacuum the reaction mixture was stirred at room temperature for 4 hours. The mixture was filtered with Celite and concentrated in vacuo to afford the alcohol **175** (0.74 g, 100%) as an oil with a 1:1.2 mixture of diastereomers without further

purification: ^{1}H NMR ($CDCl_3$) δ 7.4-7.1 (m, 5H), 4.15 (m, 2H), 3.7 (q, 2H), 3.5 (m, 1H), 2.2 (m, 2H), 1.35 & 1.25 (d, 3H), 1.25 (m, 3H); ^{31}P NMR ($CDCl_3$) δ 30.82, 30.54.

Example 176

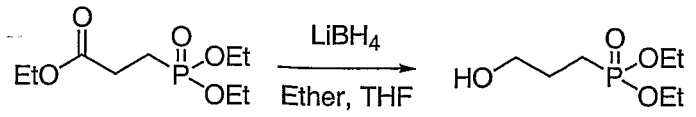
To a solution of phenol **172** (0.073 g, 0.167 mmol) dissolved in THF (1.67 mL) was added the alcohol **175** (0.075 g, 0.25 mmol), triphenylphosphine (0.087 g, 0.33 mmol), and diethyl azodicarboxylate (0.042 mL, 0.33 mmol). The reaction mixture stirred at room temperature under an inert atmosphere overnight. The residue was purified directly by chromatography on silica gel washed with methanol prior to use (80/20 – toluene/acetone) to afford the product **176** (0.065 g, 54%) with a 1:1.2 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 9.1 (dd, 1H), 8.8 (dd, 1H), 7.6 (dd, 1H), 7.5 (dd, 2H), 7.4-7.1 (m, 5H), 7.0 (t, 2H), 4.85 (s, 2H), 4.85-4.7 (m, 4H), 4.2 (q, 1H), 4.15 (m, 2H), 4.0-3.8 (m, 1H), 2.65 (m, 2H), 1.4 & 1.25 (d, 3H), 1.3 (m, 2H), 1.2 (m, 3H), 0.10 (s, 9H); ^{31}P NMR ($CDCl_3$) δ 27.84, 26.96; MS: 722 (M+1).



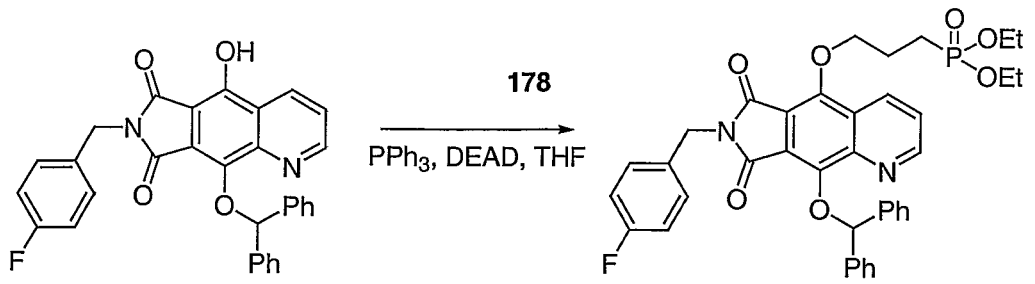
176 **177**

Example 177

A solution of the phosphonate **176** (0.030 g, 0.042 mmol) in dichloromethane (0.832 mL) was treated with trifluoroacetic acid (0.064 mL, 0.84 mmol). The reaction mixture was stirred at room temperature under an inert atmosphere for 45 minutes. The volatiles were removed in vacuo with toluene. The solid was triturated in diethylether/hexane to afford the product **177** (0.022 g, 85%) as a TFA salt with a 1:1.2 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 9.0 (dd, 1H), 8.85 (dd, 1H), 7.65 (dd, 1H), 7.5 (dd, 2H), 7.4-7.1 (m, 5H), 7.0 (t, 2H), 4.85 (s, 2H), 4.85 (m, 2H), 4.15 (m, 1H), 4.15 (m, 1H), 4.1 (m, 2H), 3.8 (m, 1H), 2.65 (m, 2H), 1.35 & 1.30 (d, 3H), 1.2 (m, 3H); ^{31}P NMR ($CDCl_3$) δ 27.86, 27.05; MS: 622 (M+1), 620 (M-1).



178



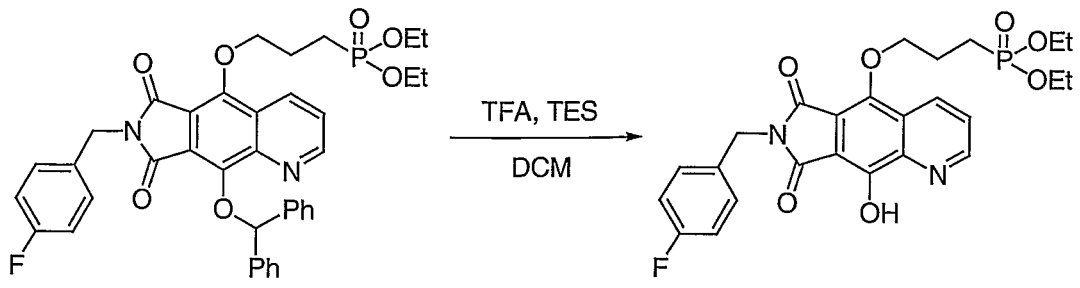
40 179

Example 178

A solution of (2-ethoxy-ethyl)-phosphonic acid diethyl ester (0.500g, 2.1 mmol) in ether (8.5 mL) and THF (1.5 mL) was treated with lithium borohydride. The reaction mixture stirred at room temperature for 1 hour and was then concentrated in vacuo. The crude mixture was partitioned between dichloromethane and water. The organic phase was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), then concentrated in vacuo. The residue was purified by silica gel chromatography (5/95 – methanol/dichloromethane) to afford (3-hydroxy-propyl)-phosphonic acid diethyl ester **178** (0.100g, 24%) as an oil: ^1H NMR ($CDCl_3$) δ 4.1 (m, 4H), 3.7 (m, 2H), 2.95 (bs, 1H), 1.85 (m, 4H), 1.30 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 33.26; MS: 197 (M+1).

Example 179

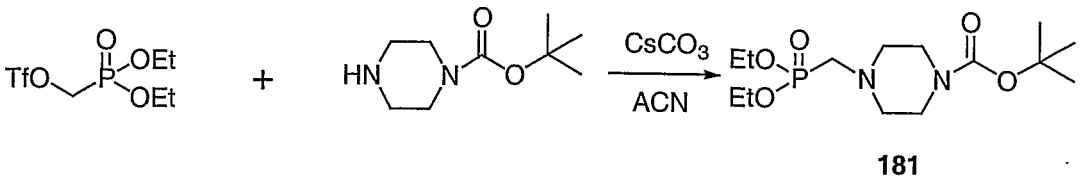
To a solution of phenol **40** (0.023 g, 0.046 mmol) dissolved in THF (0.45 mL) was added the alcohol **178** (0.013 g, 0.068 mmol), triphenylphosphine (0.024 g, 0.091 mmol), and diethyl azodicarboxylate (0.014 mL, 0.091 mmol). The reaction mixture stirred at room temperature under an inert atmosphere overnight. The residue was purified directly by silica gel chromatography (90/10 – ethylacetate/hexane) to afford the product **179** (0.024 g, 76%): ^1H NMR ($CDCl_3$) δ 9.1 (dd, 1H), 8.6 (dd, 1H), 7.9 (dd, 1H), 7.6 (m, 6H), 7.4 (dd, 2H), 7.2 (m, 6H), 7.0 (t, 2H), 4.8 (s, 2H), 4.5 (t, 2H), 4.15 (m, 2H), 2.2 (m, 2H), 2.0 (m, 2H), 1.35 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 31.48; MS: 684 (M+1).



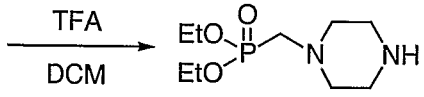
179 180

Example 180

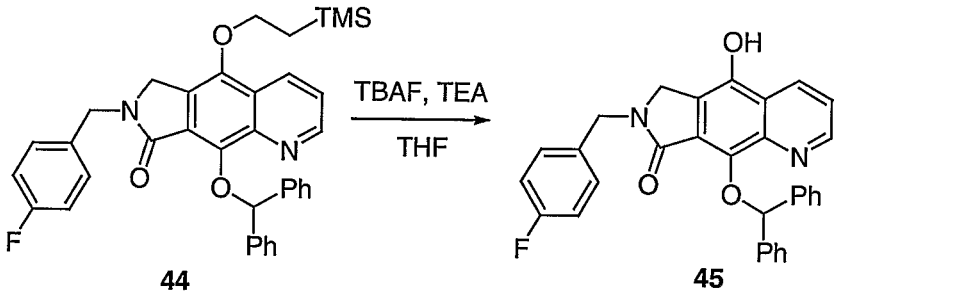
A solution of the phosphonate **179** (0.028 g, 0.041 mmol) in dichloromethane (0.5 mL) was treated with trifluoroacetic acid (0.1 mL) and triethylsilane (0.2 mL). The reaction mixture was stirred at room temperature under an inert atmosphere for 20 minutes. The volatiles were removed in vacuo with toluene. The solid was triturated in diethylether/hexane to afford the product **180** (0.020 g, 95%) as a TFA salt: ^{1}H NMR ($CDCl_3$) δ 9.0 (dd, 1H), 8.7 (dd, 1H), 7.65 (dd, 1H), 7.5 (dd, 2H), 7.0 (t, 2H), 4.85 (s, 2H), 4.6 (t, 2H), 4.15 (m, 2H), 2.25 (m, 2H), 2.05 (m, 2H), 1.35 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 31.45; MS: 517 (M+1), 516 (M-1).



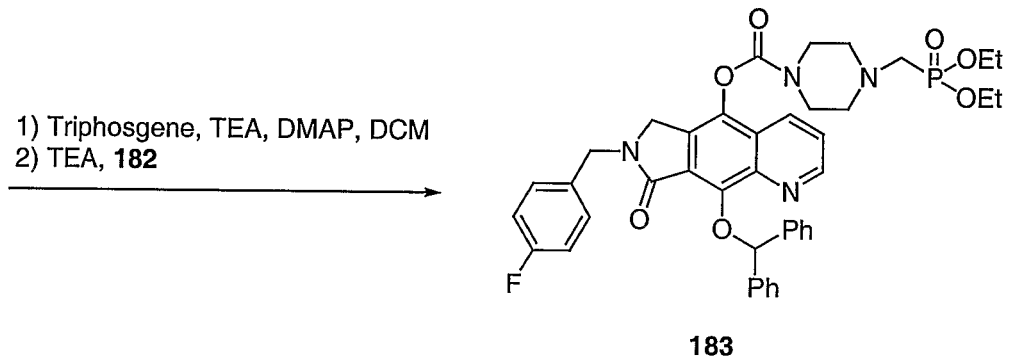
181



182



44 45



183

Example 181

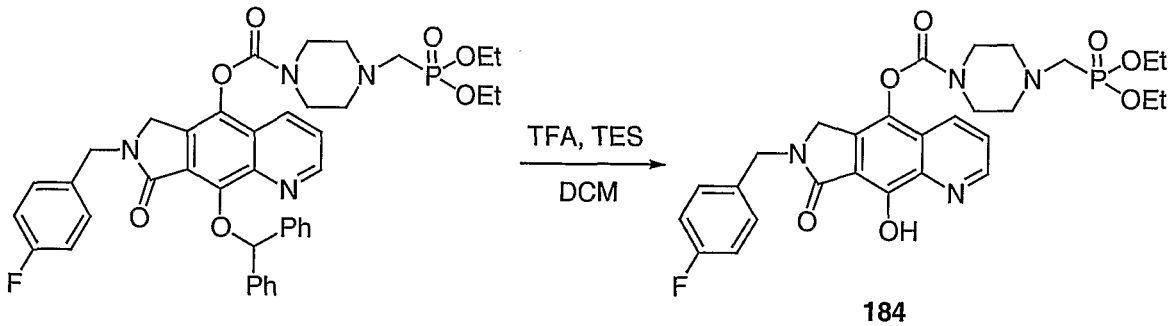
To a solution of 1-BOC-piperazine (0.200 g, 1.08 mmol) in acetonitrile (10.4 mL) was added $CsCO_3$ (1.05 g, 3.23 mmol) and then cooled to 0 °C. Trifluoromethanesulfonic acid diethoxyphosphorylmethyl ester (0.387 g, 1.29 mmol) dissolved in acetonitrile (5 mL) was added in a dropwise manner. The reaction mixture was stirred at room temperature for 1 hour upon which it was concentrated in vacuo. The reaction mixture was taken into ethylacetate then washed with saturated NH_4Cl and brine, dried ($MgSO_4$), then concentrated in vacuo. The residue was purified using silica gel chromatography (3/97 – methanol/dichloromethane) to afford the product **181** (0.310 g, 86%) as an oil: ^1H NMR ($CDCl_3$) δ 4.15 (m, 4H), 3.45 (t, 4H), 2.8 (d, 2H), 2.6 (m, 4H), 1.45 (s, 9H), 1.35 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 24.03; MS: 337 (M+1).

Example 182

A solution of the BOC protected piperazine linker phosphonate **181** (0.310 g, 0.923 mmol) in dichloromethane (6.15 mL) was treated with trifluoroacetic acid (0.711 mL, 9.23 mmol). The reaction mixture was stirred at room temperature under an inert atmosphere overnight. The volatiles were removed in vacuo with toluene to afford the free piperazine linker phosphonate **182** (0.323 g, 100%) as a TFA salt: ^{1}H NMR ($CDCl_3$) δ 11.0 (bs, 1H), 4.2 (m, 4H), 3.45 (t, 4H), 3.35 (m, 4H), 3.2 (d, 2H), 1.4 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 19.16; MS: 237 (M+1).

Example 183

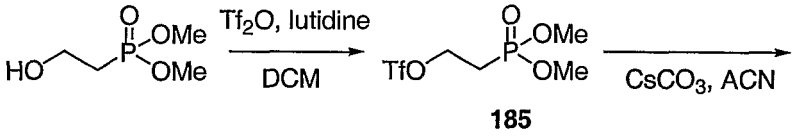
A solution of the phenol intermediate **45** (0.044 mmol) in dichloromethane (0.441 mL) was treated with triethylamine (0.025 mL, 0.176 mmol) and cat. 4-dimethylaminopyridine. The reaction mixture was cooled to 0 °C then triphosgene (0.026 g, 0.088 mmol) in a 1M solution of dichloromethane was added. The mixture stirred at room temperature under an inert atmosphere for 2 hours, then the free piperazine linker phosphonate **182** (0.046 g, 0.132 mmol) in a 1M solution of dichloromethane treated with triethylamine (0.025 mL, 0.176 mmol) was added, and the mixture was stirred overnight. The mixture was partitioned between dichloromethane and water. The organic phase was washed with saturated NH_4Cl and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel chromatography (3/97 – methanol/dichloromethane) to afford the product **183** (0.016 g, 64%): ^{1}H NMR ($CDCl_3$) δ 9.05 (dd, 1H), 8.1 (dd, 1H), 8.0 (s, 1H), 7.75 (d, 4H), 7.5 (dd, 1H), 7.4-7.m, 8H), 7.05 (t, 2H), 4.8 (s, 2H), 4.2 (s, 2H), 4.15 (m, 4H), 3.75 (m, 2H), 3.6 (m, 2H), 2.85 (d, 2H), 2.8 (m, 2H), 2.75 (m, 2H), 1.35 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 23.57; MS: 753 (M+1).



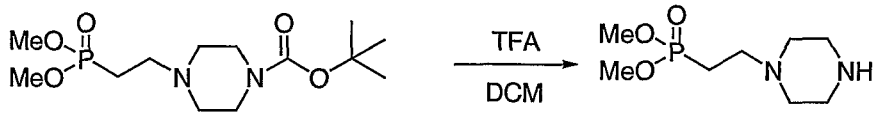
183 **184**

Example 184

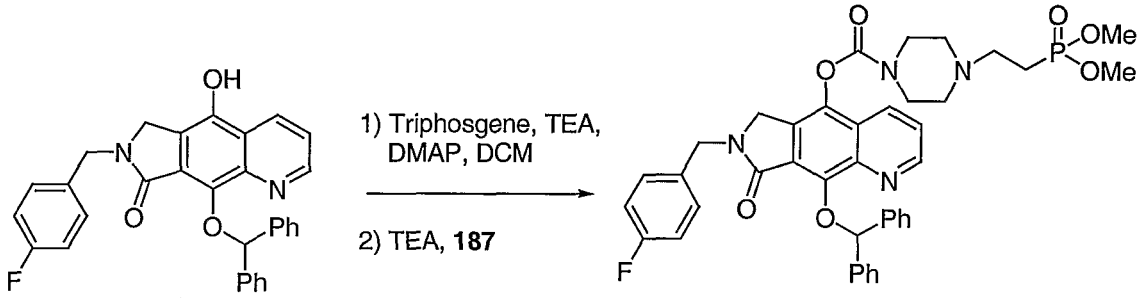
A solution of the phosphonate **183** (0.016 g, 0.021 mmol) in dichloromethane (0.5 mL) was treated with trifluoroacetic acid (0.1 mL) and triethylsilane (0.2 mL). The reaction mixture was stirred at room temperature under an inert atmosphere for 20 minutes. The volatiles were removed in vacuo with toluene. The solid was triturated in diethylether/hexane to afford the product **184** (0.0125 g, 100%) as a TFA salt: ^{1}H NMR ($CDCl_3$) δ 9.0 (dd, 1H), 8.2 (dd, 1H), 7.6 (dd, 1H), 7.3 (m, 2H), 7.05 (t, 2H), 4.75 (s, 2H), 4.35 (s, 2H), 4.2 (m, 4H), 3.95 (m, 2H), 3.75 (m, 2H), 3.2 (d, 2H), 3.2 (m, 2H), 3.1 (m, 2H), 1.4 (t, 6H); ^{31}P NMR ($CDCl_3$) δ 19.93; MS: 587 (M+1), 585 (M-1).



185



186 187



45 188

Example 185

To a solution of (2-hydroxy-ethyl)-phosphonic acid dimethyl ester (0.250 g, 1.62 mmol) in dichloromethane (4 mL) was added 2,6-lutidine (0.284 mL, 2.44 mmol). The reaction mixture was cooled to -40° C and trifluoromethanesulfonic anhydride (0.355 mL, 2.11 mmol) was added. The mixture stirred in the cold bath under an inert atmosphere for 2 hours at which point the reaction was completed as shown by ^{31}P NMR ($CDCl_3$) δ 25.7. The mixture was partitioned between dichloromethane and water both cooled by an ice-water bath. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford trifluoromethanesulfonic acid dimethoxy-phosphoryl-2-ethyl ester **185** as an oil which was immediately carried forward with no further purification or characterization.

Example 186

To a solution of 1-BOC-piperazine (0.252 g, 1.35 mmol) in acetonitrile (14.3 mL) was added $CsCO_3$ (1.32 g, 4.06 mmol) and then cooled to 0 °C. Trifluoromethanesulfonic acid dimethoxy-phosphoryl-2-ethyl ester **185** (0.464 g, 1.62 mmol) dissolved in acetonitrile (5 mL) was added in a dropwise manner. The reaction mixture was stirred at room temperature overnight upon which it was concentrated in vacuo. The reaction mixture was taken into ethylacetate then washed with saturated NH_4Cl and brine, dried ($MgSO_4$), then concentrated in vacuo. The residue was purified using silica gel chromatography (5/95 – methanol/dichloromethane) to afford the BOC protected piperazine linker phosphonate **186** (0.162 g, 31% over 2 steps) as an oil: ^1H NMR ($CDCl_3$) δ 3.75 (d, 6H), 3.4 (m, 4H), 2.65 (m, 2H), 2.4 (m, 4H), 1.95 (m, 2H), 1.45 (s, 9H); ^{31}P NMR ($CDCl_3$) δ 33.06; MS: 323 (M+1).

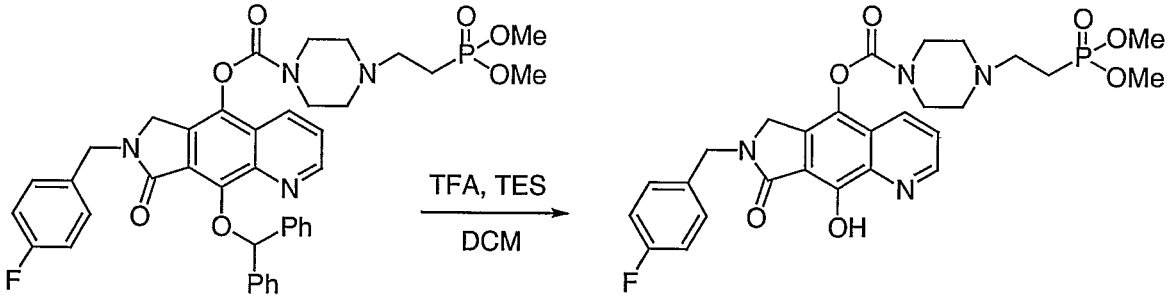
Example 187

A solution of the BOC protected piperazine linker phosphonate **186** (0.162 g, 0.503 mmol) in dichloromethane (3.35 mL) was treated with trifluoroacetic acid (0.388 mL, 5.03 mmol). The reaction mixture was stirred at room temperature under an inert atmosphere overnight. The volatiles were removed in vacuo with toluene to afford the free piperazine linker phosphonate **187** (0.169 g, 100%) as a TFA salt: ^1H NMR (CD_3OD) δ 3.8 (d, 6H), 3.45 (m, 4H), 3.2 (m, 4H), 3.15 (m, 2H), 2.3 (m, 2H); ^{31}P NMR ($CDCl_3$) δ 30.92; MS: 223 (M+1).

Example 188

A solution of the phenol intermediate **45** (0.046 mmol) in dichloromethane (0.458 mL) was treated with triethylamine (0.026 mL, 0.183 mmol) and a catalytic amount of 4-dimethylaminopyridine. The reaction mixture was cooled to 0 °C then triphosgene (0.027 g, 0.092 mmol) in a 1M solution of dichloromethane was added. The mixture was stirred at room temperature under an inert atmosphere for 2 hours, then the free piperazine linker phosphonate **187** (0.046 g, 0.137 mmol) in a 1M solution of dichloromethane treated with triethylamine (0.026 mL, 0.183 mmol) was added dropwise. The mixture was stirred overnight and then partitioned between dichloromethane and water. The organic phase was washed with saturated NH_4Cl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel chromatography (8/92 – methanol/ethylacetate) to afford the product **188** (0.019 g, 56%): ^1H NMR ($CDCl_3$) δ 9.05 (dd, 1H), 8.1 (dd, 1H), 8.05 (s,

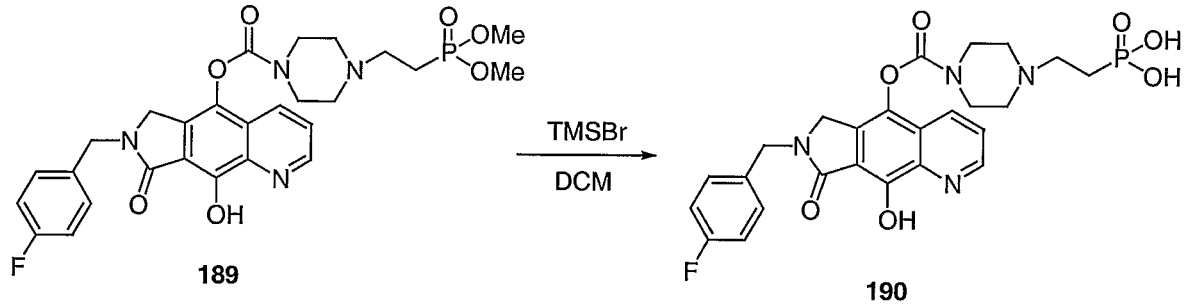
1H), 7.75 (m, 4H), 7.5 (dd, 1H), 7.4-7.1 (m, 8H), 7.1 (t, 2H), 4.8 (s, 2H), 4.2 (s, 2H), 3.8 (d, 6H), 3.6 (m, 4H), 2.75 (m, 2H), 2.55 (m, 4H), 2.1 (m, 2H); ^{31}P NMR ($CDCl_3$) δ 32.65; MS: 739 (M+1).



188 189

Example 189

A solution of the phosphonate **188** (0.019 g, 0.026 mmol) in dichloromethane (0.5 mL) was treated with trifluoroacetic acid (0.1 mL) and triethylsilane (0.2 mL). The reaction mixture was stirred at room temperature under an inert atmosphere for 20 minutes. The volatiles were removed in vacuo with toluene. The solid was triturated in diethylether/hexane to afford the product **189** (0.013 g, 74%) as a TFA salt: ^{1}H NMR ($CDCl_3$) δ 8.9 (dd, 1H), 8.15 (dd, 1H), 7.55 (dd, 1H), 7.35 (m, 2H), 7.05 (t, 2H), 4.75 (s, 2H), 4.35 (s, 2H), 4.2 (m, 2H), 3.95 (m, 2H), 3.8 (d, 6H), 3.4 (m, 4H), 3.35 (m, 2H), 2.4 (m, 2H); ^{31}P NMR ($CDCl_3$) δ 27.31; MS: 573 (M+1).

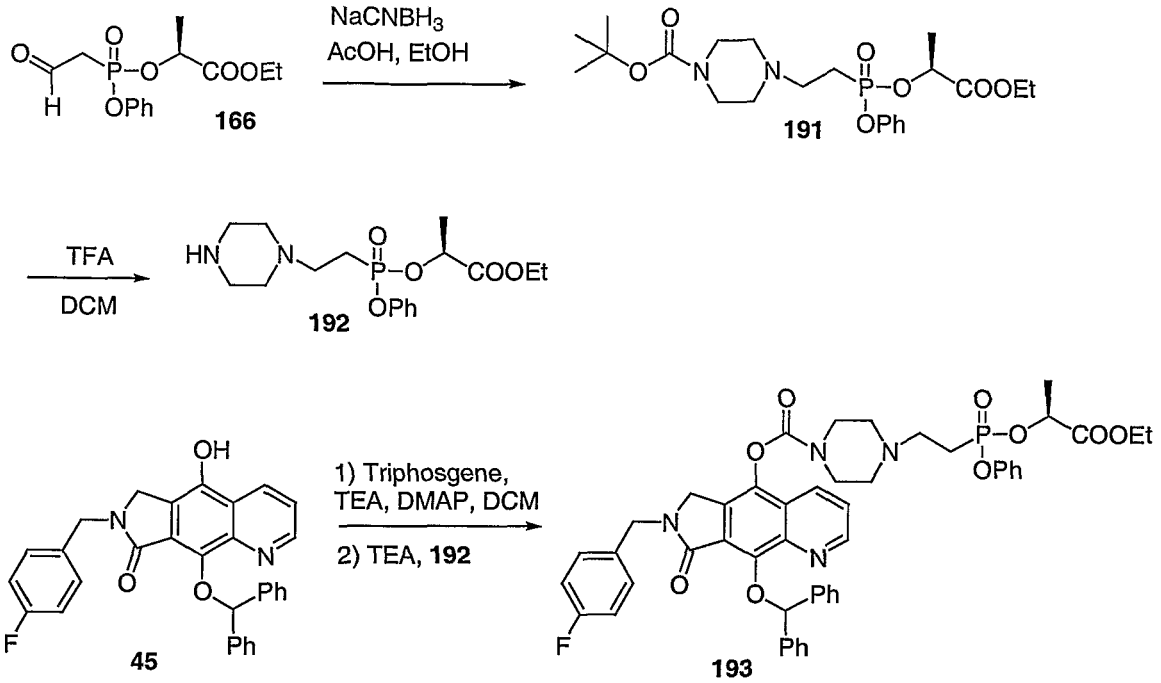


189 190

Example 190

A solution of the phosphonate **189** (0.006 g, 0.009 mmol) in dichloromethane (0.088 mL) was treated with trimethylsilane bromide (0.007 mL, 0.053 mmol). The reaction mixture was stirred at room temperature overnight under an inert atmosphere. The volatiles were removed in vacuo with methanol. The solid was washed with dichloromethane to afford the diacid **190** (0.006 g, 100%): ^{1}H NMR (CD_3OD) δ 9.3 (dd, 1H), 9.2 (dd, 1H), 8.2

(dd, 1H), 7.4 (m, 2H), 7.1 (t, 2H), 4.8 (s, 2H), 4.6 (s, 2H), 3.6-3.2 (m, 10H), 2.35 (m, 2H); ^{31}P NMR (CD_3OD) δ 21.43; MS: 545 (M+1), 543 (M-1).



Example 191

To a solution of 2-[(2-oxo-ethyl)-phenoxy-phosphinoyloxy]-propionic acid ethyl ester, aldehyde **166**, as a 1:1 mixture of DMSO (0.050 g, 0.167 mmol) and 1-BOC-piperazine (0.034 g, 0.183 mmol) dissolved in ethanol (1.67 mL) was added acetic acid (0.038 mL, 0.667 mmol). The reaction mixture was stirred at room temperature for 2.5 hours then sodium cyanoborohydride (0.021 g, 0.333 mmol) was added. The reaction mixture stirred at room temperature overnight. Saturated $NaHCO_3$ was added to the reaction mixture and was stirred for five more minutes. The mixture was concentrated in vacuo to remove most of the ethanol. Brine was added and then the crude product was extracted into ethylacetate. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (5/95 – methanol/dichloromethane) to afford the product **191** (0.050 g, 64%), an oil as a mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 7.4-7.1 (m, 5H), 5.0 (m, 1H), 4.2 (m, 2H), 3.4 (m, 4H), 2.8 (m, 2H), 2.4 (m, 4H), 2.2 (m, 2H), 1.6 & 1.35 (d, 3H), 1.4 (s, 9H), 1.2 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 28.83, 27.18; MS: 471 (M+1).

Alternatively, a solution of 2-[(2-oxo-ethyl)-phenoxy-phosphinoyloxy]-propionic acid ethyl ester **166**, as a 1:1 mixture with DMSO (0.500 g, 1.67 mmol), and piperazine-1-

carboxylic acid *tert*-butyl ester (1-BOC-piperazine, 0.340 g, 1.83 mmol) dissolved in ethanol (1.67 mL) was added 4 Å molecular sieves (0.300 g) and acetic acid (0.400 mL, 6.8 mmol). The reaction mixture was stirred at room temperature for 1.5 hours then sodium cyanoborohydride (0.212 g, 3.33 mmol) was added. The reaction mixture stirred at room temperature for 3 hours and was concentrated in vacuo then redissolved in chloroform. The mixture was washed with saturated $NaHCO_3$ and brine, dried ($NaSO_4$), filtered and concentrated. The residue was treated with diethyl ether. Solid precipitate was filtered off, and the filtrate was concentrated to afford 4-{2-[(1-Ethoxycarbonyl-ethoxy)-phenoxy-phosphoryl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester **191** (0.600 g, 77%) as an oil (mixture of two diastereomers).

Example 192

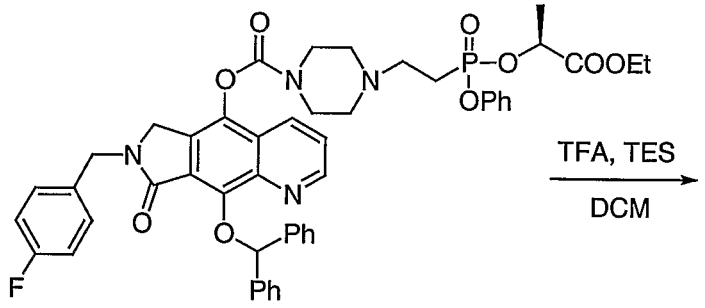
A solution of 4-{2-[(1-ethoxycarbonyl-ethoxy)-phenoxy-phosphoryl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester **191** (0.050 g, 0.106 mmol) in dichloromethane (0.709 mL) was treated with trifluoroacetic acid (0.082 mL, 1.06 mmol). The reaction mixture was stirred at room temperature under an inert atmosphere for 4 hours. The volatiles were removed in vacuo with toluene to afford the free piperazine linker phosphonate **192** (0.051 g, 100%) as a TFA salt (mixture of two diastereomers): ^{1}H NMR ($CDCl_3$) δ 10.8 (bs, 1H), 7.5-7.1 (m, 5H), 5.0 (m, 1H), 4.2 (m, 4H), 3.7 (m, 8H), 2.65 (m, 2H), 1.6 & 1.4 (d, 3H), 1.25 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 25.58, 20.86; MS: 371 (M+1).

Alternatively a solution of 4-{2-[(1-ethoxycarbonyl-ethoxy)-phenoxy-phosphoryl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester **191** (0.100 g, 0.212 mmol) in methylene chloride (2 mL) was treated with trifluoroacetic acid (0.340 mL, 4.41 mmol). The reaction mixture was stirred at room temperature under an inert atmosphere for 6 hours. The volatiles were removed in vacuo with ethyl acetate to afford the trifluoroacetate salt of 2-[phenoxy-(2-piperazin-1-yl-ethyl)-phosphinoyloxy]-propionic acid ethyl ester **192** (0.103 g, 100%) (mixture of two diastereomers).

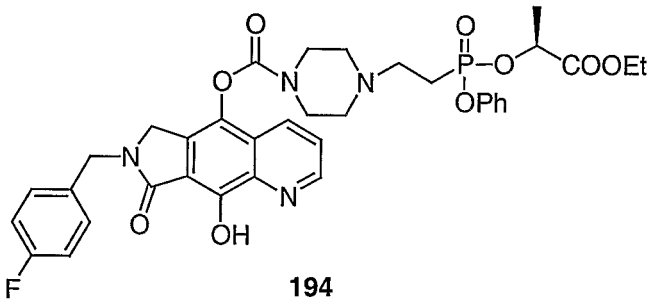
Example 193

A solution of the phenol intermediate **45** (0.039 mmol) in dichloromethane (0.386 mL) was treated with triethylamine (0.022 mL, 0.155 mmol) and cat. 4-dimethylaminopyridine. The reaction mixture was cooled to 0 °C then triphosgene (0.023 g, 0.077 mmol) in a 1M solution of dichloromethane was added. The mixture stirred at room temperature under an inert atmosphere for 2 hours, then the free piperazine linker

phosphonate **192** (0.056 g, 0.115 mmol) in a 1M solution of dichloromethane treated with triethylamine (0.022 mL, 0.155 mmol) was added, and the mixture was stirred overnight. The mixture was partitioned between dichloromethane and water. The organic phase was washed with saturated NH_4Cl and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel chromatography (5/95 – methanol/dichloromethane) to afford the product **193** (0.013 g, 50%) as a mixture of diastereomers: ^1H NMR ($CDCl_3$) δ 9.05 (dd, 1H), 8.1 (dd, 1H), 8.05 (s, 1H), 7.75 (d, 4H), 7.5 (dd, 1H), 7.4-7.1 (m, 11H), 7.05 (t, 2H), 5.1 (m, 1H), 4.8 (s, 2H), 4.2 (s, 2H), 4.15 (m, 2H), 3.8-3.4 (m, 4H), 3.0-2.2 (m, 8H), 1.6 & 1.4 (d, 3H), 1.2 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 28.30, 26.59; MS: 887 (M+1).



193

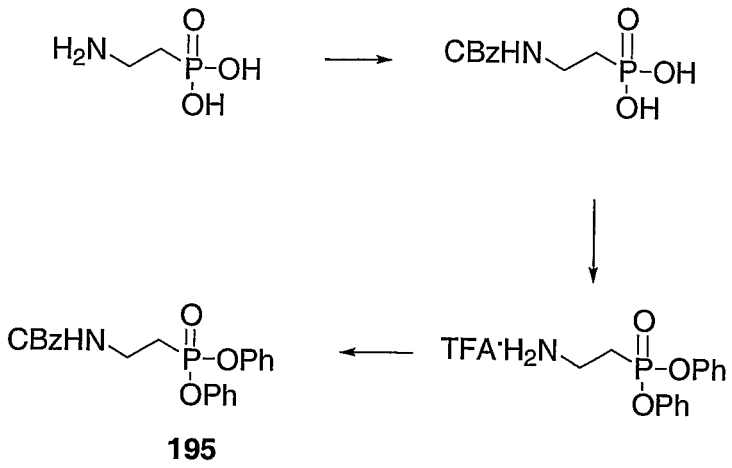


194

Example 194

A solution of the phosphonate **193** (0.013 g, 0.015 mmol) in dichloromethane (0.5 mL) was treated with trifluoroacetic acid (0.1 mL) and triethylsilane (0.2 mL). The reaction mixture was stirred at room temperature under an inert atmosphere for 20 minutes. The volatiles were removed in vacuo with toluene. The solid was triturated in diethylether/hexane to afford the product **194** (0.010 g, 80%) as a TFA salt: ^1H NMR ($CDCl_3$) δ 8.95 (dd, 1H), 8.15 (dd, 1H), 7.55 (dd, 1H), 7.35 (m, 2H), 7.3-7.1 (m, 5H), 7.05 (t, 2H), 5.0 (m, 1H), 4.75 (s, 2H), 4.35 (s, 2H), 4.2 (m, 2H), 3.8-3.6 (m, 4H), 3.4-3.0 (m,

6H), 2.5-2.7 (m, 2H), 1.6 & 1.4 (d, 3H), 1.25 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 23.39, 21.67; MS: 721 (M+1).



195

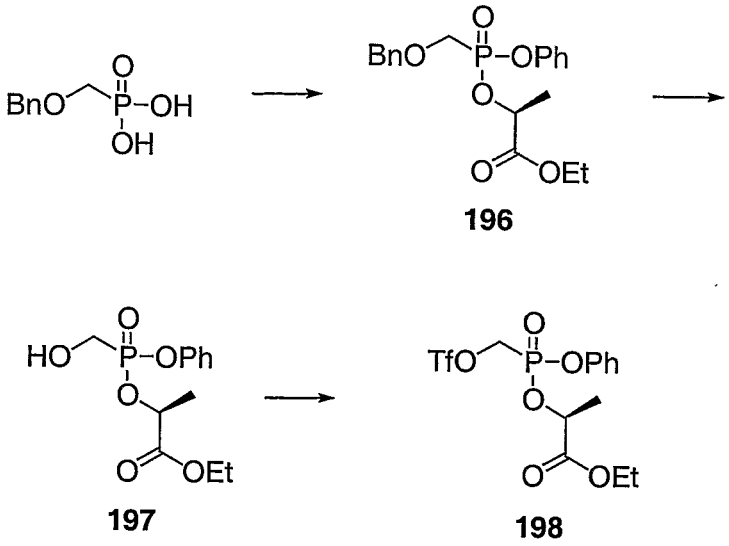
Example 195

To a solution of 2-aminoethylphosphonic acid (1.26 g, 10.1 mmol) in 2N NaOH (10.1 mL, 20.2 mmol) was added benzyl chloroformate (1.7 mL, 12.1 mmol). After the reaction mixture was stirred for 2 d at room temperature, the mixture was partitioned between Et_2O and water. The aqueous phase was acidified with 6N HCl until pH = 2. The resulting colorless solid was dissolved in MeOH (75 mL) and treated with Dowex 50WX8-200 (7 g). After the mixture was stirred for 30 minutes, it was filtered and evaporated under reduced pressure to give carbobenzoxyaminoethyl phosphonic acid (2.37 g, 91%) as a colorless solid.

To a solution of carbobenzoxyaminoethyl phosphonic acid (2.35 g, 9.1 mmol) in pyridine (40 mL) was added phenol (8.53 g, 90.6 mmol) and 1,3-dicyclohexylcarbodiimide (7.47 g, 36.2 mmol). After the reaction mixture was warmed to 70°C and stirred for 5 h, the mixture was diluted with CH_3CN and filtered. The filtrate was concentrated under reduced pressure and diluted with EtOAc. The organic phase was washed with sat. NH_4Cl, sat. $NaHCO_3$, and brine, then dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel twice (eluting 40-60% EtOAc/hexane) to give diphenyl 2-aminoethyl phosphonic acid (2.13 g, 57%) as a colorless solid.

To a solution of diphenyl 2-aminoethyl phosphonic acid (262 mg, 0.637 mmol) in iPrOH (5 mL) was added TFA (0.05 mL, 0.637 mmol) and 10% Pd/C (26 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 1 h, the mixture was filtered

through Celite. The filtrate was evaporated under reduced pressure to give diphenyl carbobenzoxyaminoethyl phosphonate **195** (249 mg, 100%) as a colorless oil.



Example 196

To a solution of benzyloxymethyl phosphonic acid (520 mg, 2.57 mmol) in CH_3CN (5 mL) was added thionyl chloride (0.75 mL, 10.3 mmol) and heated to 70°C in an oil bath. After the reaction mixture was stirred for 2 h at 70°C, the mixture was concentrated and azeotroped with toluene. To a solution of the crude chloridate in toluene (5 mL) was added tetrazole (18 mg, 0.26 mmol) at 0°C. To this mixture was added phenol (121 mg, 1.28 mmol) and triethylamine (0.18 mL, 1.28 mmol) in toluene (3 mL) at 0°C. After the reaction mixture was warmed to room temperature and stirred for 2 h, ethyl lactate (0.29 mL, 2.57 mmol) and triethylamine (0.36 mL, 2.57 mmol) in toluene (2.5 mL) were added. The reaction mixture was stirred for 16 hours at room temperature, at which time the mixture was partitioned between EtOAc and sat. NH_4Cl. The organic phase was washed with sat. NH_4Cl, 1M $NaHCO_3$, and brine, then dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 20-40% EtOAc/hexane) to give two diastereomers (isomer A and isomer B) of 2-(benzyloxymethyl-phenoxy-phosphinoyloxy)-propionic acid ethyl ester **196** (66 mg, 109 mg, 18% total) as colorless oils.

Example 197a

To a solution of benzyl phosphonate **196** isomer A (66 mg, 0.174 mmol) in EtOH (2 mL) was added 10% Pd/C (13 mg). After the reaction mixture was stirred under H_2

atmosphere (balloon) for 6 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give alcohol **197a** isomer A (49 mg, 98%) as a colorless oil.

Example 197b

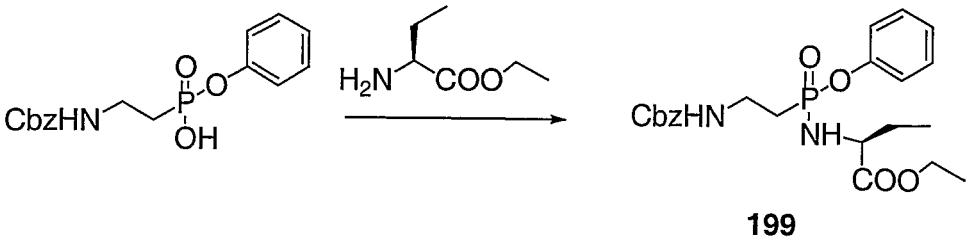
To a solution of benzyl phosphonate **196** isomer B (110 mg, 0.291 mmol) in EtOH (3 mL) was added 10% Pd/C (22 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 6 h, it was filtered through Celite. The filtrate was evaporated under reduced pressure to give alcohol **197b** isomer B (80 mg, 95%) as a colorless oil.

Example 198a

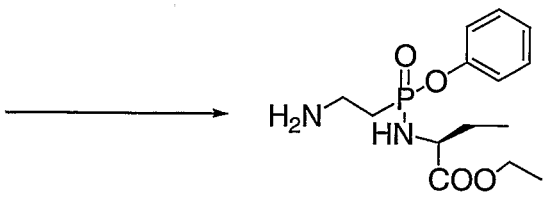
To a solution of alcohol **197a** isomer A (48 mg, 0.167 mmol) in CH_2Cl_2 (2 mL) was added 2,6-lutidine (0.03 mL, 0.250 mmol) and trifluoromethanesulfonic anhydride (0.04 mL, 0.217 mmol) at -40°C (dry ice-CH_3CN bath). After the reaction mixture was stirred for 15 min at -40°C, the mixture was warmed to 0°C and partitioned between Et_2O and 1M H_3PO_4. The organic phase was washed with 1M H_3PO_4 (3 times), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give triflate **198a** isomer A (70 mg, 100%) as a pale yellow oil.

Example 198b

To a solution of alcohol **197b** isomer B (80 mg, 0.278 mmol) in CH_2Cl_2 (3 mL) was added 2,6-lutidine (0.05 mL, 0.417 mmol) and trifluoromethanesulfonic anhydride (0.06 mL, 0.361 mmol) at -40°C (dry ice-CH_3CN bath). After the reaction mixture was stirred for 15 min at -40°C, the mixture was warmed to 0°C and partitioned between Et_2O and 1M H_3PO_4. The organic phase was washed with 1M H_3PO_4 (3 times), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give triflate **198b** isomer B (115 mg, 98%) as a pale yellow oil.



199



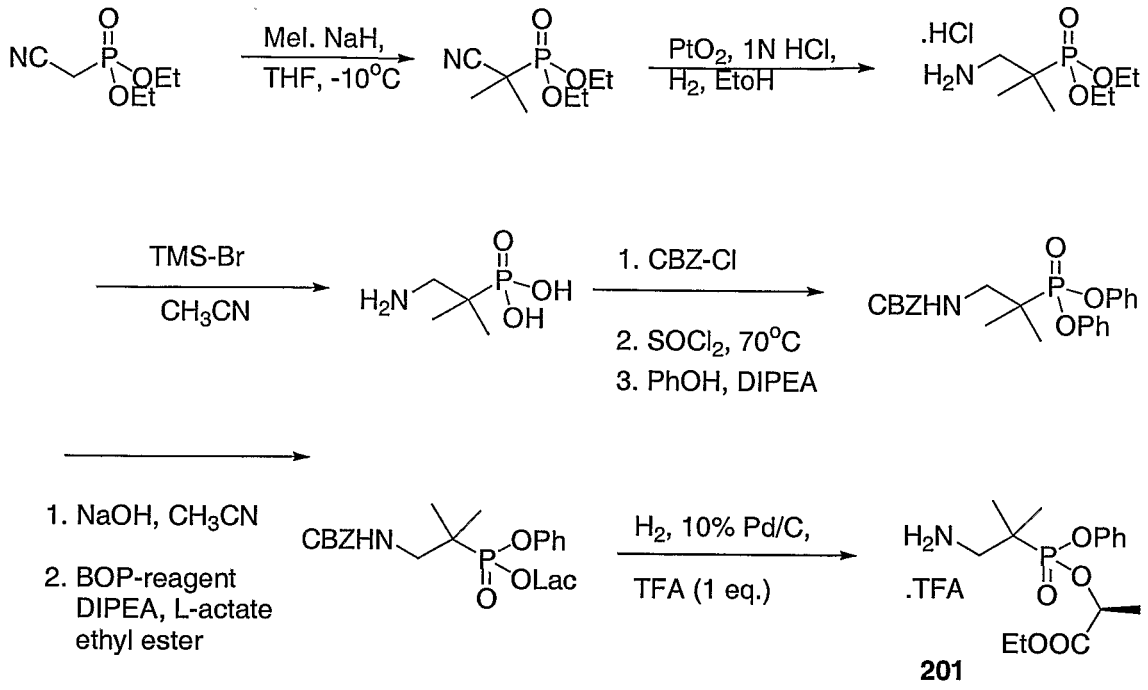
200

Example 199

To a stirred solution of phenyl 2-carbobenzoxyaminoethyl phosphonate (1 g, 3 mmol) in 30 mL of acetonitrile at room temperature under N_2 was added thionyl chloride (0.67 mL, 9 mmol). The resulted mixture was stirred at 60-70 °C for 0.5 h. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was added 30 mL of DCM, followed by DIEA (1.7 mL, 10 mmol), L-alanine butyric acid ethyl ester hydrochloride (1.7 g, 10 mmol) and TEA (1.7 mL, 12 mmol). After 4h at room temperature, the solvent was removed under reduced pressure, and the residue was diluted with DCM and washed with brine and water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (Hexane/EtOAc 1:1) to give **199** (670 mg, 50%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.33-7.11 (m, 10H), 5.70 (m, 1H), 5.10 (s, 2H), 4.13-3.53 (m, 5H), 2.20-2.10 (m, 2H), 1.76-1.55 (m, 2H), 1.25-1.19 (m, 3H), 0.85-0.71 (m, 3H); ^{31}P NMR ($CDCl_3$) δ 30.2 and 29.9; MS (ESI) 471 (M+Na).

Example 200

A solution of compound **199** (450mg) was dissolved in 9 mL of EtOH, then 0.15 mL of acetic acid and 10 % Pd/C (90 mg) was added. The resulted mixture was stirred under H2 atmosphere (balloon) for 4 h. After filtration through Celite, the filtered was evaporated under reduced pressure to afford the compound **200** (300mg, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.29-7.12 (m, 5H), 4.13-3.53 (m, 5H), 2.20-2.10 (m, 2H), 1.70-1.55 (m, 2H), 1.24-1.19 (m, 3H), 0.84-0.73(m, 3H); ^{31}P NMR ($CDCl_3$) δ 29.1 and 28.5; MS (ESI) 315 (M+1).



Example 201

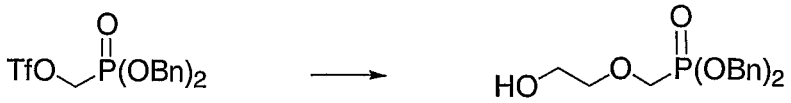
A THF solution (30 mL) of NaH (3.4 g of 60% oil dispersion, 85 mmol) was cooled to –10°C, followed by the addition of diethyl (cyanomethyl)phosphonate (5g, 28.2 mmol) and iodomethane (17 g, 112 mmol). The resulting solution was stirred at –10°C for 2 hr, then 0°C for 1 hr, was worked up, and purified to give diethyl (cyano(dimethyl)methyl) phosphonate (5 g, 86 %).

Diethyl (cyano(dimethyl)methyl) phosphonate was reduced to the amine derivative by the described procedure (J. Med. Chem. 1999, 42, 5010-5019) whereby a solution of ethanol (150 mL) and 1N HCl aqueous solution (22 mL) of diethyl (cyano(dimethyl)methyl) phosphonate (2.2 g, 10.7 mmol) was hydrogenated at 1 atmosphere in the presence of PtO_2 (1.25 g) at room temperature overnight. The catalyst was filtered through a Celite pad. The filtrate was concentrated to dryness, to give crude diethyl 2-amino-1,1-dimethyl-ethyl phosphonate (2.5g, as HCl salt).

Crude diethyl 2-amino-1,1-dimethyl-ethyl phosphonate (2.5 g) in 30 mL CH_3CN was cooled to 0°C, and treated with TMSBr (8 g, 52 mmol) for 5 hr. The reaction mixture was stirred with methanol for 1.5 hr at room temperature, concentrated, recharged with methanol, concentrated to dryness to give crude 2-Amino-1,1-dimethyl-ethyl phosphonic acid which was used for next reaction without further purification.

2-Amino-1,1-dimethyl-ethyl phosphonic acid was protected with CBZ, followed by the reaction with thionyl chloride at 70 °C. The CBZ protected dichloridate was reacted

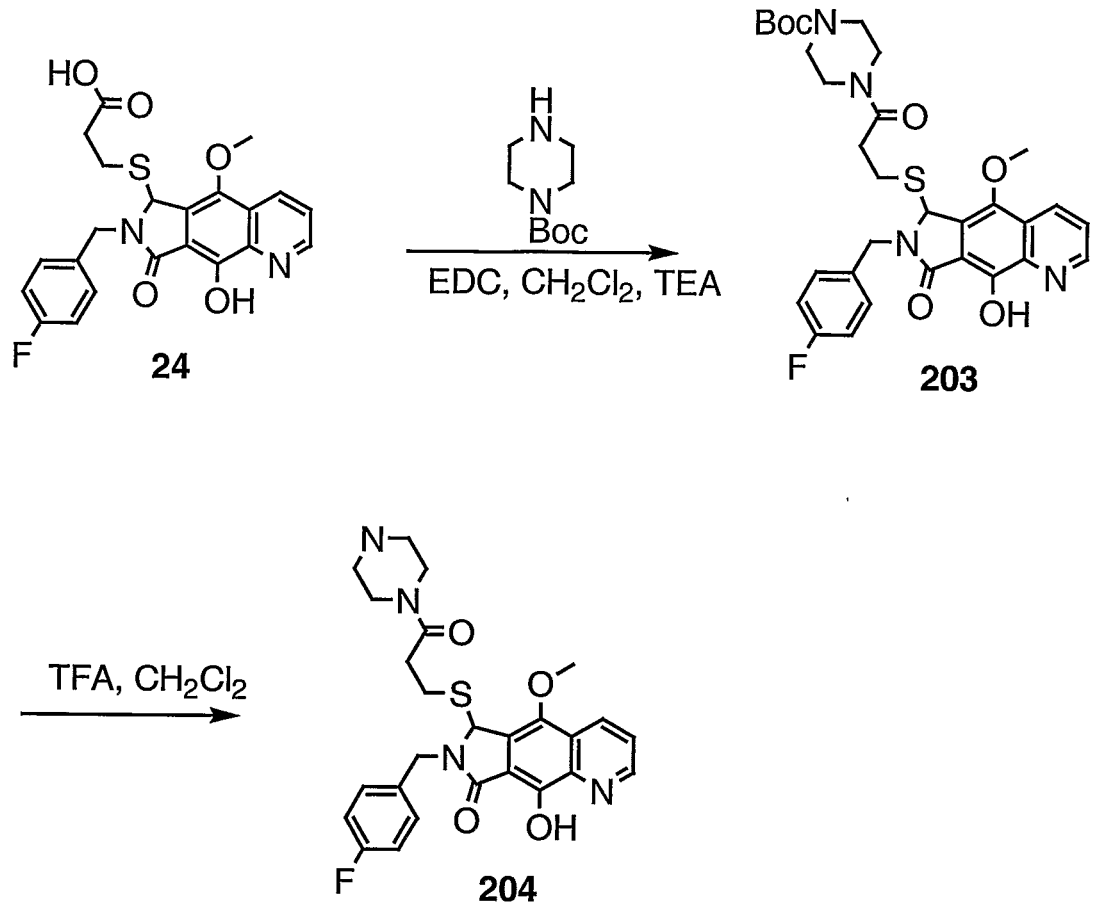
with phenol in the presence of DIPEA. Removal of one phenol, follow by coupling with ethyl L-lactate gave N-CBZ-2-amino-1,1-dimethyl-ethyl phosphonate derivative. Hydrogenation of N-CBZ derivative at 1 atmosphere in the presence of 10 % Pd/C and 1 eq. of TFA gave lactate phenyl (2-amino-1,1-dimethyl-ethyl)phosphonate **201** as the TFA salt.



202

Example 202

Powdered magnesium *tert*-butoxide (2.05 g, 12.02 mmol) was added to a solution of dibenzyl trifluoromethane sulfonic hydroxymethyl phosphonate (4.10 g, 9.66 mmol) and anhydrous ethylene glycol (5.39 mL, 96.6 mmol) in anhydrous DMF (30 mL) at 0°C. The reaction mixture was stirred at 0°C for 1.5 h, then concentrated. The residue was partitioned between EtOAc and H_2O and washed with 1 N HCl, saturated $NaHCO_3$ solution, and brine. Organic layer dried ($MgSO_4$), concentrated and purified (silica gel, 4% $MeOH/CH_2Cl_2$) to give (2-hydroxy-ethoxymethyl)-phosphonic acid dibenzyl ester **202** as a colorless oil (1.55 g, 48%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.37 (s, 10 H, Ar), 5.40-5.05 (m, 4 H, CH_2Ph), 3.84 (d, J = 8.1 Hz, 2 H, PCH_2O), 3.70-3.60 (m, 4 H, OCH_2CH_2O, OCH_2CH_2O); ^{31}P NMR (121 MHz, $CDCl_3$): δ 22.7.



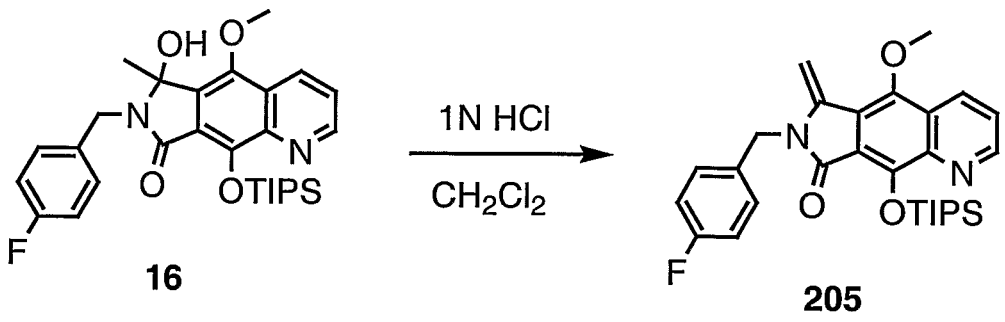
Example 203

A solution of **24** (Example 24) (38 mg, 0.086 mmol) in CH_2Cl_2 (0.86 mL) was stirred with EDC (33 mg, 0.172 mmol), TEA (12 μL, 0.086 mmol), and 1-Boc-piperazine (19 mg, 0.103 mmol) at ambient temperature for 15 h when LCMS analysis demonstrated completion of the reaction. The reaction mixture was worked up by dilution of the mixture with CH_2Cl_2 and washing the organic layer with H_2O. The organic layer was dried *in vacuo* and the residue, 4-{3-[7-(4-fluoro-benzyl)-9-hydroxy-5-methoxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-6-ylsulfanyl]-propionyl}-piperazine-1-carboxylic acid tert-butyl ester **203** was carried forward for deprotection.

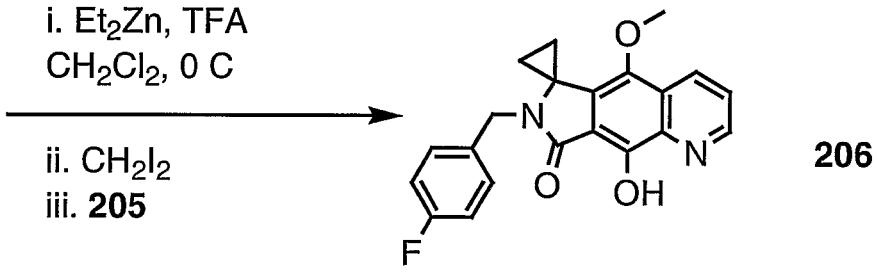
Example 204

A solution of **203** (52 mg, 0.085 mmol) in 0.8 mL of trifluoroacetic acid and 0.8 mL of CH_2Cl_2 was stirred at room temperature for 1 h when the starting material was completely consumed as detected by LCMS. The solution was dried *in vacuo* and re-dissolved in 1:1 mixture of MeOH- H_2O. The product **204** was purified by RP-HPLC using

a 5- 95% A. Buffer A contained CH_3CN-1% TFA and buffer B was H_2O-1% TFA. ^1H NMR (300 MHz, CD_3OD) δ 2.19- 2.40 (m, 4H), 3.06- 3.20 (m, 4H), 3.43- 3.56 (m, 2H), 3.63- 3.74 (m, 2H), 4.08 (s, 3H), 4.62 (d, 1H, *J*= 15 Hz), 5.16 (d, 1H, *J*= 15 Hz), 5.76 (s, 1H), 7.10 (t, 2H, *J*= 9 Hz), 7.46 (t, 2H, *J*= 8 Hz), 7.74 (dd, 1H, *J*= 4, 8 Hz), 8.69 (d, 1H, *J*= 8 Hz), 8.96 (d, 1H, *J*= 4 Hz); ^{19}F NMR (282.6 MHz, CD_3OD) δ -77.7, 60.0; EI MS (*m/z*) 511.0 $[M+H]^+$.



16 205



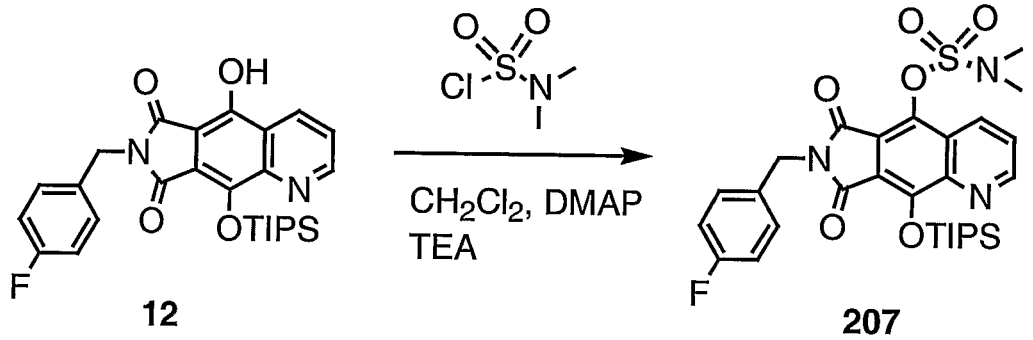
206

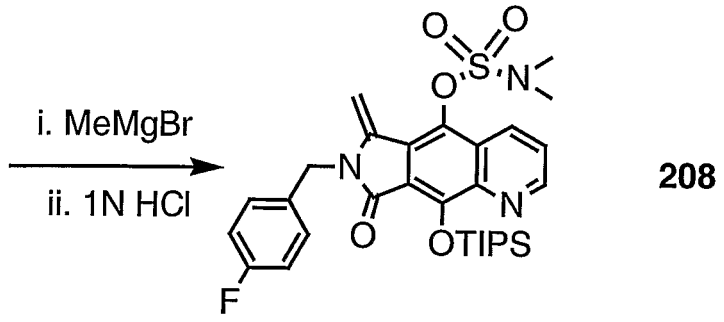
Example 205

Grignard product **16** (Example 16) was worked up by addition of ethyl acetate and stirring of the organic layer with aqueous 1N HCl for 30 minutes. The layers were separated and the organic layer was washed with the 1N HCl solution 2 more times. The organic layer was checked with LCMS to assure complete elimination of the alcohol resulted from the Grignard reaction to the eliminated product **205**. The organic layer was dried *in vacuo* and the residue was purified by column chromatography using CH_2Cl_2 to give **205**. ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, 18H, *J*= 8 Hz), 1.56 (septet, 3H, *J*= 8 Hz), 3.95 (s, 3H), 4.82 (s, 1H), 4.99 (s, 2H), 5.53 (s, 1H), 7.01 (t, 2H, *J*= 8 Hz), 7.28 (dd, 2H, *J*= 5, 9 Hz), 7.54 (dd, 1H, *J*= 4, 8 Hz), 8.46 (d, 1H, *J*= 8 Hz), 8.87 (d, 1H, *J*= 3 Hz); ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 61.06; EI MS (*m/z*) 507.4 $[M+H]^+$.

Example 206

A solution of diethylzinc (0.134 mmol, 134 μL of a 1M mixture) and 134 μL of CH_2Cl_2 was added to TFA (0.134 mmol, 10.4 μL) under a N_2 atmosphere at 0 °C. The mixture was stirred at cooled temperature for 15 minutes, then a solution of CH_2I_2 (0.134 mmol, 11 μL) in 100 μL of CH_2Cl_2 was added. After 10 minutes, a solution of **205** in 100 μL of CH_2Cl_2 was added and the ice bath removed. The reaction mixture was stirred at ambient temperature for 1 hour when LCMS analysis demonstrated complete consumption of the starting materials. The product **206** was purified by RP-HPLC using a 20- 80% A. Buffer A contained CH_3CN-1% TFA and buffer B was H_2O-1% TFA. ^1H NMR (300 MHz, CD_3OD) δ 1.58 (t, 2H, *J*= 5 Hz), 1.79 (t, 2H, *J*= 5 Hz), 3.95 (s, 3H), 4.61 (s, 2H), 7.07 (t, 2H, *J*= 9 Hz), 7.32 (dd, 2H, *J*= 5, 8 Hz), 7.84 (dd, 1H, *J*= 4, 8 Hz), 8.77 (d, 1H, *J*= 8 Hz), 8.98 (d, 1H, *J*= 4 Hz); ^{19}F NMR (282.6 MHz, CD_3OD) δ -78.0, 59.3; EI MS (*m/z*) 365.3 $[M+H]^+$, 387.3 $[M+Na]^+$.





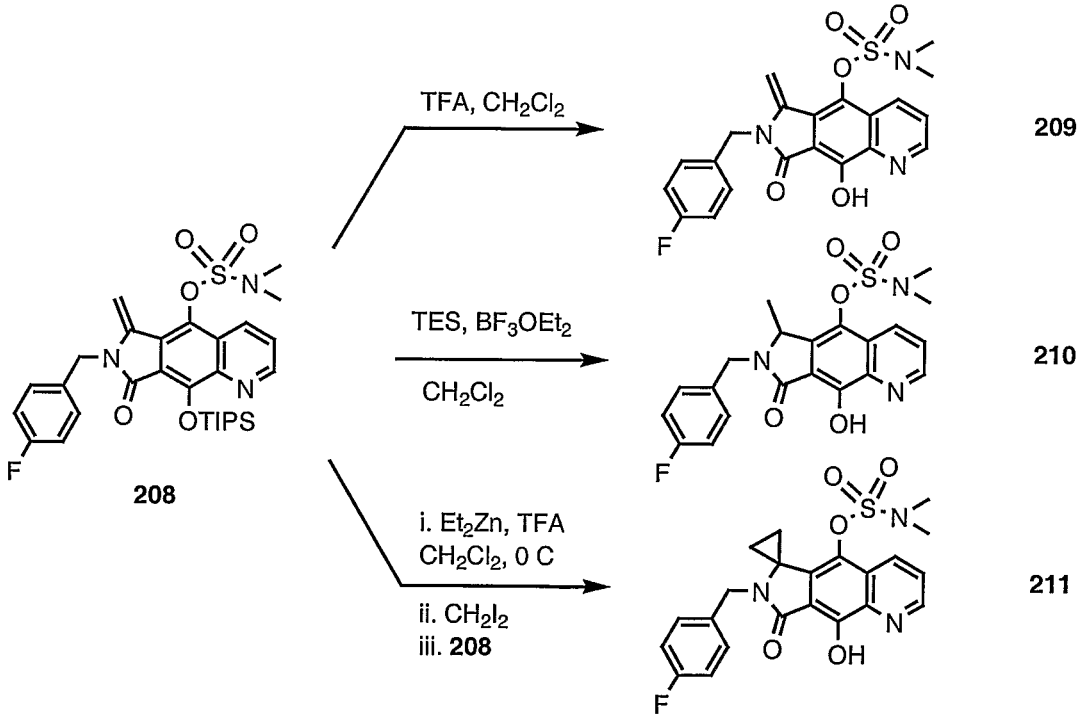
Example 207

A solution of **12** (Example 12, 65 mg, 0.131 mmol) in 1.3 mL of CH_2Cl_2 was stirred with dimethyl sulfamoyl chloride (38 mg, 0.262 mmol), TEA (73 μL, 0.63 mmol), and DMAP (2 mg, 0.013 mmol) for 2 hours at room temperature when LCMS analysis

demonstrated complete consumption of the starting materials. The reaction was worked up by dilution with CH_2Cl_2 and washing the organic layer with H_2O. The solvent was removed under reduced pressure and the product was purified by column chromatography to yield 59 mg of **207** (75%) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, 18H, *J*= 8 Hz), 1.53 (septet, 3H, *J*= 8 Hz), 3.23 (s, 6H), 4.84 (s, 2H), 7.00 (t, 2H, *J*= 8 Hz), 7.45 (dd, 2H, *J*= 6, 9 Hz), 7.65 (dd, 1H, *J*= 4, 8 Hz), 8.77 (dd, 1H, *J*= 2, 8 Hz), 8.94 (dd, 1H, *J*= 2, 4 Hz); ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 62.0; EI MS (*m/z*) 624.2 $[M+Na]^+$.

Example 208

A solution of **207** (30 mg, 0.050 mmol) in 0.25 mL of THF was stirred with 33 μL (0.10 mmol) of methylmagnesium bromide for 1 hour at room temperature. The solution was diluted with CH_2Cl_2 and stirred with aqueous 1N HCl for 30 minutes. Removal of the solvent *in vacuo* yielded 26 mg (87%) of the product **208** as a green oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, 18H, *J*= 8 Hz), 1.56 (septet, 3H, *J*= 8 Hz), 2.97 (s, 6H), 4.94 (s, 1H), 5.00 (s, 2H), 5.59 (s, 1H), 7.00 (t, 2H, *J*= 8 Hz), 7.21- 7.32 (m, 2H), 7.55- 7.62 (m, 1H), 8.50 (d, 1H, *J*= 8 Hz), 8.88 (br s, 1H); ^{19}F NMR (282.6 MHz, $CDCl_3$) δ 61.3; EI MS (*m/z*) 600.2 $[M+H]^+$, 622.2 $[M+Na]^+$.



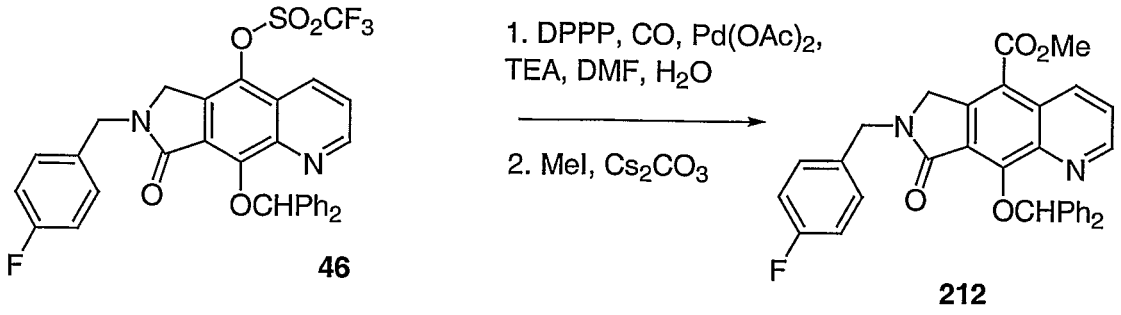
Example 209

A solution of **208** (13 mg, 0.022 mmol) and TFA (0.11 mL) and CH_2Cl_2 (0.11 mL) was allowed to stir at room temperature overnight. The solvent was removed in vacuo and the residue was purified by RP-HPLC using a 20- 80% A to give product **209**. Buffer A contained CH_3CN-1% TFA and buffer B was H_2O-1% TFA. ^1H NMR (300 MHz, $CDCl_3$) δ 3.06 (s, 3H), 3.07 (s, 3H), 5.00 (s, 2H), 5.12 (s, 1H), 5.71 (s, 1H), 6.96- 7.07 (m, 2H), 7.22- 7.33 (m, 2H), 7.71 (dd, 1H, *J*= 4, 9 Hz), 8.67 (d, 1H, *J*= 8 Hz), 9.05 (br s, 1H); ^{19}F NMR (282.6 MHz, $CDCl_3$) δ -76.2, 62.1; EI MS (*m/z*) 444.2 $[M+H]^+$, 466.1 $[M+Na]^+$.

Example 210

Under a N_2 atmosphere, a solution of **208** (14 mg, 0.023 mmol) in CH_2Cl_2 (0.23 mL) was stirred with triethylsilane (15 μL, 0.093 mmol) and boron trifluoride diethyletherate (BF_3OEt_2, 20 μL, 0.164 mmol) at ambient temperature overnight. The reaction mixture was worked up by removing the solvent under reduced pressure and precipitation from EtOAc-Hex to provide 7.5 mg of the product **210** as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.56 (d, 3H, *J*= 7 Hz), 3.16 (s, 6H), 4.42 (d, 1H, *J*= 15 Hz), 5.02 (q, 1H, *J*= 6 Hz), 5.09 (d, 1H, *J*=15 Hz), 7.06 (t, 2H, *J*= 8 Hz), 7.33(dd, 2H, *J*= 5, 9 Hz), 7.72- 7.79 (m, 1H), 8.62 (d, 1H, *J*= 9 Hz), 9.15 (br s, 1H); ^{19}F NMR (282.6 MHz, $CDCl_3$) δ -76.2, 62.5; EI MS (*m/z*) 446.2 $[M+H]^+$, 468.2 $[M+Na]^+$.Example 211

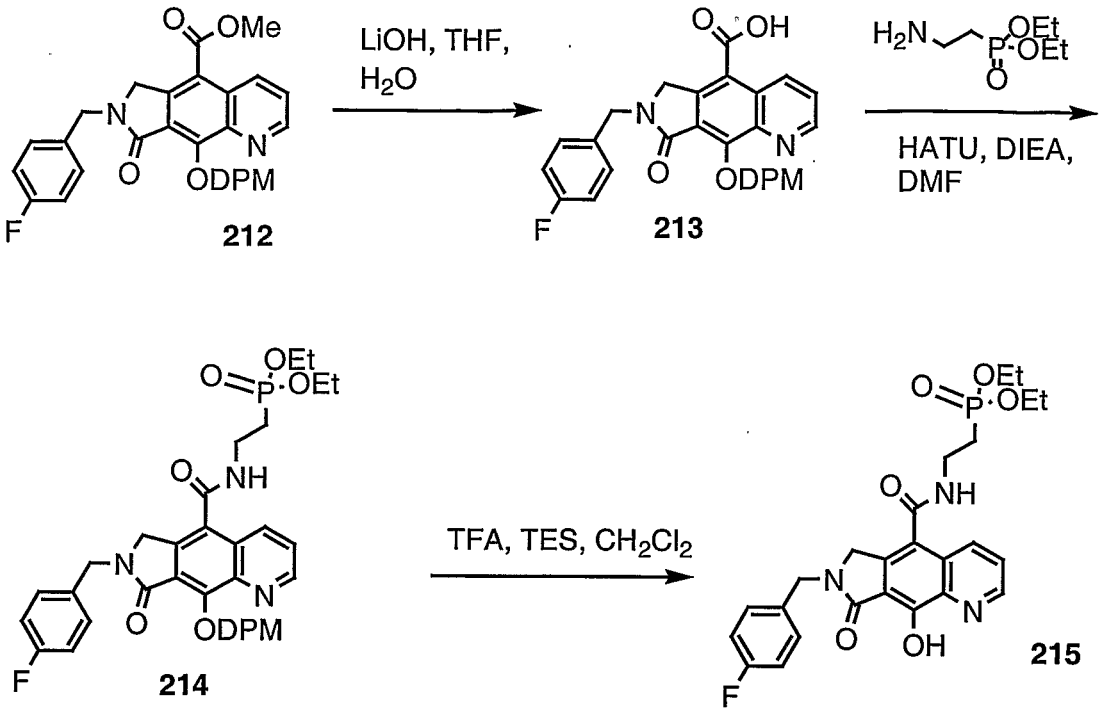
Under a N_2 atmosphere, to a solution of diethylzinc (0.074 mmol, 74 μL of a 1M mixture) and 74 μL of CH_2Cl_2 was added TFA (0.074 mmol, 5.7 μL) at 0 °C. This mixture was stirred at cooled temperature for 15 minutes when a solution of CH_2I_2 (0.074 mmol, 6 μL) in 50 μL of CH_2Cl_2 was added. After 10 minutes, a solution of **208** in 50 μL of CH_2Cl_2 was added and the ice bath removed. The reaction mixture was stirred at ambient temperature for 1 hour when LCMS analysis demonstrated complete consumption of the starting materials. The product **211** was purified by RP-HPLC using a 20- 80% A. Buffer A contained CH_3CN-1% TFA and buffer B was H_2O-1% TFA.. ^1H NMR (300 MHz, CD_3OD) δ 1.46 (br t, 2H), 2.10 (br t, 2H), 3.14 (s, 6H), 4.55 (s, 2H), 7.02 (t, 2H, *J*= 9 Hz), 7.21- 7.31 (m, 2H), 7.60-7.68 (m, 1H), 8.58- 8.65 (m, 1H), 9.05- 9.08 (m, 1H); EI MS (*m/z*) 458.2 $[M+H]^+$, 480.1 $[M+Na]^+$.



46 212

Example 212

To trifluoro-methanesulfonic acid 9-benzhydryloxy-7- (4-fluoro-benzyl)-8-oxo-7, 8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **46** (1.48 g, 2.39 mmol) and 1,3-bis(diphenylphosphino)propane (DPPP) (295 mg, 0.7 mmol) in DMF (20 mL) and water (1 mL) in a two-necked round bottom flask were added $Pd(OAc)_2$ (107 mg, 0.48 mmol). The solution was degassed under high vacuum and flushed with carbon monoxide from a balloon. The flushing was repeated five times. TEA (0.733 mL, 3.26 mmol) was introduced. The mixture was heated under CO atmosphere for 2.5 hours and cooled down to the room temperature. MeI (0.74 mL, 12 mmol) and Cs_2CO_3 were added and stirring was continued under a nitrogen atmosphere for 45 minutes. The mixture was diluted with EtOAc (300 mL), washed with water, 1N aqueous HCl and brine, dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography on a silica gel column eluting with 15% to 35% of EtOAc in hexane to afford 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid methyl ester **212**, (0.9g, 1.69 mmol, 70%) as a yellow solid. ^1H NMR ($CDCl_3$): δ9.25 (d, 1H), 9.05 (m, 1H), 7.80 (d, 4H), 7.56 (dd, 1H), 7.0-7.4 (m, 11H), 4.85 (s, 2H), 4.55 (s, 2H), 3.95 (s, 3H); MS: 555 (M+Na).



Example 213

A solution of 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid methyl ester **212** (54 mg, 0.10 mmol) in 1.0 mL of a 1:1:1 mixture of THF: MeOH: H_2O was stirred with LiOH (9.7 mg, 0.41 mmol) overnight when the starting materials were completely consumed as judged by TLC (DPM = benzhydryl, Ph_2CH-). The reaction mixture was dried under reduced pressure and the residue was dissolved in EtOAc. The organic layer was stirred with saturated aqueous NH_4Cl for 30 minutes. The aqueous layer was checked by TLC to assure complete transfer of the products to the organic layer. The organic layer was dried in vacuo to yield 45.5 mg (87%) of 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid **213** as a white solid. The product was carried on without purification. MS (*m/z*) 519.2 $[M+H]^+$, 541.2 $[M+Na]^+$.

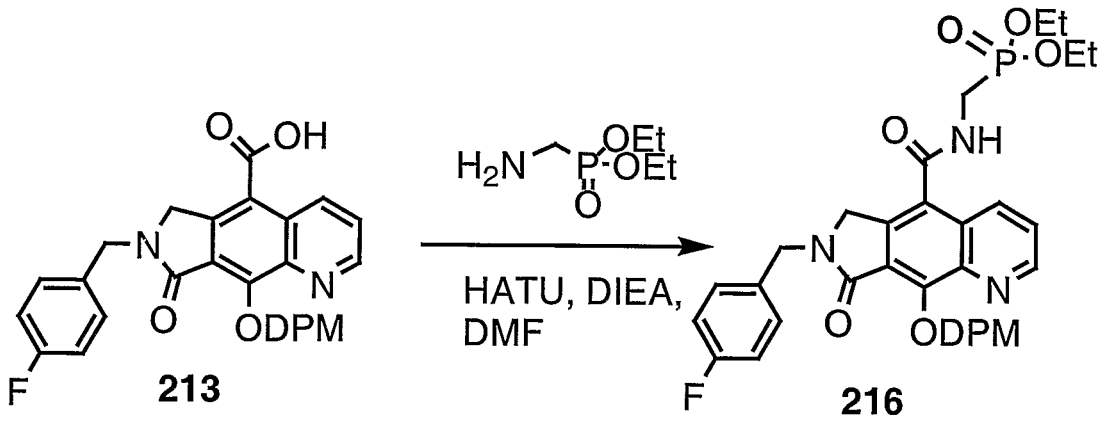
Alternatively, methyl ester **212** (0.071g, 0.1334mmol) was dissolved in 2.4 mL of tetrahydrofuran and 0.6 mL of DI H_2O. To this was added LiOH (0.013g, 0.5338mmol) and mixture stirred at room temperature. After 15 hours, starting material consumed. Diluted with dichloromethane, washed with 1M HCl solution, dried (Na_2SO_4), concentrated to give **213** (0.068g, 0.1313 mmol, 98%.) ^1H NMR (CD_3SOCD_3) δ 9.25 (d, 1H), 9.12 (dd, 1H), 8.17 (s, 1H), 7.75 (d, 5H), 7.37 (dd, 2H), 7.24 (m, 6H), 4.82 (s, 2H), 4.59 (s, 2H.) MS: 517 (M-1.)

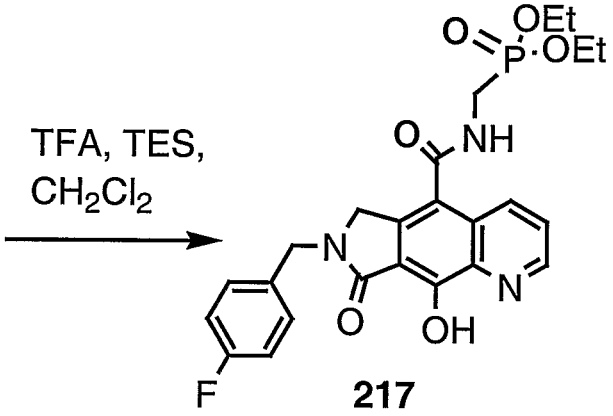
Example 214

A solution of the oxalate salt ($HO_2CCO_2^-$) of diethyl(aminoethyl)phosphonate (12 mg, 0.042 mmol) in 0.21 mL of DMF was mixed with DIEA (15 μL, 0.084 mmol) until the reaction became clear. To this solution was added **213** (11 mg, 0.021 mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (16 mg, 0.042 mmol). This mixture was stirred at room temperature for 2 hours when it was warmed to 60 °C with a heat gun for 1 minute. LCMS analysis demonstrated complete consumption of the starting materials. The reaction mixture was directly loaded onto a silica gel column and the product was quickly eluted with a gradient of EtOAc-10% MeOH/EtOAc to provide 12.7 mg (88%) of the product **214**. ^{1}H NMR (300 MHz, CD_3OD) δ 1.29 (t, 6, *J*= 7 Hz), 2.18 (dt, 2H, *J*= 7, 18 Hz), 3.53- 3.65 (m, 2H), 4.08 (septet, 4H, *J*= 7 Hz), 4.46 (s, 2H), 4.83 (s, 2H), 7.06- 7.25 (m, 8H), 7.40 (dd, 2H, *J*= 5, 9 Hz), 7.61- 7.68 (m, 6H), 8.04 (s, 1H), 8.44 (d, 1H, *J*= 7 Hz), 9.04-9.09 (m, 1H); ^{31}P (121.4 MHz, CD_3OD) δ 29.5; MS (*m/z*) 682.1 $[M+H]^+$, 704.2 $[M+Na]^+$.

Example 215

A solution of **214** (12.7 mg, 0.019 mmol) in 0.19 mL of CH_2Cl_2 was stirred with TFA (144 μL, 1.9 mmol) and TES (304 μL, 1.9 mmol) for 45 minutes under a N_2 atmosphere. TLC and LCMS analysis indicated complete reaction at that time. The reaction was worked up by removing the solvent under reduced pressure. The residue was purified by crystallization from EtOAc-Hex to yield 8.6 mg (71%) of (2-{[7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-amino}-ethyl)-phosphonic acid diethyl ester **215** as a yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ 1.33 (t, 6H, *J*= 7 Hz), 2.24 (dt, 2H, *J*= 19, 7 Hz), 3.70 (septet, 2H, *J*= 8 Hz), 4.09- 4.17 (m, 4H), 4.61 (s, 2H), 4.78 (s, 2H), 7.10 (t, 2H, *J*= 9 Hz), 7.41 (dd, 2H, *J*= 6, 8 Hz), 7.76 (br d, 1H, *J*= 5 Hz), 8.71 (d, 1H, *J*= 9 Hz), 8.95 (br s, 1H); ^{31}P (121.4 MHz, CD_3OD) δ 29.5; MS (*m/z*) 516.3 $[M+H]^+$, 1030.9 $[2M]^+$, 1053.0 $[2M+Na]^+$.



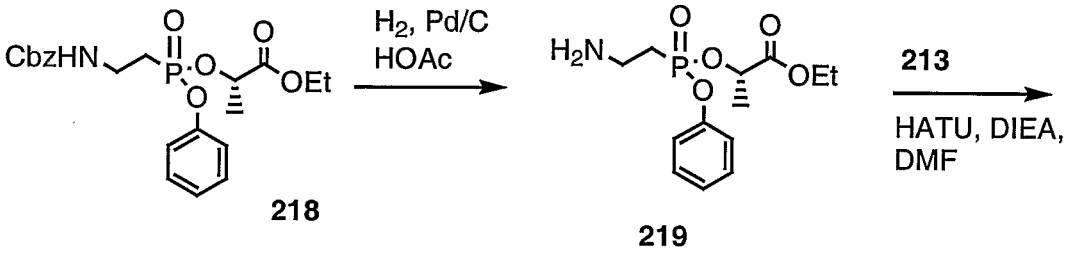


Example 216

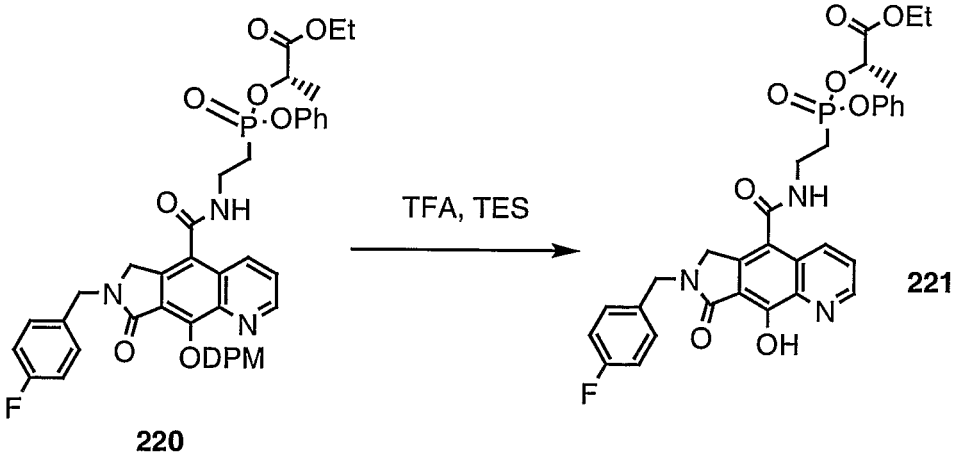
A solution of oxalate salt of diethyl(aminomethyl)phosphonate (8 mg, 0.031 mmol) in 0.31 mL of DMF and DIEA (22 μL, 0.124 mmol) was added to **213** (16 mg, 0.031 mmol) and HATU (24 mg, 0.062 mmol). The solution was stirred at ambient temperature for 2 hours when another batch of the amine and the coupling reagent equivalent to the above amounts were added. The reaction was heated with a heat gun to 60 °C for 1 minute and the reaction was analyzed by LCMS. The reaction mixture was loaded onto a flash column and ({[9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-amino}-methyl)-phosphonic acid diethyl ester **216** was eluted with EtOAc- 10% MeOH to provide 20 mg (97%) of a clear oil. MS (*m/z*) 668.1 $[M+H]^+$, 690.3 $[M+Na]^+$.

Example 217

A solution of **216** (20 mg, 0.030 mmol) in 0.30 mL of CH_2Cl_2 was stirred with TFA (231 μL, 3.00 mmol) and TES (479 μL, 3.00 mmol) for 30 minutes when the starting materials were completely consumed as judged by TLC and LCMS. The reaction was worked up by removal of the solvent in vacuo and crystallizing the product from EtOAc-Hex to provide 10 mg (66%) of ({[7-(4-Fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-amino}-methyl)-phosphonic acid diethyl ester **217** as a yellow solid. ^{1}H NMR (300 MHz, CD_3OD) δ 1.32 (t, 6H, *J*= 7 Hz), 3.96 (d, 2H, *J*= 12 Hz), 4.16 (septet, 4H, *J*= 7 Hz), 4.56 (s, 2H), 4.79 (s, 2H), 7.10 (t, 2H, *J*= 9 Hz), 7.39 (dd, 2H, *J*= 9 Hz), 7.76 (br s, 1H), 8.66 (d, 1H, *J*= 8 Hz), 8.95 (br s, 1H); ^{31}P (121.4 MHz, CD_3OD) δ 23.2; ^{19}F NMR (282.6 MHz, CD_3OD) δ -76.2, 59.9; MS (*m/z*) 502.5 $[M+H]^+$, 1003.0 $[2M]^+$, 1025.1 $[2M+Na]^+$.



218 **219**



220 **221**

Example 218

S-lactate ester **218**

Example 219

A solution of 2-[(2-benzyloxycarbonylamino-ethyl)-phenoxy-phosphinoyloxy]-propionic acid ethyl ester **218** (240 mg, 0.551 mmol) with approximately 50% purity and a ratio of 2:1 of diastereomers was dissolved in 5.5 mL of ethanol with acetic acid (63 μL, 1.10 mmol). To this solution was added 36 mg of 10% Pd/C and the solution was degassed under a hydrogen atmosphere three times. The solution was vigorously stirred at room temperature for 3 hours when TLC showed complete consumption of the starting materials. The mixture was filtered through a pad of Celite and dried to provide 174 mg (87%) of 2-[(2-amino-ethyl)-phenoxy-phosphinoyloxy]-propionic acid ethyl ester; compound with acetic acid **219** as a clear oil.

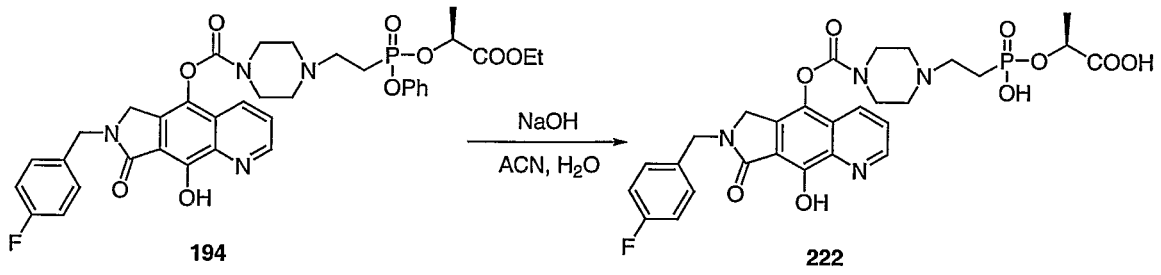
Example 220

A solution of 13.5 mg of **213** in 0.13 mL of DMF was stirred with HATU (20 mg, 0.052 mmol) at room temperature for 10 minutes. To this solution was added a premixed solution of **219** (28 mg, 0.078 mmol) of approximately 50% purity in 0.130 mL of DMF and DIEA (13.4 mg, 0.104 mmol). The reaction mixture was gently heated with a heat gun for 30 seconds and then the reaction was allowed to proceed at room temperature for 2 hours when LCMS demonstrated complete consumption of the carboxylic acid. The reaction mixture was loaded onto a silica gel column and purified with EtOAc- 10% MeOH to provide 9.5 mg of 3-[(2-{[9-Benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-amino}-ethyl)-phenoxy-phosphinoyl]-2-methyl-propionic acid ethyl ester **220** which was carried on to the next step.

Example 221

A solution of **220** (9.5 mg, 11.8 μmol) was stirred with 0.12 mL of dry dichloromethane with trifluoroacetic acid (93 μL, 1.18 mmol) and triethylsilane (189μL, 1.18 mmol) for 1 hour at room temperature when TLC showed complete consumption of the starting materials. The reaction mixture was dried *in vacuo* and azeotroped from dichloromethane three times. The solid product was triturated with EtOAc- Hex to get 6 mg of 2-[(2-{[7-(4-Fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-amino}-ethyl)-phenoxy-phosphinoyloxy]-propionic acid ethyl ester **221** as a pale yellow solid. The NMR of the two diastereomers in $CDCl_3$ is broad and indicates presence of rotamers. VT NMR in DMSO at 85 °C resulted in drastic sharpening of the peaks. ^1H

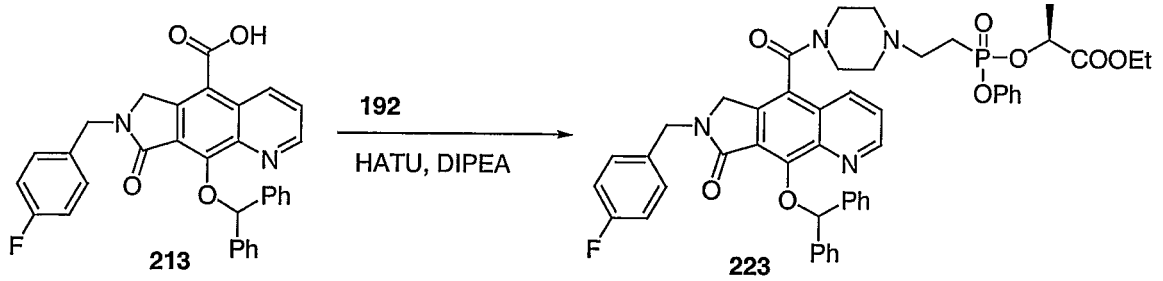
NMR (300 MHz, DMSO- *d6*, 85 °C) δ 1.15- 1.26 (m, 3H), 1.35 and 1.47 (d, 3H, *J*= 7 Hz), 2.23- 2.45 (m, 2H), 3.58- 3.57 (m, 2H), 4.08- 4.19 (m, 2H), 4.56 (s, 2H), 4.69 (s, 2H), 4.93- 5.04 (m, 1H), 7.14 (t, 2H, *J*= 9 Hz), 7.18- 7.23 (m, 3H), 7.35- 7.42 (m, 4H), 7.65 (dd, 1H, *J*= 4, 8 Hz), 8.42 (br s, 1H), 8.55 (d, 1H, *J*= 9 Hz), 8.92 (d, 1H, *J*= 4H); ^{31}P (121.4 MHz, DMSO-*d6*, 85 °C) δ 26.1, 28.3; MS (*m/z*) 636.5 $[M+H]^+$.



194 222

Example 222

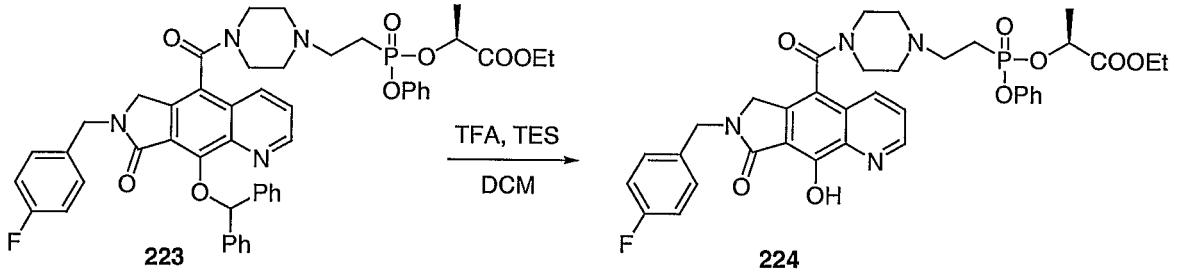
A solution of the trifluoroacetate salt of 4-{2-[(1-ethoxycarbonyl-ethoxy)-phenoxy-phosphoryl]-ethyl}-piperazine-1-carboxylic acid 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **194** (0.045 g, 0.054 mmol) in acetonitrile (ACN, 0.68 mL) and water (0.68 mL) was treated with an aqueous solution of NaOH (0.162 mL, 1M). The reaction mixture was stirred at room temperature for 3 hours. The mixture was cooled to 0° C, then acidified with a 2N aqueous solution of HCl to pH=1. Acetonitrile was removed in vacuo then purified by reversed phase HPLC to afford the trifluoroacetate salt of 4-{2-[(1-carboxy-ethoxy)-hydroxy-phosphoryl]-ethyl}-piperazine-1-carboxylic acid 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester; compound with trifluoro-acetic acid **222** (0.032 g , 80%): ^{1}H NMR (CD_3OD) δ 9.0 (d, 1H), 8.5 (d, 1H), 7.75 (dd, 1H), 7.4 (dd, 2H), 7.1 (t, 2H), 4.8 (s, 2H), 4.45 (s, 2H), 4.3-3.7 (m, 4H), 3.7-3.35 (m, 6H), 2.2 (m, 2H), 1.55 (d, 3H); ^{31}P NMR ($CDCl_3$) δ 19.8; MS: 617 (M+1).



213 223

Example 223

A solution of the 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid **213** (0.415 g, 0.80 mmol) and HATU (0.608 g, 1.60 mmol) in N,N-dimethylformamide (DMF) (2.5 mL) was stirred under an inert atmosphere at room temperature for 5 minutes. To the solution was added a premixed solution of 2-[phenoxy-(2-piperazin-1-yl-ethyl)-phosphinoyloxy]-(*S*)-propionic acid ethyl ester: compound with trifluoroacetic acid **192** (0.580 g, 1.20 mmol), N,N-Diisopropylethylamine (DIPEA) (0.700 mL, 4.0 mmol) in DMF (3.5 mL). The reaction mixture was stirred at room temperature for 5 hours. The mixture was diluted with ethyl acetate, washed with saturated $NaHCO_3$ (twice), water (twice) and brine (twice), dried ($NaSO_4$), and concentrated. The residue was purified by silica gel chromatography (5/95 – methanol/methylene chloride) to afford 2-[(2-{4-[9-benzyhydryloxy-7-(4-fluoro-benzyl-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-piperazin-1-yl}-ethyl)-phenoxy-phosphinoyloxy]-(*S*)-propionic acid ethyl ester **223** (0.625 g, 90%) as mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 9.07 (dd, 1H), 8.15 (s, 1H), 8.05 (dd, 1H), 7.75 (d, 4H), 7.52 (dd, 1H), 7.4-7.1 (m, 13H), 7.05 (t, 2H), 5.02 (m, 1H), 5.0-4.6 (dd, 2H), 4.4-4.0 (dd, 2H), 4.17 (m, 2H), 4.0-3.5 (m, 3H), 3.0 (m, 2H), 2.7-2.5 (m, 3H), 2.4-2.1 (m, 4H), 1.6 & 1.4 (d, 3H), 1.25 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 28.3, 26.5; MS: 871 (M+1).

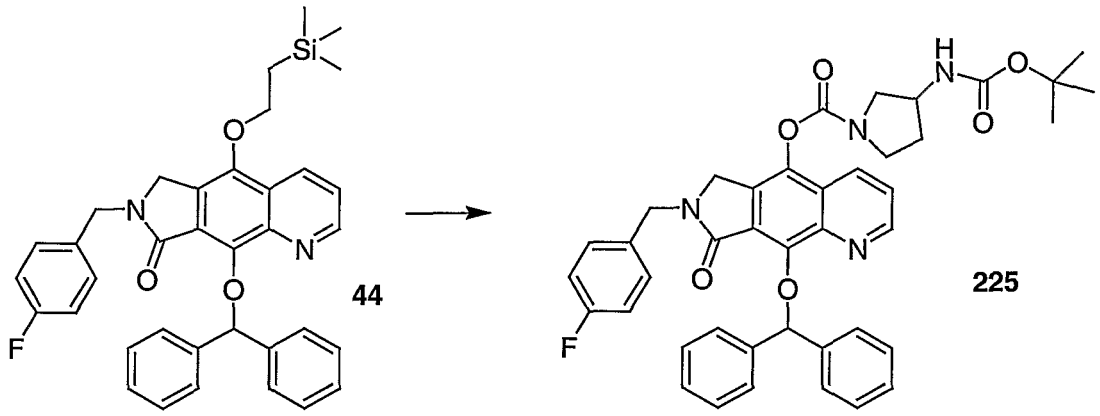


223 224

Example 224

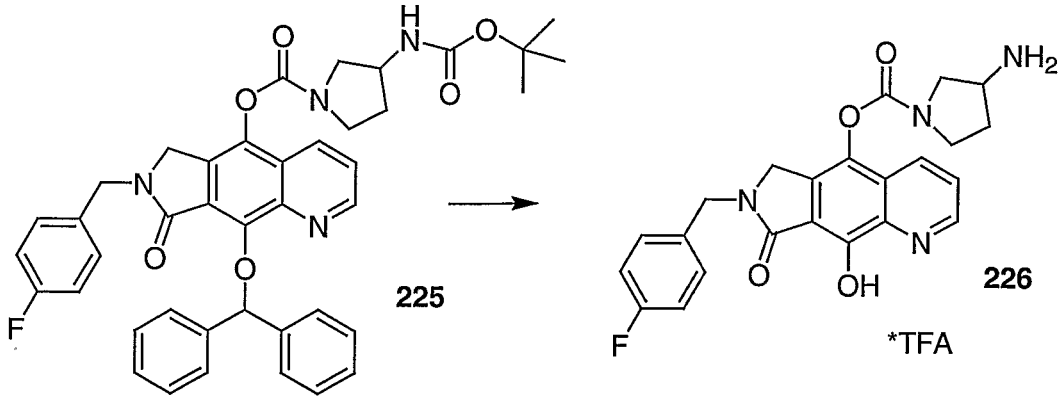
A solution of 2-[(2-{4-[9-benzyhydryloxy-7-(4-fluoro-benzyl-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-piperazin-1-yl}-ethyl)-phenoxy-phosphinoyloxy]-propionic acid ethyl ester **223** (0.420 g, 0.483 mmol) in methylene chloride (2 mL) was treated with trifluoroacetic acid (0.4 mL) and triethylsilane (0.8 mL). The reaction mixture was stirred at room temperature under an inert atmosphere for 40 minutes. The volatiles were removed in vacuo with toluene. The product was triturated in diethyl ether/hexane with sonicaton to afford the trifluoroacetate salt of 2-{[2-4-2-[7-(4-fluoro-benzyl)-9-

hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl]-acetyl}-piperazin-1-yl)-ethyl]-phenoxy-phosphinoyloxy}-propionic acid ethyl ester **224** (0.370 g, 94%): ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.15 (dd, 1H), 7.67 (dd, 1H), 7.35-7.1 (m, 7H), 7.05 (t, 2H), 5.0 (m, 1H), 5.0-4.6 (m, 2H), 4.6-4.25 (m, 2H), 4.25-3.95 (m, 5H), 3.7-2.8 (m, 8H), 2.7-2.5 (m, 2H), 1.6 & 1.4 (d, 3H), 1.25 (t, 3H); ^{31}P NMR ($CDCl_3$) δ 23.0, 21.0; MS: 705 (M+1).



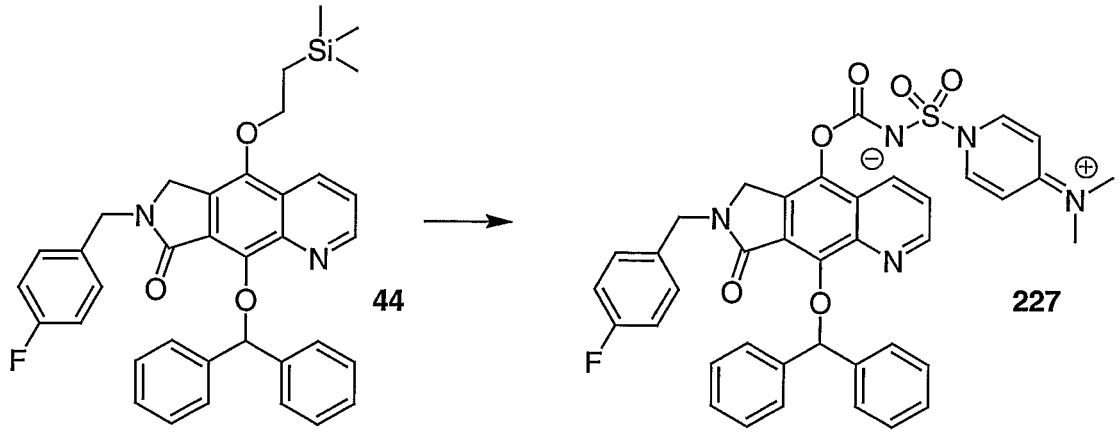
Example 225

Trimethylsilylethyl ether **44** (0.03g, 0.0508 mmol) was dissolved in 2 mL dry tetrahydrofuran. To this was added triethylamine (0.028mL, 0.2032 mmol) and 1 M tetrabutylammonium fluoride solution in tetrahydrofuran (0.1016mL, 0.1016mmol.) Stirred at room temperature 10 minutes until starting material consumed. Diluted with dichloromethane, washed with washed with 1M HCl solution, saturated brine, concentrated to give crude. Dissolved in 1.5 mL dichloromethane, added catalytic dimethylaminopyridine, triethylamine (0.16mL, 0.6 mmol) and cooled to 0° C. To this was added triphosgene (0.03g, 0.1016 mmol) and stirred 40 minutes. BOC-aminopyrrolidine (0.038g, 0.2032 mmol) was then added and stirred at room temperature for 10 minutes. The mixture was diluted with dichloromethane, washed with 1M HCl, brine, concentrated volatiles to give crude product. Chromatographed (10% to 30% acetone/toluene) to give **225** (0.0108g, 0.0153mmol, 30%.) ^{1}H NMR ($CDCl_3$) δ 9.03 (dd, 1H), 8.11 (d, 1H), 8.03 (s, 1H), 7.74 (d, 4H), 7.50 (dd, 1H), 7.27 (m, 8H), 7.07 (dd, 2H), 4.80 (s, 2H), 4.65 (br s, 1H), 4.30 (br s, 1H), 4.24 (s, 2H), 3.95 (br s, 1H), 3.74 (m, 2H), 3.58 (m, 2H), 1.48 (s, 9H) MS: 703 M+1)



Example 226

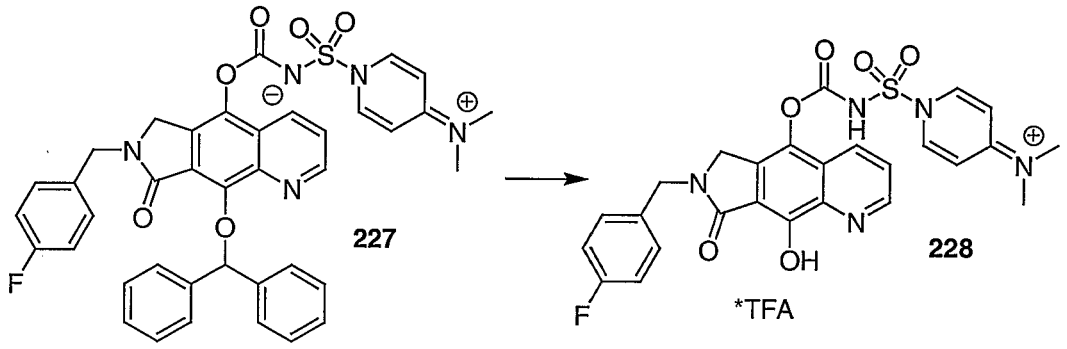
Carbamate **225** (0.0108g, 0.0153mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Then dissolved in 0.3 mL dichloromethane, 0.3 ml trifluoroacetic acid. Stirred at room temperature for one hour. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethyl ether/hexanes to give the trifluoroacetate salt of 3-amino-pyrrolidine-1-carboxylic acid 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **226** (0.0057g, 0.0104mmol, 68%.) ^{1}H NMR (CD_3SOCD_3) δ 9.00 (s, 1H), 8.41 (s, 1H), 8.21 (s, 1H), 7.76 (dd, 1H), 7.36 (dd, 2H), 7.22 (dd, 2H), 4.72 (s, 2H), 4.36 (s, 2H), 3.93-3.35 (m, 7H) ^{19} F NMR: -73.9 MS: 437 (M+1), 435 (M-1)



Example 227

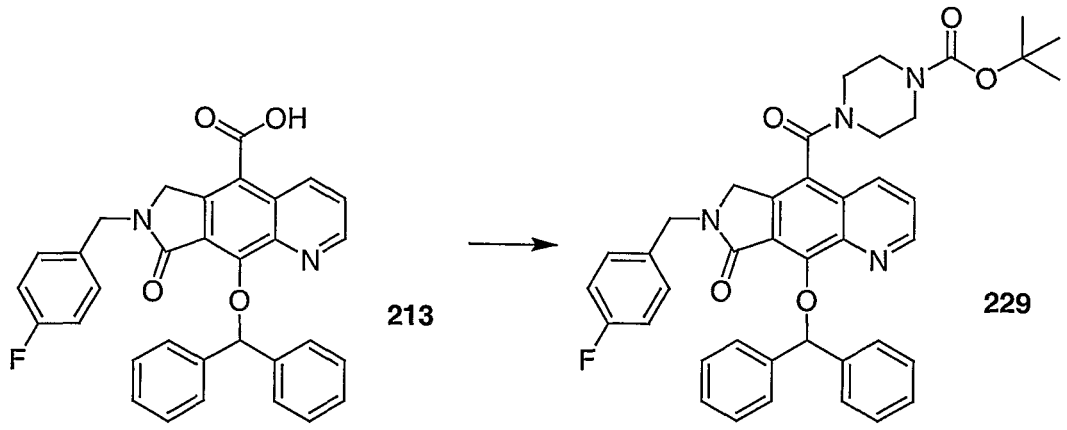
2-Amino-1,2,4 thiadiazole (0.006g, 0.06mmol) and triethylamine (0.0376mL, 0.27mmol) were added to 1 mL dichloromethane and cooled to 0° C. To this was slowly

added chlorosulfonylisocyanate (0.007mL, 0.08mmol) at 0° C. Stirred thirty minutes until starting material consumed. Simultaneously, in a separate flask trimethylsilylethyl ether **44** was dissolved in 0.5 mL tetrahydrofuran. To this was added triethylamine (0.0376mL, 0.27mmol) and 1M tetrabutylammonium fluoride in tetrahydrofuran (0.135, 0.135mmol) and stirred at room temperature. After 20 minutes, diluted with dichloromethane, washed with 1M HCl solution and brine, concentrated to give crude. At 0° C, dissolved in 0.5mL dichloromethane and added to the solution prepared *in situ* above. Stirred at 0° C for 5minutes, catalytic DMAP added, then stirred for one hour at room temperature. Diluted with dichloromethane, washed with 1M HCl solution, brine, concentrated to give crude. Chromatographed (5 to 30% methanol/dichloromethane) to give dimethylaminopyridine adduct **227** (0.033g, 0.046mmol, 68%.) ^{1}H NMR ($CDCl_3$) δ 8.97 (dd, 1H), 8.54 (d, 2H), 8.19 (d, 1H), 8.00 (s, 1H), 7.72 (d, 4H), 7.42 (dd, 1H), 7.26-7.14 (m, 7H), 7.02 (dd, 2H), 6.52 (d, 2H), 4.74 (s, 2H), 4.17 (s, 2H), 3.22 (s, 6H.) MS: 718 (M+1).



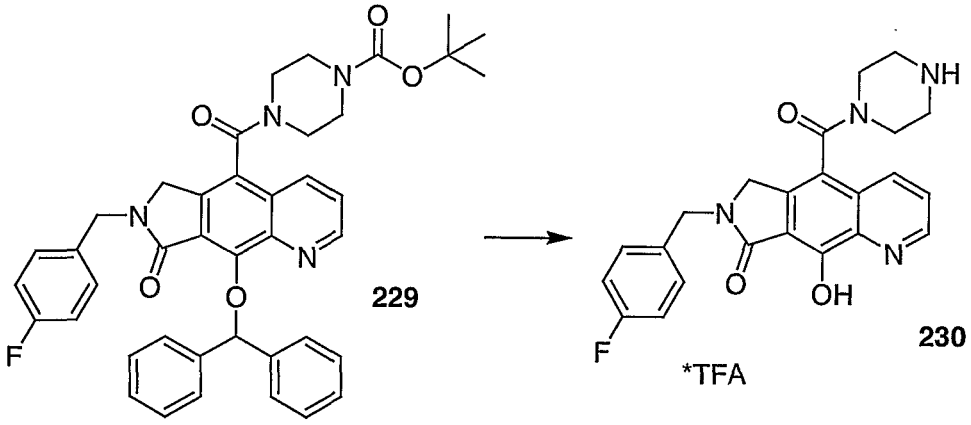
Example 228

Carbamate **227** (0.007 gm, 0.0097 mmol) was dissolved in 0.25 mL of dichloromethane. To this was added 0.1mL of triethylsilane and 0.05mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethyl ether/hexanes to give **228** (0.004g, 0.0073mmol, 75%.) ^{1}H NMR (CD_3SOCD_3) δ 9.22 (d, 1H), 9.09 (s, 1H), 8.47 (s, 1H), 8.19 (s, 1H), 8.01 (s, 1H), 7.37 (s, 2H), 7.19 (s, 1H), 6.96 (s, 2H), 4.76 (s, 2H), 4.45 (s, 2H), 3.21 (d, 6H.) ^{19}F NMR: -75.95 MS: 552 (M+1), 550 (M-1)



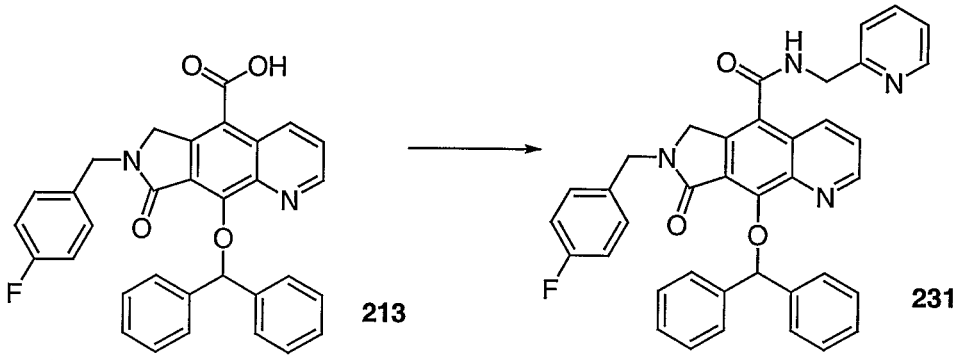
Example 229

Carboxylic acid **213** (0.015g, 0.029mmol) was dissolved in 0.8 mL of dimethylformamide. To this was added BOC-piperazine (0.0116g, 0.058 mmol), triethylamine (0.012mL, 0.087mmol), 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.011g, 0.058mmol), 1-Hydroxybenzotriazole hydrate (0.0059g, 0.0435mmol) and stirred at room temperature. After 15 hours, starting material was consumed. Dilute with dichloromethane, washed with 1M HCl solution, saturated brine solution, dried (Na_2SO_4), concentrated to give crude product. Chromatographed (10 to 50% ethyl acetate/hexanes) to give 4-[9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester **229** (0.009g, 0.013mmol, 45%.) ^{1}H NMR ($CDCl_3$) 9.075 (s, 1H), 8.15 (s, 1H), 8.03 (d, 1H), 7.74 (dd, 4H), 7.53 (dd, 1H), 7.27 (m, 8H), 7.04 (dd, 2H), 4.91 (d, J=17Hz, 1H), 4.69 (d, J=17Hz, 1H), 4.41 (d, J=17Hz, 1H), 4.055 (d, J=17Hz, 1H), 3.55-2.96 (br m, 8H), 1.44 (s, 9H.) MS: 687 (M+1).



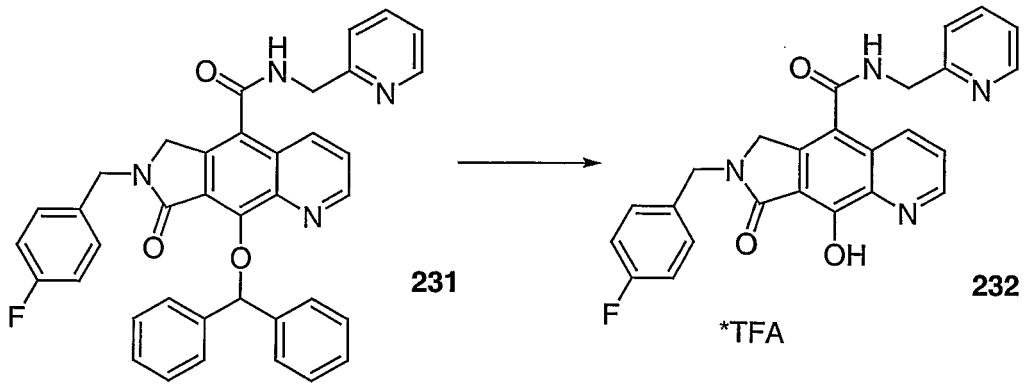
Example 230

Carboxamide **229** (0.0108g, 0.0153mmol) was dissolved in 1 mL of dichloromethane. To this was added 0.4 mL of triethylsilane and 0.2 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Then dissolved in 0.6 mL dichloromethane, 0.6 ml trifluoroacetic acid. Stirred at room temperature for one hour. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethyl ether/hexanes to give 7-(4-fluoro-benzyl)-9-hydroxy-5-(piperazine-1-carbonyl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **230** (0.039g, 0.0682mmol, 100%.) ^{1}H NMR (CD_3SOCD_3) δ 98.97 (s, 2H), 8.32 (d, 1H), 7.74 (s, 1H), 7.36 (dd, 2H), 7.19 (dd, 2H), 4.86 (d, 1H), 4.58 (d, 1H), 4.42 (d, 1H), 4.34 (d, 1H), 3.9-2.90 (m, 8H.) ^{19}F NMR: -74.202 MS: 421 (M+1), 419 (M-1)



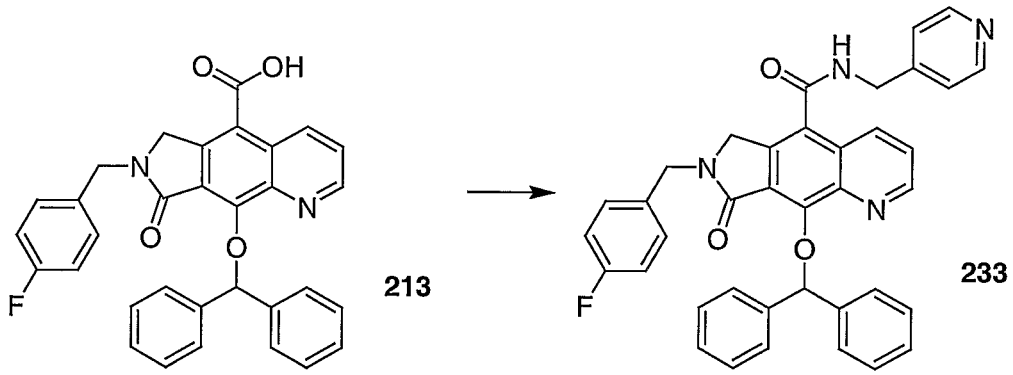
Example 231

Carboxylic acid **213** (0.010g, 0.0193mmol) was dissolved in 0.3 mL of dimethylformamide. To this was added 2-aminomethylpyridine (0.004g, 0.0386 mmol), triethylamine (0.008mL, 0.058mmol), 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.074g, 0.0386mmol), 1-Hydroxybenzotriazole hydrate (0.0039g, 0.029mmol) and stirred at room temperature. After 15 hours, starting material was consumed. Dilute with dichloromethane, washed with 1M HCl solution, saturated brine solution, dried (Na_2SO_4), concentrated to give crude product. Chromatographed (0 to 8% methanol/dichloromethane) to give 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid (pyridin-2-ylmethyl)-amide **231** (0.007g, 0.011mmol, 59%.) ^{1}H NMR ($CDCl_3$) 8.94 (s, 1H), 8.45 (d, 2H), 8.05 (s, 1H), 7.70 (d, 4H), 7.57-7.17 (m, 12H), 7.05 (d, 2H), 4.78 (s, 1H), 4.69 (d, J=5Hz, 1H), 4.38 (s, 1H). MS: 609 (M+1).



Example 232

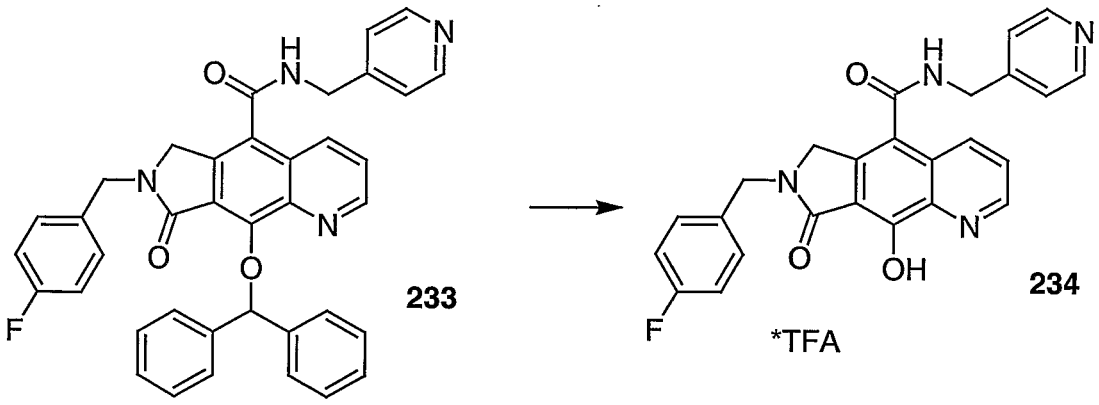
Carboxamide **231** (0.225g, 0.355mmol) was dissolved in 1 mL of dichloromethane. To this was added 0.5mL of triethylsilane and 0.25mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethyl ether/hexanes to give 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid (pyridin-2-ylmethyl)-amide **232** (0.11g, 0.20mmol, 56%.) ^{1}H NMR (CD_3SOCD_3) δ 9.18 (s, 1H), 8.96 (d, 1H), 8.65 (dd, 2H), 8.09 (dd, 1H), 7.76 (dd, 1H), 7.64 (dd, 1H), 7.36 (dd, 2H), 7.22 (dd, 2H), 4.70 (s, 4H), 4.54 (s, 2H). ^{19}F NMR: -75.37 MS: 443 (M+1), 441 (M-1)



Example 233

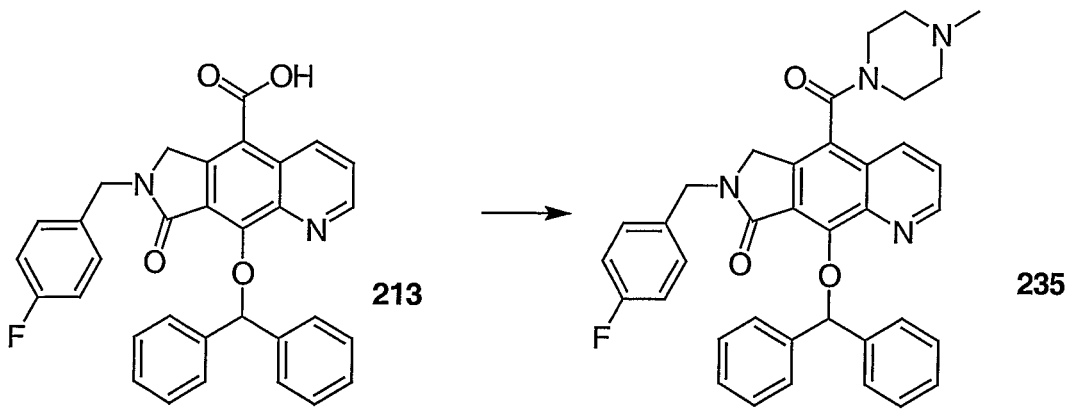
Carboxylic acid **213** (0.010g, 0.0193mmol) was dissolved in 0.3 mL of dimethylformamide. To this was added 4-aminomethylpyridine (0.004mL, 0.0386 mmol), triethylamine (0.008mL, 0.058mmol), 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.074g, 0.0386mmol), 1-Hydroxybenzotriazole hydrate (0.0039g, 0.029mmol) and stirred at room temperature. After 15 hours, starting material was consumed. Dilute with dichloromethane, washed with 1M HCl solution, saturated brine

solution, dried (Na_2SO_4), concentrated to give crude product. Chromatographed (0 to 8% methanol/dichloromethane) to give **233** (0.0048g, 0.008mmol, 41%.) ^{1}H NMR ($CDCl_3$) δ 8.71 (s, 1H), 8.66 (d, 2H), 7.99 (dd, 2H), 7.65 (s, 1H), 7.51 (s, 4H), 7.34 (m, 9H), 7.05 (dd, 2H), 4.69 (s, 2H), 4.25 (d, 2H), 4.00 (s, 2H). MS: 609 (M+1).



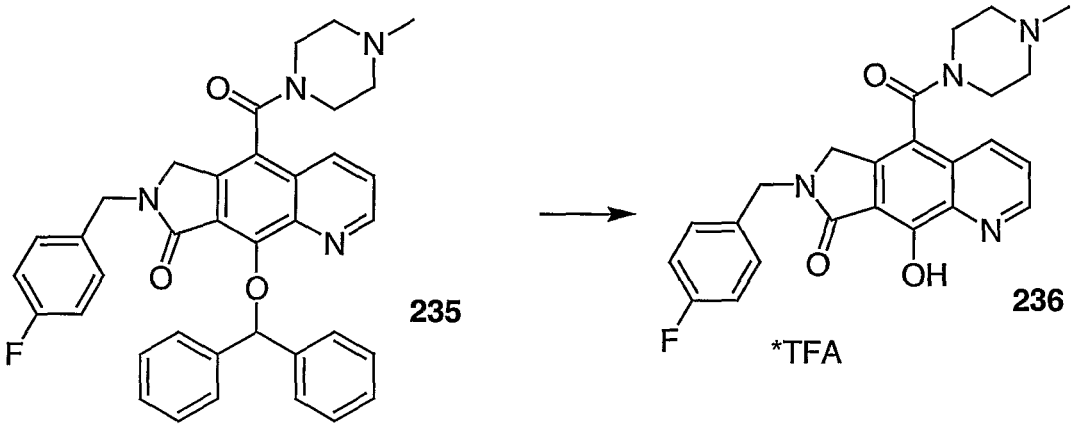
Example 234

Carboxamide **233** (0.137g, 0.225mmol) was dissolved in 1 mL of dichloromethane. To this was added 0.5mL of triethylsilane and 0.25mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethyl ether/hexanes to give 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid (pyridin-4-ylmethyl)-amide **234** (0.114g, 0.20mmol, 91%.) ^{1}H NMR (CD_3SOCD_3) δ 9.24 (dd, 1H), 8.98 (d, 1H), 8.77 (dd, 2H), 8.53 (d, 1H), 7.79 (dd, 3H), 7.40 (dd, 2H), 7.23 (dd, 2H), 4.71 (s, 4H), 4.56 (s, 2H). ^{19}F NMR: -74.906 MS: 443 (M+1), 441 (M-1)



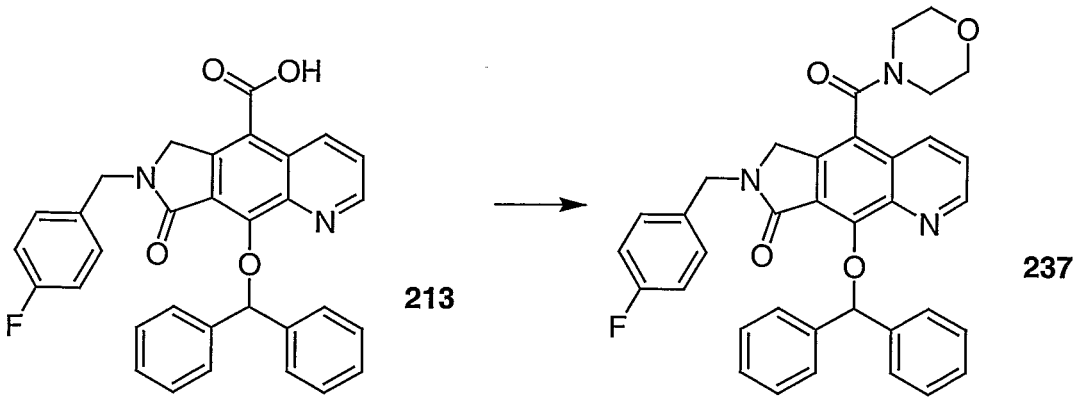
Example 235

Carboxylic acid **213** (0.020g, 0.0386 mmol) was dissolved in 0.4 mL of dimethylformamide. To this was added methyl piperazine (0.0085mL, 0.077 mmol), diisopropylethylamine (0.027 mL, 0.154mmol), *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.029g, 0.0777mmol) and stirred at room temperature. After 15 hours, starting material was consumed. Dilute with dichloromethane, washed with saturated brine solution, dried (Na_2SO_4), concentrated to give crude product. Chromatographed (0 to 8% methanol/dichloromethane) to give **235** (0.017g, 0.028 mmol, 73%.) ^{1}H NMR ($CDCl_3$) δ 9.06 (dd, 1H), 8.13 (s, 1H), 8.05 (dd, 1H), 7.76 (dd, 4H), 7.53 (dd, 1H), 7.27 (m, 8H), 7.06 (dd, 2H), 4.93 (d, J=15Hz, 1H), 4.72 (d, J=15Hz, 1H), 4.36 (d, J=15Hz, 1H), 4.066 (d, J=15Hz, 1H), 3.88-2.97 (m, 8H), 2.28 (s, 3H.) MS: 601 (M+1).



Example 236

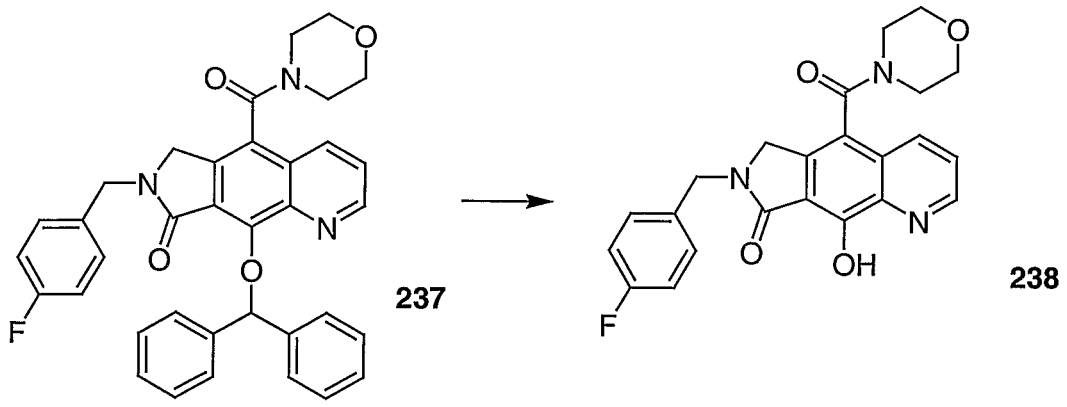
Carboxamide **235** (0.015g, 0.025mmol) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethyl ether/hexanes to give 7-(4-fluoro-benzyl)-9-hydroxy-5-(4-methyl-piperazine-1-carbonyl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **236** (0.0135g, 0.227mmol, 91%.) ^{1}H NMR 90 °C(CD_3SOCD_3) δ 8.98 (dd, 1H), 8.28 (d, 1H), 7.74 (dd, 1H), 7.40 (dd, 2H), 7.21 (dd, 2H), 4.72 (s, 4H), 4.40 (s, 4H), 3.5 (br s, 4H), 2.81 (s, 3H.) ^{19} F NMR: -74.688 MS: 436 (M+1), 434 (M-1)



213 237

Example 237

Carboxylic acid **213** (0.10g, 0.193mmol) was dissolved in 2 mL of dimethylformamide. To this was added morpholine (0.0337mL, 0.386 mmol), diisopropylethylamine (0.135mL, 0.772mmol), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 0.146g, 0.386mmol) and stirred at room temperature. After 15 hours, starting material was consumed. Dilute with dichloromethane, washed with 1M HCl solution, saturated brine solution, dried (Na_2SO_4), concentrated to give crude product. Chromatographed (0 to 5% methanol/dichloromethane) to give pure product (0.06g, 0.102mmol, 53%.) ^{1}H NMR ($CDCl_3$) δ 9.08 (dd, 1H), 8.15 (s, 1H), 8.06 (dd, 1H), 7.76 (dd, 4H), 7.55 (dd, 1H), 7.30 (m, 8H), 7.07 (dd, 2H), 4.95 (d, J=15Hz, 1H), 4.70 (d, J=15Hz, 1H), 4.42 (d, J=15Hz, 1H), 4.14 (d, J=15Hz, 1H), 3.94-3.79 (m, 4H), 3.41 (m, 2H), 2.99 (m, 2H.) MS: 588 (M+1).

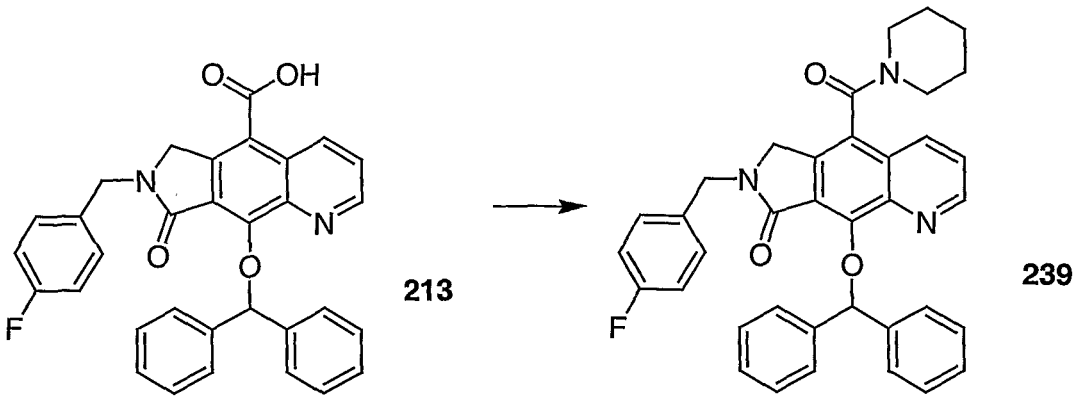


237 238

Example 238

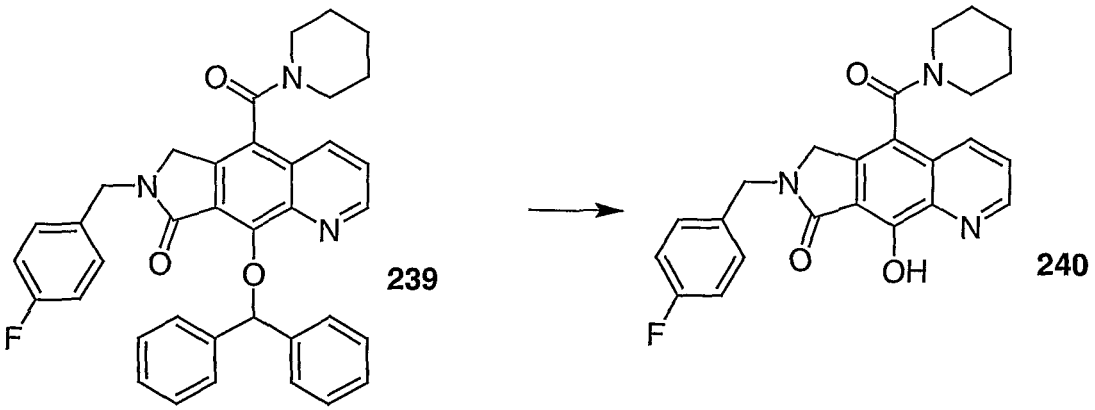
Carboxamide **237** (0.06g, 0.102mmol) was dissolved in 1 mL of dichloromethane. To this was added 0.4 mL of triethylsilane and 0.2mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles,

azeotroped with toluene to give crude. Triturated twice with 1:1 diethyl ether/hexanes to give 7-(4-fluoro-benzyl)-9-hydroxy-5-(morpholine-4-carbonyl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **238** (0.0459g, 0.109mmol, 100%.) ^{1}H NMR ($CDCl_3$) δ 9.05 (dd, 1H), 8.20 (d, 1H), 7.64 (dd, 1H), 7.35 (m, 2H), 7.08 (dd, 2H), 4.91 (d, J=15Hz, 1H), 4.68 (d, J=15Hz, 1H), 4.59 (d, J=15Hz, 1Hz), 4.24 (d, J=15Hz, 1H), 3.99 (m, 3H), 3.5 (s, 2H), 3.18 (s, 2H.) MS: 436 (M+1), 434 (M-1)



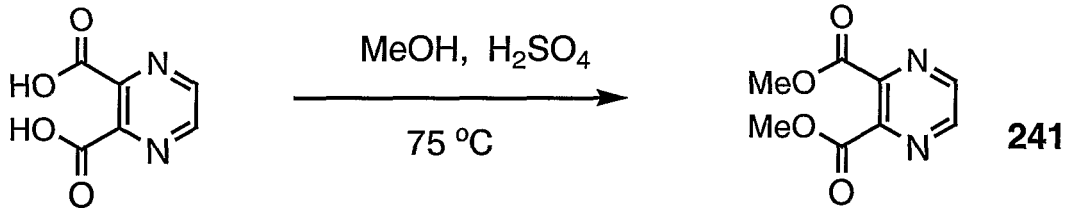
Example 239

Carboxylic acid **213** (0.018g, 0.0347mmol) was dissolved in 0.5 mL of dimethylformamide. To this was added piperidine (0.0068mL, 0.0695 mmol), diisopropylethylamine (0.024mL, 0.139mmol), HATU (0.027g, 0.0695mmol) and stirred at room temperature. After 2.5 hours, starting material was consumed. Dilute with ethyl acetate, washed with 2.5% LiCl solution, saturated brine solution, dried (Na_2SO_4), concentrated to give crude **239**. ^{1}H NMR ($CDCl_3$) δ 9.04 (dd, 1H), 8.12 (s, 1H), 8.06 (d, 1H), 7.75 (dd, 4H), 7.52 (dd, 1H), 7.30 (m, 8H), 7.06 (dd, 2H), 4.94 (d, J=15Hz, 1H), 4.69 (d, J=15Hz, 1H), 4.40 (d, J=15Hz, 1H), 4.07 (d, J=15Hz, 1H), 3.91 (s, 1H), 3.71 (s, 1H), 3.28 (s, 1H), 3.18 (s, 1H), 2.0-1.28 (m, 6H.) MS: 586 (M+1).



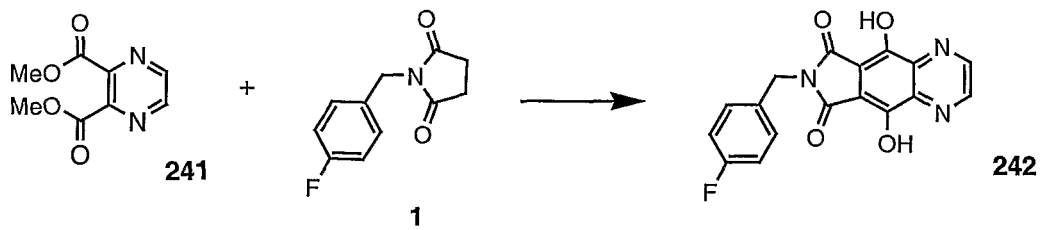
Example 240

Carboxamide **239** (crude) was dissolved in 0.5 mL of dichloromethane. To this was added 0.2 mL of triethylsilane and 0.1 mL of trifluoroacetic acid. Stirred at room temperature and after ten minutes complete by TLC. Concentrated off volatiles, azeotroped with toluene to give crude. Triturated twice with 1:1 diethyl ether/hexanes to give 7-(4-fluoro-benzyl)-9-hydroxy-5-(piperidine-1-carbonyl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **240** (0.0084 g, 0.02 mmol, 58% for 2 steps.) ^{1}H NMR ($CDCl_3$) δ 8.97 (dd, 1H), 8.17 (d, 1H), 7.60 (dd, 1H), 7.34 (dd, 2H), 7.07 (dd, 2H), 4.91 (d, J=15Hz, 1H), 4.66 (d, J=15Hz, 1H), 4.56 (d, J=15Hz, 1Hz), 4.22 (d, J=15Hz, 1H), 3.91 (s, 1H), 3.75 (s, 1H), 3.11 (s, 2H), 1.7-1.3 (m, 6H.) MS: 420 (M+1), 418 (M-1)



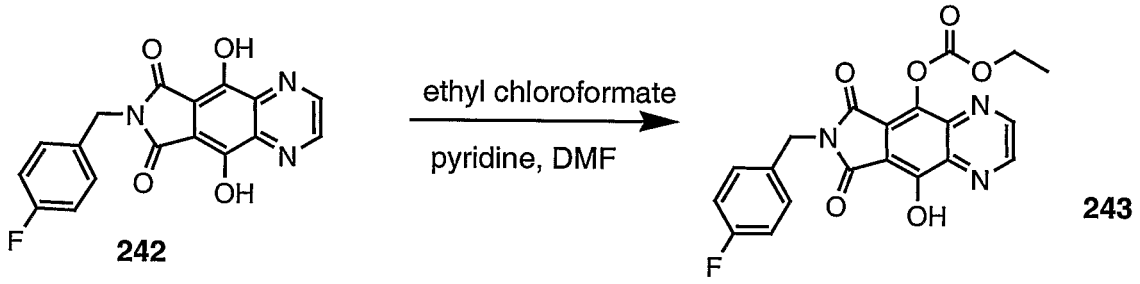
Example 241

To a mixture of pyrazine-2,3-dicarboxylic acid (20 g, 119 mmol, 1 equiv.) was added MeOH (80 mL) followed by dropwise addition of concentrated H_2SO_4 (36 mL, 680 mmol, 5.7 equiv.) over 45 minutes. This method is similar to that that cited for a different substrate (*J. Am. Chem. Soc.*, *73*, 1951, 5614 - 5616). The reaction was heated at 75 °C for 16 hours and then cooled and quenched with water (200 mL). It was extracted with EtOAc (4 x 60 mL) and the organic layer washed several times with water (3 x 50 ml), saturated $NaHCO_3$ (50 ml), brine solution (50 mL). It was dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield pyrazine-2,3-dicarboxylic acid methyl ester **241** as a brown solid (47 %, 10.97 g, 55.9 mmol). ^{1}H NMR (300 MHz) $CDCl_3$ δ 8.79 (d, *J* = 2.7 Hz, 2 H), 4.05 (s, 3 H), 4.04 (s, 3 H). TLC Rf: 0.7 ethyl acetate / methanol (9/1)



Example 242

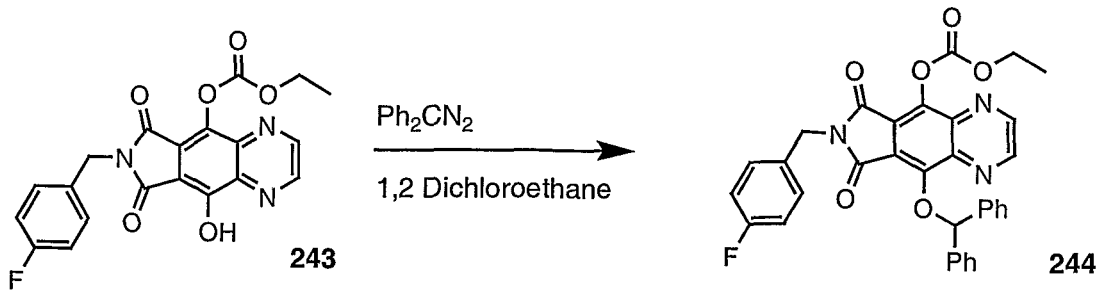
Into a flask containing pyrazine-2,3-dicarboxylic acid methyl ester **241** (10.70 g, 54.6 mmol, 1 equiv.) was added THF (150 mL) under a nitrogen atmosphere followed by 1-(4-Fluoro-benzyl)-pyrrolidine-2,5-dione **1** (11.30 g, 54.6 mmol, 1 equiv.). MeOH (1.8 mL) was then added and at O °C was added NaH (4.8 g, 120.1 mmol, 2.2 equiv.) carefully in four portions. Refluxing was carried out for 20 hours after which the reaction was cooled and placed in a 0 °C icebath. HCl (6 N, 30 mL, H_20) was slowly added while vigorously stirring. The resulting solid was filtered, and washed thoroughly with water followed by ether. It was then dried in a vacuum oven (60 °C,12 hours) to realize 8.7 gm (47 %, 25.66 mmol) of 7-(4-fluoro-benzyl)-5,9-dihydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione **242**. ^1H NMR (300 MHz) $CDCl_3$ δ 7.15 - 7.33 (m, 5 H), 5.91 (s, 2 H), 3.96 (s, 3 H), 3.88 (s, 3 H). MS: 340.3 (M+1).



242 **243**

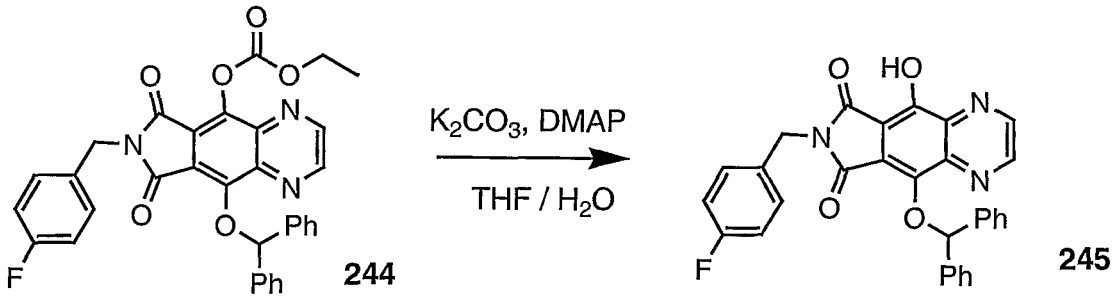
Example 243

7-(4-Fluoro-benzyl)-5,9-dihydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione **242** (1 g, 2.95 mmol, 1 equiv.) was dissolved in DMF (30 ml, 0.1 M) and pyridine (477 µL, 5.89 mmol, 2 equiv.) before ethyl chloroformate was added (237 µL, 2.95 mmol, 1 equiv.). The reaction was stirred for 16 hours before being quenched with HCl (30 ml, 1 N) and extracted with ethyl acetate (2 x 30 mL). The organic layer washed several times with water (4 x 30 mL), saturated $NaHCO_3$ (50 mL), brine solution (50 mL). It was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Recrystallization was carried out in ethyl acetate and Hexanes to yield carbonic acid ethyl ester 7-(4-fluoro-benzyl)-9-hydroxy-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoxalin-5-yl ester **243** as a light brown solid (98%, 1.20 g, 2.89 mmol). ^1H NMR (300 MHz) $CDCl_3$ δ 9.09 (d, J = 6 Hz, 1 H), 8.97 (d, J = 6 Hz, 1 H), 8.65 (bs, 1 H), 7.46 (d, J = 4.8 Hz, 2 H), 7.03 (d, J = 4.8 Hz, 2 H), 4.85 (s, 2 H), 4.04 (q, J = 2.8 Hz, 2 H), 1.43 (q, J = 2.8 Hz, 3 H). MS: 412.6 (M+1).



Example 244

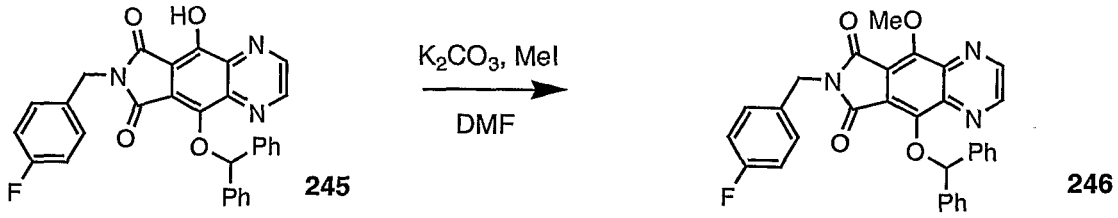
Carbonic acid mono-[1-(1-benzyl-4-methylene-2,5-dioxo-pyrrolidin-3-ylidene)-ethyl] ester **243** (1.1 g, 2.68 mmol, 1 equiv.) was dissolved in 1, 2 dichloroethane (50 mL, 0.055 M) and to this was added diphenyldiazomethane (1.05 g, 5.35 mmol, 2 equiv.) and heated at 70 °C under a nitrogen atmosphere for 24 hours. The reaction was concentrated *in vacuo* and purified by silica gel chromatography using 4/1 Hexanes / Ethyl acetate to obtain carbonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoxalin-5-yl ethyl ester **244** (70 %, 1085 mg, 1.87 mmol). ^{1}H NMR (300 MHz) $CDCl_3$ δ 9.09 (d, J = 6 Hz, 1 H), 8.97 (d, J = 6 Hz, 1 H), 8.65 (bs, 1 H), 7.46 (d, J = 4.8 Hz, 2 H), 7.03 (d, J = 4.8 Hz, 2 H), 4.85 (s, 2 H), 4.04 (q, J = 2.8 Hz, 2 H), 1.43 (q, J = 2.8 Hz, 3 H). MS: 600.2 (M+23). TLC R_f: 0.3 Hexanes / Ethyl acetate (7/3)



Example 245

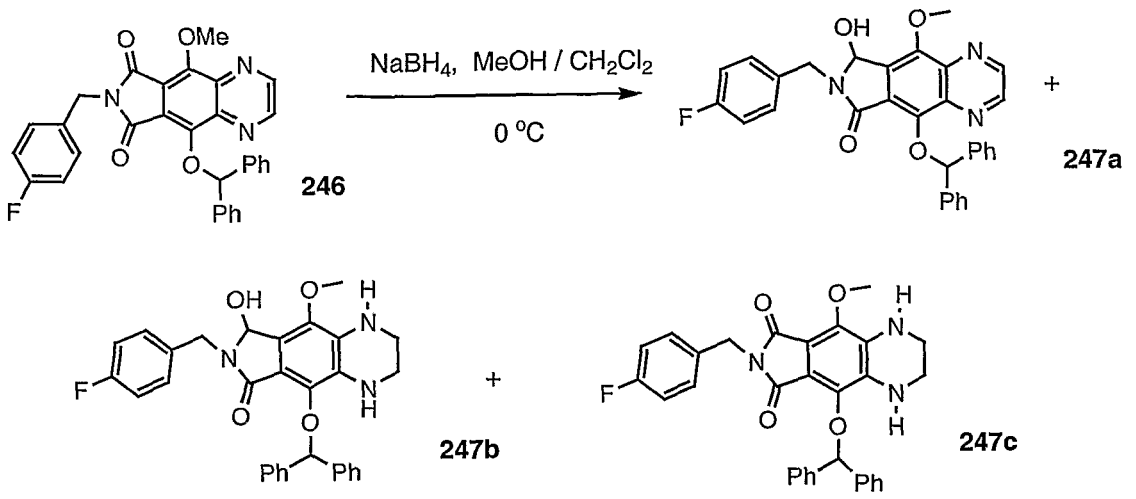
Carbonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoxalin-5-yl ester ethyl ester **244** (500 mg, 0.87 mmol) was dissolved in THF (9 mL, 0.1 M) along with DMAP (211 mg, 1.73 mmol, 2 equiv.). A solution of K_2CO_3 (1.20 g, 8.66 mmol, and 10 equiv.) was dissolved separately in H_2O (6 mL) before being transferred to the reaction mixture. The reaction was allowed to stir for 18 hours and quenched with HCl (20 mL, 1 N) and extracted with ethyl acetate (2 x 30 mL). The organic layer was washed with saturated NH_4Cl solution (25 mL), brine solution (25 mL) and dried

over Na_2SO_4 and concentrated *in vacuo* to yield 5-benzhydryloxy-7-(4-fluoro-benzyl)-9-hydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione **245** (94 %, 413 mg, 0.82 mmol). ^{1}H NMR (300 MHz) $CDCl_3$ δ 9.08 (d, J = 1.5 Hz, 1 H), 8.92 (d, J = 1.5 Hz, 1 H), 7.67 (s, 1 H), 7.67 – 7.42 (dd, J_1 = 1.5 Hz, J_2 = 8.4 Hz, 4 H), 7.43 – 7.48 (m, 2 H), 7.19 – 7.27 (m, 7 H), 7.03 - 7.20 (m, 1 H), 4.86 (s, 2 H). MS: 528.0 (M+23). TLC R_f: 0.2 Hexanes / Ethyl acetate (8/2)



Example 246

Into a flask containing 5-benzhydryloxy-7-(4-fluoro-benzyl)-9-hydroxy-pyrrolo[3,4-g]quinoxaline-6,8-dione **245** (350 mg, 0.69 mmol, 1 equiv.) was added DMF (20 mL) followed by K_2CO_3 (478 mg, 3.46 mmol, 5 equiv.). To this was added MeI (983 µL, 6.93 mmol, 10 equiv.) under a nitrogen atmosphere and stirred for 16 hours. To the reaction was then added water (50 mL) and extracted with ethyl acetate (2 x 40 mL). The organic layer was washed several times with water (3 x 30 mL), saturated $NaHCO_3$ (40 mL), brine solution (30 mL). It was dried over Na_2SO_4, filtered and concentrated *in vacuo* before being purified by silica gel chromatography using 3/2 Hexanes / ethyl acetate to obtain 5-benzhydryloxy-7-(4-fluoro-benzyl)-9-methoxy-pyrrolo[3,4-g]quinoxaline-6,8-dione **246** (78 %, 280 mg, 0.54 mmol) as a yellow solid. ^{1}H NMR (300 MHz) $CDCl_3$ δ 9.03 (d, J = 1.5 Hz, 1 H), 8.97 (d, J = 1.5 Hz, 1 H), 7.75 (s, 1 H), 7.60 (dd, J_1 = 1. 5 Hz, J_2 = 8.4 Hz, 4 H), 7.43 – 7.48 (m, 2 H), 7.19 – 7.27 (m, 7 H), 7.03 - 7.20 (m, 1 H), 4.86 (s, 2 H), 4.37 (s, 3 H). MS: 542.0 (M+23). TLC R_f: 0.5 Hexanes / Ethyl acetate (1/1)



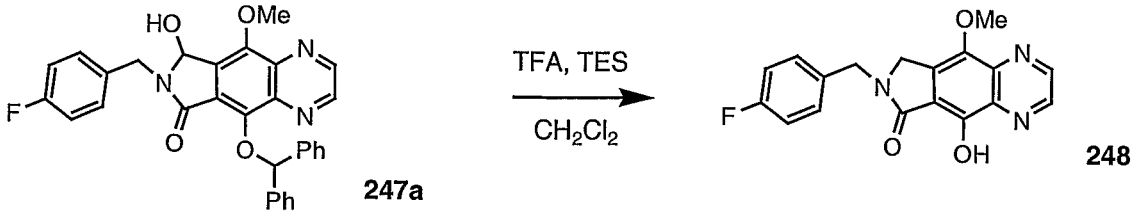
Example 247

5-Benzhydryloxy-7-(4-fluoro-benzyl)-9-methoxy-pyrrolo[3,4-g]quinoxaline-6,8-dione **246** (10 mg, 0.019 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (0.2 mL) and MeOH (0.5 mL) under a nitrogen atmosphere at 0 °C. Sodium borohydride ($NaBH_4$) was added (115 µL, 0.057 mmol, 3 equiv., 0.5 M). The reaction was allowed to stir for 1 hour and then quenched with water (5 mL) and extracted with ethyl acetate (2 x 5 mL). The organic layer was washed several times with water (2 x 10 mL), brine solution (10 mL). It was dried over Na_2SO_4, filtered and concentrated *in vacuo* and purified by preparatory thin-layer chromatography (PTLC) using 3/2 Hexanes / Ethyl acetate to obtain 5-benzhydryloxy-7-(4-fluoro-benzyl)-8-hydroxy-9-methoxy-7,8-dihydro-pyrrolo[3,4-g]quinoxalin-6-one **247a** (34 %, 3 mg) and reduced species: 5-benzhydryloxy-7-(4-fluoro-benzyl)-8-hydroxy-9-methoxy-1,2,3,4,7,8-hexahydro-pyrrolo[3,4-g]quinoxalin-6-one **247b** (21 %, 2 mg) and 5-benzhydryloxy-7-(4-fluoro-benzyl)-9-methoxy-1,2,3,4-tetrahydro-pyrrolo[3,4-g]quinoxaline-6,8-dione **247c** (34 %, 3.4 mg).

247a: ^{1}H NMR (300 MHz) $CDCl_3$ δ 8.86 (d, J = 1.8 Hz, 1 H), 8.82 (d, J = 1.8 Hz, 1 H), 7.69 (s, 1 H), 7.69 – 7.56 (m, 1 H), 7.54 – 7.56 (m, 1 H), 7.16 – 7.32 (m, 10 H), 7.01 – 7.17 (s, 2 H), 5.78 (bs, 1 H), 5.18 (d, J = 14.7 Hz, 1 H), 4.38 (d, J = 13.5 Hz,1 H), 4.18 (s, 3 H), 3.83 (s, 2 H). MS: 544.0(M+23). TLC R_f: 0.3 Hexanes / Ethyl acetate (3/2)

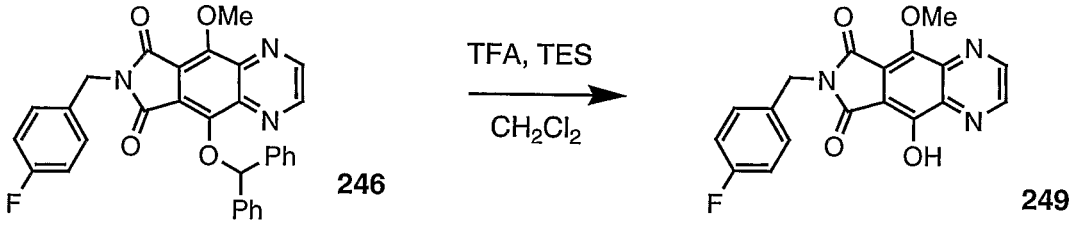
247b: ^{1}H NMR (300 MHz) $CDCl_3$ δ 7.27 – 7.7.40 (m, 12 H), 6.95 – 7.01 (m, 2 H), 4.70 (s, 2 H), 4.01 (s, 3 H), 3.32 (t, J = 3.9 Hz, 2 H), 3.13 (t, J = 5.1 Hz, 2 H), 2.75 (s, 2 H). MS: 545.9 (M+23). TLC R_f: 0.25 Hexanes / Ethyl acetate (1/1)

247c: ^{1}H NMR (300 MHz) $CDCl_3$ δ 7.27 – 7.7.40 (m, 12 H), 5.58 (bs,1 H), 5.01 (d, *J* = 14.1 Hz, 1 H), 4.21 (d, *J* = 9.6 Hz, 1 H), 3.85 (s, 3 H), 3.32 - 3.45 (m, 2 H), 3.02 – 3.05 (t, *J* = 5.1 Hz, 2 H), 1.63 (bs, 2 H). R_f: 0.2 Hexanes / Ethyl acetate (1/1)



Example 248

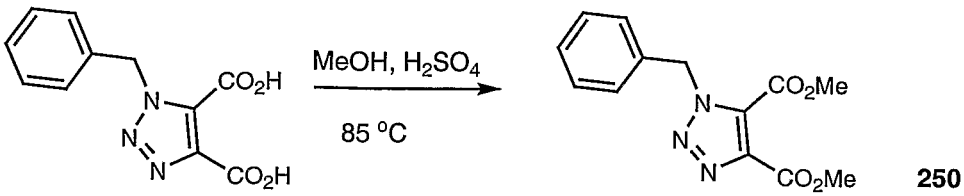
Into a flask containing 5-benzhydryloxy-7-(4-fluoro-benzyl)-8-hydroxy-9-methoxy-7,8-dihydro-pyrrolo[3,4-g]quinoxalin-6-one **247a** (20 mg, 0.038 mmol, 1 equiv.) was added CH_2Cl_2 (1 mL) under a nitrogen atmosphere. Triethylsilane (200 µL) was added followed by trifluoroacetic acid (200 µL). The reaction was allowed to stir for 1 hour and then concentrated *in vacuo* until thoroughly dried. To the oil was Hexanes / Ethyl ether (15 mL, 1/1 ratio) and sonicated. The resulting solid was then filtered, washed in hexanes, and air dried to give 7-(4-fluoro-benzyl)-5-hydroxy-9-methoxy-7,8-dihydro-pyrrolo[3,4-g]quinoxalin-6-one **248** (38 %, 7.2 mg, 0.0.14 mmol). ^{1}H NMR (300 MHz) $CDCl_3$ δ 8.95 (d, *J* =13. 8 Hz, 2 H), 7.23 - 7.27 (m, 2 H), 6.96 –7.05 (s, 2 H), 4.79 (2 H), 4.55 (s, 2 H), 4.14 (s, 3 H). ^{19}F NMR (300 MHz) $CDCl_3$ δ 62.80. MS: 340.1 (M+1)



Example 249

Into a flask containing 5-benzhydryloxy-7-(4-fluoro-benzyl)-9-methoxy-pyrrolo[3,4-g]quinoxaline-6,8-dione **246** (10 mg, 0.019 mmol, 1 equiv.) was added CH_2Cl_2 (1 mL) and under a nitrogen atmosphere was added triethylsilane (200 µL) followed by trifluoroacetic acid (200 µL). The reaction was allowed to stir for 1.5 hours and concentrated *in vacuo* until thoroughly dried. To the oil was added Hexanes / Ethyl ether (20 mL, 1/1 ratio) and sonicated. The resulting solid was filtered, washed in hexanes and air dried to give 7-(4-

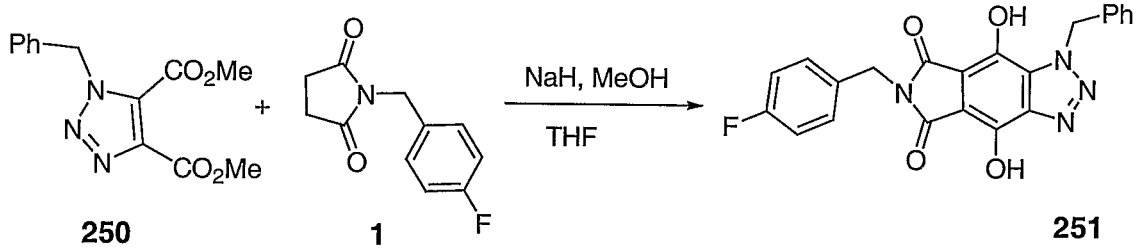
fluoro-benzyl)-5-hydroxy-9-methoxy-pyrrolo[3,4-g]quinoxaline-6,8-dione **249** (67 %, 4.6 mg, 0.015 mmol). ^{1}H NMR (300 MHz) $CDCl_3$ δ 9.07 (d, J = 1.8 Hz, 1 H), 8.97 (d, J = 1.8 Hz, 1 H), 7.23 -7.27 (m, 2 H), 6.96 – 7.05 (s, 2 H), 4.87 (s, 2 H), 4.46 (s, 3 H). ^{19}F NMR (300 MHz) $CDCl_3$ δ 62.77 MS: 354.0 (M+1)



250

Example 250

To commercially available, 1-benzyl-1H-[1,2,3]triazole-4,5-dicarboxylic acid (4.5 g, 18.2 mmol, 1 equiv.) was added MeOH (30 mL) followed by dropwise addition of H_2SO_4 (5.5 mL, 103.75 mmol, 5.7 equiv.) over 20 minutes by a method similar to *J. Am. Chem. Soc.*, 73, 1951, 5614-5616. The reaction was heated at 85 °C for 2 h. The reaction was cooled and quenched with water (100 mL). It was extracted with ethyl acetate (4 x 40 mL) and the organic layer washed several times with water (3 x 50 mL), saturated $NaHCO_3$ (50 mL), brine solution (50 mL). It was dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield 1-Benzyl-1H-[1,2,3]triazole-4,5-dicarboxylic acid dimethyl ester **250** as a brown solid (76 %, 3.85 g, 55.9 mmol). ^{1}H NMR (300 MHz) $CDCl_3$ δ 7.15 - 7.33 (m, 5 H), 5.41 (s, 2 H), 3.92 (s, 3 H), 3.84 (s, 3 H).

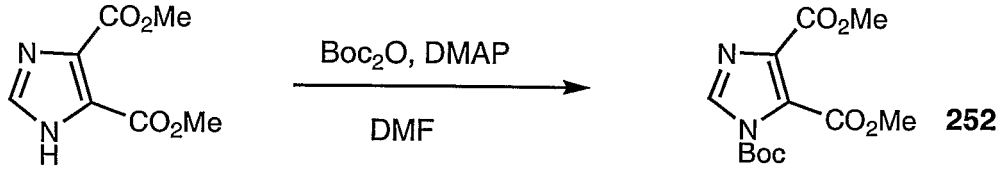


250 **1** **251**

Example 251

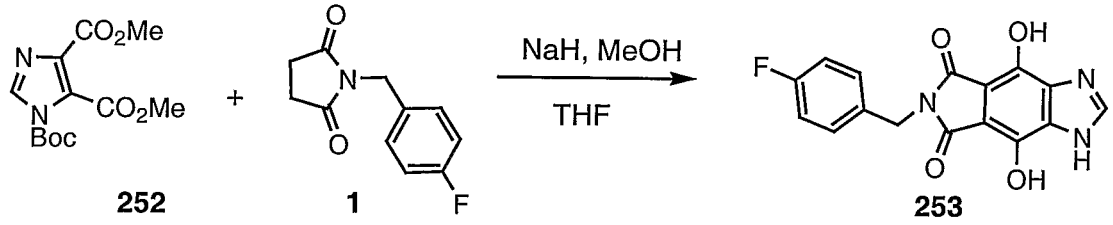
Into a flask containing 1-benzyl-1H-[1,2,3]triazole-4,5-dicarboxylic acid dimethyl ester **250** (3.75 g, 13.64 mmol, 1 equiv.) was added THF (150 mL) under a nitrogen followed by 1-(4-fluoro-benzyl)-pyrrolidine-2,5-dione **1** (2.82 g, 13.64 mmol, 1 equiv.). Methanol (MeOH, 1.1 mL) was added and at O °C was added NaH (1.20 g, 29.99 mmol, 2.2 equiv., 60 % dispersion) carefully in four portions. Refluxing was carried out for 20 hours after which the reaction was cooled and placed in a 0 °C icebath. HCl (6 N, 20 mL, H_20) was slowly added while vigorously stirring. The resulting solid was filtered, and washed

thoroughly with water followed by ether. It was then dried in a vacuum oven (60 °C, overnight) to realize 3.34 gm (60 %, 8.18 mmol) of 1-benzyl-6-(4-fluoro-benzyl)-4,8-dihydroxy-1H-pyrrolo[3',4':4,5]benzo[1,2-d][1,2,3]triazole-5,7-dione **251**. ^{1}H NMR (300 MHz) CD_3OD δ 9.51 (b, 1 H), 7.45 – 7.35 (m, 8 H), 7.15 - 7.33 (m, 2 H), 5.92 (s, 2 H), 4.78 (s, 2 H).



Example 252

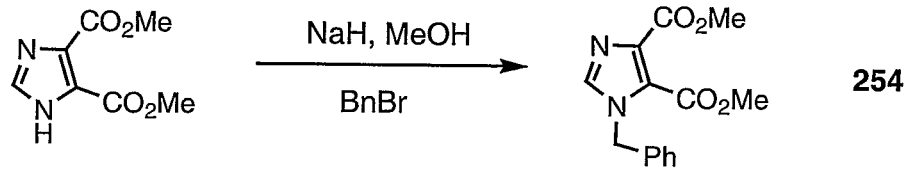
1H-Imidazole-4,5-dicarboxylic acid dimethyl ester (2 g, 10.87 mmol, 1 equiv.) was dissolved in THF (55 mL, 0.2 M) and DMAP (1.46 g, 11.95 mmol, 1.1 equiv.) before Di-*tert*-butyl dicarbonate (3.50 g, 16.29 mmol, 1.4 equiv.) was added. The reaction was stirred for 16 hours before being quenched with saturated NH_4Cl (30 mL) and extracted with ethyl acetate (2 x 30 mL) and the organic layer washed several times with water (4 x 30 mL), brine solution (50 mL). It was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Imidazole-1,4,5-tricarboxylic acid 1-tert-butyl ester 4,5-dimethyl ester **252** (3.85 g, 100%, 10.87 mmol). ^{1}H NMR (300 MHz) $CDCl_3$ δ 8.02 (s, 1 H), 3.99 (s, 3 H), 3.92 (s, 3 H). MS: 306.8 (M+23). TLC R_f: 0.6 Hexanes / Ethyl acetate (1/1)



Example 253

Into a flask containing imidazole-1,4,5-tricarboxylic acid 1-*tert*-butyl ester 4,5-dimethyl ester **252** (3.85 g, 13.55 mmol, 1 equiv.) was added THF (55 mL) under a nitrogen atmosphere followed by 1-(4-fluoro-benzyl)-pyrrolidine-2,5-dione **1** (2.80 g, 13.55 mmol, 1 equiv.). MeOH (0.4 mL) was added and at O °C was added NaH (1.20 g, 29.81 mmol, 2.2 equiv., 60 % dispersion) carefully in four portions. Refluxing was carried out for 20 hours after which the reaction was cooled and placed in a 0 °C icebath. HCl (6 N, 30 mL, H_20)

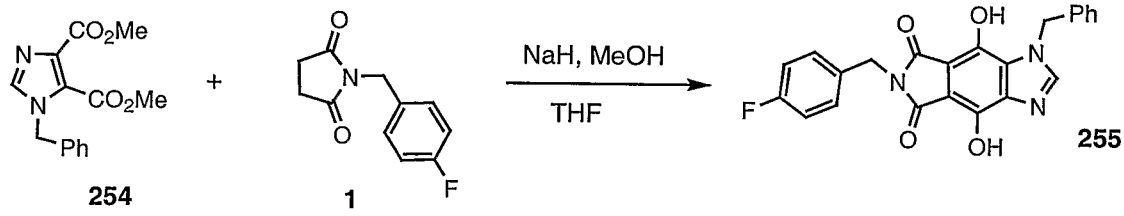
was slowly added while vigorously stirring. The resulting solid was filtered, and washed thoroughly with water followed by ether. It was then dried in a vacuum oven (60 °C, overnight) to realize 2.70 gm of a crude solid which was recrystallized with dioxane (650 mL). 6-(4-fluoro-benzyl)-4,8-dihydroxy-1H-1,3,6-triaza-s-indacene-5,7-dione **253** 1.65 g, 5.01 mmol). ^{1}H NMR (300 MHz) DMSO d_6 δ 8.64 (s, 1 H), 7.25 - 7.35 (m, 2 H), 7.10 – 7.29 (m, 2 H), 4.66 (s, 2 H). ^{19}F NMR (300 MHz) $CDCl_3$ δ 61.34. MS: 328.1 (M+1)



254

Example 254

1H-Imidazole-4,5-dicarboxylic acid dimethyl ester (1.5 g, 8.15 mmol, 1 equiv.) was dissolved in MeOH (10 mL) and benzyl bromide (1.16 mL, 9.77 mmol, 1.1 equiv.) before sodium hydride (360 mg, 1.1 equiv., 60% dispersion) and sodium iodide (200 mg) was added. The reaction was stirred for 16 hours before being quenched with saturated NH_4Cl (30 mL) and extracted with ethyl acetate (2 x 30 mL) and the organic layer washed several times with water (4 x 30 mL), brine solution (50 mL). It was dried over Na_2SO_4, filtered and concentrated *in vacuo*. 1-Benzyl-1H-imidazole-4,5-dicarboxylic acid dimethyl ester **254** (2.01 g, 90 %, 7.33 mmol). ^{1}H NMR (300 MHz) $CDCl_3$ δ 7.58 (s, 1 H), 7.33 – 7.42 (m, 3 H), 7.14 – 7.18 (m, 2 H), 5.41 (s, 2 H), 3.92 (s, 3 H), 3.84 (s, 3 H). MS: 275.1 (M+1)

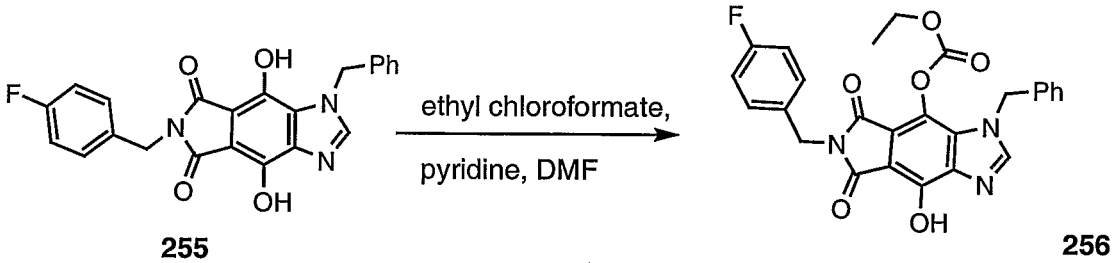


254 **1** **255**

Example 255

Into a flask containing1-benzyl-1H-imidazole-4,5-dicarboxylic acid dimethyl ester **254** (2.80 g, 10.22 mmol, 1 equiv.) was added THF (35 mL) under a nitrogen atmosphere followed by 1-(4-Fluoro-benzyl)-pyrrolidine-2,5-dione **1** (2.2 g, 10.22 mmol, 1 equiv.). MeOH (0.5 mL) was then added and at O °C was added NaH (940 mg, 23.49 mmol, 2.2 equiv.) carefully in four portions. Refluxing was carried out for 20 hours after which the

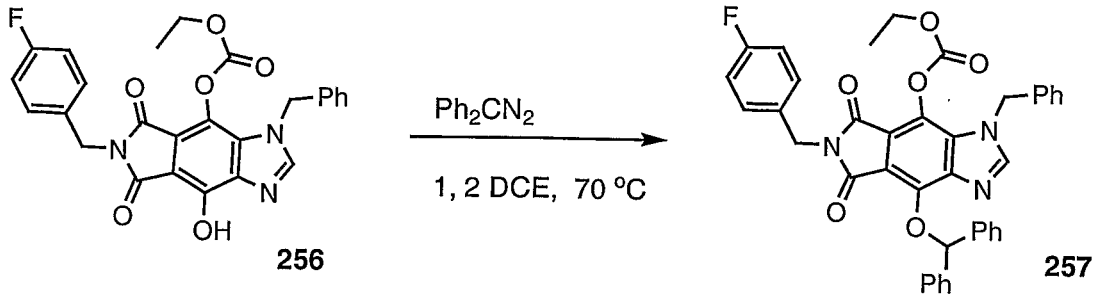
reaction was cooled and placed in a 0 °C icebath. HCl (6 N, 30 mL, H_20) was slowly added while vigorously stirring. The resulting solid was filtered, and washed thoroughly with water followed by ether. It was then dried in a vacuum oven (60 °C,12 hours) to realize 4.20 gm of a crude solid. It was recrystallized with dioxane (700 ml) to realize 1-benzyl-6-(4-fluoro-benzyl)-4,8-dihydroxy-1H-1,3,6-triaza-s-indacene-5,7-dione **255** (1.74 g, 41 %, 4.19 mmol). ^{1}H NMR (300 MHz) DMSO d_6 δ 10.40 (bs, 1 H), 8.73 (s, 1 H), 7.22 – 7.7.43 (m, 3 H), 7.05 – 7.18 (m, 2 H), 5.65 (s, 2 H), 4.60 (s, 2 H). MS: 418.1 (M+1).



255 **256**

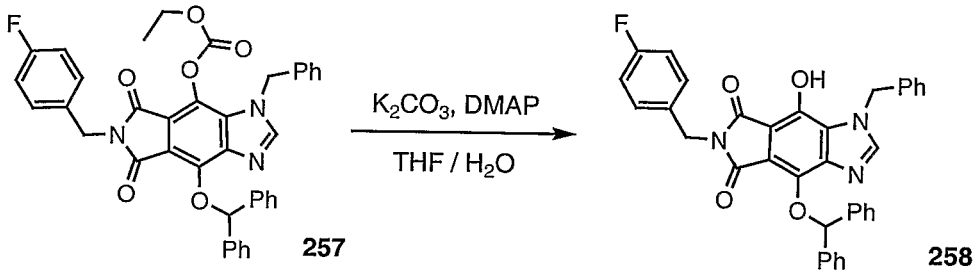
Example 256

1-Benzyl-6-(4-fluoro-benzyl)-4,8-dihydroxy-1H-1,3,6-triaza-s-indacene-5,7-dione **255** (1g, 2.39 mmol, 1 equiv.) was dissolved in a flask containing DMF (24 mL, 0.1 M) and pyridine (290 µL, 2.88 mmol, 1.5 equiv.). Ethyl chloroformate was added (231 µL, 2.88 mmol, 1.2 equiv.) under a nitrogen atmosphere. The reaction was stirred for 16 hours before being quenched with saturated NH_4Cl (30 mL) and extracted with ethyl acetate (2 x 30 mL) and the organic layer washed several times with water (4 x 30 mL), saturated $NaHCO_3$ (50 mL), brine solution (50 mL). It was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Trituration was carried out with Hexanes / Ethyl acetate (1 / 4, 100 mL) to remove the corresponding biscarbonate to give carbonic acid 3-benzyl-6-(4-fluoro-benzyl)-8-hydroxy-5,7-dioxo-3,5,6,7-tetrahydro-1,3,6-triaza-s-indacen-4-yl ester ethyl ester **256** (13 %, 145 mg, 0.296 mmol). ^{1}H NMR (300 MHz) DMSO d_6 δ 8.63 (s, 1 H), 7.45 – 7.35 (m, 6 H), 7.15 - 7.33 (m, 4 H), 5.59 (s, 2 H), 4.63 (s, 2 H), 3.98 (q, J = 6.9 Hz, 2 H), 1.17 (t, J = 6.9 Hz, 3 H). MS: 490.2 (M+1). TLC R_f: 0.6 Ethyl acetate.



Example 257

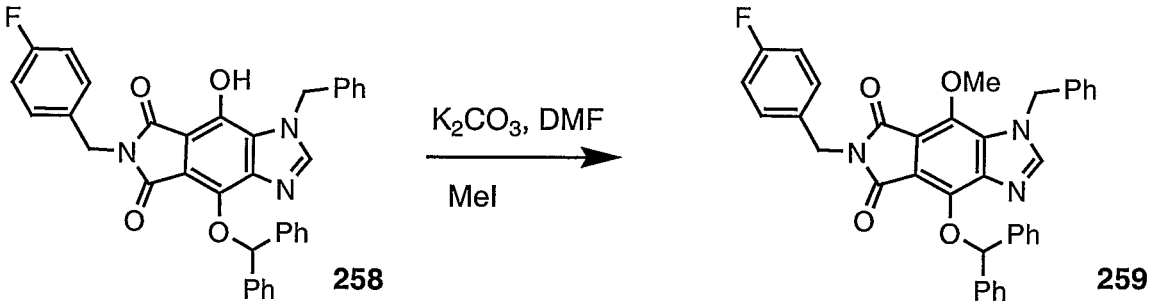
Carbonic acid 3-benzyl-6-(4-fluoro-benzyl)-8-hydroxy-5,7-dioxo-3,5,6,7-tetrahydro-1,3,6-triaza-s-indacen-4-yl ester ethyl ester **256** (140 mg, 0.28 mmol, 1 equiv.) was dissolved in 1, 2 dichloroethane (20 mL) and to this was added diphenyldiazomethane (72 mg, 0.37 mmol, 1.3 equiv.) and heated at 70 °C under a nitrogen atmosphere for 24 hours. The reaction was then concentrated *in vacuo* and purified by silica gel chromatography using 7/3 Hexanes / Ethyl acetate to obtain carbonic acid 8-benzhydryloxy-3-benzyl-6-(4-fluoro-benzyl)-5,7-dioxo-3,5,6,7-tetrahydro-1,3,6-triaza-s-indacen-4-yl ester ethyl ester **257** (78 %, 135 mg, 0.22 mmol). ^{1}H NMR (300 MHz) $CDCl_3$ δ 8.17 (s, 1 H), 7.91 (s, 1 H), 7.68 (d, J = 7.2 Hz, 4 H), 7.21 – 7.42 (m, 12 H), 6.95 – 7.06 (s, 4 H), 5.49 (s, 2 H), 4.76 (s, 2 H), 4.11 (q, J = 6.9 Hz, 2 H), 1.17 (t, J = 6.9 Hz, 3 H). MS: 678.1 (M+23). TLC R_f: 0.3 Hexanes / Ethyl acetate (7/ 3)



Example 258

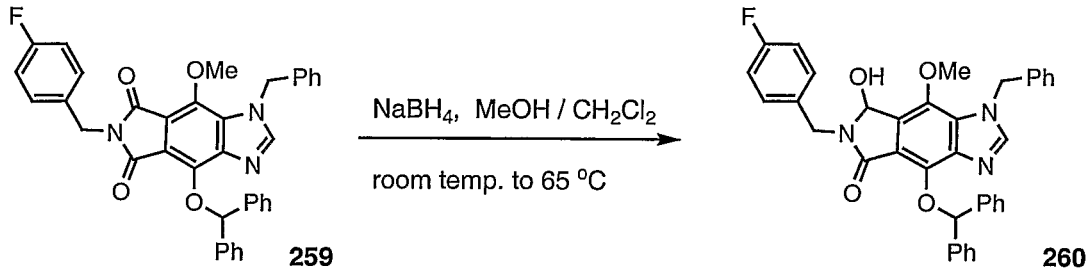
Carbonic acid 8-benzhydryloxy-3-benzyl-6-(4-fluoro-benzyl)-5,7-dioxo-3,5,6,7-tetrahydro-1,3,6-triaza-s-indacen-4-yl ester ethyl ester **257** (130 mg, 0.20 mmol) was dissolved in THF (5 mL, 0.1 M) along with DMAP (24 mg, 0.40 mmol, 2 equiv.). A solution of K_2CO_3 (276 mg, 1.99 mmol, 10 equiv.) was dissolved separately in H_2O (6 mL) before transferring to the reaction mixture. The reaction was allowed to stir for 18 hr and quenched with HCl (20 mL, 1 N) and extracted with ethyl acetate (2 x 30 ml). The organic layer was washed with saturated NH_4Cl solution (25 mL), brine solution (25 mL) and dried over Na_2SO_4 and concentrated *in vacuo* to yield 4-Benzhydryloxy-1-benzyl-6-(4-fluoro-

benzyl)-8-hydroxy-1H-1,3,6-triaza-s-indacene-5,7-dione **258** (94 %, 103 mg, 0.188 mmol) as an off white oil. ^{1}H NMR (300 MHz) $CDCl_3$ δ 8.28 (bs, 1 H), 7.94 (s, 1 H), 7.89 (s, 1 H), 7.64 – 7.43 (m, 4 H), 7.17 – 7.43 (m, 12 H), 6.98 – 7.04 (s, 2 H), 5.57 (s, 2 H), 4.77 (s, 2 H). MS: 584.1 (M+1).



Example 259

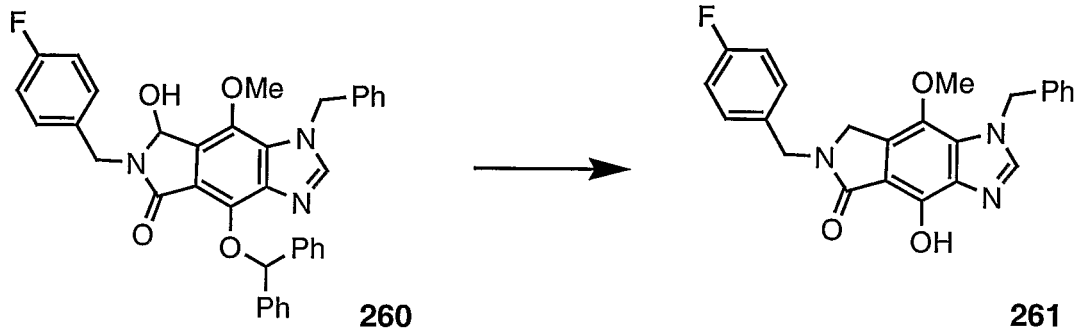
Benzhydryloxy-1-benzyl-6-(4-fluoro-benzyl)-8-hydroxy-1H-1,3,6-triaza-s-indacene-5,7-dione **258** (103 mg, 0.177 mmol, 1 equiv.) was added to a flask containing DMF (4 mL) followed by K_2CO_3 (122 mg, 0.88 mmol, 5 equiv.). To this was added methyl iodide (MeI, 109 µL, 1.76 mmol, 10 equiv.) under a nitrogen atmosphere and stirred for 16 hours. To the reaction was added water (50 mL) and extracted with ethyl acetate (2 x 40 mL). The organic layer was washed several times with water (3 x 30 mL), saturated $NaHCO_3$ (40 mL), brine solution (30 mL). It was dried over Na_2SO_4, filtered and concentrated *in vacuo* and purified by silica gel chromatography using 7/3 Hexanes / Ethyl acetate to obtain 4-benzhydryloxy-1-benzyl-6-(4-fluoro-benzyl)-8-methoxy-1H-1,3,6-triaza-s-indacene-5,7-dione **259** (73 %, 75 mg, 0.125 mmol). ^{1}H NMR (300 MHz) $CDCl_3$ δ 8.09 (s, 1 H), 7.94 (s, 1 H), 7.88 (s, 1 H), 7.64 – 7.43 (m, 4 H), 7.41 – 7.46 (m, 2 H), 7.17 – 7.43 (m, 10 H), 6.98 – 7.04 (m, 3 H), 5.56 (s, 2 H), 4.80 (s, 2 H), 3.84 (s, 3 H). MS: 620.1 (M+23). TLC R_f: 0.6 Hexanes / Ethyl acetate (1 / 1).



Example 260

4-Benzhydryloxy-1-benzyl-6-(4-fluoro-benzyl)-8-methoxy-1H-1,3,6-triaza-s-indacene-5,7-dione **259** (54 mg, 0.092 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (2 mL) and MeOH (0.5 mL) and under a nitrogen atmosphere. Sodium borohydride ($NaBH_4$, 736 μL, 0.37 mmol, 4 equiv., 0.5 M) was added. The reaction was allowed to stir for 1 hour at room temperature and heated to 65 °C for 2 hours before being quenched with water (5 mL) and extracted with ethyl acetate (2 x 5 mL). The organic layer was washed several times with water (2 x 10 mL), brine solution (10 mL). It was dried over Na_2SO_4, filtered and concentrated *in vacuo* and purified by preparatory thin-layer chromatography (PTLC) using 3/2 Hexanes / Ethyl acetate to obtain **260** (51 %, 28 mg, 0.047 mmol).

^{1}H NMR (300 MHz) $CDCl_3$ δ 7.86 (d, *J* = 7.2 Hz, 2 H), 7.59 (d, *J* = 7.2 Hz, 2 H), 7.46 – 7.32 (m, 4 H), 7.32 – 7.21 (m, 4 H), 7.03 – 7. 18 (m, 6 H), 6.91- 7.01 (m, 2 H), 5.95 (bs, 1 H), 5.56 (s, 2 H), 5.62 – 5.52 (m, 1 H), 5.28 (d, *J* = 15.9 Hz, 1 H), 5.14 (d, *J* = 15.9 Hz, 1 H), 4.49 (d, *J* = 15.9 Hz, 1 H), 3.37 (s, 3 H). MS: 622.0 (M+23). TLC R_f: 0.25 Hexanes / Ethyl acetate (3 / 2)

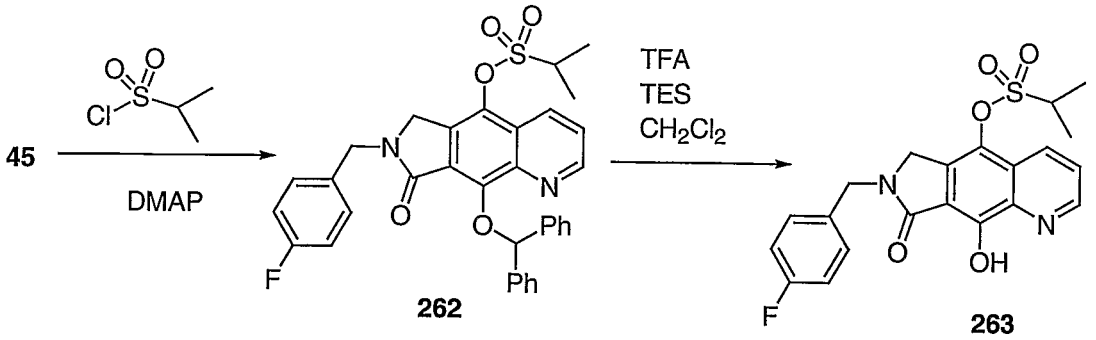


260 **261**

Example 261

4-Benzhydryloxy-1-benzyl-6-(4-fluoro-benzyl)-7-hydroxy-8-methoxy-6,7-dihydro-1H-1,3,6-triaza-s-indacen-5-one **260** (28 mg, 0.047 mmol, 1 equiv.) was added to CH_2Cl_2 (1 mL) under a nitrogen atmosphere. Triethylsilane (200 μL) was added, followed by trifluoroacetic acid (200 μL). The reaction was allowed 1 hour and concentrated *in vacuo* until thoroughly dried. Hexanes / Ethyl ether (15 mL, 1/1 ratio) was added to the oil and sonicated. The resulting solid was then filtered and washed in Hexanes and air dried to give 7-(4-fluoro-benzyl)-5-hydroxy-9-methoxy-7,8-dihydro-pyrrolo[3,4-g]quinoxalin-6-one **261** (100 %, 20 mg, 0.047 mmol) as a light gray powder.

^{1}H NMR (300 MHz) $CDCl_3$ δ 9.11 (bs 1 H), 7.86 (s, 1 H), 7.33 – 7.23 (m, 5 H), 7.01 7.07 (s, 4 H), 5.57 (s, 2 H), 4.71 (s, 2 H), 4.37 (s, 2 H), 3.57 (s, 3 H). ^{19}F NMR (300 MHz) $CDCl_3$ δ 62.25. MS: 418.2 (M+1)

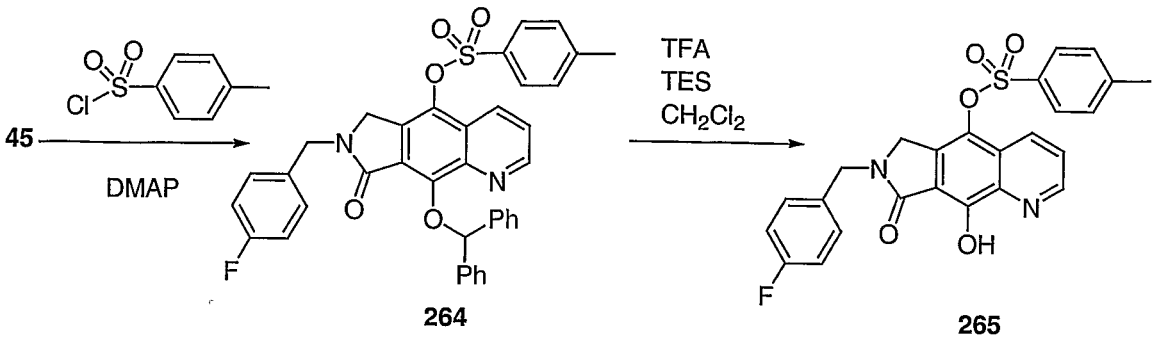


Example 262

To 0.051 mmol crude **45** was added triethylamine (100 µl), DMAP (catalytic amount) and isopropylsulfonyl chloride (18 µl, 0.154 mmol). The reaction mixture was stirred at room temperature for 24 hours under an inert atmosphere. The reaction was monitored by TLC (EtOAc/hexane 3/7) (R_f **44** = 0.5, R_f **45** = 0, R_f **262** = 0.2) and LC/MS. After completion of the reaction, the mixture was diluted with EtOAc (20mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (ethylacetate/hexane – 3/7) to afford propane-2-sulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **262** (8.7 mg, 29%).

Example 263

To a solution of **262** (8.7mg, 0.015 mmol) dissolved in dichloromethane (1 mL) was added trifluoroacetic acid (100 µl) and triethylsilane (200 µl). The reaction mixture was stirred at room temperature for 30 min under an inert atmosphere then concentrated in vacuo. The residue was triturated with diethyl ether/hexane (1/1) to afford the trifluoroacetate salt of propane-2-sulfonic acid 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **263** (5.3 mg, 0.010 mmol, 68%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.4 (d, 1H), 7.6 (m, 1H), 7.3 (m, 2H), 7.0 (t, 2H), 4.8 (s, 2H), 4.6(s, 2H), 3.7 (m, 1H), 1.7 (m, 6H); MS: 431 (M+1).

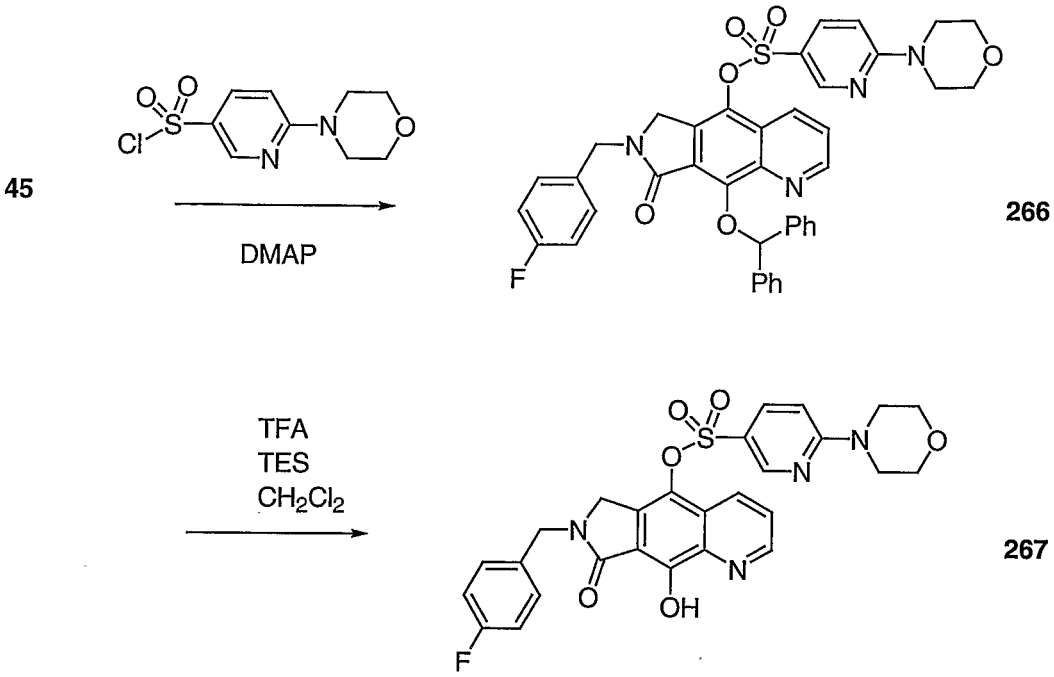


Example 264

Triethylamine (100 µl), DMAP (catalytic amount) and p-tosyl-chloride (30 mg, 0.154 mmol) were added to 0.051 mmol **45**. The reaction mixture was stirred at room temperature for 24 hours under an inert atmosphere. The reaction was monitored by TLC (EtOAc/hexane 3/7) (R_f **44** = 0.5, R_f **45** = 0, R_f **264** = 0.3) and LC/MS. After completion of the reaction, the mixture was diluted with EtOAc (20mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (ethylacetate/hexane – 3/7) to afford toluene-4-sulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **264** (15.3 mg, 47%).

Example 265

To a solution of **264** (15.3mg, 0.015 mmol) dissolved in dichloromethane (1 mL) was added trifluoroacetic acid (100 µl) and triethylsilane (200 µl). The reaction mixture was stirred at room temperature for 1/2 hours under an inert atmosphere then concentrated in vacuo. The residue was triturated with diethyl ether/hexane (1/1) to afford the trifluoroacetate salt of toluene-4-sulfonic acid 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **265** (11.6 mg, 0.020 mmol, 83%) as a yellow solid: ^1H NMR ($CDCl_3$) δ 8.9 (d, 1H), 8.0 (d, 1H), 7.8 (m, 1H), 7.3 (m, 6H), 7.0 (t, 2H), 5.3 (s, 1H, OH), 4.7 (s, 2H), 4.4 (s, 2H), 2.4 (s, 3H); MS: 479 (M+1).

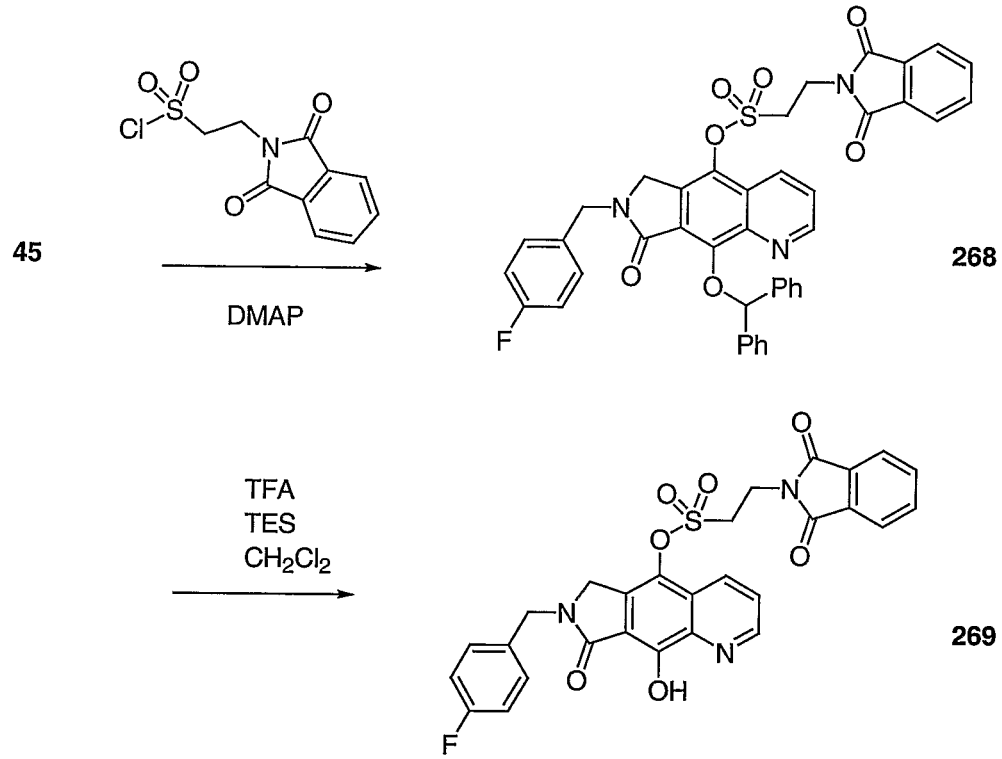


Example 266

Triethylamine (50 µl), DMAP (catalytic amount) and 6-Morpholin-4-yl-pyridine-3-sulfonyl chloride (26.3 mg, 0.10 mmol) were added to 0.034 mmol **45**. The reaction mixture was stirred at room temperature for 18 hours under an inert atmosphere. The reaction was monitored by TLC (EtOAc/hexane 3/7) (R_f **44** = 0.5, R_f **45** = 0, R_f **266** = 0.3) and LC/MS. After completion of the reaction, the mixture was diluted with EtOAc (20mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (ethylacetate/hexane – 3/7) to afford 6-morpholin-4-yl-pyridine-3-sulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **266** (14.6 mg, 59%).

Example 267

To a solution of **266** (14.6 mg, 0.020 mmol) dissolved in dichloromethane (1 mL) was added trifluoroacetic acid (100 µl) and triethylsilane (200 µl). The reaction mixture was stirred at room temperature for 1/2 hours under an inert atmosphere then concentrated in vacuo. The residue was triturated with diethyl ether/hexane (1/1) to afford the TFA salt of 6-morpholin-4-yl-pyridine-3-sulfonic acid 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **267** (9.0 mg, 68%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 8.9 (d, 1H), 8.6 (s, 1H), 8.0 (dd, 1H), 7.7 (dd, 1H), 7.5 (m, 1H), 7.3 (m, 2H), 7.0 (t, 2H), 6.5 (d, 2H), 4.8 (s, 2H), 4.6 (s, 2H), 3.7 (d, 4H), 3.6 (d, 4H); MS: 551 (M+1).



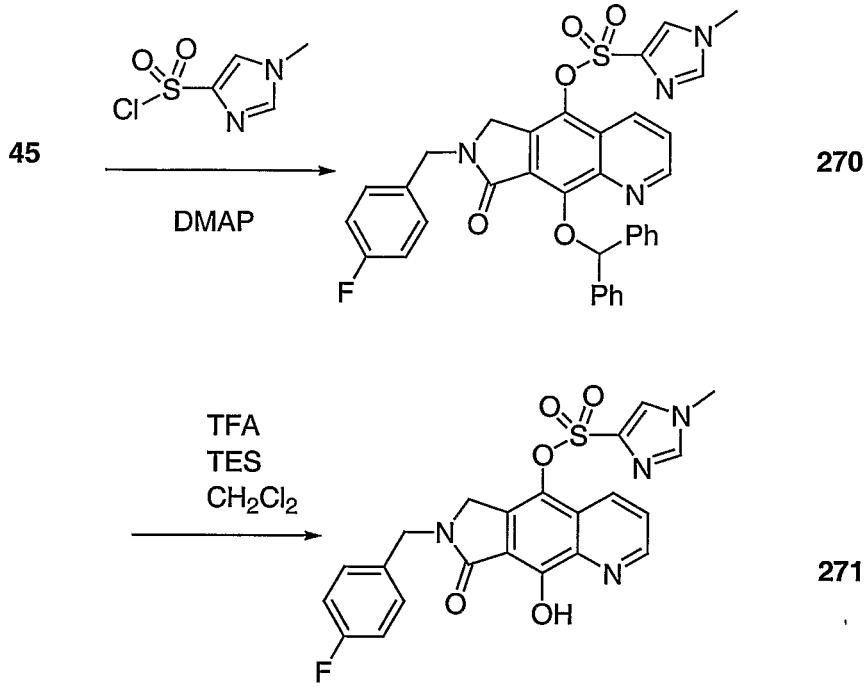
Example 268

Triethylamine (50 µl), DMAP (catalytic amount) and 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethanesulfonyl chloride (27.4 mg, 0.10 mmol) were added to 0.034 mmol **45**. The reaction mixture was stirred at room temperature for 18 hours under an inert atmosphere. The reaction was monitored by TLC (EtOAc/hexane 3/7) (R_f **44** = 0.5, R_f **45** = 0, R_f **268** = 0.4) and LC/MS. After completion of the reaction, the mixture was diluted with EtOAc (20mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (ethylacetate/hexane – 3/7) to afford 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethanesulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **268** (12.2 mg, 50%).

Example 269

To a solution of **268** (12.2 mg, 0.017 mmol) dissolved in dichloromethane (1 mL) was added trifluoroacetic acid (100 µl) and triethylsilane (200 µl). The reaction mixture was stirred at room temperature for 1/2 hours under an inert atmosphere then concentrated in vacuo. The residue was triturated with diethyl ether/hexane (1/1) to afford 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethanesulfonic acid 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-

dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **269**, TFA salt, (9.0 mg, 76%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.5 (dd, 1H), 7.9 (m, 2H), 7.8 (m, 2H), 7.7 (m, 1H), 7.3 (m, 2H), 7.0 (t, 2H), 4.8 (s, 2H), 4.6 (s, 2H), 4.4 (q, 2H), 3.9 (q, 2H); MS: 562 (M+1).



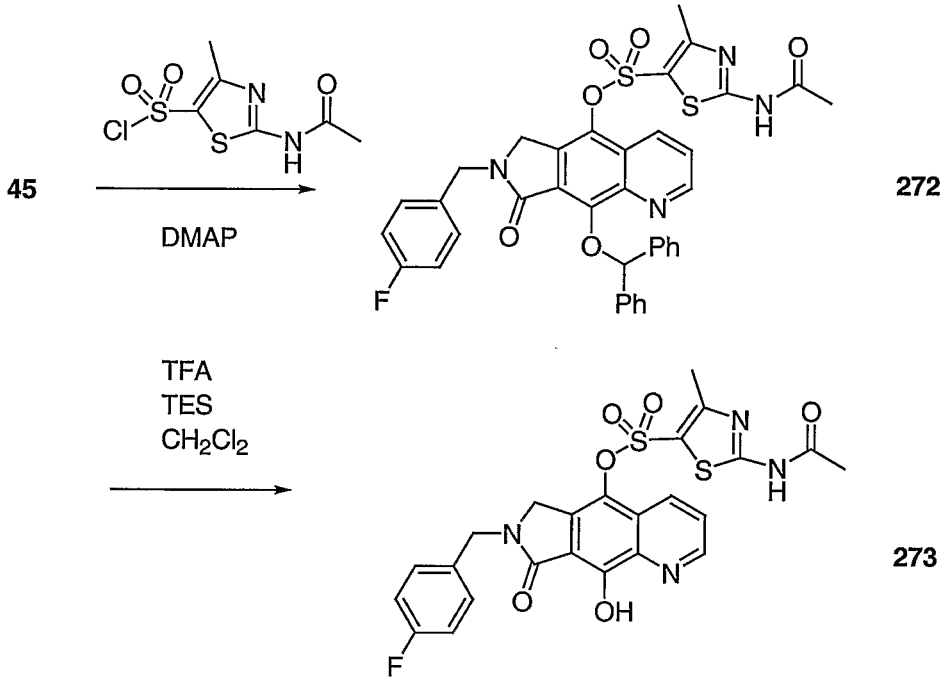
Example 270

Triethylamine (50 µl), DMAP (catalytic amount) and 1-methyl-1H-imidazole-4-sulfonyl chloride (18.1 mg, 0.10 mmol) were added to 0.034 mmol crude **45**. The reaction mixture was stirred at room temperature for 18 hours under an inert atmosphere. The reaction was monitored by TLC (EtOAc/hexane 3/7) (R_f**44** = 0.5, R_f**45** = 0, R_f**270** = 0.05) and LC/MS. After completion of the reaction, the mixture was diluted with EtOAc (20mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude mixture of 1-methyl-1H-imidazole-4-sulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **270**.

Example 271

To a solution of crude **270** dissolved in dichloromethane (1 mL) was added trifluoroacetic acid (100 µl) and triethylsilane (200 µl). The reaction mixture was stirred at room temperature for 1/2 hours under an inert atmosphere then concentrated in vacuo. The residue was purified by HPLC to afford 1-methyl-1H-imidazole-4-sulfonic acid 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **271**, TFA salt,

(2.5 mg) as a yellow solid: ^{1}H NMR (CD_3OD) δ 8.9 (d, 1H), 8.4 (d, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 7.6 (m, 1H), 7.4 (m, 2H), 7.1 (t, 2H), 4.8 (s, 2H), 4.5(s, 2H), 3.8 (s, 3H); MS: 469 (M+1). HPLC conditions: mobile phase A was 0.1% TFA in water, mobile phase b was 0.1% TFA in CH_3CN; gradient from 5% to 60% B in 20 min; flow rate was 20 mL/min; column was Phenomenex, luna 5μ, C18(2), 150mm x 21.1mm.

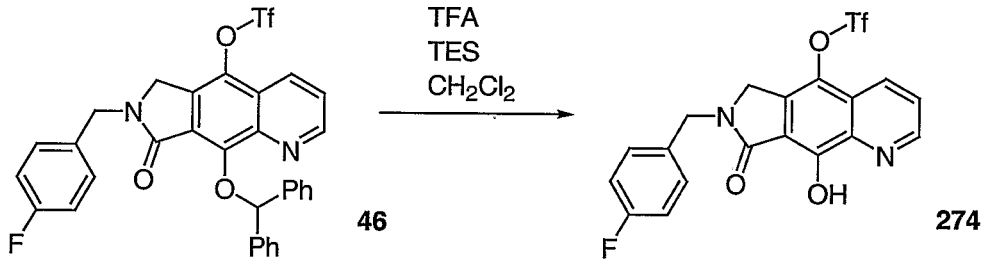


Example 272

Triethylamine (50 μl), DMAP (catalytic amount) and 2-acetylamino-4-methyl-thiazole-5-sulfonyl chloride (25.5 mg, 0.10 mmol) were added to 0.034 mmol **45**. The reaction mixture was stirred at room temperature for 18 hours under an inert atmosphere. The reaction was monitored by TLC (EtOAc/hexane 3/7) (R_f**44** = 0.5, R_f**45** =0, R_f**272** = 0.2) and LC/MS. After completion of the reaction, the mixture was diluted with EtOAc (20mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (ethylacetate/hexane – 3/7) to afford 2-acetylamino-4-methyl-thiazole-5-sulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **272** (18.9 mg, 79%).

Example 273

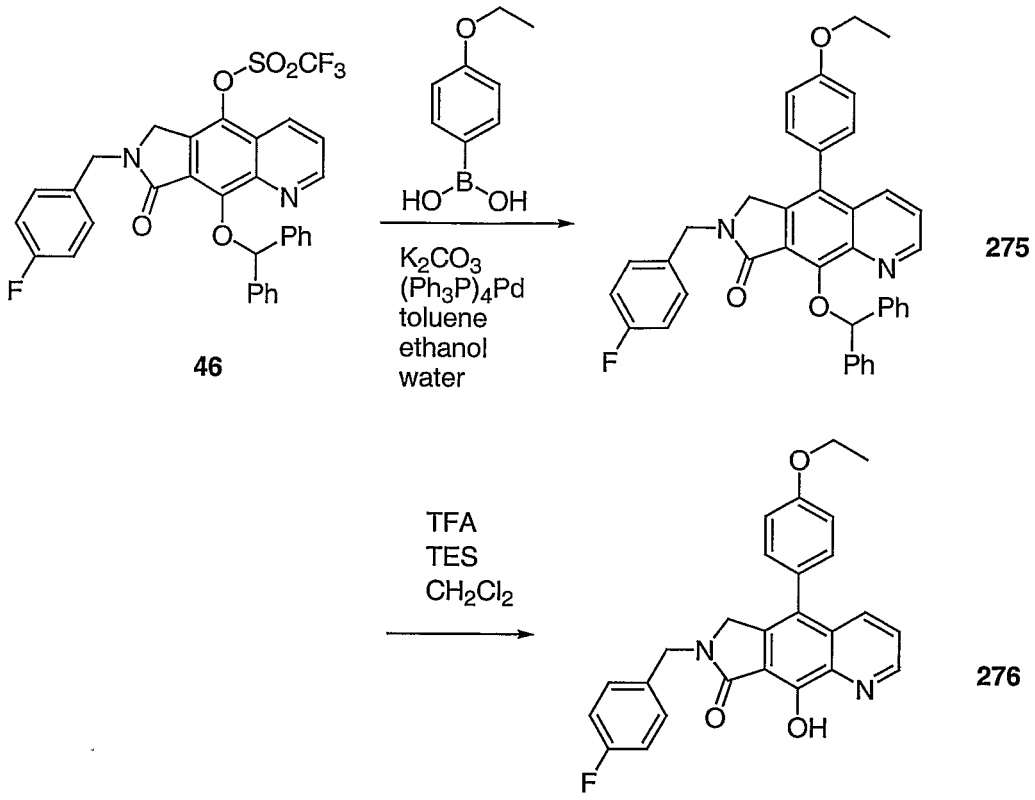
To a solution of **272** (18.9 mg, 0.027 mmol) dissolved in dichloromethane (1 mL) was added trifluoroacetic acid (100 µl) and triethylsilane (200 µl). The reaction mixture was stirred at room temperature for 1/2 hours under an inert atmosphere then concentrated in vacuo. The residue was triturated with diethyl ether/hexane (1/1) to afford 2-acetylamino-4-methyl-thiazole-5-sulfonic acid 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **273**, TFA salt, (13.2 mg, 74%) as a yellow solid: ^{1}H NMR (CD_3OD) δ 8.9 (d, 1H), 8.2 (d, 1H), 7.6 (m, 1H), 7.4 (m, 2H), 7.1 (t, 2H), 4.7 (s, 2H), 4.4 (s, 2H), 2.23 (s, 3H), 2.21 (s, 3H); MS: 543 (M+1).



46 **274**

Example 274

To a solution of trifluoro-methanesulfonic acid 9-benzhydryloxy-7- (4-fluoro-benzyl)-8-oxo-7, 8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **46** (28 mg, 0.045 mmol) dissolved in dichloromethane (2 mL) was added trifluoroacetic acid (100 µl) and triethylsilane (200 µl). The reaction mixture was stirred at room temperature for 1/2 hours under an inert atmosphere then concentrated in vacuo. The residue was triturated with diethyl ether/hexane (1/1) to afford trifluoro-methanesulfonic acid 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7, 8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **274,** (13.7 mg, 0.03 mmol, 67%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.4 (d, 1H), 7.7 (dd, 1H), 7.3 (dd, 2H), 7.1 (t, 2H), 4.8 (s, 2H), 4.6 (s, 2H); MS: 457 (M+1).

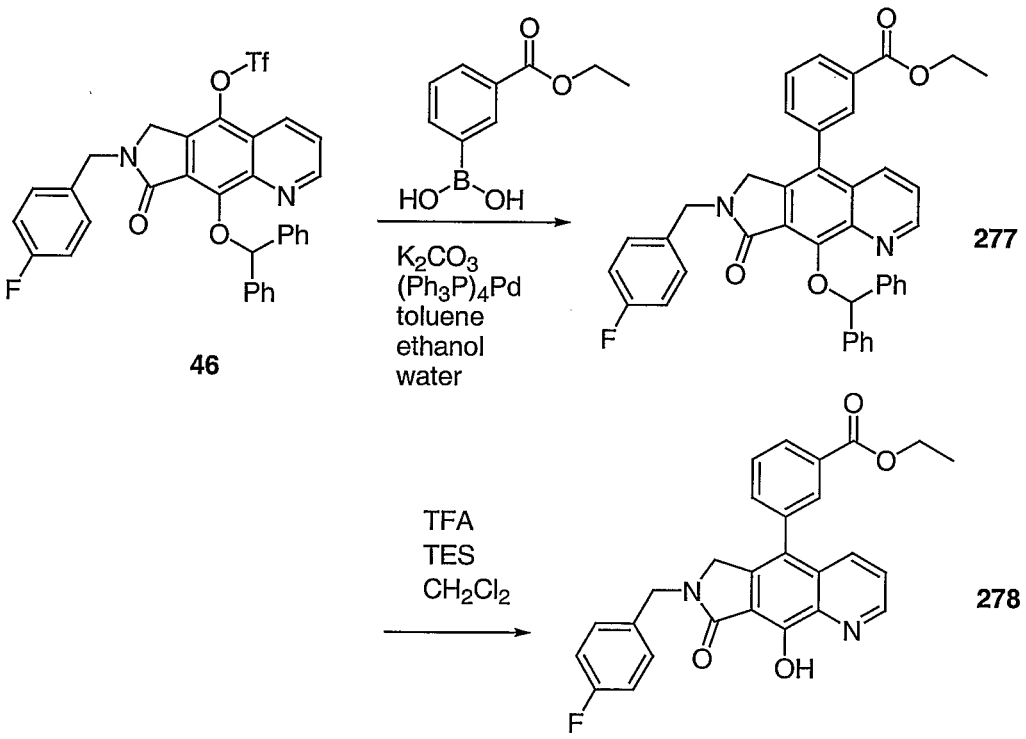


Example 275

To a solution of trifluoro-methanesulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **46** (40 mg, 0.064 mmol) dissolved in toluene (3 mL) / ethanol (0.6 mL) / water (0.4 mL) was added K_2CO_3 (27 mg, 0.192 mmol), 4-ethoxyphenolboronic acid (22 mg, 0.128 mmol) and tetrakis-(triphenylphosphine)-palladium(0) (15 mg, 0.013mmol). The reaction mixture in the flask was flashed with argon three times. It was then heated to 120°C under argon 3 hours. The reaction was monitored by TLC (EtOAc/hexane 3/7) (R_f **46** = 0.6, R_f **275** = 0.4) and LC/MS. After cooling to room temperature, the mixture was diluted with EtOAc (20mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (ethylacetate/hexane – 1/3) to afford 9-benzhydryloxy-5-(4-ethoxy-phenyl)-7-(4-fluoro-benzyl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **275** (8.0 mg, 21%) as a solid: ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.1 (s, 1H), 7.9 (d, 1H), 7.8-7.5 (dd, 4H), 7.5 (s, 1H), 7.4 (dd, 2H), 7.3-7.1 (m, 10H), 7.0 (t, 2H), 4.8 (s, 2H), 4.1 (m, 2H), 4.0 (s, 1H), 1.4 (t, 3H); MS: 595 (M+1).

Example 276

To a solution of 9-benzhydryloxy-5-(4-ethoxy-phenyl)-7-(4-fluoro-benzyl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **275** (8 mg, 0.013 mmol) dissolved in dichloromethane (1 mL) was added trifluoroacetic acid (100 µl) and triethylsilane (200 µl). The reaction mixture was stirred at room temperature for 1/2 hours under an inert atmosphere then concentrated in vacuo. The residue was triturated with diethyl ether/hexane (1/1) to afford 5-(4-ethoxy-phenyl)-7-(4-fluoro-benzyl)-9-hydroxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **276**, TFA salt, (1.8 mg, 0.003 mmol, 25%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.1 (d, 1H), 7.7 (m, 2H), 7.6 (dd, 1H), 7.5 (dd, 2H), 7.2 (dd, 2H), 7.1 (t, 2H), 4.7 (s, 2H), 4.2(s, 2H), 4.1 (m, 2H), 1.5 (t, 3H); MS: 429 (M+1).



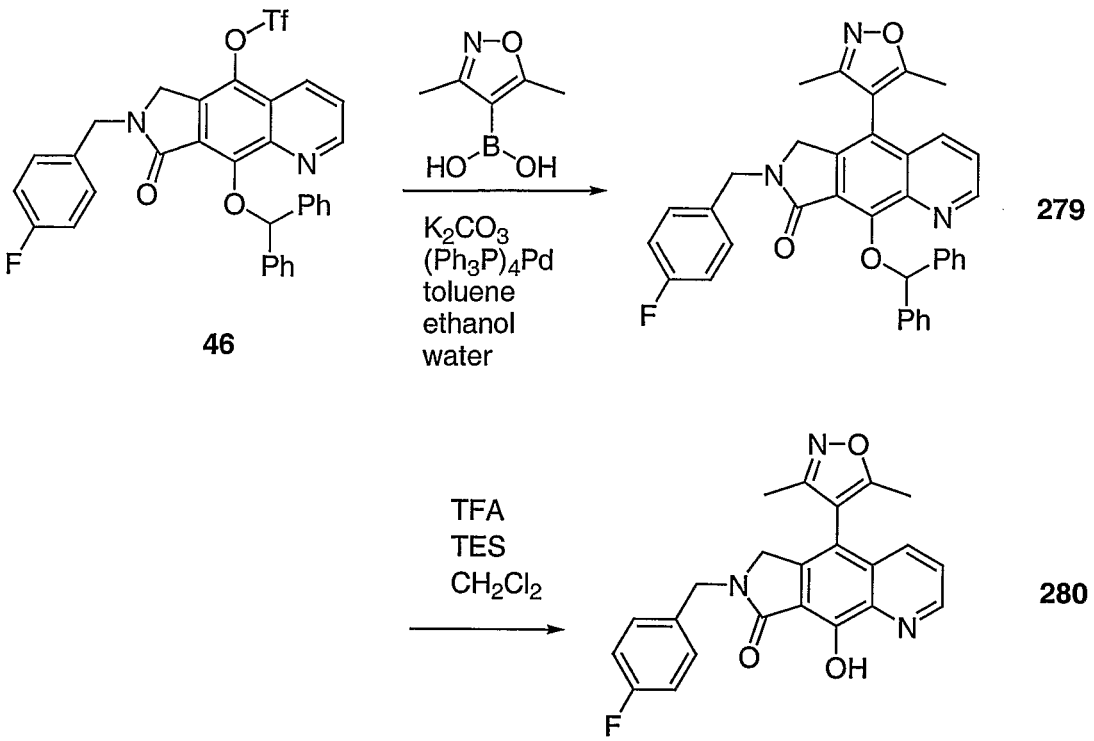
Example 277

To a solution of trifluoro-methanesulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **46** (43 mg, 0.07 mmol) dissolved in toluene (3 mL) / ethanol (0.6 mL) / water (0.4 mL) was added K_2CO_3 (29 mg, 0.21 mmol), (3-ethoxycarbonylphenyl)boronic acid (28 mg, 0.14 mmol) and tetrakis-(triphenylphosphine)-palladium(0) (16 mg, 0.014mmol). The reaction mixture in the flask was flashed with argon three times. It was then heated to 120°C under argon 3 hours. The reaction was monitored by TLC (EtOAc/hexane 3/7) (R_f **46** = 0.6, R_f **277** = 0.3) and LC/MS.

After cooling to room temperature, the mixture was diluted with EtOAc (20mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to afford crude 3-[9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl]-benzoic acid ethyl ester **277.**

Example 278

To a solution of **277** dissolved in dichloromethane (2 mL) was added trifluoroacetic acid (200 µl) and triethylsilane (400 µl). The reaction mixture was stirred at room temperature for 1/2 hours under an inert atmosphere then concentrated in vacuo. The residue was redissolved in DMSO (1mL) and purified by prep-HPLC to afford 3-[7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl]-benzoic acid ethyl ester **278**, TFA salt, (25 mg, 0.003 mmol, 44% in two steps) as a yellow solid: ^1H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.2 (d, 1H), 8.0 (s, 1H), 7.7 (m, 1H), 7.6 (dd, 1H), 7.5 (dd, 2H), 7.0 (m, 2H), 7.1 (t, 2H), 4.7 (dd, 2H), 4.4(q, 2H), 4.3 (dd, 2H), 1.4 (t, 3H); MS: 457 (M+1). HPLC conditions: mobile phase A was 0.1% TFA in water, mobile phase b was 0.1% TFA in CH_3CN; gradient from 5% to 60% B in 20 min; flow rate was 20 mL/min; column was Phenomenex, luna 5µ, C18 (2), 150mm x 21.1mm.



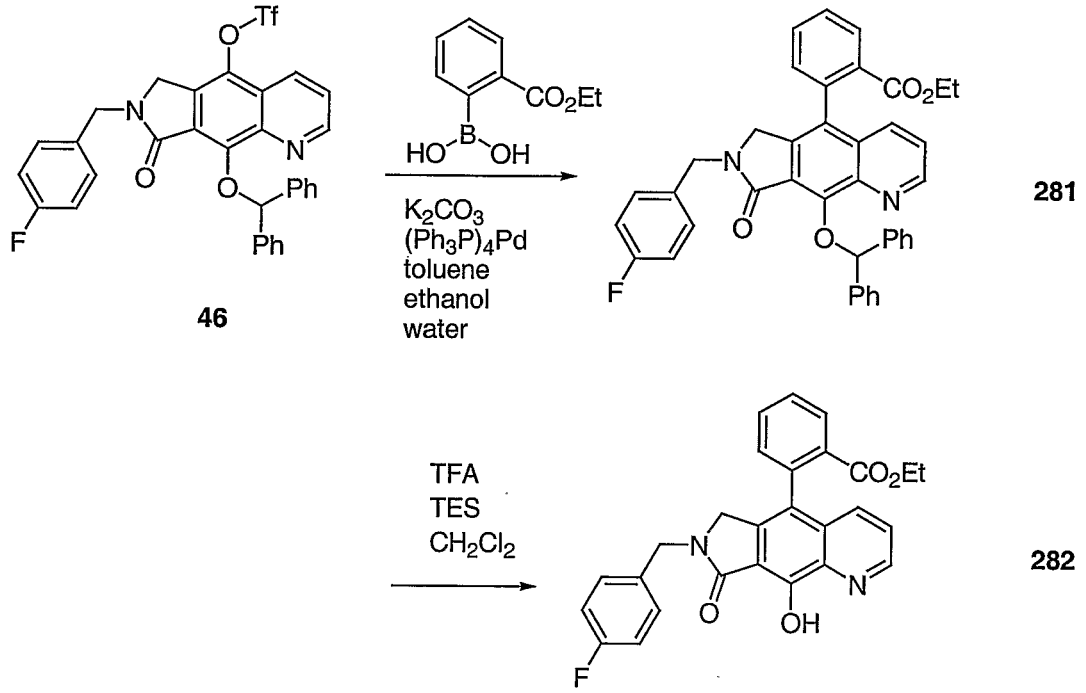
Example 279

To a solution of trifluoro-methanesulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **46** (23.6 mg, 0.038 mmol) dissolved in toluene (3 mL) / ethanol (0.6 mL) / water (0.4 mL) was added K_2CO_3 (16 mg, 0.11 mmol), 3,5-dimethylisoxazole-4-boronic acid (11 mg, 0.076 mmol) and tetrakis-(triphenylphosphine)-palladium(0) (9 mg, 0.007mmol). The reaction mixture in the flask was flashed with argon three times. It was then heated to 120°C under argon 3 hours. The reaction was monitored by LC/MS. After cooling to room temperature, the mixture was diluted with EtOAc (20mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to afford crude 9-benzhydryloxy-5-(3,5-dimethyl-isoxazol-4-yl)-7-(4-fluoro-benzyl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **279.**

Example 280

To a solution of **279** dissolved in dichloromethane (1 mL) was added trifluoroacetic acid (100 µl) and triethylsilane (200 µl). The reaction mixture was stirred at room temperature for 1/2 hours under an inert atmosphere then concentrated in vacuo. The residue was dissolved in DMSO (1mL) and purified by prep-HPLC to remove Ph_3PO. The crude mixture was diluted with EtOAC and extracted with 1N HCl. The aqueous phase containing product **280** was re-purified by HPLC to afford 5-(3,5-dimethyl-isoxazol-4-yl)-

7-(4-fluoro-benzyl)-9-hydroxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **280**, (0.4mg) as a TFA salt solid: ^{1}H NMR (CD_3OD) δ 9.0 (d, 1H), 8.1 (d, 1H), 8.0 (s, 1H), 7.7 (m, 1H), 7.4 (dd, 1H), 7.1 (t, 2H), 4.8 (s, 2H), 4.2(s, 2H), 2.0 (s, s, 2x3H); MS: 404 (M+1). HPLC conditions: mobile phase A was 0.1% TFA in water, mobile phase b was 0.1% TFA in CH_3CN; gradient from 5% to 60% B in 20 min; flow rate was 20 mL/min; column was Phenomenex, luna 5μ, C18 (2), 150mm x 21.1mm.



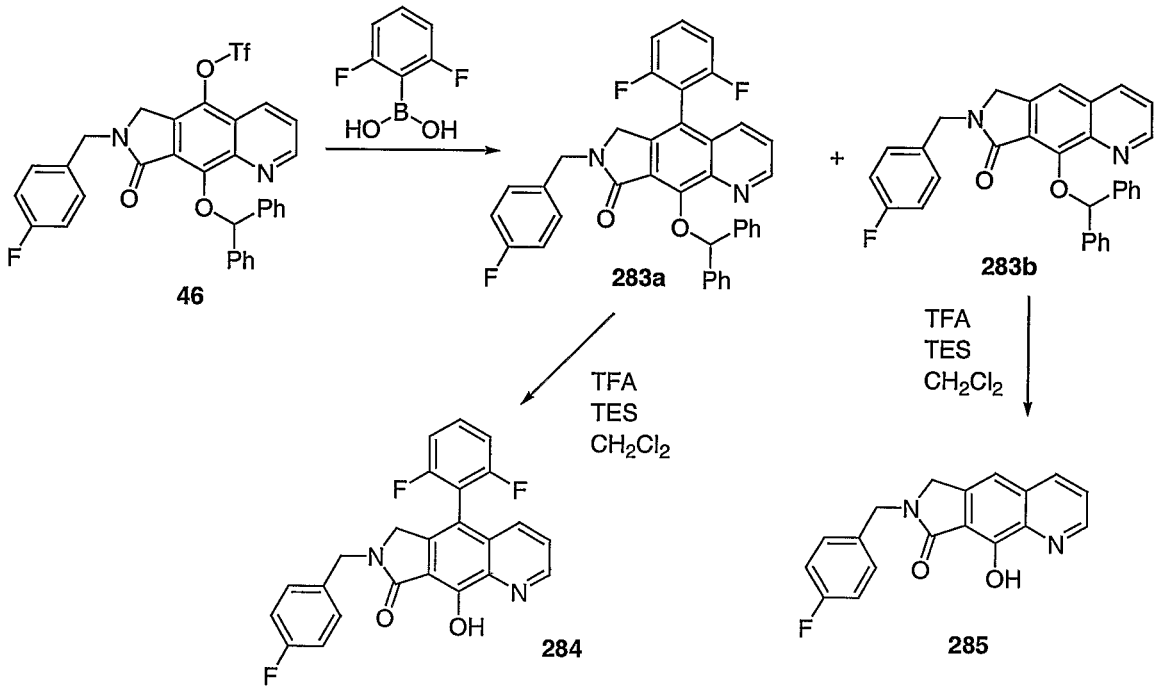
46 **281** **282**

Example 281

To a solution of trifluoro-methanesulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **46** (33.5 mg, 0.05 mmol) dissolved in toluene (3 mL) / ethanol (0.6 mL) / water (0.4 mL) was added K_2CO_3 (22 mg, 0.15 mmol), (2-ethoxycarbonylphenyl)boronic acid (22 mg, 0.10 mmol) and tetrakis-(triphenylphosphine)-palladium(0) (12.5 mg, 0.01mmol). The reaction mixture in the flask was flashed with argon three times. It was then heated to 120°C under argon 3 hours. The reaction was monitored by TLC (EtOAc/hexane 3/7) (R_f **46** = 0.6, R_f **281** = 0.5) and LC/MS. After cooling to room temperature, the mixture was diluted with EtOAc (20mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with EtOAc/Hexane (3/7) to afford pure 2-[9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl]-benzoic acid ethyl ester **281**, 9mg, 26.8% .

Example 282

To a solution of **281** dissolved in dichloromethane (2 mL) was added trifluoroacetic acid (200 µl) and triethylsilane (400 µl). The reaction mixture was stirred at room temperature for 1/2 hours under an inert atmosphere then concentrated in vacuo. . The residue was triturated with diethyl ether/hexane (1/1) to afford 2-[7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl]-benzoic acid ethyl ester **282**, TFA salt, (2.5 mg) as a yellow solid: ^{1}H NMR (CD_3OD) δ 8.9 (d, 1H), 8.0 (d, 1H), 8.0 (s, 1H), 7.8-7.6 (m, 3H), 7.5 (dd, 1H), 7.3 (m, 2H+1H), 7.0 (t, 2H), 4.7 (dd, 2H), 4.1(dd, 2H), 3.7 (m, 2H), 0.6 (t, 3H); MS: 457 (M+1).



Example 283

To a solution of trifluoro-methanesulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **46** (40 mg, 0.064 mmol) dissolved in toluene (3 mL) / ethanol (0.6 mL) / water (0.4 mL) was added K_2CO_3 (29 mg, 0.16 mmol), (2, 6-difluorophenyl)boronic acid (20 mg, 0.128 mmol) and tetrakis-(triphenylphosphine)-palladium(0) (15 mg, 0.01mmol). The reaction mixture in the flask was flashed with argon three times. It was then heated to 120 °C under argon for 3 hours. The reaction was monitored by TLC (EtOAc/hexane 3/7) (R_f **46** = 0.6, R_f **283a** = 0.4, R_f **283b** = 0.3) and LC/MS. After cooling to room temperature, the mixture was diluted with EtOAc (20mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase

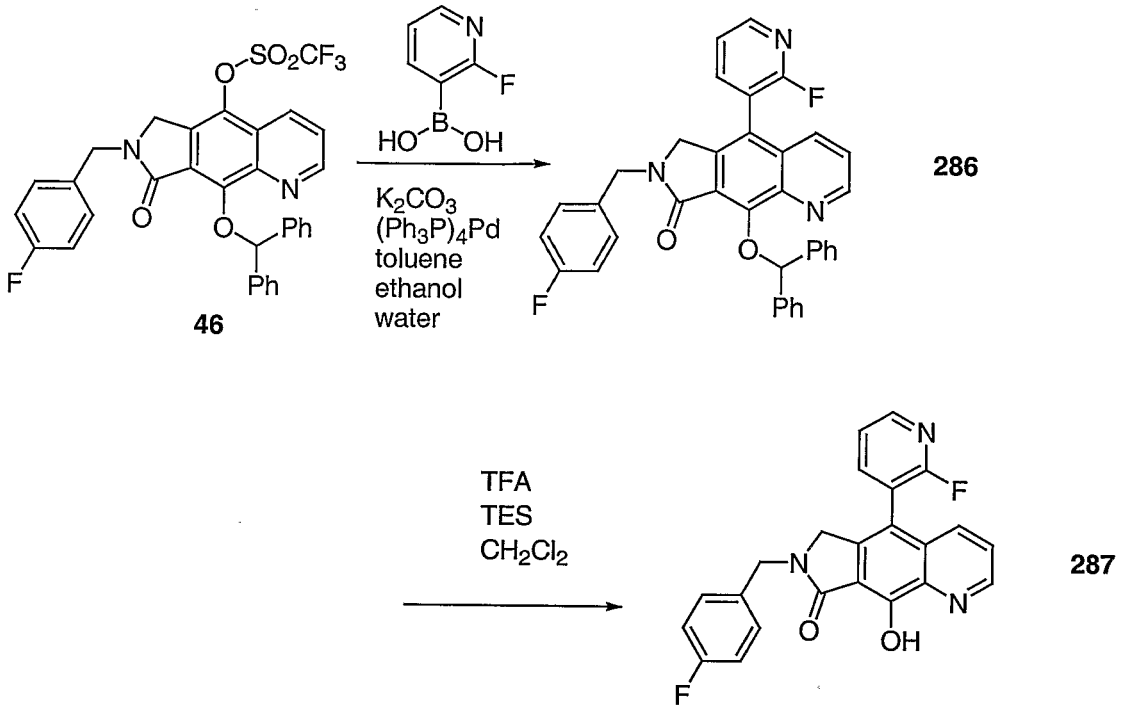
was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel with EtOAc/Hexane (3/7) to separate pure 9-benzhydryloxy-5-(2,6-difluoro-phenyl)-7-(4-fluoro-benzyl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **283a**, 6mg, 17%; and pure 9-benzhydryloxy-7-(4-fluoro-benzyl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **283b**, 11.0mg, 36%.

Example 284

To a solution of **283a** (9mg) dissolved in dichloromethane (1 mL) was added trifluoroacetic acid (100 µl) and triethylsilane (200 µl). The reaction mixture was stirred at room temperature for 1/2 hours under an inert atmosphere then concentrated in vacuo. . The residue was triturated with diethyl ether/hexane (1/1) to afford 5-(2,6-difluoro-phenyl)-7-(4-fluoro-benzyl)-9-hydroxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **284**, TFA salt, (3.2 mg) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.0 (d, 1H), 7.6 (m, 1H), 7.5 (dd, 1H), 7.2 (m, 2H), 7.1 (m, 4H), 4.7 (s, 2H), 4.2(s, 2H); MS: 421 (M+1).

Example 285

To a solution of **283b** (11mg) dissolved in dichloromethane (1 mL) was added trifluoroacetic acid (100 µl) and triethylsilane (200 µl). The reaction mixture was stirred at room temperature for 1/2 hours under an inert atmosphere then concentrated in vacuo. . The residue was triturated with diethyl ether/hexane (1/1) to afford 7-(4-fluoro-benzyl)-9-hydroxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **285**, TFA salt, (3.9 mg) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 9.1 (d, 1H), 8.3 (d, 1H), 7.6 (m, 1H), 7.35 (s, 1H), 7.33 (m, 2H), 7.0 (t, 2H), 4.8 (s, 2H), 4.4(s, 2H); MS: 309 (M+1).



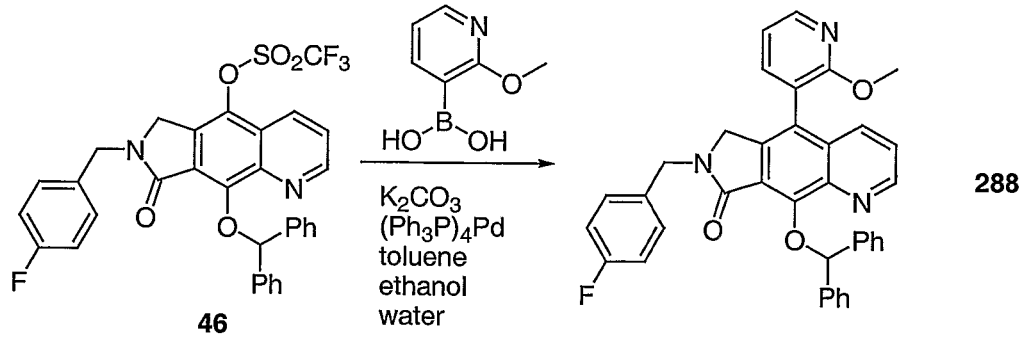
Example 286

To a solution of trifluoro-methanesulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **46** (40 mg, 0.064 mmol) dissolved in toluene (3 mL) / ethanol (0.6 mL) / water (0.4 mL) was added K_2CO_3 (29 mg, 0.16 mmol), 2-fluoropyridine-3-boronic acid (18 mg, 0.128 mmol) and tetrakis-(triphenylphosphine)-palladium(0) (15 mg, 0.01mmol). The reaction mixture in the flask was flashed with argon three times. It was then heated to 120°C under argon 3 hours. The reaction was monitored by TLC (EtOAc/hexane 3/7) (R_f **46** = 0.6, R_f **286** = 0.1) and LC/MS. After cooling to room temperature, the mixture was diluted with EtOAc (20mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with EtOAc/Hexane (1/1) to afford pure 9-benzhydryloxy-7-(4-fluoro-benzyl)-5-(2-fluoro-pyridin-3-yl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one (**15**), 10.6mg, 29%.

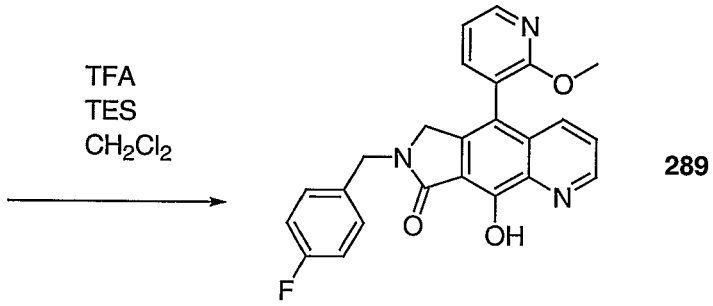
Example 287

To a solution of **286** (10.6mg) dissolved in dichloromethane (1 mL) was added trifluoroacetic acid (100 µl) and triethylsilane (200 µl). The reaction mixture was stirred at room temperature for 1/2 hours under an inert atmosphere then concentrated in vacuo. The residue was purified by HPLC to afford 7-(4-fluoro-benzyl)-5-(2-fluoro-pyridin-3-yl)-9-hydroxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **287**, TFA salt, (3.2 mg) as a yellow

solid: ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.4 (d, 1H), 7.9 (d, 1H), 7.8 (dd, 1H), 7.5 (m, 1H), 7.4 (m, 1H), 7.3 (m, 2H), 7.0 (t, 2H), 4.7 (dd, 2H), 4.2(dd, 2H); MS: 404 (M+1). HPLC conditions: mobile phase A was 0.1% TFA in water, mobile phase b was 0.1% TFA in CH_3CN; gradient from 5% to 60% B in 20 min; flow rate was 20 mL/min; column was Phenomenex, luna 5μ, C18(2), 150mm x 21.1mm.



46 288



289

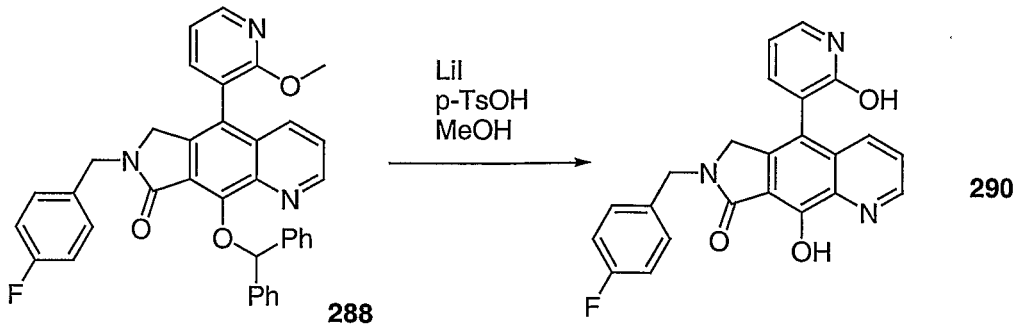
Example 288

To a solution of trifluoro-methanesulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **46** (40 mg, 0.064 mmol) dissolved in toluene (3 mL) / ethanol (0.6 mL) / water (0.4 mL) was added K_2CO_3 (29 mg, 0.16 mmol), 2-methoxypyridine-3-boronic acid (20 mg, 0.128 mmol) and tetrakis-(triphenylphosphine)-palladium(0) (15 mg, 0.01mmol). The reaction mixture in the flask was flashed with argon three times. It was then heated to 120°C under argon 3 hours. The reaction was monitored by TLC (EtOAc/hexane 3/7) (R_f **46** = 0.6, R_f **288** = 0.1) and LC/MS. After cooling to room temperature, the mixture was diluted with EtOAc (20mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel with EtOAc/Hexane (1/1) to afford pure 9-benzhydryloxy-7-(4-fluoro-benzyl)-5-(2-methoxy-pyridin-3-yl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one (**17**), 18.0mg, 48%.

Alternatively, according to a modified Suzuki coupling method of C. H. Chen; Tetrahedron Letter; EN; 44; 5747-5750; 2003, to a solution of trifluoro-methanesulfonic acid 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester **46** (266.2 mg, 0.428 mmol) dissolved in toluene (5 mL) was added Na_2CO_3 (2M in water, 500µl), 2-methoxypyridine-3-boronic acid (164 mg, 1.07 mmol) and tetrakis-(triphenylphosphine)-palladium(0) (100 mg, 0.086mmol). The reaction mixture in the flask was flashed with argon three times. It was then heated to 120°C under argon 4 hours. The reaction was monitored by TLC (EtOAc/hexane 3/7) (R_f**1** = 0.6, R_f**17** = 0.1) and LC/MS. After cooling to room temperature, the mixture was diluted with EtOAc (20mL) and washed with 1N HCl, saturated $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with EtOAc/Hexane (1/1) to afford pure 9-benzhydryloxy-7-(4-fluoro-benzyl)-5-(2-methoxy-pyridin-3-yl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **288**, 125mg, 50%. ^{1}H NMR ($CDCl_3$) δ 9.0 (dd, 1H), 8.3 (dd, 1H), 8.2 (s, 1H), 7.8 (dd, 4H), 7.7 (dd, 1H), 7.4 (dd, 1H), 7.3-7.1 (m, 8H), 7.0 (m, 2H+1H), 4.7 (dd, 2H), 4.1(dd, 2H), 3.8 (s, 1H); MS: 582 (M+1).

Example 289

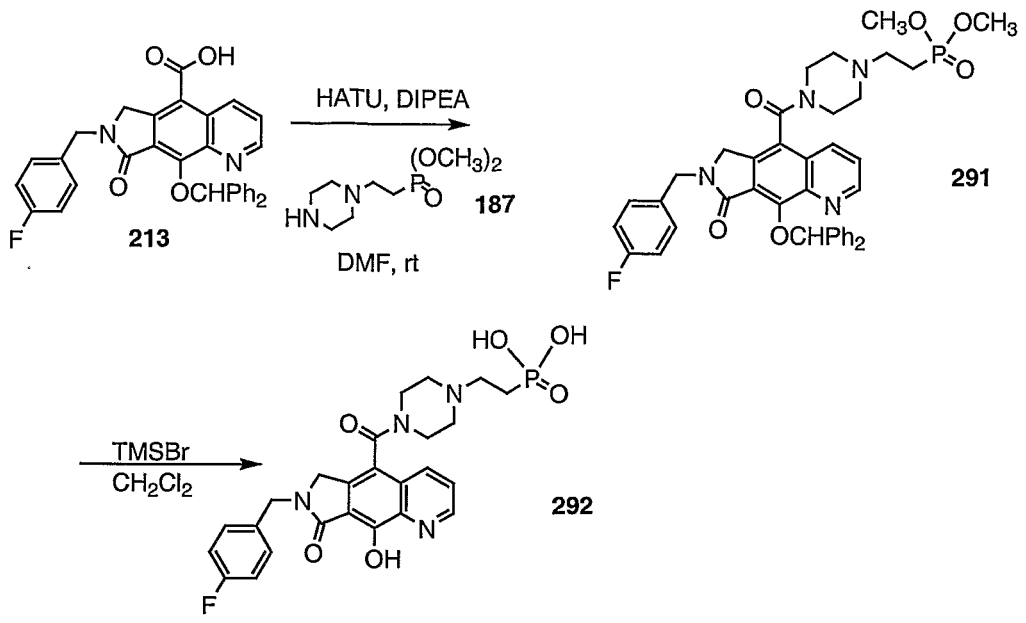
To a solution of **288** (18mg) dissolved in dichloromethane (1 mL) was added trifluoroacetic acid (100 µl) and triethylsilane (200 µl). The reaction mixture was stirred at room temperature for 1/2 hours under an inert atmosphere then concentrated in vacuo. The residue was purified by HPLC to afford 7-(4-fluoro-benzyl)-5-(2-methoxy-pyridin-3-yl)-9-hydroxy-6, 7-dihydro-pyrrolo[3,4-g]quinolin-8-one **289**, TFA salt, (11.6 mg, 68%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 9.0 (d, 1H), 8.3 (d, 1H), 7.9 (d, 1H), 7.5 (m, 2H), 7.2 (m, 1H+1H), 7.0 (m, 2H+1H), 4.7 (dd, 2H), 4.1(dd, 2H), 3.8 (s, 1H); MS: 416 (M+1). HPLC conditions: mobile phase A was 0.1% TFA in water, mobile phase b was 0.1% TFA in CH_3CN; gradient from 5% to 60% B in 20 min; flow rate was 20 mL/min; column was Phenomenex, luna 5µ, C18(2), 150mm x 21.1mm.



288 290

Example 290

To a solution of 9-benzhydryloxy-7-(4-fluoro-benzyl)-5-(2-methoxy-pyridin-3-yl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **288** (99mg, 0.17mmol) dissolved in methanol (20 mL) was added p-toluenesulfonic acid monohydrate (390 mg, 2.05 mmol) and lithium iodide (1.37 g, 10.26 mmol). The reaction mixture was heated to 120°C under nitrogen for 10 hours. The reaction was monitored by LC/MS. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in 2mL DMSO and 100 µl of TFA. It was purified by HPLC to afford 7-(4-fluoro-benzyl)-9-hydroxy-5-(2-hydroxy-pyridin-3-yl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **290**, TFA salt, (44.4 mg, 51%) as a yellow solid: ^{1}H NMR (CD_3OD) δ 8.9 (dd, 1H), 8.2(dd, 1H), 7.7 (m, 1H+1H), 7.6 (d, 2H), 7.4 (m, 2H), 7.1 (m, 2H), 6.6 (t, 1H), 4.8 (dd, 2H), 4.3(d, 2H); MS: 402 (M+1). HPLC conditions: mobile phase A was 0.1% TFA in water, mobile phase b was 0.1% TFA in CH_3CN; gradient from 5% to 60% B in 20 min; flow rate was 20 mL/min; column was Phenomenex, luna 5µ, C18(2), 150mm x 21.1mm.



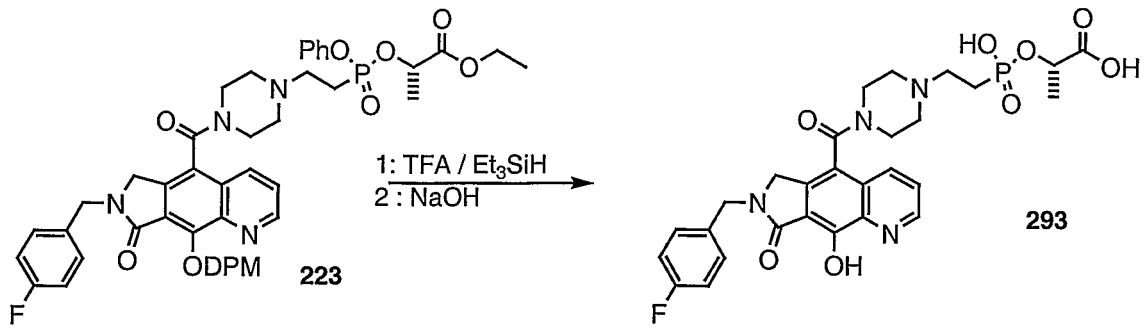
Example 291

To a solution of the trifluoroacetate salt of (2-piperazin-1-yl-ethyl)-phosphonic acid dimethyl ester **187** (0.023 g, 0.077 mmol) in 1 ml DMF was added diisopropylethylamine (33 μL, 0.192 mmol). This mixture was added to a solution of 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid **213** (0.020 g, 0.038 mmol) that had been mixed with HATU (0.0293 g, 0.077 mmol) in 1 ml of DMF. The reaction was stirred at rt under inert atmosphere for 3h, at which time TLC in 100% EtOAc showed complete consumption of starting material. The reaction mixture was introduced directly onto silica gel (99/1 EtOH/Et_3N) to give 20 mg of (2-{4-[9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-piperazin-1-yl}-ethyl)-phosphonic acid dimethyl ester **291** after flash chromatography.

Example 292

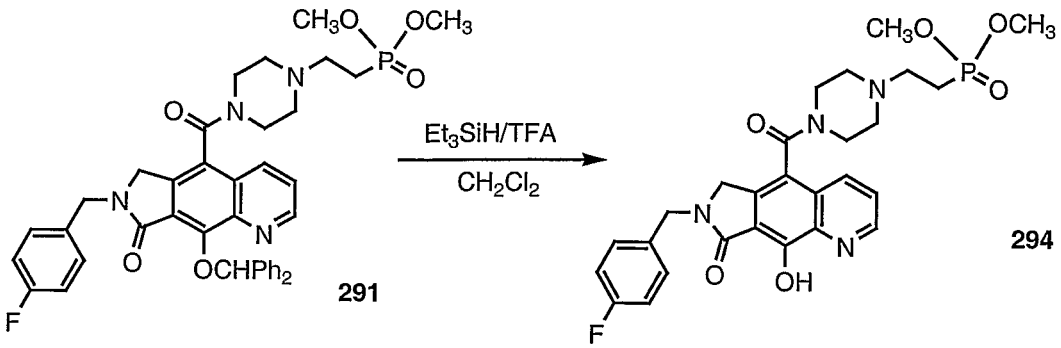
An excess of trimethylsilyl bromide (TMSBr, 0.015 g, 0.1 mmol) was added to (2-{4-[9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-piperazin-1-yl}-ethyl)-phosphonic acid dimethyl ester **291** in 1 mL of CH_2Cl_2. After stirring at room temperature (rt) for 16h, volatiles were removed under vacuum and the residue was triturated with Et_2O to provide pure the HBr salt of (2-{4-[7-(4-Fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-piperazin-1-yl}-ethyl)-phosphonic acid **292** (12 mg, 95 %) as a yellow solid. ^{1}H NMR (DMSO) δ : 8.95 (d, 1H), 8.75 (d, 1H), 8.54 (1H, d), 8.35 (bm, 1H), 7.78 (m, 2H), 7.52 (m, 2H), 7.4-7.32

(bm, 2H), 7.15 (t, 2H), 4.85 (bm, 1H) 4.45 (bm, 2H) 2.04 (bm, 2H); ^{31}P NMR (DMSO) δ 19.9; MS: 529 (M+H).



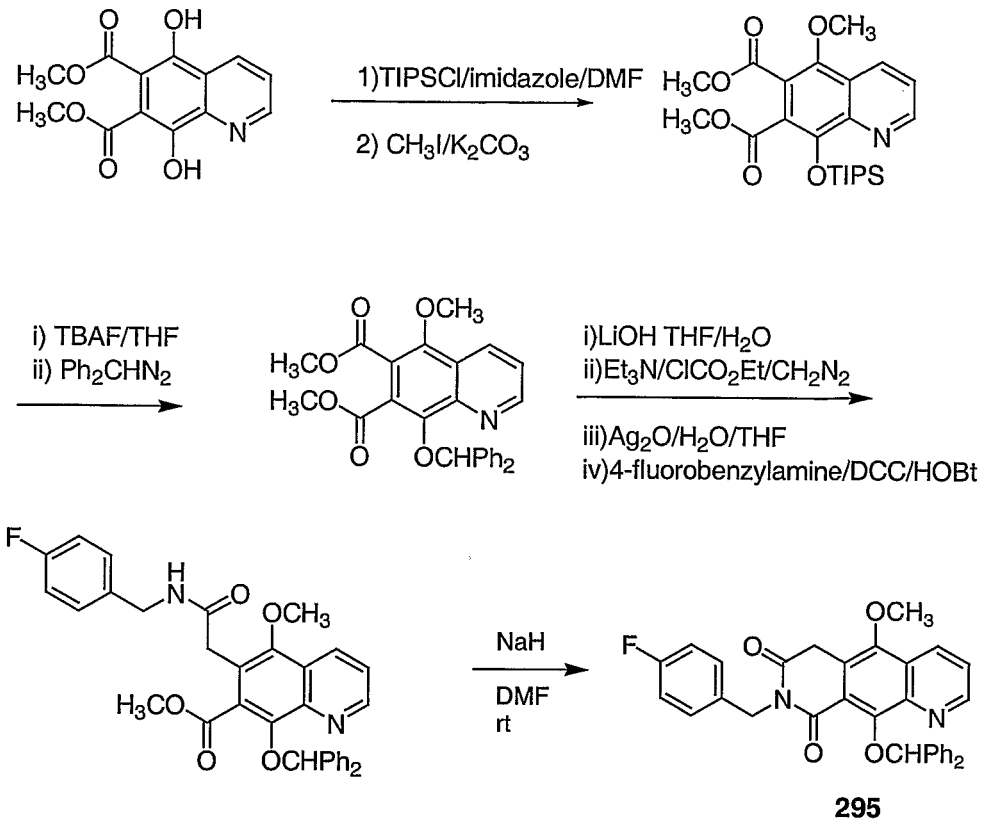
Example 293

To a solution of 2-[(2-{4-[9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-piperazin-1-yl}-ethyl)-phenoxy-phosphinoyloxy]-propionic acid ethyl ester **223** (15 mg, 0.017 mmol) in 1ml CH_2Cl_2 at rt was added an excess of TFA (10 μL, 0.085 mmol) and triethylsilane (30 μL, 0.17 mmol). The reaction was stirred under N_2 with monitoring via LC/MS. After 8h, the volatiles were removed by vacuum and the residue dissolved in 1mL of a 1/1 mixture of acetonitrile/water. 50 μL of 1M NaOH was added and the reaction was stirred at rt overnight. At this time, the product was introduced directly onto reverse phase HPLC to afford, after lyophilization, 2-[(2-{4-[7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-piperazin-1-yl}-ethyl)-hydroxy-phosphinoyloxy]-propionic acid as the trifluoroacetate salt, **293** (5 mg, 39 %). ^{1}H NMR (D_2O) δ : 9.10 (d, 1H), 8.95-8.72 (bm, 1H), 8.14 (bs, 1H), 7.20-7.3 (bm, 2H), 6.92-7.08 (bs, 2H), 4.65-4.25 (m, 4H), 3.78-3.65 (bs, 1H), 3.62-3.10 (bm, 9H), 2.75 (d, 2H), 1.95 (m, 2H), 1.35 (d, 3H); ^{31}P NMR (D_2O) δ 19.5; MS : 629 (M+H).



Example 294

To (2-{4-[9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-piperazin-1-yl}-ethyl)-phosphonic acid dimethyl ester **291** (5 mg, 0.0069 mmol) in 1mL CH_2Cl_2 is added CF_3CO_2H (6 μL, 0.035 mmol) and triethylsilane (12 μL, 0.07 mmol). After 2h, the volatile reaction components were removed by vacuum and the residue was washed with diethyl ether to give (2-{4-[7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-piperazin-1-yl}-ethyl)-phosphonic acid **294** as the trifluoroacetate salt (4.5 mg, 97%): ^{1}H NMR (CD_3OD) δ : 8.90 (d, 0.7H) 8.74 (d, 0.3H), 8.45 (d, 0.3H), 8.31 (d, 0.7H), 7.75 (dd, 0.7H), 7.55 (dd, 0.3H), 7.40 (m, 2H), 7.12 (m, 2H), 4.54 (s, 2H), 4.15 (bs, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.62-3.40 (bs, 2H), 3.12 (bs, 2H), 2.45-2.30(m, 2H); ^{19}F NMR (CD_3OD) δ -78, -127; ^{31}P NMR (CD_3OD) δ 29; MS: 556 (M+H).



295

Example 295

Imidazole (0.74 g, 10.8 mmol) and chlorotriisopropylsilane (TIPSCl, 1.15 g, 6.0 mmol) were added to 5,8-dihydroxy-quinoline-6,7-dicarboxylic acid dimethyl ester (prepared by the method in Oguchi, S. *Bulletin of the Chemical Society of Japan* **1974**, *47*, 1291, 1.5g, 5.4 mmol) in 20 mL DMF. The reaction was stirred for 48 h at rt and then the reaction was partitioned between 0.5 L methyl t-butyl ether and 150 mL saturated aq. LiCl. The organic layer was dried over Na_2SO_4 and the solvent removed by rotary evaporation. The residue (1.4 g, 3.2 mmol) was redissolved in 25 mL DMF and treated with K_2CO_3 (0.66 g, 4.8 mmol) followed by methyl iodide (MeI, 0.6g, 4.8 mL) at rt. After 2h, the reaction mixture was concentrated and purified by introduction of the reaction mixture onto silica gel for flash chromatography (4/1 hexanes/ethyl acetate) to give 5-methoxy-8-triisopropylsilanyloxy-quinoline-6,7-dicarboxylic acid dimethyl ester (1.4 g, 59 % overall yield) : ^{1}H NMR ($CDCl_3$) δ 8.85 (d, 1H), 8.45 (d, 1H), 7.50 (dd, 1H), 4.05 (s, 3H), 3.95 (s, 3H), 3.90 (s, 3H), 1.45 (septet, 3H), 1.05 (d, 9H); MS: 448 (M+H).

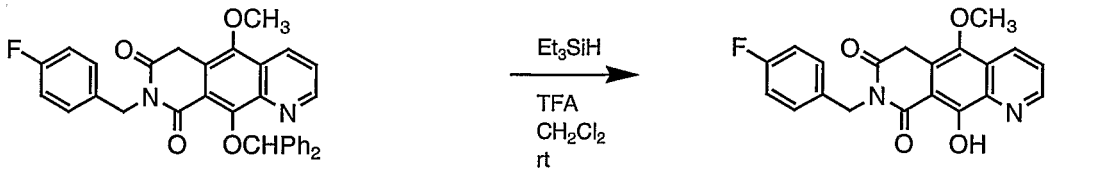
A 1M solution of TBAF in THF (4 ml) was added to 5-methoxy-8-triisopropylsilanyloxy-quinoline-6,7-dicarboxylic acid dimethyl ester (0.85g, 1.9 mmol) in 20 ml dry THF. The reaction was stirred at rt for 1h, at which time the reaction mixture was concentrated and the residue dissolved in 100 mL diethyl ether and washed with 25 mL 1N

HCl, followed by 25 mL of saturated aq. NaCl. The organic layer was concentrated and the residue was dissolved in 40 mL dichloroethane. Diphenyldiazomethane (0.7g, 3.8 mmol) was added and the reaction temperature was raised to 70 °C for 24h. The reaction mixture was concentrated and the residue chromatographed on silica gel (1/1 hexanes/EtOAc) to give 8-benzhydryloxy-5-methoxy-quinoline-6,7-dicarboxylic acid dimethyl ester (0.8 g, 61 % yield overall). ^{1}H NMR ($CDCl_3$) δ 8.85 (d, 1H), 8.45 (d, 1H), 7.45 (dd, 1H), 3.98 (s, 3H), 3.85 (s, 3H), 3.74 (s, 3H); MS : 480 (M+Na).

Lithium hydroxide (LiOH, 0.07g, 2.95 mmol) was added to 8-benzhydryloxy-5-methoxy-quinoline-6,7-dicarboxylic acid dimethyl ester (0.27g, 0.59 mmol) in 1 mL 3/1 THF/H_2O. The reaction was heated at 45 °C and after 24 h, the reaction was diluted with 50 mL dichloromethane and acidified with 1 mL 0.1 M HCl. The organic layer was dried over Na_2SO_4 and concentrated to give 180 mg of an oil which was dissolved in 5 mL THF, triethylamine (0.168g, 1.2 mmol) and ethyl chloroformate (0.064g, 0.6 mmol). After 2h, the reaction was diluted with diethyl ether and washed with brine. The organic layer was dried over Na_2SO_4 and the organic layer decanted from drying agent. The ether layer was cooled to 0 °C and a solution of ca. 0.3 M diazomethane in diethyl ether (4 mL, ca. 1.2 mmol) was added dropwise. After stirring for 24h to effect diazotization, the ether layer was removed along with excess diazomethane via rotary evaporation. The resulting residue was dissolved in 4 mL of 1/1 THF/water, and silver(I) oxide (0.035g, 0.15mmol) was added. The reaction was heated to 60 °C for a period of 4h, then the reaction mixture was diluted with 50 mL EtOAc and acidified with 10 ml 1N HCl. The organic layer was dried over Na_2SO_4 and concentrated. The resulting residue was then taken up in 2 mL THF, and treated with hydroxybenzotriazole (HOBt, 0.08 g, 0.6 mmol), dicyclohexylcarbodiimide (DCC, 0.12 g, 0.6 mmol) and 4-fluorobenzylamine (0.07 g, 0.6 mmol). After a period of 16h, the reaction was introduced directly to chromatography on silica gel (100 % diethyl ether) to give 8-benzhydryloxy-6-[(4-fluoro-benzylcarbamoyl)-methyl]-5-methoxy-quinoline-7-carboxylic acid methyl ester (0.12 g, 38 % overall yield): ^{1}H NMR ($CDCl_3$) δ 8.85 (d, 1H), 8.35 (d, 1H), 7.60-6.8 (cm, 12H), 6.15 (s, 1H), 4.30 (m, 2H), 3.95 (s, 3H), 3.75 (s, 3H), 3.65 (s, 2H), 3.54 (t, 1H); MS : 587 (M+Na).

A 60 % sodium hydride (NaH) mineral oil dispersion (0.002 g, 0.06 mmol was added to a solution of 8-benzhydryloxy-6-[(4-fluoro-benzylcarbamoyl)-methyl]-5-methoxy-quinoline-7-carboxylic acid methyl ester (0.020 g, 0.04 mmol) in 1mL of anhydrous DMF. The resulting indigo-tinted solution was stirred at rt for a period of 30 min, and then diluted

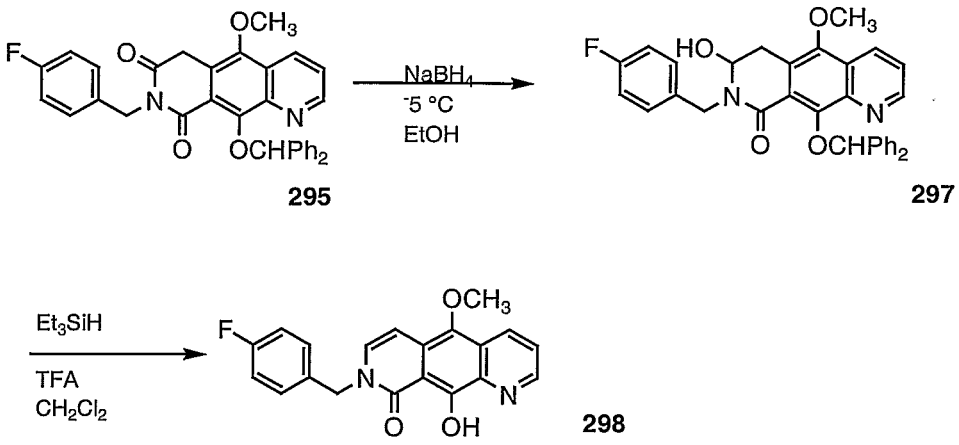
with diethyl ether (50 ml) and washed with sat. aq. NH_4Cl (25 mL). The organic layer was dried over Na_2SO_4 and solvent was removed by rotary evaporation. The residue was purified by silica gel chromatography (1/1 hexanes/diethyl ether and then 100% MeOH to elute product fractions) to give 9-benzhydryloxy-7-(4-fluoro-benzyl)-10-methoxy-5H-1,7-diaza-anthracene-6,8-dione **295** (9 mg, 48 %).



295 **296**

Example 296

9-Benzhydryloxy-7-(4-fluoro-benzyl)-10-methoxy-5H-1,7-diaza-anthracene-6,8-dione **295** (6 mg, 0.01 mmol) in 1mL CH_2Cl_2 was treated with 0.1mL trifluoroacetic acid and 0.05 mL triethylsilane. After 1h, volatiles were removed and the product was purified via trituration with diethyl ether to give the trifluoroacetate salt of 7-(4-Fluoro-benzyl)-9-hydroxy-10-methoxy-5H-1,7-diaza-anthracene-6,8-dione **296** (5 mg, 62%): ^1H NMR (CDCl3) δ 12.98 (s, 1H), 9.10 (d, 1H), 8.35 (d, 1H), 7.65 (m, 1H), 7.55 (m, 2H), 7.04 (t, 2H), 5.2 (s, 2H), 4.75 (s,1H), 4.20 (s, 1H), 3.95 (s, 3H); MS: 367 (M+Na).



295 **297** **298**

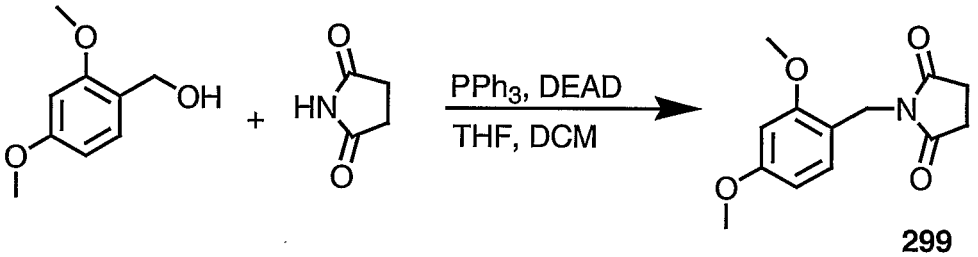
Example 297

Sodium borohydride ($NaBH_4$, 0.021 g, 0.56mmol) was added to 9-benzhydryloxy-7-(4-fluoro-benzyl)-10-methoxy-5H-1,7-diaza-anthracene-6,8-dione **295** (30 mg, 0.056 mmol) in 1 mL EtOH at $^-5$ °C. The reaction was stirred at low temperature for a period of 2h, then

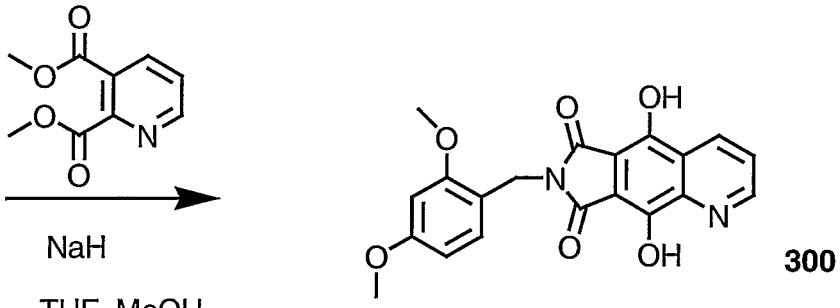
the reaction was diluted with CH_2Cl_2 (25 mL) and washed with 10 mL sat. aq. sodium bicarbonate solution. The aqueous layer was then washed twice with 25 ml portions of CH_2Cl_2 and the combined organic layers washed with brine and dried over Na_2SO_4. The reduction product was purified on silica gel (100% Et_2O) to give 6 mg of 9-benzhydryloxy-7-(4-fluoro-benzyl)-10-methoxy-5H-1,7-diaza-anthracene-6-hydroxy, 8-one **297**.

Example 298

9-Benzhydryloxy-7-(4-fluoro-benzyl)-10-methoxy-5H-1,7-diaza-anthracene-6-hydroxy, 8-one **297** (6mg, 0.01 mmol) was dissolved in 1mL CH_2Cl_2 and treated with 0.1mL trifluoroacetic acid and 0.1 mL triethylsilane. After 1hr, volatiles were removed and the product was purified via trituration with diethyl ether to give the trifluoroacetate salt of 7-(4-Fluoro-benzyl)-9-hydroxy-10-methoxy-7H-1,7-diaza-anthracen-8-one **298** (2 mg, 38%). ^{1}H NMR (CD_3OD) δ 9.35 (d, 1H), 8.75 (d, 1H), 7.80 (dd, 1H), 7.33 (m, 2H), 7.08 (m, 3H), 6.85 (d, 1H), 5.15 (s, 2H), 3.95 (s, 3H).; MS : 351 (M+H).



299



300

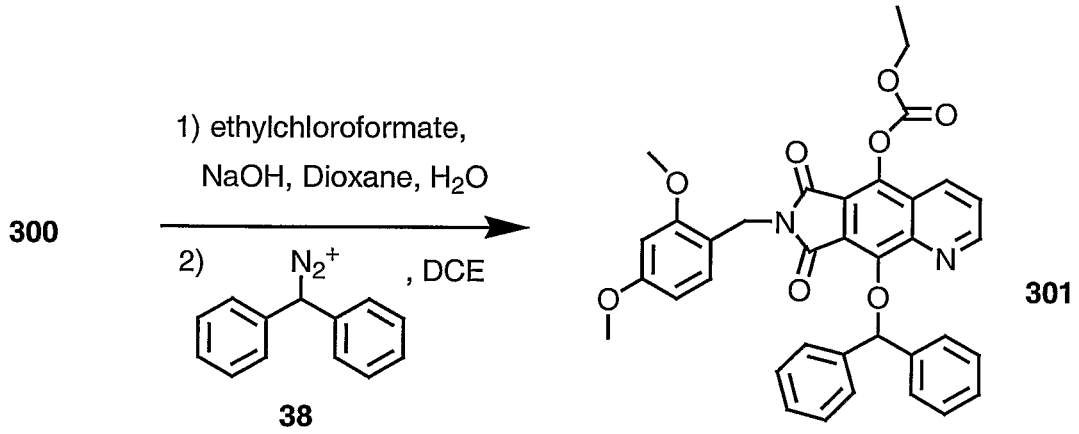
Example 299

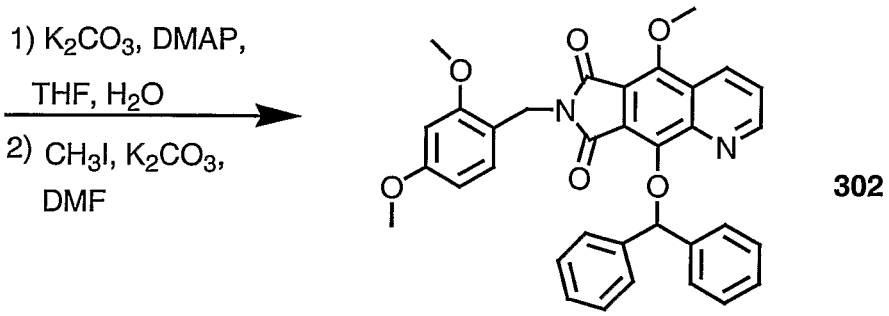
To 2,4-dimethoxybenzyl-alcohol (4.3 g, 25.6 mmol) and pyrrolidine-2,5-dione (succinimide, 1.2 g, 12.2 mmol) dissolved in tetrahydrofuran (25 ml) and dichloromethane (25 ml) was added triphenyphosphine (6.4 g, 24.4 mmol). After cooling to 0° C, diethylazidodicarboxylate (DEAD, 4.25 g, 24.4 mmol) was added dropwise to the reaction mixture. The reaction mixture was then allowed to warm to room temperature and kept at room temperature with stirring overnight. Following concentration in vacuo, 100 ml of a (1:1)hexane/ether solution was added and this mixture was stored at 0° C overnight. The

resulting solid precipitate was filtered off and the filtrate was concentrated in vacuo. The resulting residue was purified by silica gel chromatography (3/1 – ethyl acetate/hexane) to afford 1-(2,4-dimethoxy-benzyl)-pyrrolidine-2,5-dione **299** (1.4 g, 5.6 mmol, 46%). ^{1}H NMR ($CDCl_3$) δ 7.07 (d, 1H), 6.38 (m, 2H), 4.60 (s, 2H), 3.76 (s, 3H), 2.62 (s, 4H).

Example 300

To 1-(2,4-dimethoxy-benzyl)-pyrrolidine-2,5-dione **299** (1.4 g, 5.6 mmol) and pyridine-2,3-dicarboxylic acid dimethyl ester (1.13 g, 5.8 mmol) dissolved in tetrahydrofuran (60 ml) and methanol (7.0 ml) was added a 60% dispersion of sodium hydride in mineral oil (NaH, 492 mg, 12.3 mmol). The reaction mixture was warmed to 80 °C and kept at 80 °C with stirring overnight. The reaction mixture was placed in an ice bath and titrated to a pH of 4 with 1 M HCl. 200 ml of ether was added and the resulting yellow solid was collected by filtration. The solid was washed twice with ether, twice with water, and dried under high vacuum with heating to provide 7-(2,4-dimethoxy-benzyl)-5,9-dihydroxy-pyrrolo[3,4-g]quinoline-6,8-dione **300** (1.1 g, 52%). ^{1}H NMR (d-DMSO) δ 10.8 (broad, 2H), 9.0 (d, 1H), 8.67 (d, 1H), 7.72 (m, 1H), 6.90 (d, 1H), 6.5 (d, 1H), 6.38 (dd, 1H), 4.58 (s, 2H), 3.76 (s, 3H), 3.66 (s, 3H). MS: 382.1 (M+1)





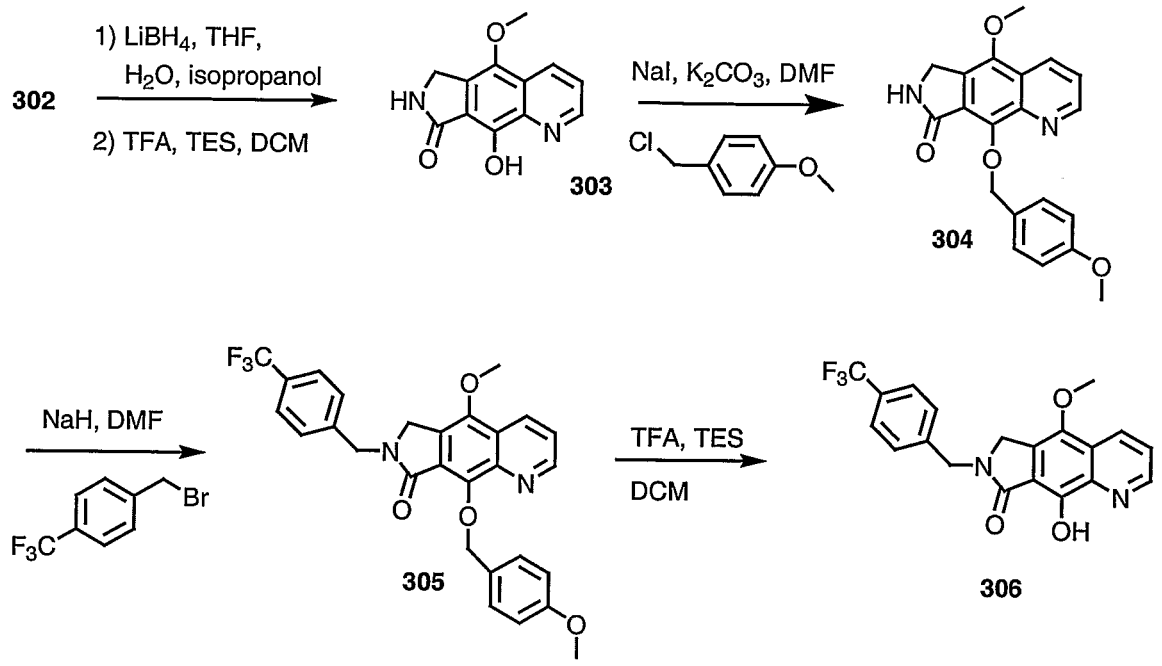
Example 301

7-(2,4-Dimethoxy-benzyl)-5,9-dihydroxy-pyrrolo[3,4-g]quinoline-6,8-dione **300** (1.1 g, 2.9 mmol) was dissolved in dioxane (14.5 ml) and H_2O (9.7 ml) and cooled to 0° C. To this reaction mixture was added 1.0 M NaOH (5.8 ml, 5.8 mmol), followed by ethylchloroformate (347.3 mg, 3.2 mmol). After stirring at 0° C for 30 minutes, dioxane (10 ml) and ethylchloroformate (51 mg, 0.5 mmol) were added and the reaction stirred for another 30 minutes at 0 °C. The reaction mixture was quenched with the addition of acetic acid (0.6 ml) and concentrated *in vacuo*. The crude mixture was diluted with ethyl acetate and washed once with 5% citric Acid (aqueous), twice with water, once with brine, and dried over magnesium sulfate. The resulting residue was dissolved in 1,2-dichloroethane (30 ml) and diphenyl-methanediazonium **38** (diphenyldiazomethane, 1.1 g, 5.6 mmol) was added. The reaction mixture was then stirred overnight at room temperature. Following dilution with dichloromethane, the reaction mixture was washed with once with water, once with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel chromatography (1/1 - Hexanes/Ethyl Acetate) to afford carbonic acid 9-benzhydryloxy-7-(2,4-dimethoxy-benzyl)-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester ethyl ester **301** (1.2 g, 1.9 mmol, 66 %). ^{1}H NMR ($CDCl_3$) δ 9.10 (dd, 1H), 8.40 (dd, 1H), 7.95 (s, 1H), 7.68 (m, 1H), 7.60 (d, 4H), 7.15 (m, 6H), 7.0 (d, 1H), 6.40 (d, 1H), 6.36 (d, 1H), 4.80 (s, 2H), 4.35 (q, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 1.31 (t, 3H). MS: 641.2 (M+23).

Example 302

Potassium carbonate (2.6 g, 19.0 mmol) and N,N-dimethyl-aminopyridine (DMAP, 0.464 g, 3.8 mmol) were added to carbonic acid 9-benzhydryloxy-7-(2,4-dimethoxy-benzyl)-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester ethyl ester **301** (1.2 g, 1.9 mmol) dissolved in tetrahydrofuran (40 ml) and water (20 ml) was added. After stirring overnight at room temperature, the reaction mixture was concentrated *in vacuo* and diluted with ethyl acetate. It was washed twice with 5% citric Acid (aqueous), twice with water, once with brine, dried over magnesium sulfate, and concentrated in vacuo. The resulting residue was dissolved in dimethylformamide (10 ml). To this reaction mixture was added potassium carbonate (1.24 g, 9.0 mmol) and iodomethane (methyl iodide, MeI, 2.55 g, 18.0 mmol). After stirring overnight at room temperature, the reaction mixture was diluted with ethyl acetate, washed twice with 5% citric acid, twice with water, once with brine, and concentrated in vacuo to afford 9-benzhydryloxy-7-(2,4-dimethoxy-benzyl)-5-methoxy-

pyrrolo[3,4-g]quinoline-6,8-dione **302** (1.1 g, 1.9 mmol, 100 %). ^{1}H NMR (d-DMSO) δ 9.16 (dd, 1H), 8.60 (dd, 1H), 7.82 (s, 1H), 7.75 (m, 1H), 7.54 (d, 4H), 7.16 (m, 6H), 6.82 (d,1H), 6.56 (d, 1H), 6.44 (dd, 1H), 4.66 (s, 2H), 4.10 (s, 3H), 3.76 (s, 3H), 3.70 (s, 3H). MS: 583.2 (M+23).



Example 303

9-Benzhydryloxy-7-(2,4-dimethoxy-benzyl)-5-methoxy-pyrrolo[3,4-g]quinoline-6,8-dione **302** (500 mg, 0.89 mmol) was dissolved in tetrahydrofuran (6.0 ml), water (1.2 ml), and isopropanol (2.4 ml) and cooled to 0° C. Lithium borohydride ($LiBH_4$, 96.9 mg, 4.45 mmol) was then added and the reaction mixture was removed from the ice bath and stirred at room temperature for 2 hours. After quenching with acetic acid (0.5 ml), the reaction mixture was diluted with ethyl acetate, washed with twice with water, once with brine, and concentrated *in vacuo*. The resulting residue was dissolved in dichloromethane (9.2 ml) and triethylsilane (1.8 ml), and cooled to 0° C. After adding trifluoroacetic acid (3.6 ml), the reaction mixture was warmed to room temperature and stirred at room temperature for 1 hour. The mixture was concentrated in vacuo and the resulting residue was redissolved in trifluoroacetic acid (10 ml) and triethylsilane (2 ml). It was then warmed to 75° C and stirred at 75° C for 2 hours. The reaction mixture was concentrated in vacuo and azeotroped three times with a (1:1) toluene/tetrahydrofuran solution. The resulting residue was triturated three times with a (3:1) hexane/ether mixture. The remaining solid

in the filter funnel and reaction flask was dissolved in methanol, combined, and concentrated in vacuo to afford 9-hydroxy-5-methoxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **303** (240 mg, 113%). ^{1}H NMR (d-DMSO) δ 8.84 (dd, 1H), 8.58 (broad, 1H), 8.50 (dd, 1H), 7.60 (m, 1H), 4.60 (s, 2H), 3.94 (s, 3H). MS: 231.1 (M+1).

Example 304

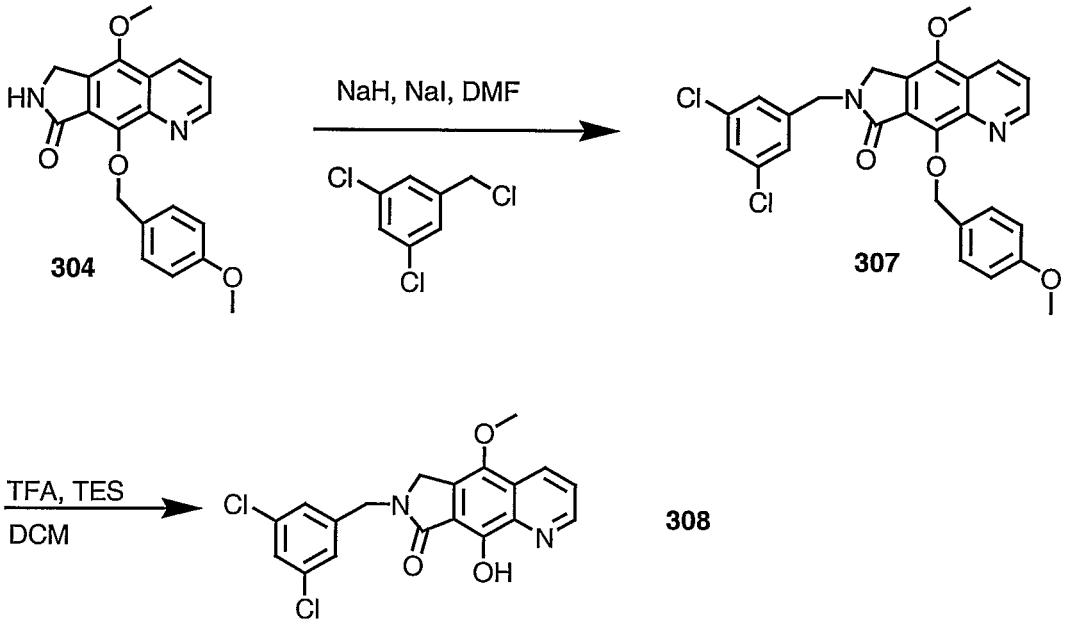
Potassium carbonate (60.1 mg, 0.435 mmol), 4-methoxybenzylchloride (41 mg, 0.26 mmol), and sodium iodide (6.3 mg, 0.043 mmol) were added to 9-hydroxy-5-methoxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **303** (20 mg, 0.087 mmol) dissolved in dimethylformamide 8 (0.4 ml). The reaction mixture was warmed to 60 °C and stirred at 60 °C for one hour. After cooling the reaction mixture to 0 °C, acetic acid (0.06 ml) was added and the mixture was concentrated in vacuo. The residue was diluted with ethyl acetate and washed once with 5% Citric Acid, twice with water, once with brine, and concentrated in vacuo. The residue was purified by silica gel chromatography (9/1 - dichloromethane/methanol) to afford 5-methoxy-9-(4-methoxy-benzyloxy)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **304** (16 mg, 0.046 mmol, 53 %). ^{1}H NMR ($CDCl_3$) δ 9.0 (dd, 1H), 8.64 (dd, 1H), 7.51 (d, 2H), 7.46 (m, 1H), 6.80 (d, 2H), 6.50 (broad, 1H), 5.60 (s, 2H), 3.98 (s, 3H), 3.72 (s, 3H). MS: 351.1 (M+1).

Example 305

5-Methoxy-9-(4-methoxy-benzyloxy)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **304** (25.4 mg, 0.073 mmol,) was dissolved in dimethylformamide (0.4 ml) and cooled to 0° C. Sodium hydride (3.6 mg, 0.095 mmol) was added, followed by stirring at 0° C for 5 minutes. 4-trifluoromethyl-benzylbromide (21.0 mg, 0.088 mmol) was added and the reaction mixture was allowed to warm to room temperature and kept at room temperature with stirring for 5 minutes. It was cooled to 0° C, quenched with acetic acid (0.030 ml), and concentrated in vacuo. The mixture was diluted with ethyl acetate, washed twice with water. once with brine, dried over magnesium sulfate, and concentrate in vacuo. The residue was purified by silica gel chromatography (99/1 - ethyl acetate/acetic acid) to afford 5-Methoxy-9-(4-methoxy-benzyloxy)-7-(4-trifluoromethyl-benzyl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **305** (13 mg, 0.026 mmol, 35 %). ^{1}H NMR δ 9.15 (dd, 1H), 8.60 (dd, 1H), 7.60 (m, 4H), 7.40 (d, 2H), 6.80 (d, 2H), 5.85 (s, 2H), 4.80 (s, 2H), 4.42 (s, 2H), 3.98 (s, 3H), 3.86 (s, 3H). MS: 509.2 (M+1).

Example 306

To 5-methoxy-9-(4-methoxy-benzyloxy)-7-(4-trifluoromethyl-benzyl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **305** (13 mg, 0.026 mmol) dissolved in dichloromethane (0.200 ml) was added triethylsilane (TES, 0.05 ml) and trifluoroacetic acid (TFA, 0.100 ml). After stirring at room temperature for 15 minutes, the reaction mixture was concentrated in vacuo and azeotroped three times with a (1:1) tetrahydrofuran to toluene mixture. The resulting residue was then triturated three times with a (3:1) hexane to ether mixture to afford 9-hydroxy-5-methoxy-7-(4-trifluoromethyl-benzyl)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **306** (7 mg, 0.014 mmol, 54%). ^{1}H NMR (CD_3OD) δ 9.0 (dd, 1H), 8.58 (dd, 1H), 7.60 (d, 2H), 7.40 (d, 2H), 4.80 (s, 2H), 4.50 (s, 2H), 3.95 (s, 3H). ^{19}F NMR δ -63, -76.2. MS: 389.1 (M+1).



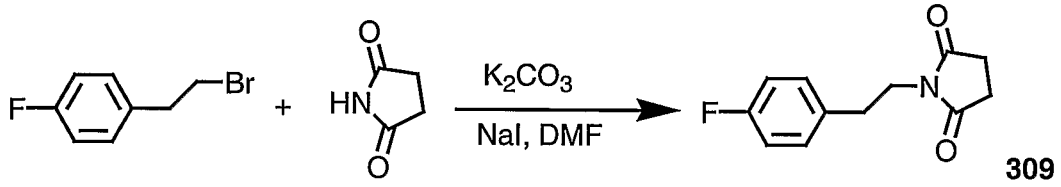
Example 307

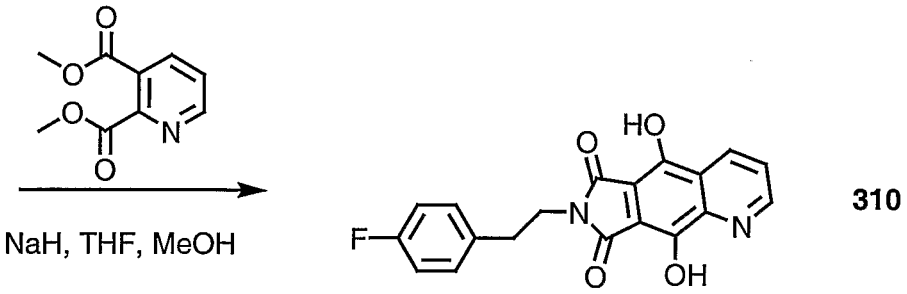
5-Methoxy-9-(4-methoxy-benzyloxy)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **304** (17 mg, 0.049 mmol) was dissolved in dimethylformamide (0.3 ml) and cooled to 0° C. After adding sodium hydride (2.5 mg, 0.064 mmol), the reaction was stirred for 5 minutes at 0° C. 3, 5-Dichlorobenzylchloride (11.5 mg, 0.059 mmol) and a catalytic amount of sodium iodide were then added. The reaction mixture was warmed to room temperature and stirred at room temperature for 30 minutes. It was then cooled to 0° C, acidified with acetic acid (0.030 ml), and concentrated *in vacuo*. The resulting residue was diluted with ethyl acetate, washed twice with water, once with brine, and concentrated in vacuo. The residue was

purified by silica gel chromatography (99/1 - ethyl acetate/acetic acid) to afford 7-(3,5-dichloro-benzyl)-5-methoxy-9-(4-methoxy-benzyloxy)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **307** (7 mg, 40 %). ^{1}H NMR ($CDCl_3$) δ 9.0 (dd, 1H), 8.40 (dd, 1H), 7.60 (d, 2H), 7.55 (m, 1H), 7.20 (m, 3H), 6.80 (d, 2H), 5.60 (s, 2H), 4.75(s, 2H), 4.40 (s, 2H), 3.95 (s, 3H), 3.75 (s, 3H). MS: 509.1 (M+1).

Example 308

In a manner similar to the protocol described in Example 306, 7-(3,5-dichloro-benzyl)-5-methoxy-9-(4-methoxy-benzyloxy)-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **307** (17 mg, 0.049 mmol) was deprotected to provide 7-(3,5-dichloro-benzyl)-9-hydroxy-5-methoxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **308** (10 mg, 0.020 mmol, 41%). ^{1}H NMR (CD_3OD) δ 9.0 (dd, 1H), 8.60 (d, 1H), 7.60 (m, 1H), 7.20 (m, 3H) 4.75 (s, 2H), 4.45 (s, 2H), 4.0 (s, 3H). ^{19}F δ -76. MS: 390.1 (M+1).





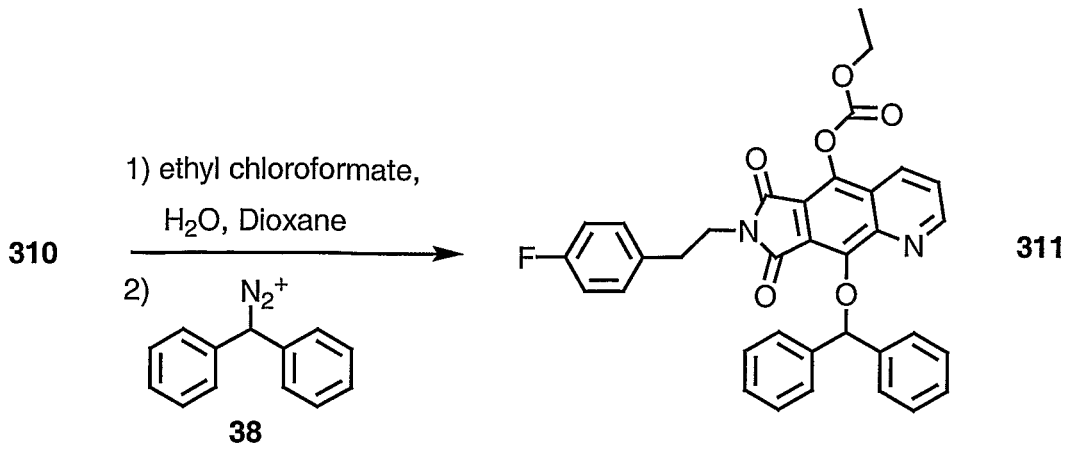
Example 309

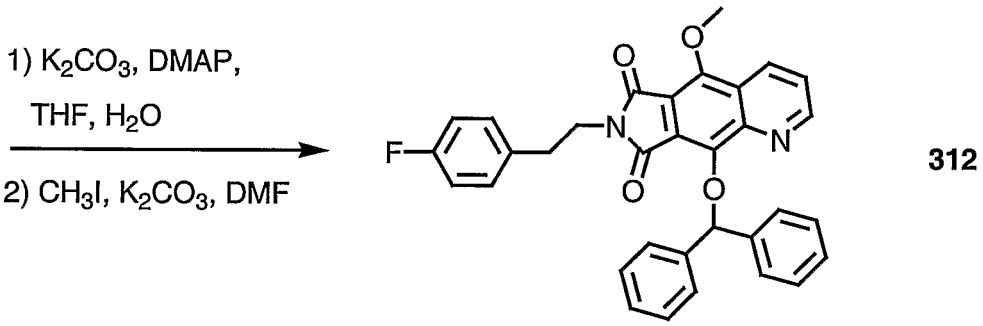
To a solution of 1-(2-bromo-ethyl)-4-fluoro-benzene (587 mg, 3.7 mmol) and pyrrolidine-2,5-dione (succinimide, 733.3 mg, 7.4 mmol) in dimethylformamide (15 ml) was added potassium carbonate (2.0 g, 14.8 mmol) and sodium iodide (277 mg, 1.9 mmol). The reaction mixture was warmed to 60° C and kept at 60° C overnight with stirring. The reaction mixture was cooled to room temperature and concentrated in vacuo. The concentrate was diluted with ethyl acetate and washed twice with a saturated sodium bicarbonate aqueous solution, twice with water, once with brine, and concentrated in vacuo.

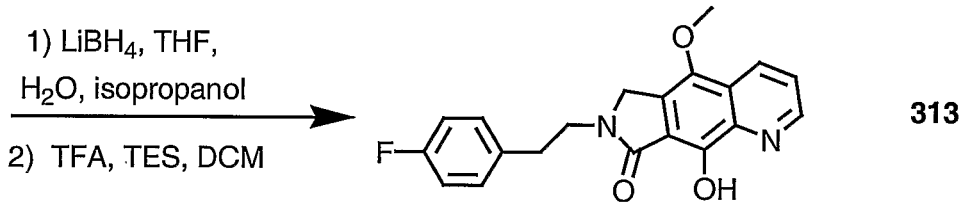
The residue was purified by silica gel chromatography (100% ethylacetate) to afford 1-[2-(4-fluoro-phenyl)-ethyl]-pyrrolidine-2,5-dione **309** (570 mg, 2.6 mmol, 70%) as a solid. ^{1}H NMR ($CDCl_3$) δ 7.14 (m, 2H), 6.94 (t, 2H), 3.68 (t, 2H), 2.84 (t, 2H), 2.63 (s, 4H).

Example 310

To 1-[2-(4-Fluoro-phenyl)-ethyl]-pyrrolidine-2,5-dione **309** (270 mg, 1.22 mmol and pyridine-2,3-dicarboxylic acid dimethyl ester (261.6 mg, 1.34 mmol) dissolved in tetrahydrofuran (12.0 ml) and methanol (1.4 ml) was added a 60% dispersion of sodium hydride in mineral oil (108 mg, 2.7 mmol). The reaction mixture was warmed to 80° C and kept at 80° C with stirring overnight. The reaction mixture was then placed in an ice bath and titrated to a pH of 4 with 1 M HCl. Two hundred (200) ml of diethylether was then added and the resulting yellow solid was collected by filtration. The solid was washed twice with ether, twice with water, and dried under high vacuum with heating to provide 7-[2-(4-fluoro-phenyl)-ethyl]-5,9-dihydroxy-pyrrolo[3,4-g]quinoline-6,8-dione **310** (250 mg, 0.71 mmol, 58%). ^{1}H NMR (d-DMSO) δ 10.7 (broad, 1H), 8.98 (dd, 1H), 8.66 (dd, 1H), 7.73 (m, 1H), 7.18 (m, 2H), 7.04 (t, 2H), 3.72 (t, 2H), 2.86 (t, 2H). MS: 353.1 (M+1).







Example 311

7-[2-(4-Fluoro-phenyl)-ethyl]-5,9-dihydroxy-pyrrolo[3,4-g]quinoline-6,8-dione **310** (250 mg, 0.71 mmol).was dissolved in dioxane (3.6 ml) and H_2O (2.4 ml) and cooled to 0 °C. After 1.0 M NaOH (1.42 ml, 1.42 mmol) and ethylchloroformate (84.6 mg, 0.78 mmol) were added, the reaction was stirred at 0° C for one hour . The reaction mixture was quenched with the addition of acetic acid (0.6 ml) and concentrated in vacuo. The crude mixture was diluted with ethyl acetate and washed once with 5% Citric Acid (aqueous), twice with water, once with brine, dried over magnesium sulfate, and concentrated in vacuo. The resulting residue was dissolved in 1,2-dichloroethane (4.0 ml) and to this was added diphenyl-methanediazonium **38** (252 mg, 1.3 mmol). The reaction mixture was then stirred overnight at room temperature. Following dilution with dichloromethane, the reaction mixture was washed with once with water, once with brine, dried over magnesium sulfate,

and concentrated in vacuo. The residue was then purified by silica gel chromatography (1/1 - hexane/ethyl acetate) to afford carbonic acid 9-benzhydryloxy-7-[2-(4-fluoro-phenyl)-ethyl]-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester ethyl ester **311** (251 mg, 0.425 mmol,65%). ^{1}H NMR (d-DMSO) δ 9.19 (dd, 1H), 8.52 (dd, 1H), 7.90 (s, 1H), 7.80 (m, 1H), 7.54 (m, 4H), 7.20 (m, 8H), 7.02 (t, 2H), 4.24 (q, 2H), 3.79 (t, 2H), 2.90 (t, 2H), 1.25 (t, 3H). MS: 599.2 (M+23).

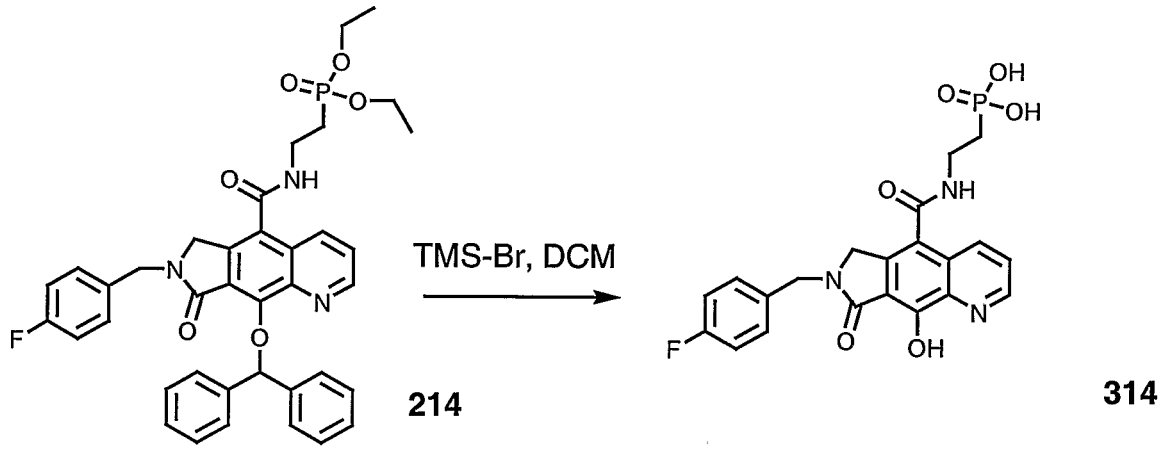
Example 312

To carbonic acid 9-benzhydryloxy-7-[2-(4-fluoro-phenyl)-ethyl]-6,8-dioxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinolin-5-yl ester ethyl ester **311** (140 mg, 0.24 mmol) dissolved in tetrahydrofuran (0.50 ml) and water (0.25 ml) was added potassium carbonate (345.4 mg, 2.5 mmol) and N,N-dimethyl-aminopyridine (DMAP, 29.3 mg , 3.8 mmol). After stirring overnight at room temperature, the reaction mixture was concentrated in vacuo and diluted with ethyl acetate. It was then washed twice with 5% citric Acid (aqueous), twice with water, once with brine, dried over magnesium sulfate, and concentrated in vacuo. The resulting residue was dissolved in dimethylformamide (3.0 ml). To this solution was added potassium carbonate (179 mg, 1.3 mmol) and iodomethane (319 mg, 2.6 mmol). After stirring overnight at room temperature, the reaction mixture was diluted with ethyl acetate. It was then washed twice with 5% citric Acid, twice with water, once with brine, and concentrated in vacuo to afford 9-benzhydryloxy-7-[2-(4-fluoro-phenyl)-ethyl]-5-methoxy-pyrrolo[3,4-g]quinoline-6,8-dione **312** (130 mg, 0.24 mmol, 100%). ^{1}H NMR ($CDCl_3$) δ 9.16 (dd, 1H), 8.58 (dd, 1H), 7.82 (s, 1H), 7.74 (m, 1H), 7.55 (m, 4H), 7.20 (m, 8H), 7.0 (t, 2H), 4.04 (s, 3H), 3.87 (t, 2H), 2.91 (t, 2H). MS: 555.2 (M+23).

Example 313

9-Benzhydryloxy-7-(2,4-dimethoxy-benzyl)-5-methoxy-pyrrolo[3,4-g]quinoline-6,8-dione **312** (130 mg, 0.24 mmol) was dissolved in tetrahydrofuran (1.6 ml), water (0.64 ml), and isopropanol (0.32 ml) and cooled to 0° C. Lithium borohydride (26.6 mg, 1.22 mmol) was then added and the reaction mixture was removed from the ice bath and stirred at room temperature for 2 hours. After quenching with acetic acid (0.12 ml), the reaction mixture was diluted with ethyl acetate. It was then washed with twice with water, once with brine, and concentrated in vacuo. The resulting residue was dissolved in dichloromethane (1.2 ml) and triethylsilane (0.6 ml) and trifluoroacetic acid (3.6 ml). The reaction mixture

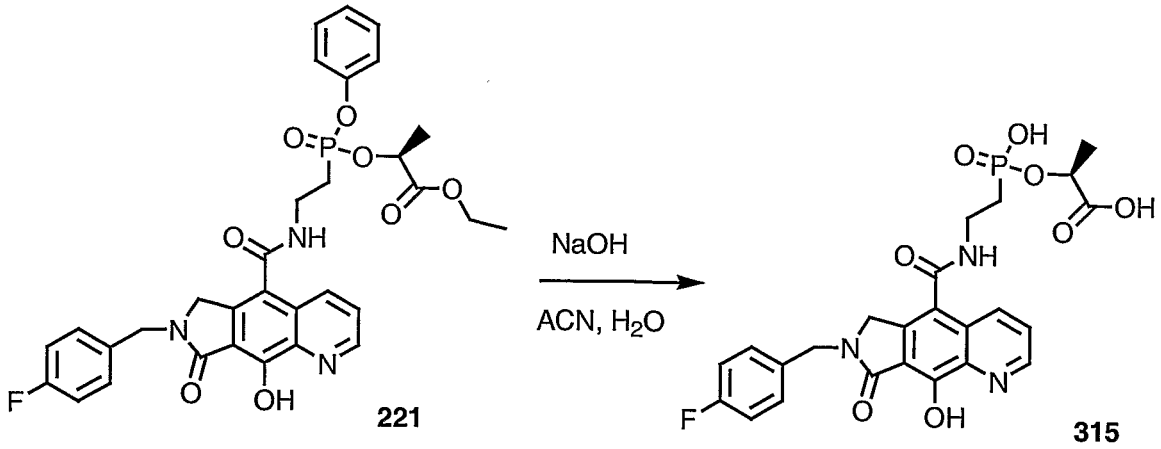
was then stirred at room temperature for 1 hour. The mixture was then concentrated in vacuo and azeotroped three times with a (1:1) toluene/tetrahydrofuran solution. The resulting residue was triturated three times with a (3:1) hexane/ether mixture and the remaining solid in the filter funnel and reaction flask was dissolved in methanol, combined, and concentrated *in vacuo* to afford 7-[2-(4-Fluoro-phenyl)-ethyl]-9-hydroxy-5-methoxy-6,7-dihydro-pyrrolo[3,4-g]quinolin-8-one **313** (40 mg, 0.086 mmol, 36%). ^{1}H NMR (d-DMSO) δ 8.85 (dd, 1H), 8.648 (dd, 1H), 7.65 (m, 1H), 7,28 (t, 2H), 7.06 (t, 2H), 4.60 (s, 2H), 3.95 (s, 3H), 3.68 (t, 2H), 2.95 (t, 2H). ^{19}F NMR δ 60.0, -75.6. MS: 353.1 (M+1).



214 **314**

Example 314

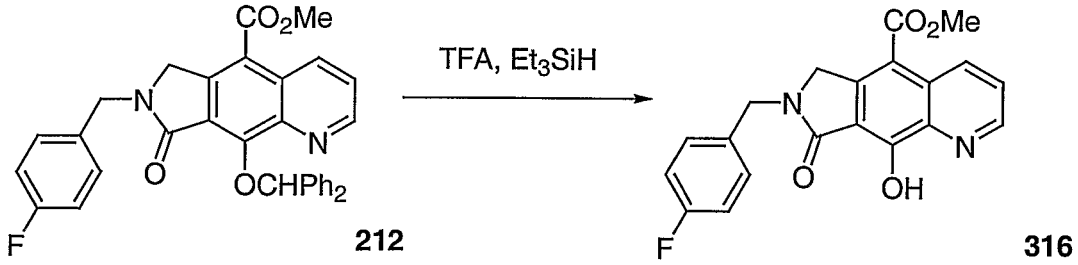
To (2-{[9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-amino}-ethyl)-phosphonic acid diethyl ester **214** (16 mg, 0.023 mmol) dissolved in dichloromethane (0.30 ml) was added trimethylsilylbromide (TMS-Br, 39 mg, 0.25 mmol). After 4 hours of stirring at room temperature, more trimethylsilylbromide (24 mg, 0.16 mmol) was added and the reaction mixture stirred for another 2 hours. The reaction mixture was cooled to 0° C, quenched with methanol (1.0 ml), and concentrated *in vacuo*. It was then triturated three times (3/1 - hexane/ether) and the remaining residue in the flask and filter was dissolved in methanol, combined, and concentrated in vacuo. The residue was dissolved in dimethysulfoxide (0.40 ml), filtered through a glass plug, and purified by reverse-phase preparatory HPLC to provide (2-{[7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-amino}-ethyl)-phosphonic acid **314** (7 mg, 0.012 mmol, 52%). ^{1}H NMR (CD_3OD) δ 8.96 (d, 1H), 8.77 (d, 1H), 7.78 (m, 1H), 7.42 (m, 2H), 7.10 (t, 2H), 4.80 (s, 2H), 4.63 (s, 2H), 3.72 (m, 2H), 2.16 (m, 2H). ^{31}P δ 25.0. ^{19}F δ -78.0, -116.0. MS: 460.1 (M+1).



221 315

Example 315

To 2-[(2-{[7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-amino}-ethyl)-phenoxy-phosphinoyloxy]-propionic acid ethyl ester **221** (15 mg, 0.024 mmol) dissolved in acetonitrile (0.10 ml) and water (0.05 ml) was added 1.0 M NaOH (0.072 ml). The reaction mixture was stirred at room temperature for 3 hours, cooled to 0° C, and quenched with 1.0 M HCl (0.1 ml). The mixture was concentrated in vacuo and the resulting residue was redissolved in dimethylsulfoxide, filtered through a glass plug, and purified by reverse phase preparatory HPLC to afford 2-[(2-{[7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carbonyl]-amino}-ethyl)-hydroxy-phosphinoyloxy]-propionic acid **315** (9 mg, 0.014 mmol, 60 %). ^{1}H NMR (CD_3OD) δ 9.0 (d, 1H), 8.80 (d, 1H), 7.80 (m,1H), 7.42 (M, 2H), 7.10 (t, 2H), 4.80 (d, 2H), 4.62 (s, 2H), 3.75 (m, 2H), 2.20 (m, 2H), 1.46 (d, 3H). ^{31}P δ 27.8. ^{19}F δ -78.0, -118.0. MS: 532.1 (M+1).

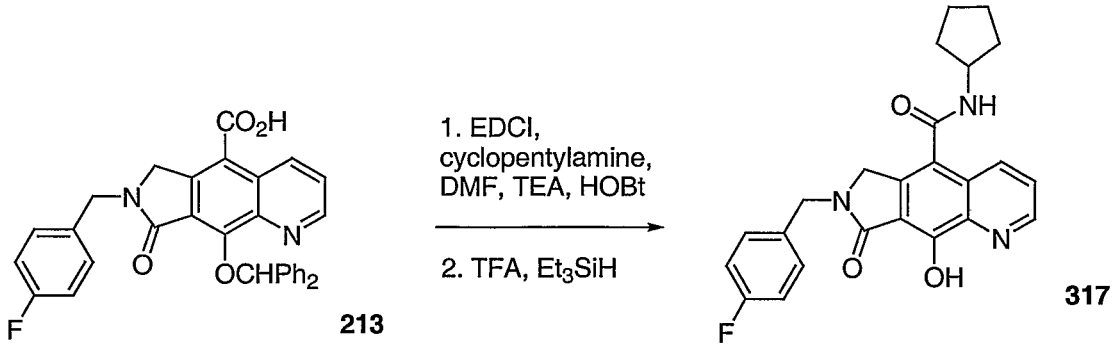


212 316

Example 316

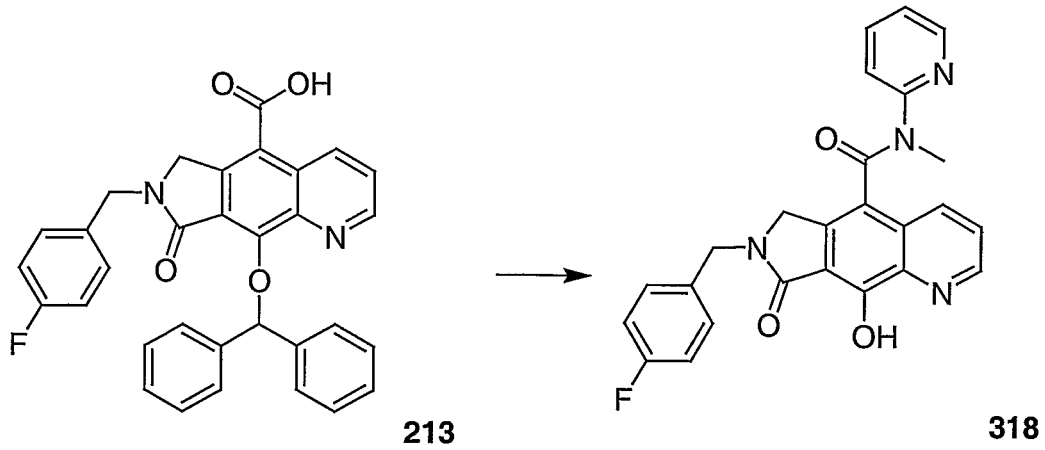
To a solution of 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid methyl ester **212** (3 mg, 0056 mmol) in dichloromethane (1 mL) were added TFA (0.1 mL) and triethylsilane (0.2 mL). Stirring was

continued at the room temperature for 1 hour and the volatiles were evaporated *in vacuo*. The residue was triturated in Et_2O/hexane to afford 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid methyl ester **316** (2.0 mg, 100%) as a yellow solid: ^1H NMR ($CDCl_3$) δ 9.5 (d, 1H), 9.0 (m, 1H), 7.66 (dd, 1H), 7.35 (dd, 2H), 7.0 (t, 2H), 4.8 (s, 2H), 4.7 (s, 2H), 4.0 (s, 3H); MS: 365 (M-1).



Example 317

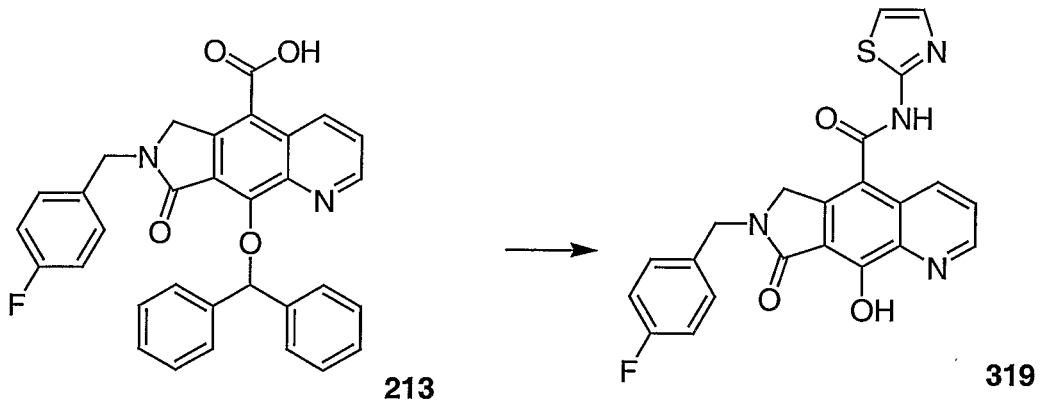
To a solution of 9-benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid **213** (6 mg, 0.0116 mmol) in DMF (0.5 mL) at the room temperature were added triethylamine (TEA, 5 μL, 0.034 mmol), cyclohexylamine (2.3 μL, 0.022 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 4.4 mg, 0.022 mmol) and 1-hydroxybenzotriazole (HOBt, 2.3 mg, 0.0174 mmol). The solution was stirred under a nitrogen atmosphere for 5 hours and diluted with EtOAc. The organic layer was washed with water, 1N aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed on a silica gel column eluting with EtOAc/hexane to afford the protected final product, which was treated in dichloromethane (1 mL) with TFA (0.1 mL) and triethylsilane (0.2 mL) at the room temperature for 1 hour. The volatiles were evaporated *in vacuo* and the residue was triturated in Et_2O/hexane to afford 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid cyclopentylamide **317** (2.6 mg, 54%) as yellow solid. ^1H NMR ($CDCl_3$) δ 8.96 (dd, 1H), 8.53 (d, 1H), 7.62 (dd, 1H), 7.27 (m, 2H), 7.04 (t, 2H), 6.34 (m, 1H), 4.63 (s, 2H), 4.48 (m, 3H), 2.2 (m, 2H), 1.50-1.90 (m, 6H); MS: 418 (M-1).



213 318

Example 318

9-Benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid **213** (0.02 g, 0.0386 mmol) was dissolved in 0.3 mL of dimethylformamide. To this was added 2-methylaminopyridine (0.0079mL, 0.0772 mmol), diisopropylethylamine (0.027mL, 0.1544mmol), *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.03 g, 0.0772 mmol) and stirred at room temperature. After 15 hours, starting material was consumed. Purified by reverse phase HPLC (0.1% TFA, H_2O/ACN) to give 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid methyl-pyridin-2-yl-amide **318** (0.0017 g, 0.003 mmol, 8%.) ^{1}H NMR ($CDCl_3$) δ 9.02 (dd, 1H), 8.50 (d, 1H), 8.18 (d, 1H), 7.65 (dd, 1H), 7.38 (m, 5H), 7.08 (dd, 2H), 4.94 (dd, J=15Hz, 11Hz, 2H), 4.49 (d, J=17Hz, 1H), 4.19 (d, J=17Hz, 1H), 3.61 (s, 3H.) MS: 443 (M+1).

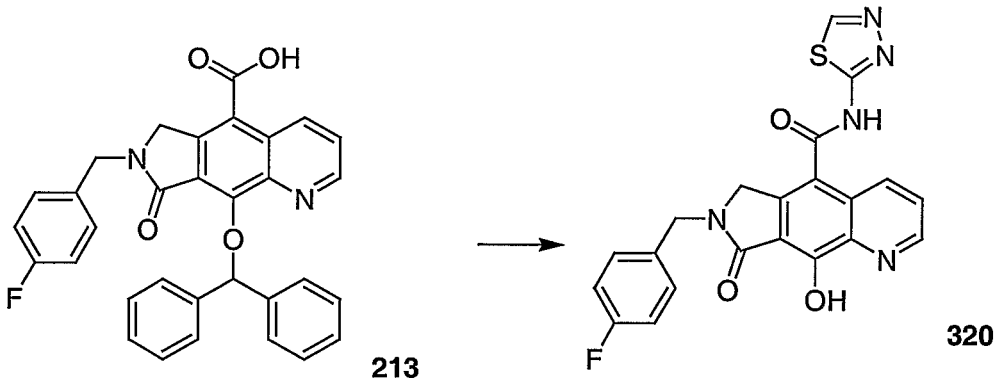


213 319

Example 319

9-Benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid **213** (0.02g, 0.0386mmol) was dissolved in 0.3 mL of

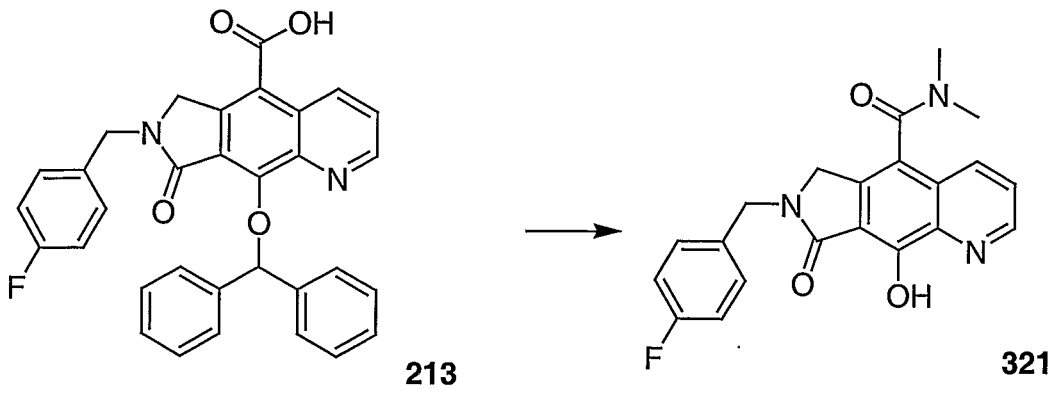
dimethylformamide. To this was added 2-aminothiazole (0.0077mL, 0.0772 mmol), diisopropylethylamine (0.027mL, 0.1544mmol), *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.03 g, 0.0772 mmol) and stirred at room temperature. After 15 hours, starting material was consumed. Purified by reverse phase HPLC (0.1% TFA, H_2O/ACN) to give 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid thiazol-2-ylamide **319** (0.01 g, 0.023 mmol, 60%.) ^{1}H NMR ($CDCl_3$) δ 9.02 (dd, 1H), 8.61 (d, 1H), 7.65 (dd, 1H), 7.55 (d, 1H), 7.38 (dd, 2H), 7.21 (d, 1H), 7.07 (dd, 2H), 4.78 (s, 2H), 4.67 (s, 2H.) MS: 435 (M+1).



213 **320**

Example 320

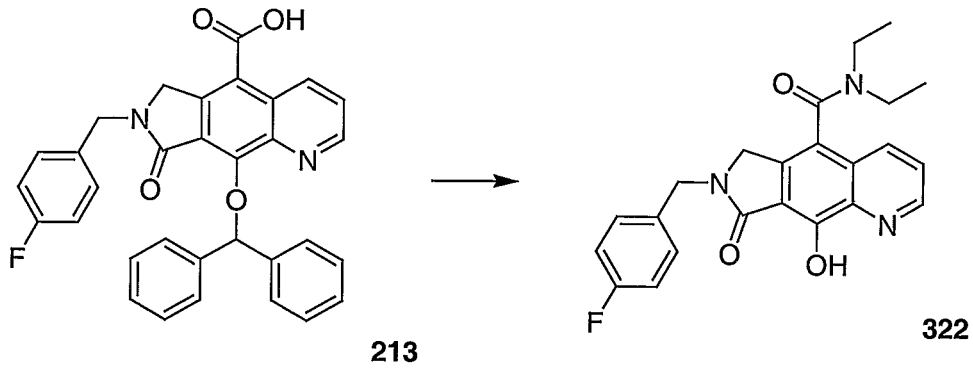
9-Benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid **213** (0.02g, 0.0386mmol) was dissolved in 0.3 mL of dimethylformamide. To this was added 2-amino-1,3,4-thiadiazole (0.0078mL, 0.0772 mmol), diisopropylethylamine (0.027mL, 0.1544mmol), *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.03 g, 0.0772 mmol) and stirred at room temperature. After 15 hours, starting material was consumed. Purified by reverse phase HPLC (0.1% TFA, H_2O/ACN) to give 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid [1,3,4]thiadiazol-2-ylamide **320** (0.0066 g, 0.015 mmol, 40%.) ^{1}H NMR ($CDCl_3$) δ 9.02 (dd, 1H), 8.81 (s, 1H), 8.65 (d, 1H), 7.65 (dd, 1H), 7.38 (dd, 2H), 7.05 (dd, 2H), 4.74 (s, 2H), 4.64 (s, 2H.) MS: 436 (M+1).



213 321

Example 321

9-Benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid **213** (0.02g, 0.0386mmol) was dissolved in 0.3 mL of dimethylformamide. To this was added dimethylamine (2M in THF) (0.0386 mL, 0.0772 mmol), diisopropylethylamine (0.027 mL, 0.1544 mmol), *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.03 g, 0.0772 mmol) and stirred at room temperature. After 15 hours, starting material was consumed. Purified by reverse phase HPLC (0.1% TFA, H_2O/ACN) to give 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid dimethylamide **321** (0.014 g, 0.037 mmol, 97%.) ^{1}H NMR ($CDCl_3$) δ 9.07 (dd, 1H), 8.18 (d, 1H), 7.65 (dd, 3H), 7.03(dd, 2H), 4.79 (dd, 2H), 4.53 (d, J=17Hz, 1H), 4.25 (d, J=17Hz, 1H), 3.24 (s, 3H), 3.21 (s, 3H.) MS: 380 (M+1).



213 322

Example 322

9-Benzhydryloxy-7-(4-fluoro-benzyl)-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid **213** (0.02g, 0.0386mmol) was dissolved in 0.3 mL of dimethylformamide. To this was added diethylamine (0.0056 mL, 0.0772 mmol), diisopropylethylamine (0.027 mL, 0.1544 mmol), *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-

tetramethyluronium hexafluorophosphate (0.03 g, 0.0772 mmol) and stirred at room temperature. After 15 hours, starting material was consumed. Purified by reverse phase HPLC (0.1% TFA, H_2O/ACN) to give 7-(4-fluoro-benzyl)-9-hydroxy-8-oxo-7,8-dihydro-6H-pyrrolo[3,4-g]quinoline-5-carboxylic acid diethylamide **322** (0.0134g, 0.033mmol, 86%.) ^{1}H NMR ($CDCl_3$) δ 9.07 (dd, 1H), 8.18 (d, 1H), 7.65 (m, 3H), 7.07(dd, 2H), 4.72 (dd, 2H), 4.56 (d, J=17Hz, 1H), 4.23 (d, J=17Hz, 1H), 3.66 (q, 2H), 3.11 (q, 2H), 1.35 (t, 3H), 0.965 (t, 3H.) MS: 408 (M+1).

Example 323 HIV Integrase Assay (IC_{50} determination)

IC50 is the inhibitory concentration that reduces the strand transfer activity of recombinant integrase by 50%.

HIV Integrase assay was carried out in Reacti-Bind High Binding Capacity Streptavidin coated plates (Pierce # 15502) in 100 μl reactions following the method of Hazuda etal *Nucleic Acids Res.* (1994) 22:1121-22. The wells of the plate are rinsed once with PBS. Each well is then coated at room temperature for 1 h with 100 μl of 0.14 μM double-stranded donor DNA of Hazuda etal.

After coating, the plate was washed twice with PBS. 3'processing of the donor DNA is started by adding 80 μl of Integrase/buffer mixture (25 mM HEPES, pH 7.3, 12.5 mM DTT, 93.75 mM NaCl, 12.5 mM $MgCl_2$, 1.25% Glycerol, 0.3125 μM integrase) to each well. 3'-Processing was allowed to proceed for 30 min at 37 °C, after which, 10 μl of test compound and 10 μl of 2.5 μM digoxigenin (DIG)-labeled, double-stranded Target DNA, according to Hazuda etal, were added to each well to allow strand transfer to proceed for 30 min at 37 °C. The plate was then washed three times with 2X SSC for 5 min and rinsed once with PBS. For detection of integrated product, 100 μl of a 1/2000 dilution of HRP-conjugated anti-DIG antibody (Pierce #31468) were added to each well and incubated for 1 hour. The plate was then washed three times for 5 min each, with 0.05% Tween-20 in PBS. For signal development and amplification, 100 μl of SuperSignal ELISA Femto Substrate (Pierce #37075) were added to each well. Chemiluminescence (in relative light units) was read immediately at 425 nm in the SPECTRAmax GEMINI Microplate Spectrophotometer using the end point mode at 5 sec per well. For IC_{50} determinations, eight concentrations of test compounds in a 1/2.2 dilution series were used. Certain compounds of the invention, including those in Tables 1-5, had a strand transfer IC_{50} less than about 10 μM.

Example 324 Anti-HIV Assay (EC_{50} determination)

EC50 (also commonly referred to as ED50 or IC50) is the effective concentration that inhibits 50% of viral production, 50% of viral infectivity, or 50% of the virus-induced cytopathic effect.

Anti-HIV assay was carried out in 96-well Clear Bottom Black Assay Plate (Costar # 3603) in 100 μl of culture medium, using the CellTiter-Glo™ Reagent (Promega # G7570) for signal detection. MT-2 cells (1.54×10^4 cells) were infected with wild-type virus at an m.o.i. of about 0.025, and grown in the presence of various drug concentrations (serial 5-fold dilutions) in 100 μl of RPMI medium containing 10% FBS, 2% glutamine, 1% HEPES and 1% penicillin/streptomycin for 5 days. At the end of the incubation period, 100 μl of CellTiter-Glo™ Reagent was added to each well in the Assay Plate and the chemiluminescence (in relative light units) was measured after 10 mins of incubation with the Wallac Victor^2 1420 MultiLabel Counter. Certain compounds of the invention, including those in Tables 1-5, had an anti-HIV MT2 EC_{50} less than about 10 μM.

Example 325 Cytotoxicity Assay (CC_{50} determination)

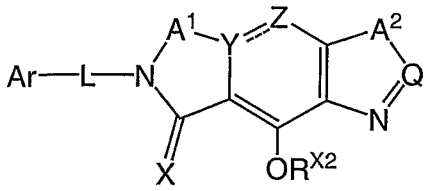
For the determination of compound cytotoxicity, the plate and reagents are the same as those of anti-HIV assay. Uninfected MT-2 cells (1.54×10^4 cells)were grown in the presence of various drug concentrations (serial 3-fold dilutions) in 100 μl of RPMI medium containing 10% FBS, 2% glutamine, 1% HEPES and 1% penicillin/streptomycin for 5 days. At the end of the incubation period, 100 μl of CellTiter-Glo™ Reagent was added to each well in the assay plate and the chemiluminescence (in relative light units) was measured after 10 mins of incubation with the Wallac Victor^2 1420 MultiLabel Counter. Certain compounds of the invention, including those in Tables 1-5, had cytotoxicity MT2 CC_{50} less than about 10 μM.

The foregoing specification teaches the principles of the present invention, with Examples provided for the purpose of illustration, and fully discloses how to make and use the present invention. The invention is not limited to the particular embodiments described herein but includes all modifications within the scope of the appended claims and their equivalents. Those skilled in the art will recognize through routine experimentation that various changes and modifications can be made without departing from the scope of this invention.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and fully set forth.

We claim:

1. A compound having the structure:



wherein:

A^1 and A^2 are 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;

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

Y=Z is ;

L is selected from a bond, O, S, S–S, S(=O), $S(=O)_2$, $S(=O)_2NR$, 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, 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;

X is selected from O, S, NH, NR, N–OR, $N–NR_2$, $N–CR_2OR$ and $N–CR_2NR_2$;

Ar is selected from 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;

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

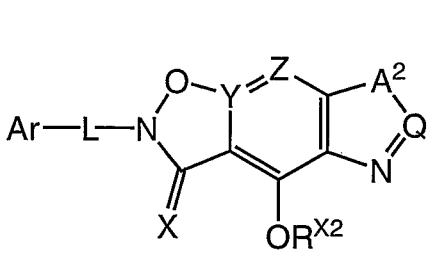
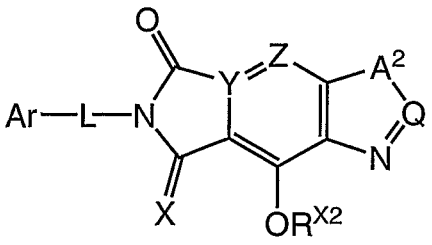
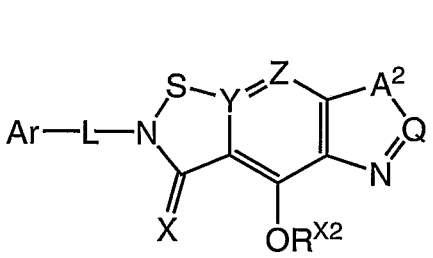
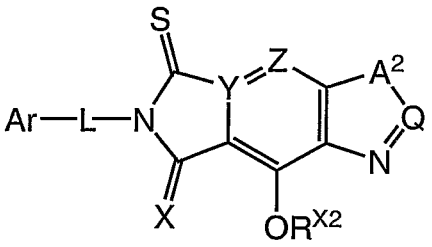
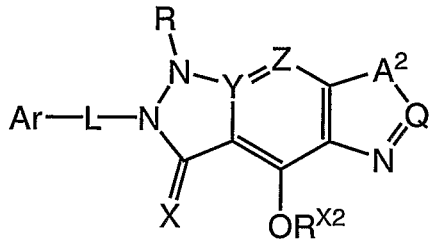
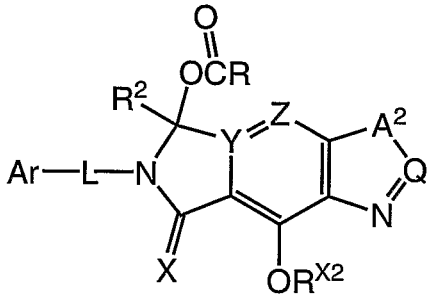
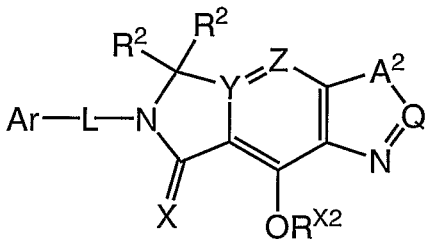
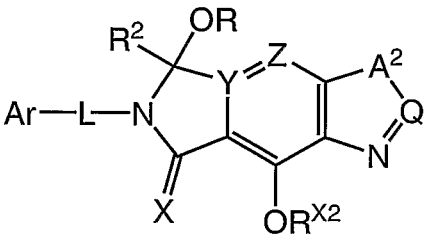
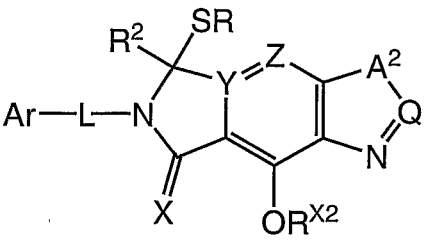
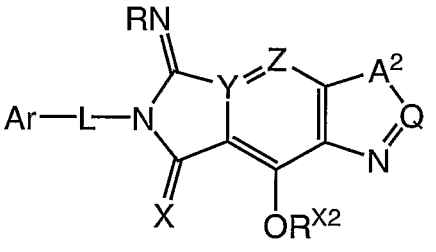
R is independently selected from H, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl, polyethyleneoxy, phosphonate, phosphate, and a prodrug moiety;

R^{X2} is independently selected from H, 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, polyethyleneoxy, phosphonate, phosphate, a prodrug, a pharmaceutically acceptable prodrug, a prodrug moiety, a protecting group, and a phosphonate prodrug moiety;

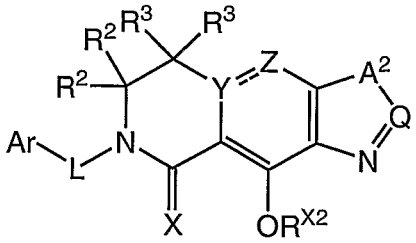
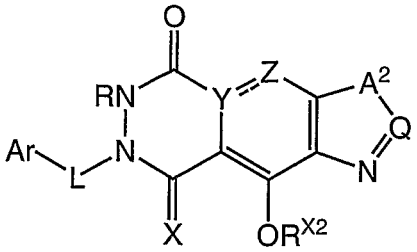
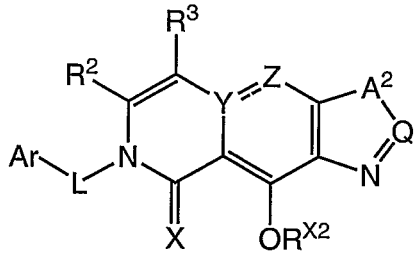
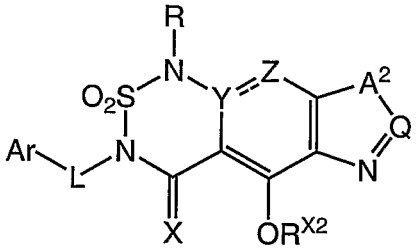
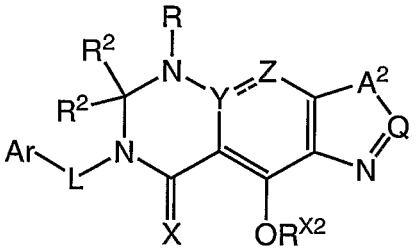
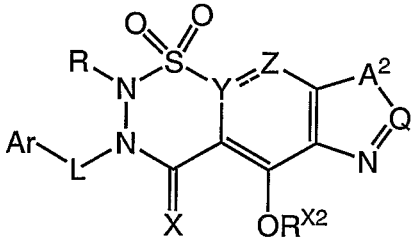
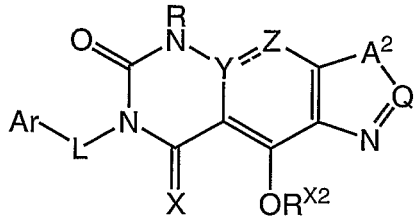
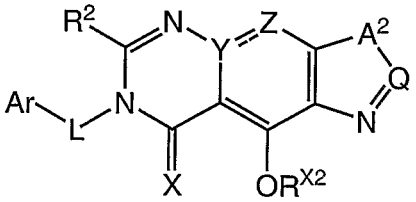
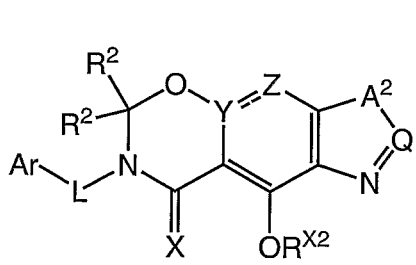
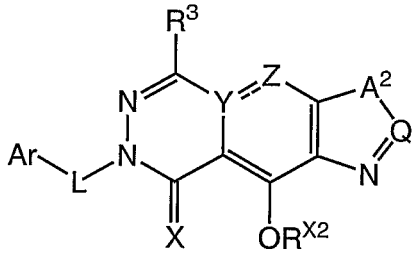
and the salts, solvates, resolved enantiomers and purified diastereomers thereof;

with the proviso that when Y=Z is C=C(OH), X is O, A^1 is C(=O), A^2 is $C(R^2)=C(R^3)$, and Q is CH, then L is not a bond.

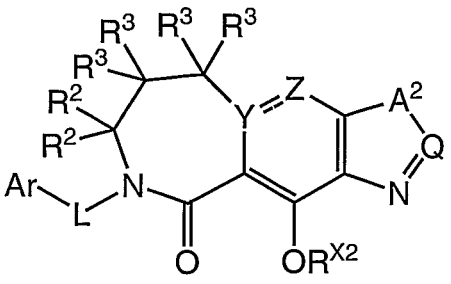
2. A compound of claim 1 selected from the structures:

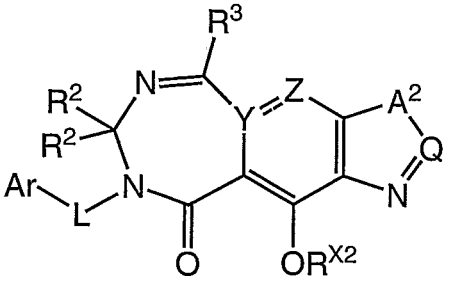









and


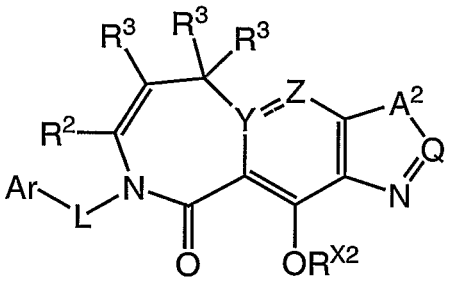
3. A compound of claim 1 selected from the structures:

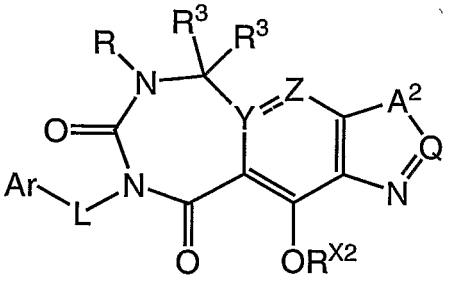









and


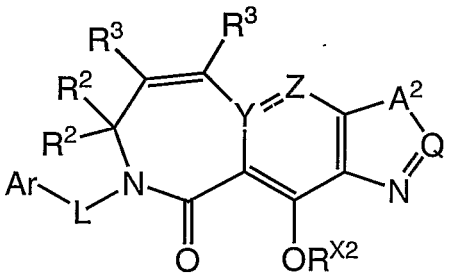
4. A compound of claim 1 selected from the structures:

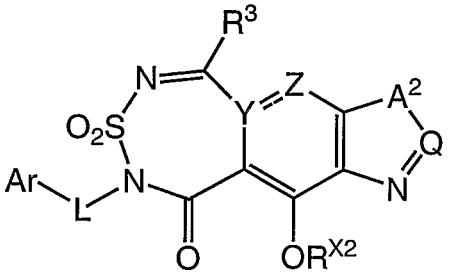




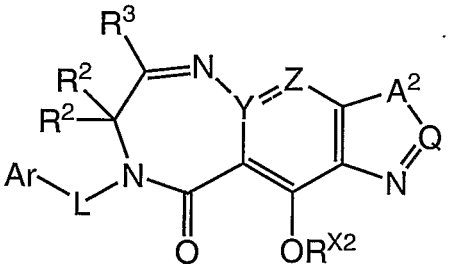




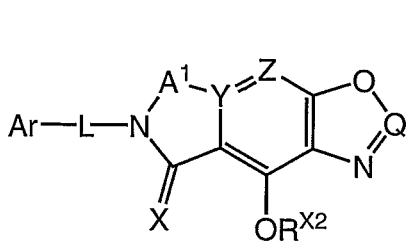


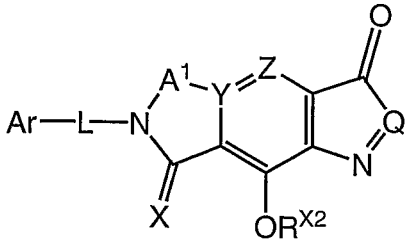


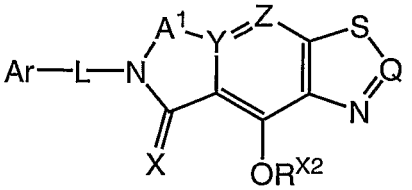
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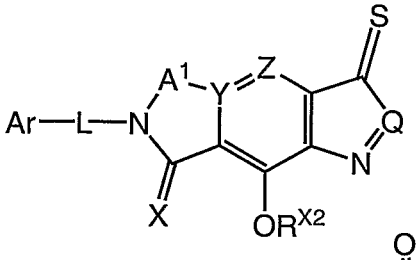


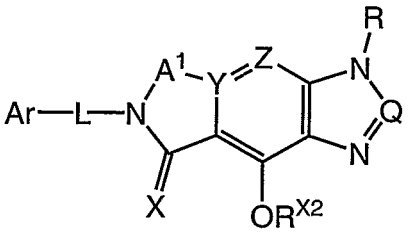
5. A compound of claim 1 selected from the structures:

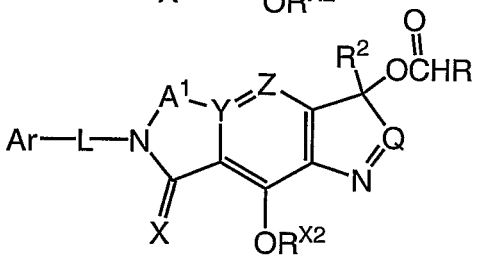


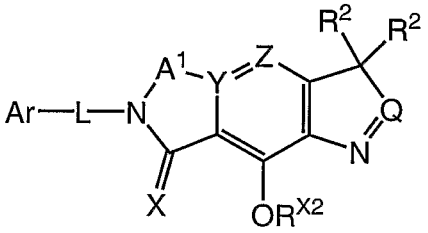


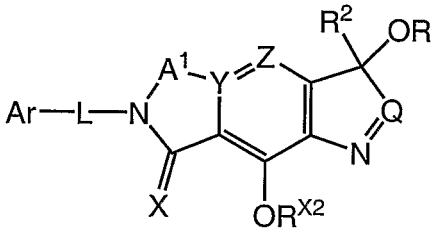




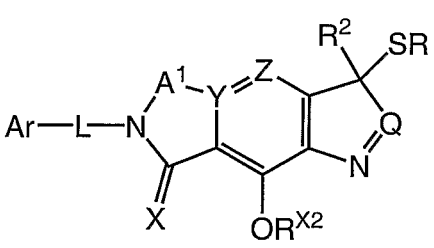


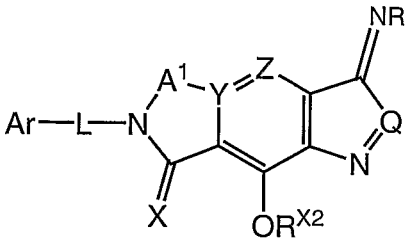




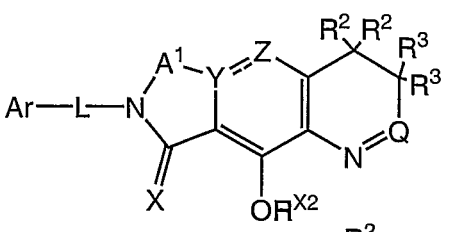


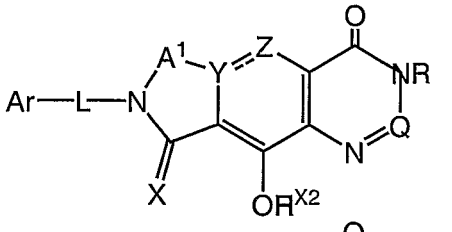
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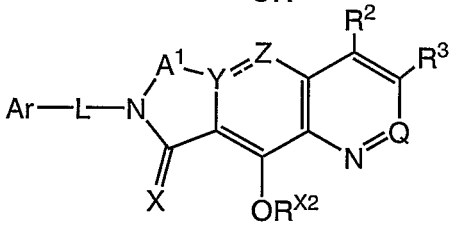


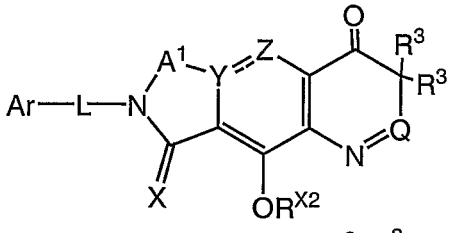


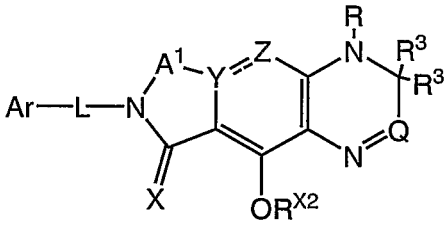
6. A compound of claim 1 selected from the structures:

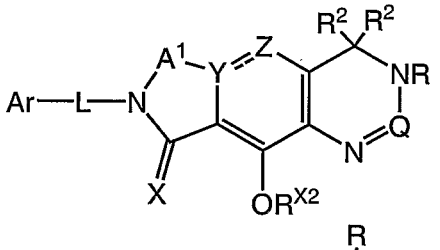


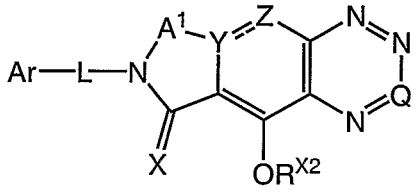


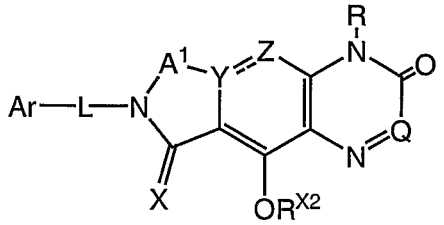




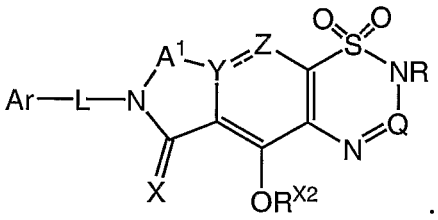






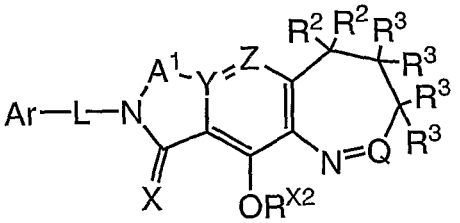


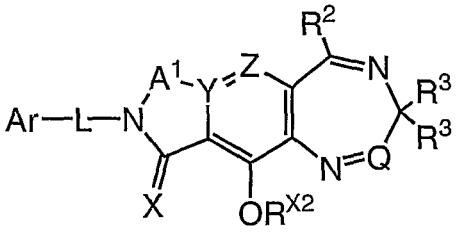
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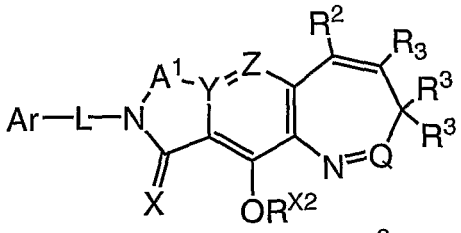


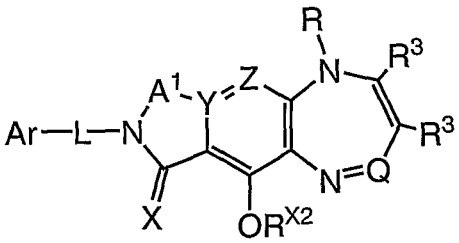
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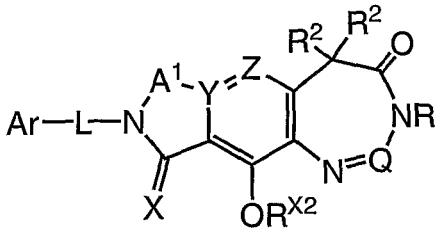
7. A compound of claim 1 selected from the structures:

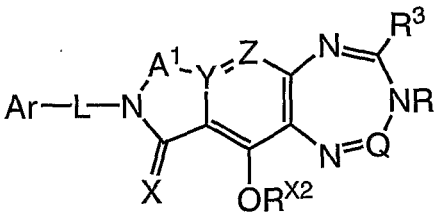




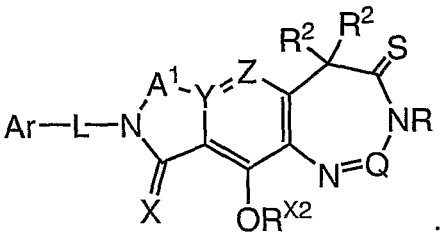






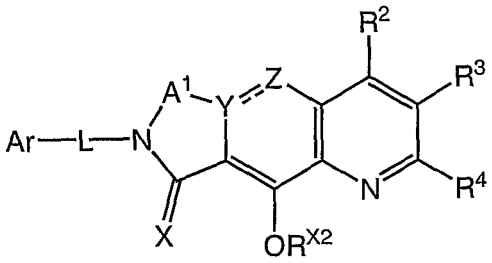


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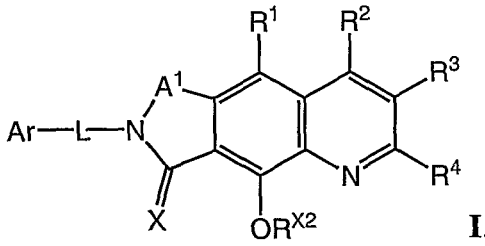


.

8. A compound of claim 6 having the structure:

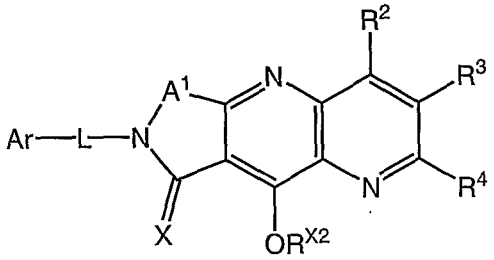


9. A compound of claim 6 having Formula I:



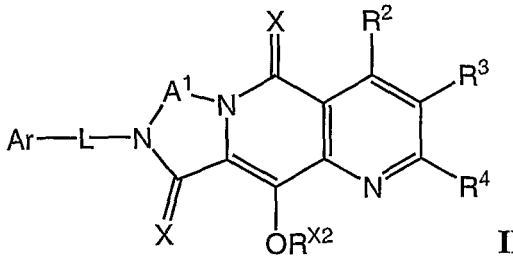
I.

10. A compound of claim 6 having Formula II:



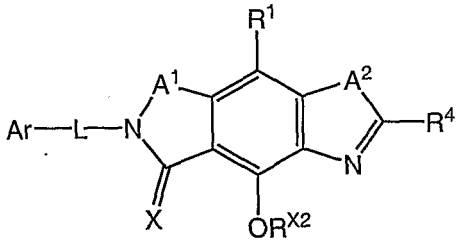
II.

11. A compound of claim 6 having Formula III:



III.

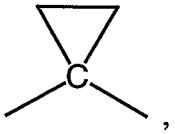
12. A compound of claim 1 having Formula IV:



IV.

13. A compound of claim 1 comprising at least one phosphonate group.

14. A compound of claim 1 wherein substituted alkyl, substituted alkylene, substituted alkyenylene, substituted alkynylene, substituted carbocycle, substituted aryl, and substituted heteroaryl are independently substituted with one or more substituents selected from 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_3-C_{12} carbocycle, C_6-C_{20} aryl, C_2-C_{20} heteroaryl, polyethyleneoxy, phosphonate, phosphate, and a prodrug moiety.

15. The compound of claim 1 wherein A^1 is CH_2, $C(CH_3)_2$, , CH_2-CH_2, $C(CH_3)_2-CH_2$, or $CH_2-CH_2-CH_2$.

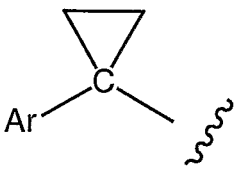
16. The compound of claim 9 wherein X is O; L is CH_2; and Ar is substituted phenyl.

17. The compound of claim 16 wherein Ar is 4-fluorophenyl.

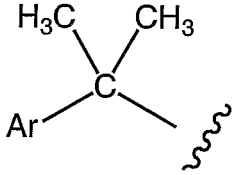
18. The compound of claim 9 wherein X is O; and R^2, R^3 and R^4 are each H.

19. The compound of claim 9 wherein X is O; A^1 is CH_2; and R^2, R^3 and R^4 are each H.

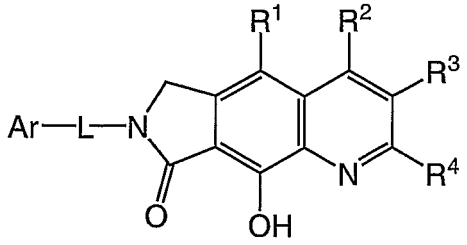
20. The compound of claim 1 wherein Ar-L is selected from the structures:



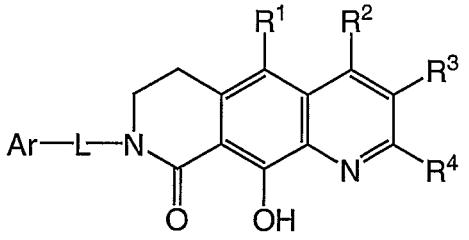
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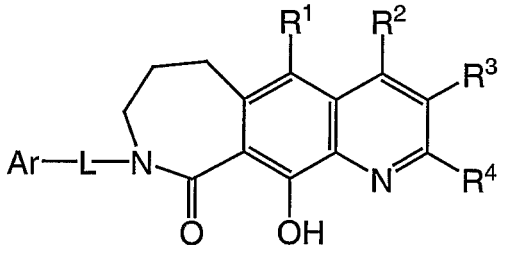
21. A compound of claim 9 comprising Formula Ia, Ib, or Ic:



Ia

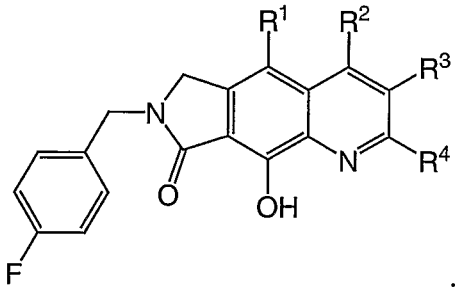


Ib

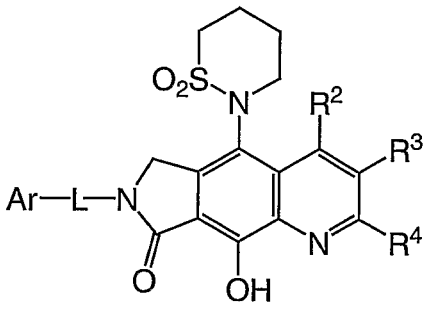


Ic .

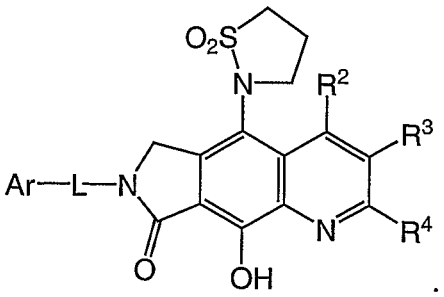
22. A compound of claim 9 having the structure:



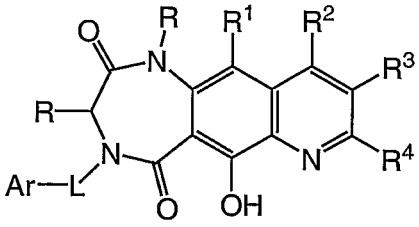
23. A compound of claim 22 selected from the structures:



and

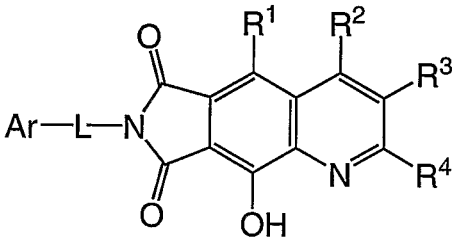


24. A compound of claim 9 having Formula Id:



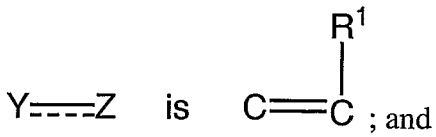
Id .

25. A compound of claim 9 having the structure:



with the proviso that when R^1 is OH, and R^2, R^3, and R^4 are H, then L is not a bond.

26. A compound of claim 1 wherein

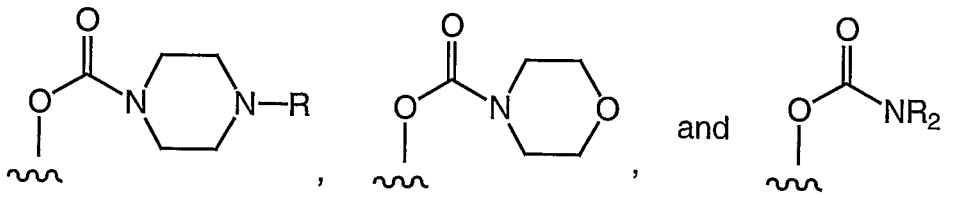


; and

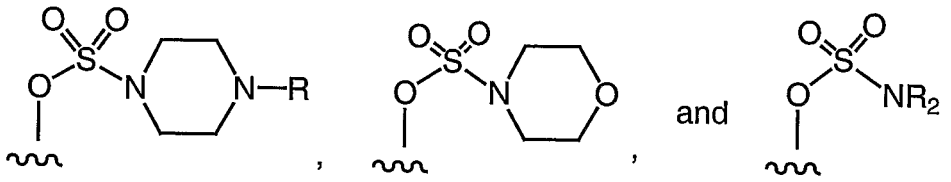
R^1 is CR_3, $C(=O)NR_2$, $OC(=O)OR$, $OC(=O)NR_2$, $OC(=O)R$, OSO_2NR_2 (sulfamate), NR_2, $NRSO_2R$, SR, $S(O)R$, SO_2R or SO_2NR_2 (sulfonamide).

27. The compound of claim 26 wherein at least one R comprises a prodrug moiety.

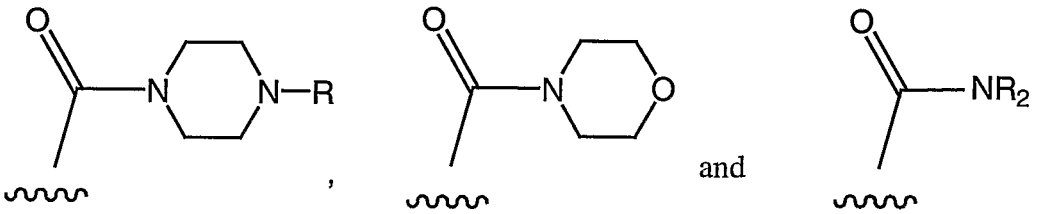
28. A compound of claim 1 wherein at least one of R^1, R^2, R^3, and R^4 is selected from the structures:



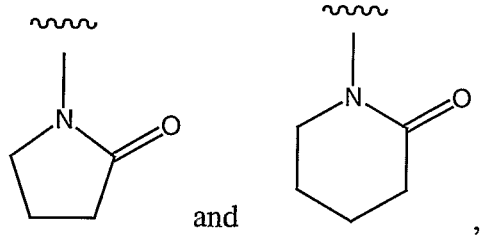
29. A compound of claim 1 wherein at least one of R^1, R^2, R^3, and R^4 is selected from the structures:



30. A compound of claim 1 wherein at least one of R^1, R^2, R^3, and R^4 is selected from the structures:

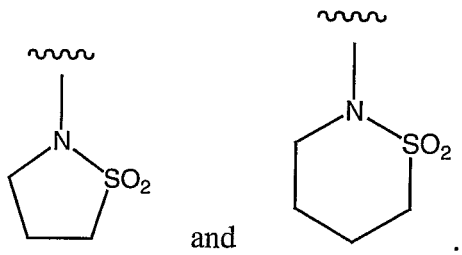


31. A compound of claim 1 wherein at least one of R^1, R^2, R^3, and R^4 comprise a lactam having the structures:

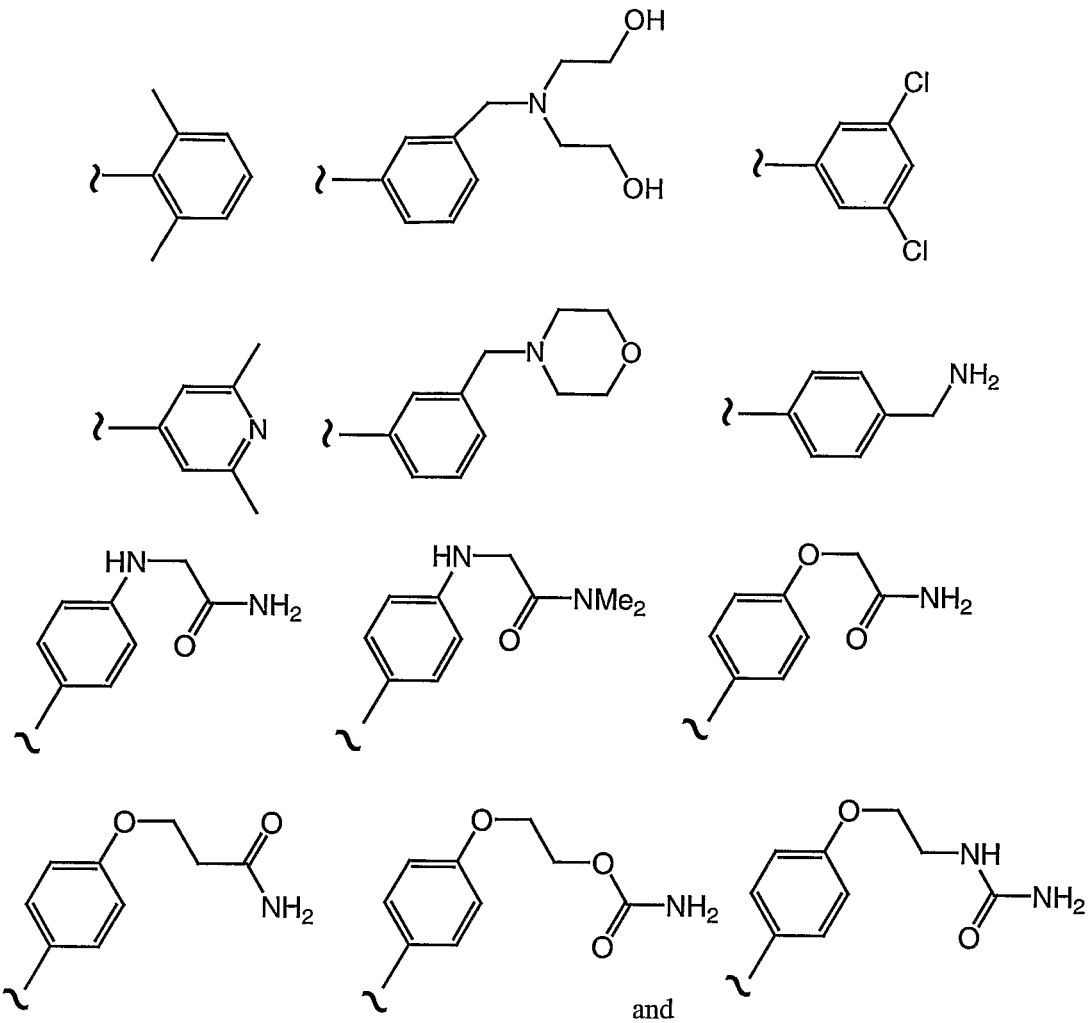


, or

a sultam having the structures:



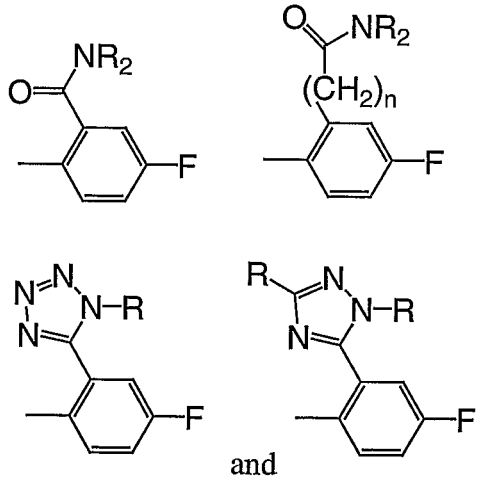
32. A compound of claim 1 wherein Ar is selected from the structures:



and

where the wavy line ~ indicates the covalent attachment site to L.

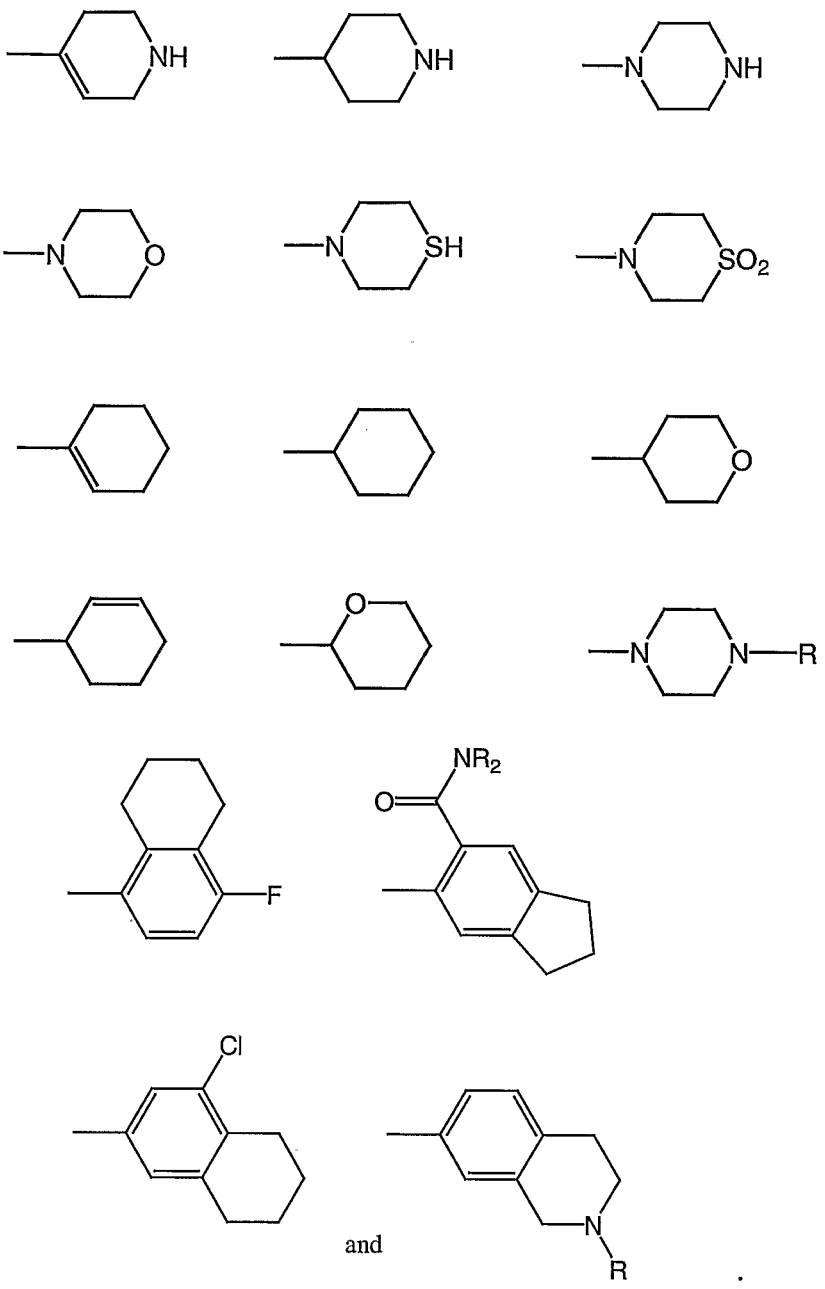
33. A compound of claim 1 wherein Ar is selected from the structures:



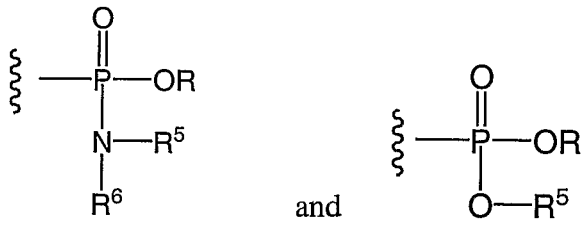
and

where n is 1 to 6.

34. A compound of claim 1 wherein Ar is selected from the structures:

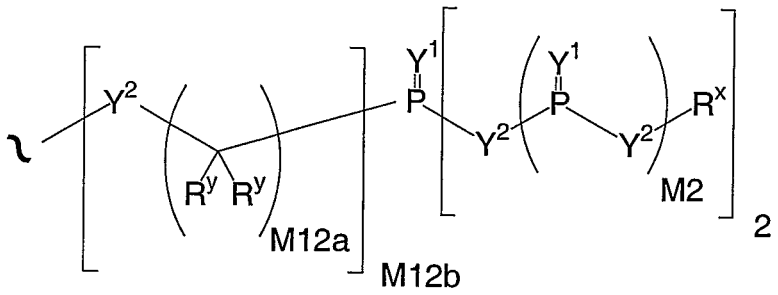


35. A compound of claim 1 comprising a prodrug moiety selected from the structures:



wherein R^5 is $-CR_2CO_2R^7$ where R^6 and R^7 are independently H or C_1–C_8 alkyl.

36. The compound of claim 1 comprising a phosphonate or prodrug moiety having the structure:



wherein:

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

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

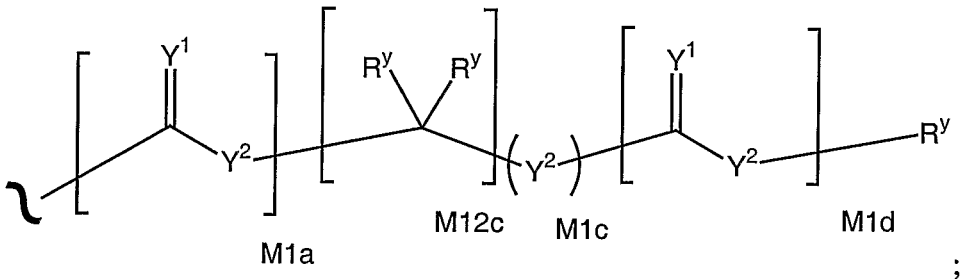
M2 is 0, 1 or 2;

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

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

R^y is independently H, C_1–C_6 alkyl, C_1–C_6 substituted alkyl, 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; and

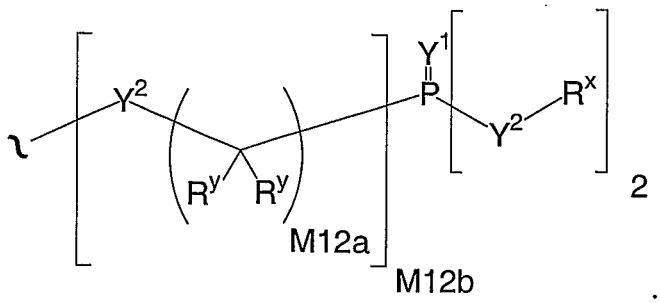
R^x is independently H, C_1–C_6 alkyl, C_1–C_6 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, or a protecting group, or the formula:



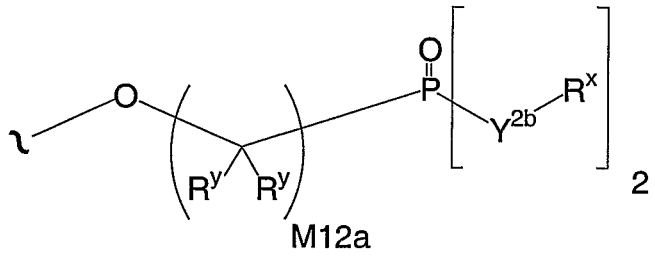
;

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.

37. The compound of claim 36 wherein the phosphonate or prodrug moiety has the structure:

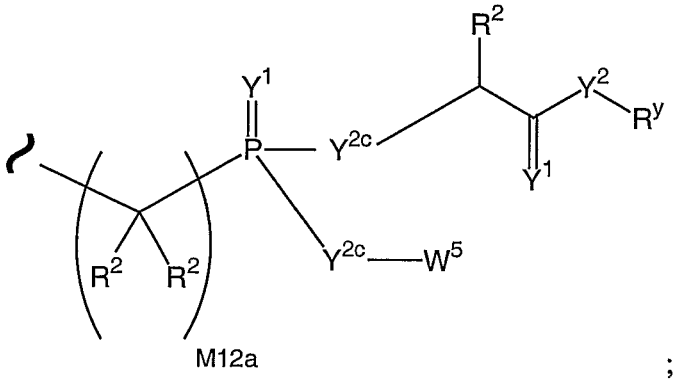


38. The compound of claim 37 wherein the phosphonate or prodrug moiety has the structure:



where Y^{2b} is O or $N(R^x)$.

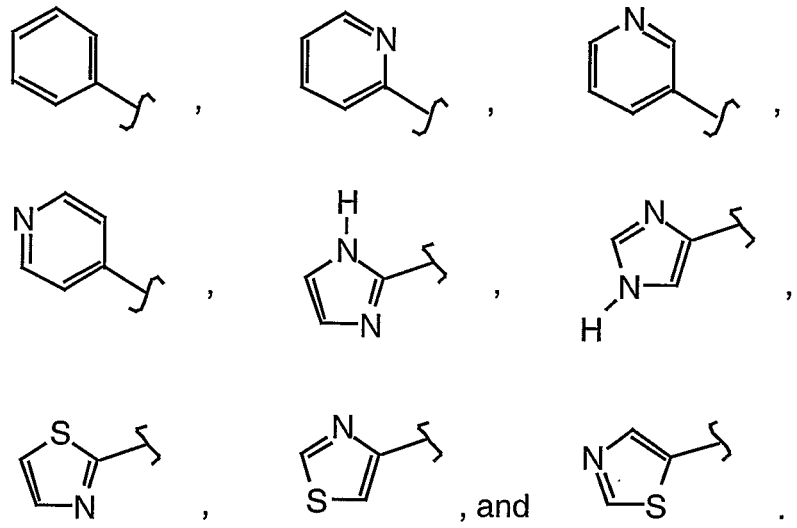
39. The compound of claim 37 wherein the phosphonate or prodrug moiety has the structure:



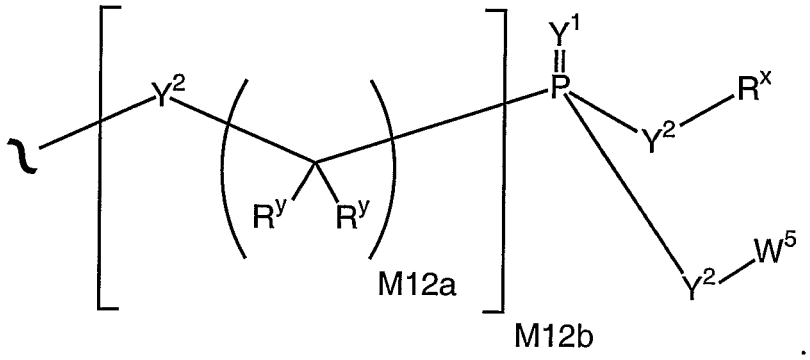
;

where W^5 is a carbocycle, and Y^{2c} is O, $N(R^y)$ or S.

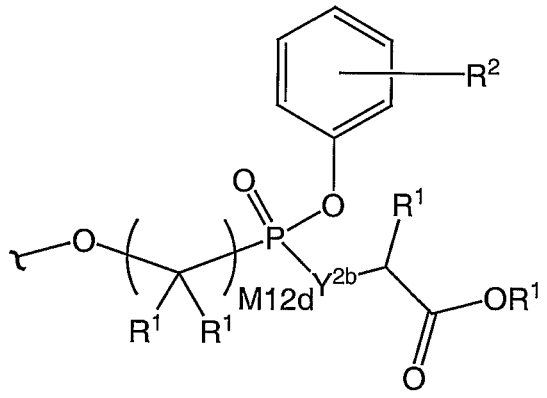
40. The compound of claim 39 wherein W^5 is selected from the structures:



41. The compound of claim 37 wherein the phosphonate or prodrug moiety has the structure:

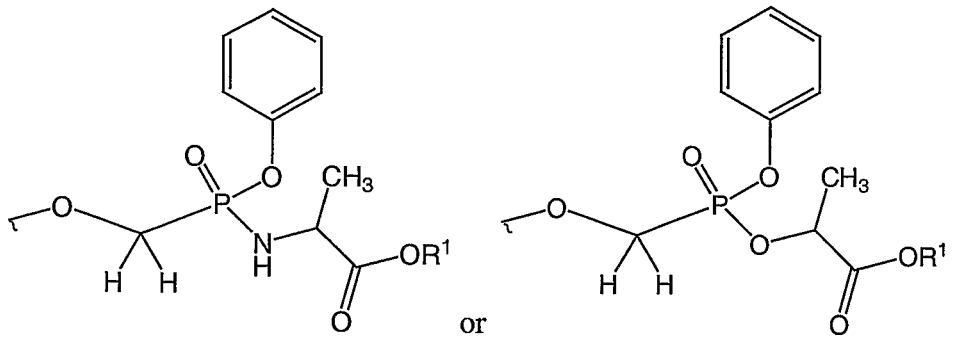


42. The compound of claim 41 wherein the phosphonate or prodrug moiety has the structure:



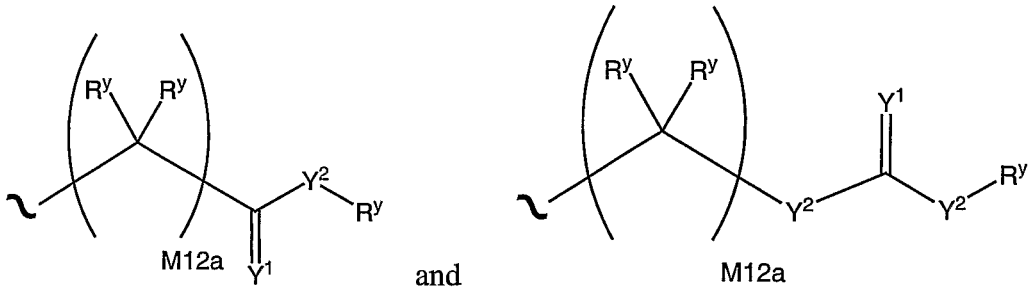
wherein Y^{2b} is O or $N(R^x)$; M12d is 1, 2, 3, 4, 5, 6, 7 or 8; R^1 is H or C_1–C_6 alkyl; and the phenyl carbocycle is substituted with 0 to 3 R^2 groups where R^2 is C_1–C_6 alkyl or substituted alkyl.

43. The compound of claim 42 wherein the phosphonate or prodrug moiety has the structure:



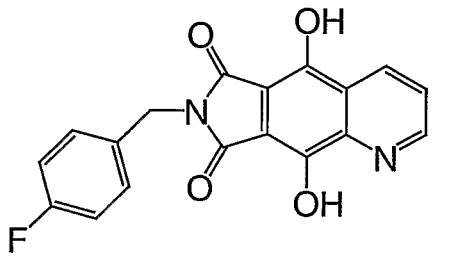
or

44. The compound of claim 36 wherein R^x is selected from the structures:

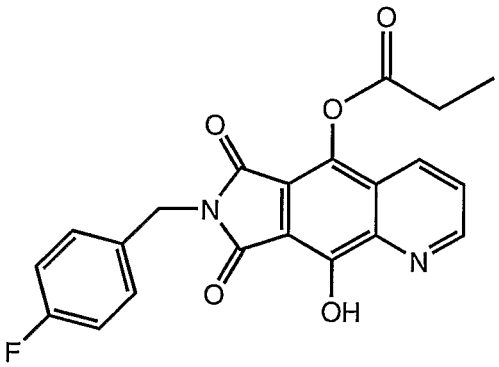


and

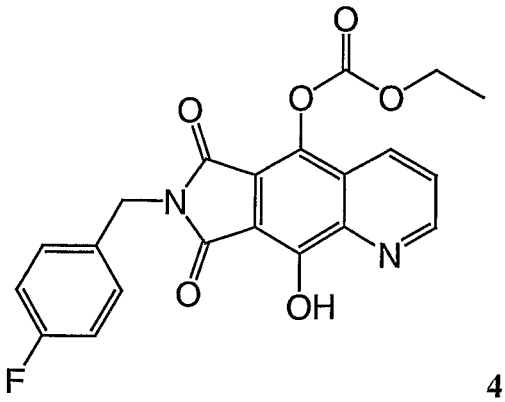
45. A compound of claim 9 selected from the structures:



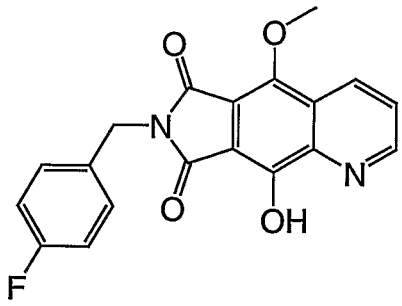
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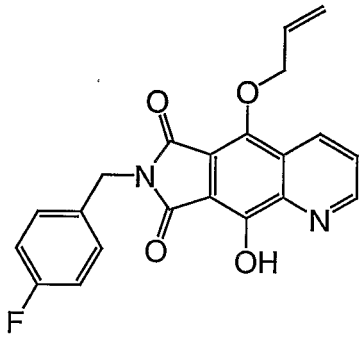
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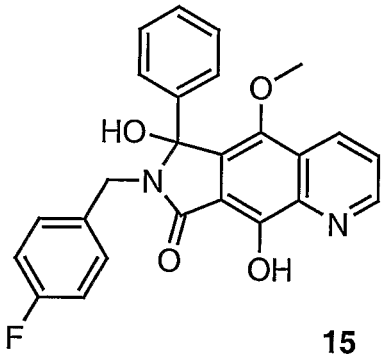
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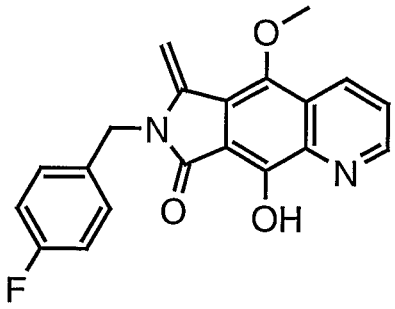
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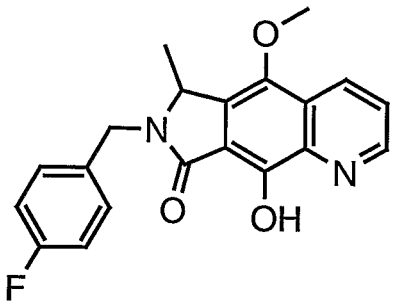
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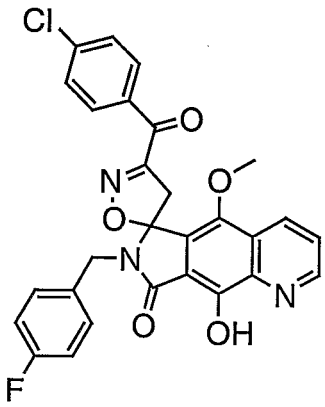
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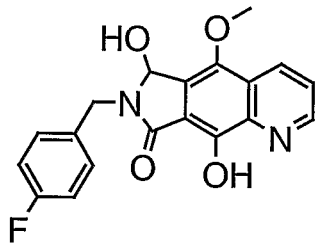
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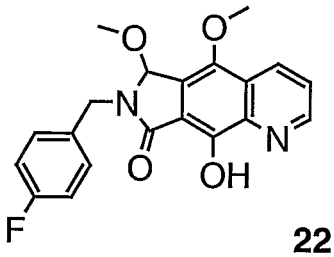
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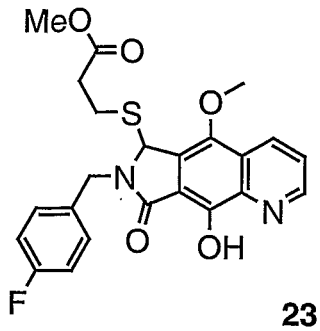
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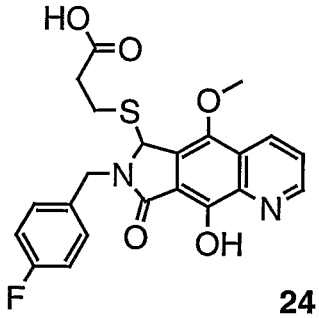
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22

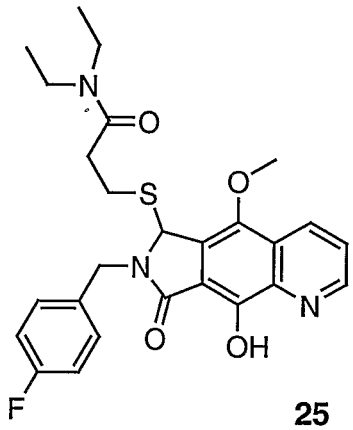


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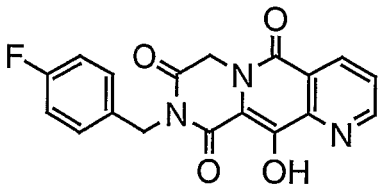
24

and



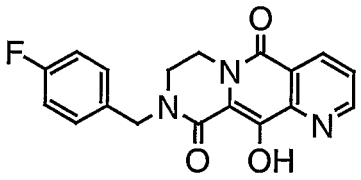
25

46. A compound of claim 11 selected from the structures:



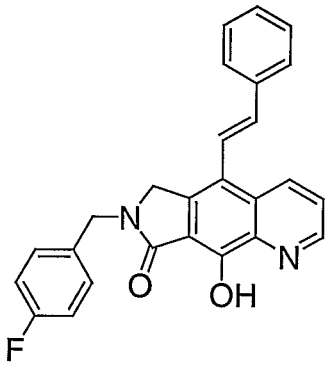
32

and

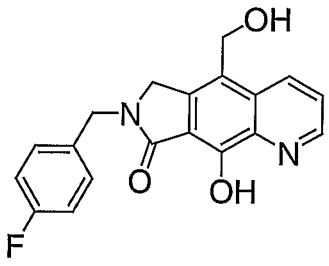


37

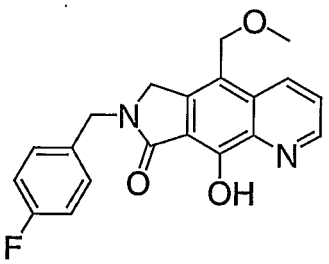
47. A compound of claim 9 selected from the structures:



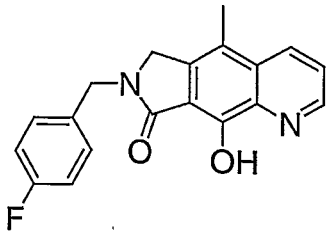
48



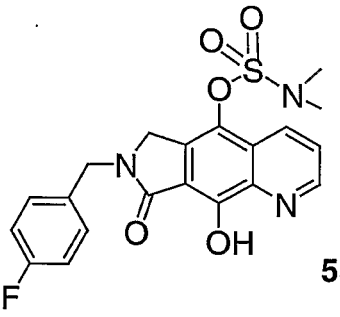
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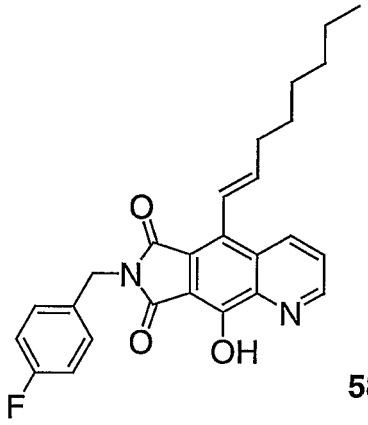
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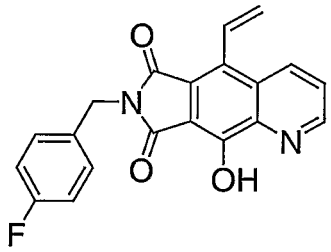
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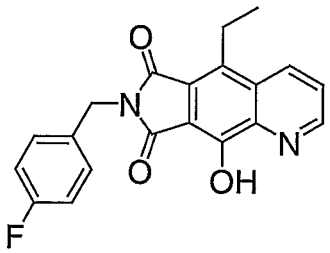
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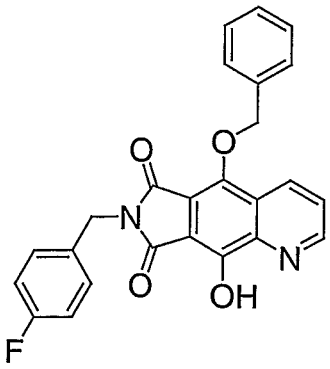
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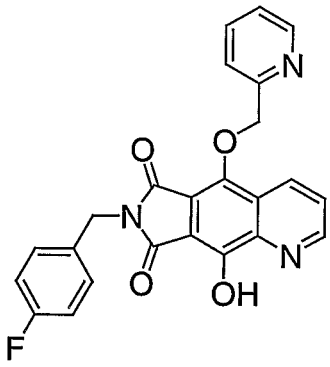
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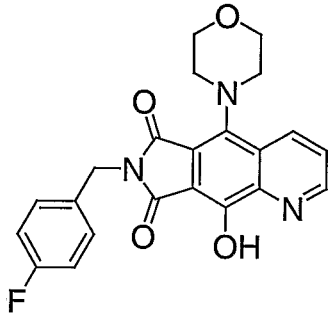
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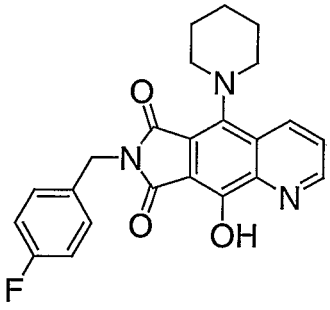
64



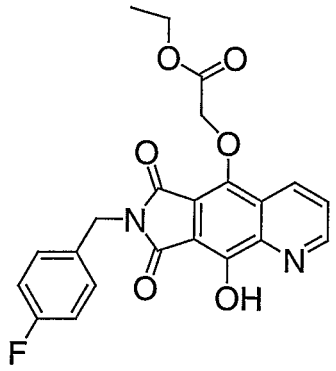
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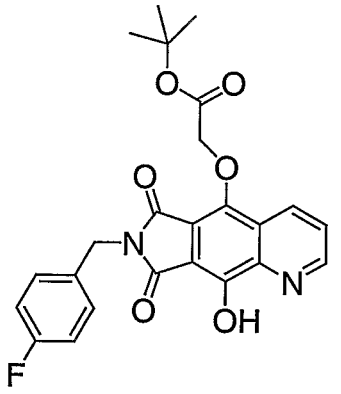
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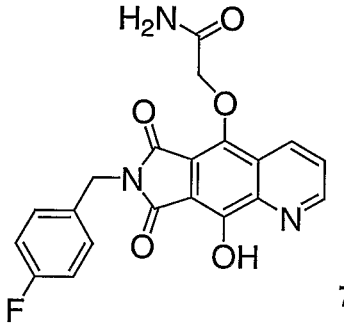
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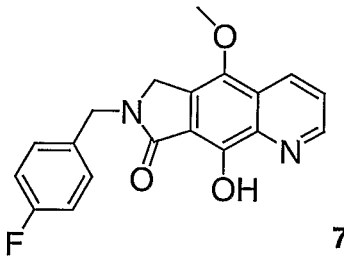
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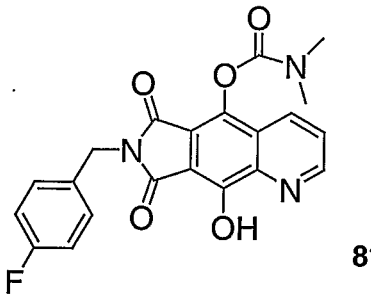
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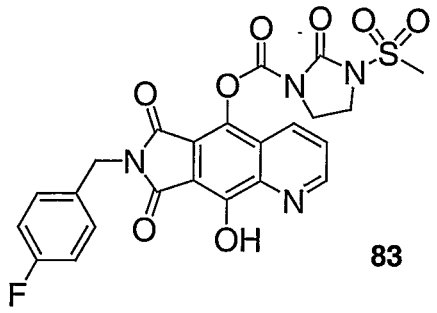
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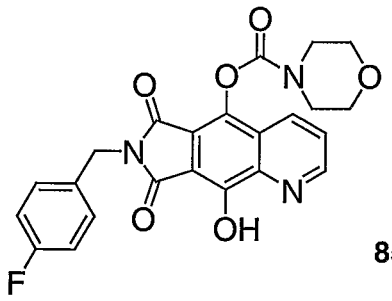
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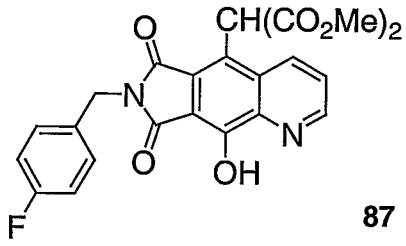
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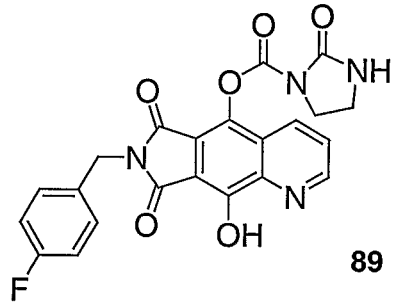
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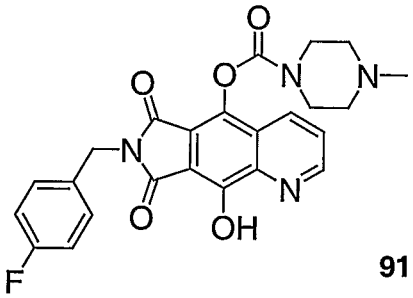
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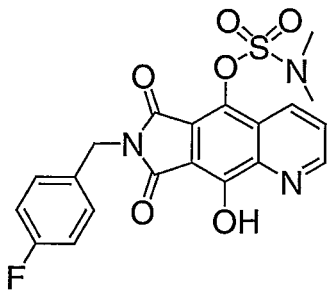
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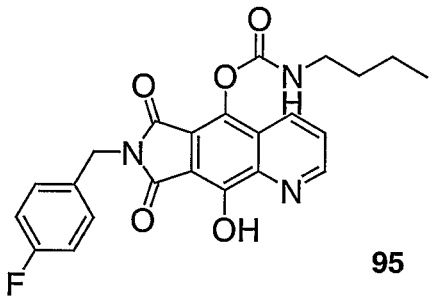
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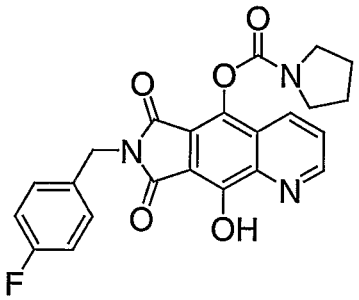
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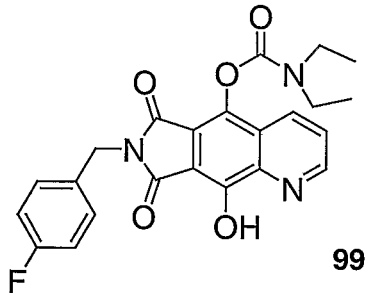
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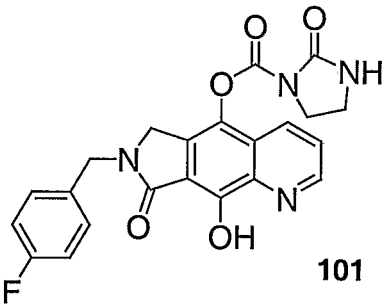
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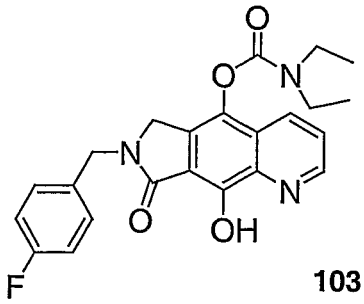
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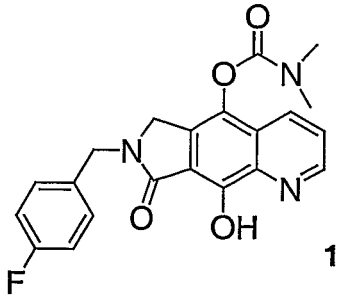
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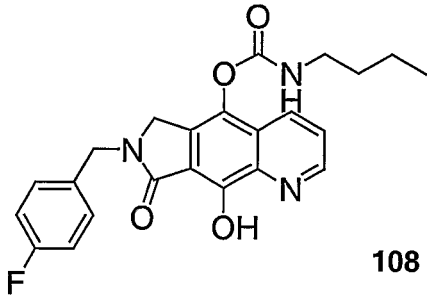
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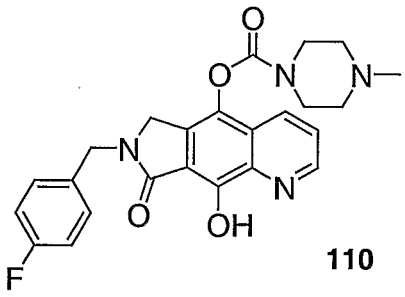
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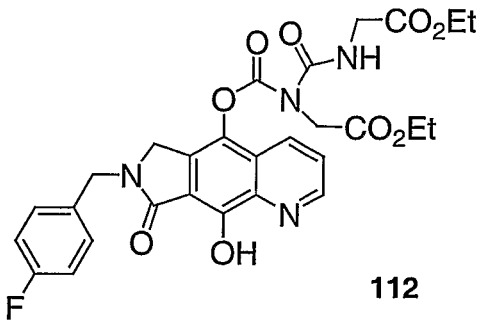
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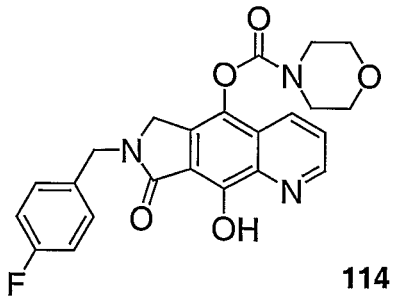
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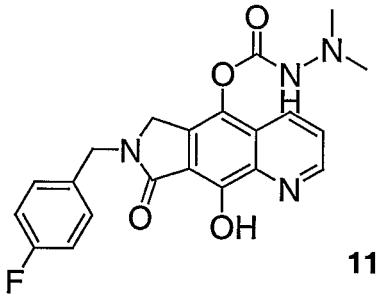
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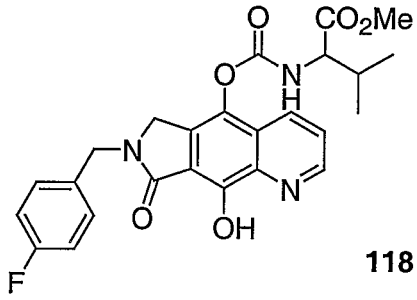
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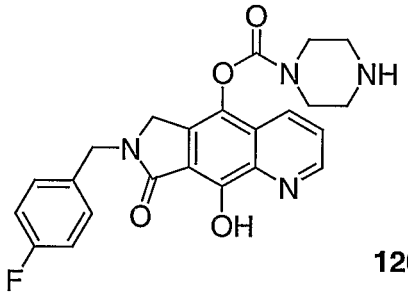
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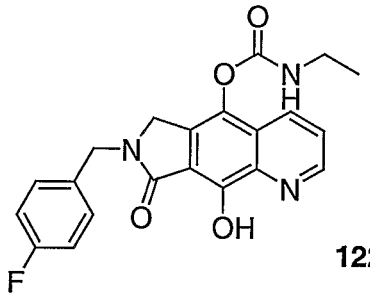
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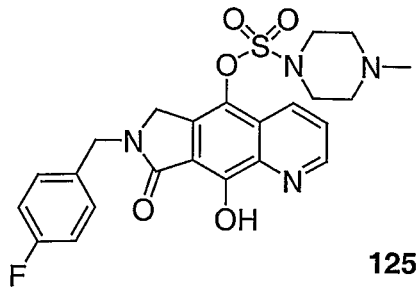
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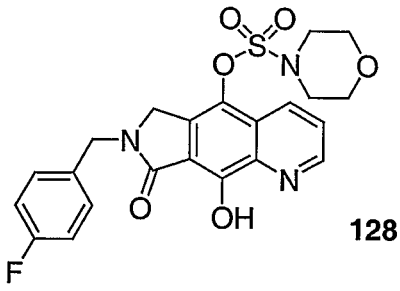
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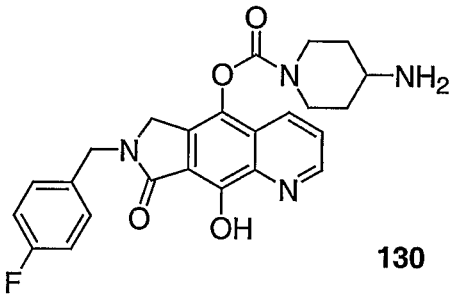
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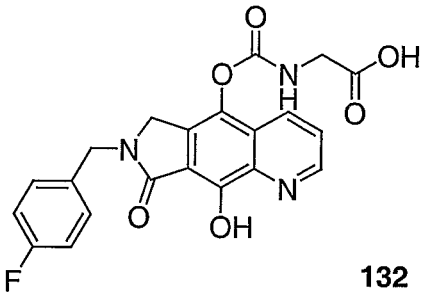
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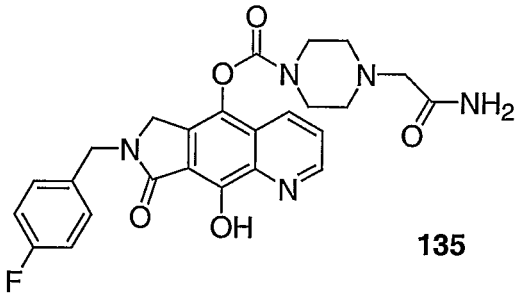
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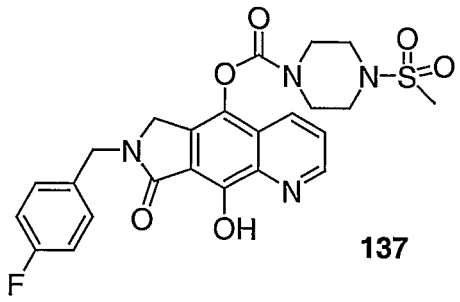
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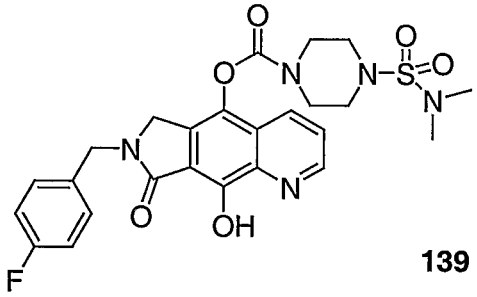
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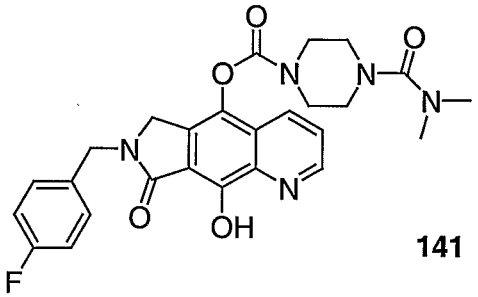
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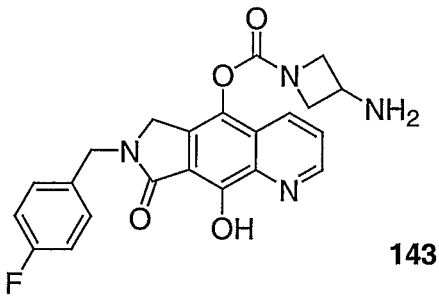
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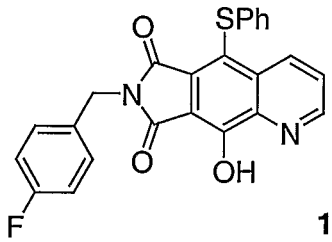
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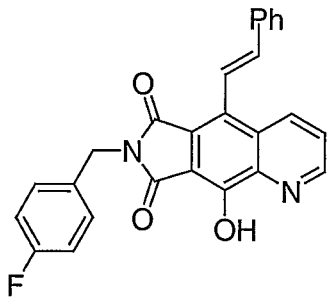
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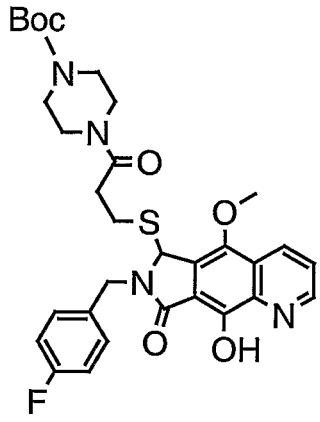
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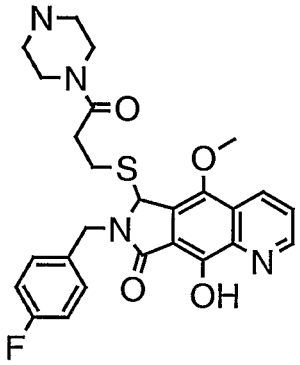
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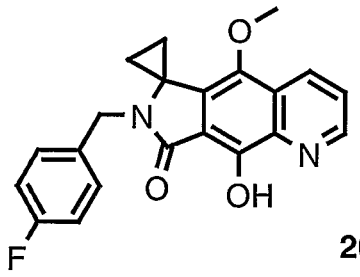
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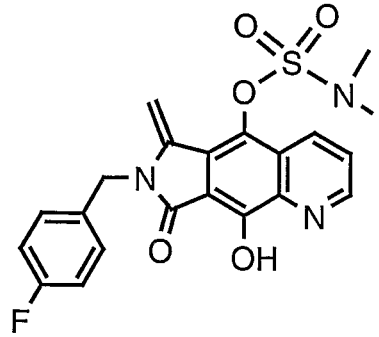
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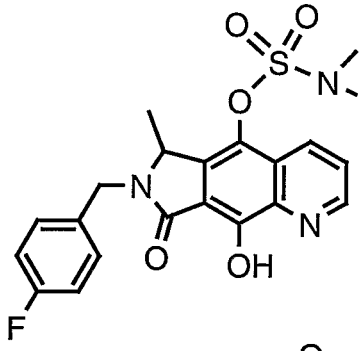
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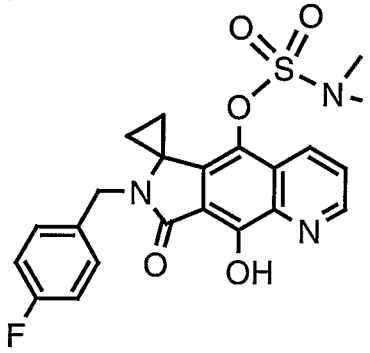
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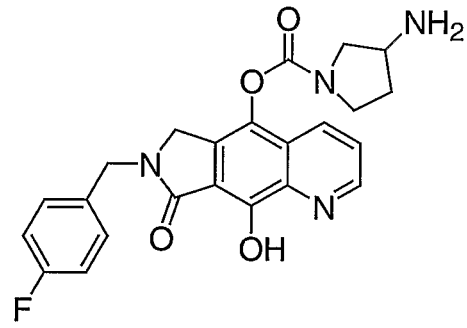
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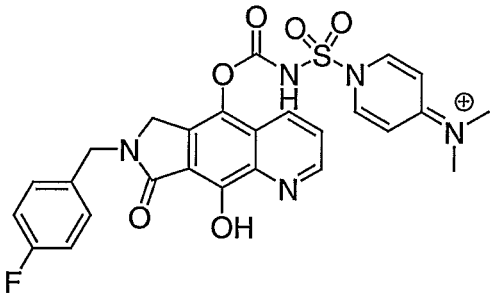
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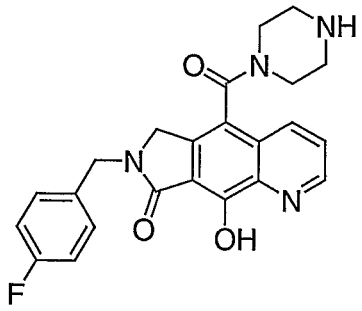
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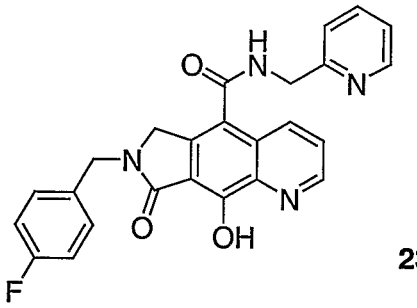
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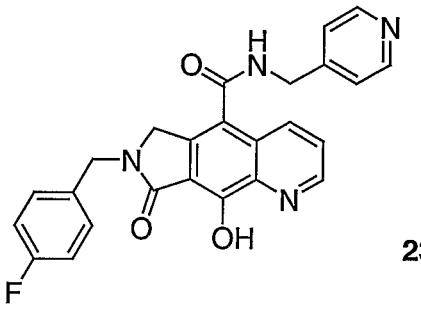
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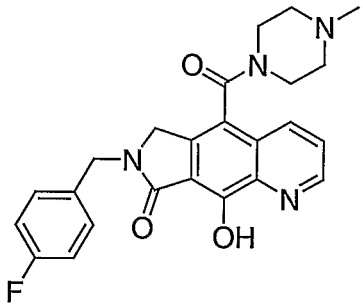
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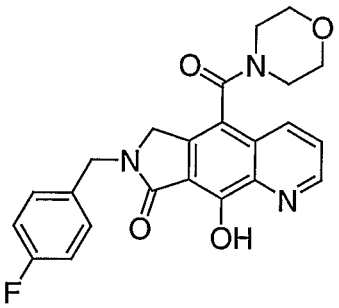
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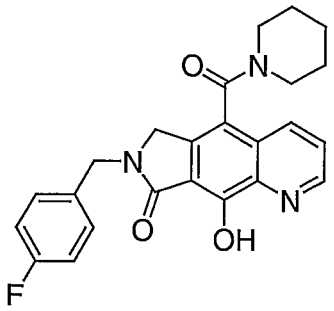
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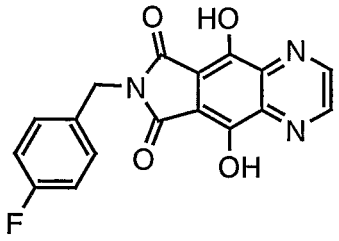
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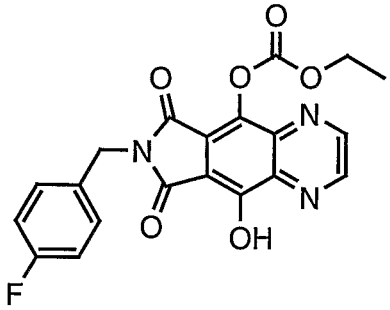
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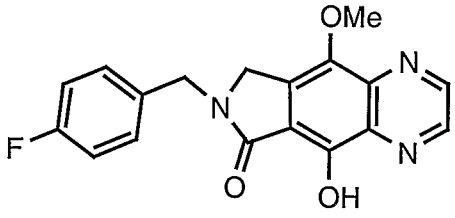
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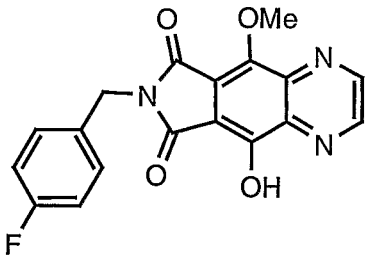
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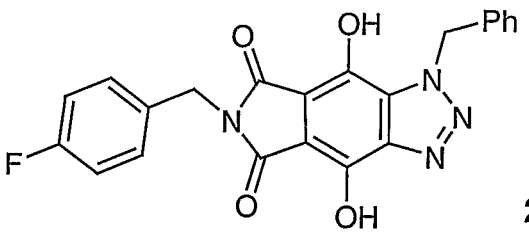
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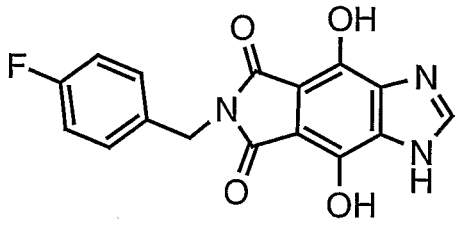
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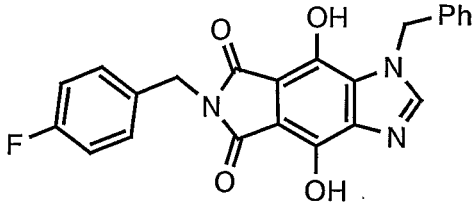
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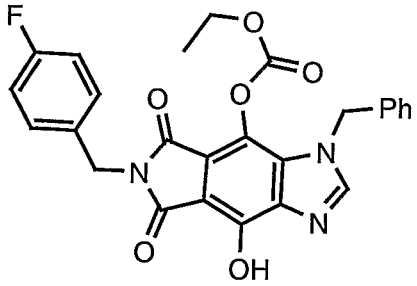
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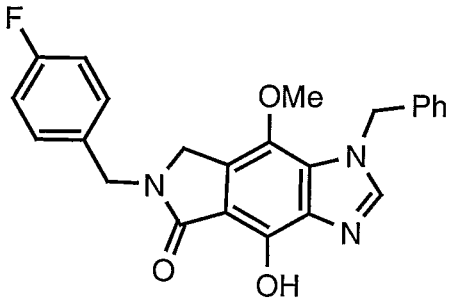
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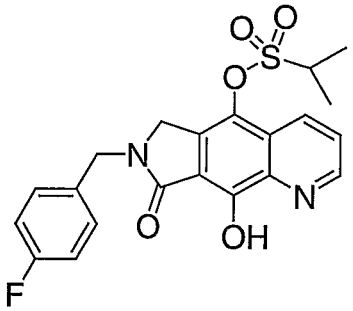
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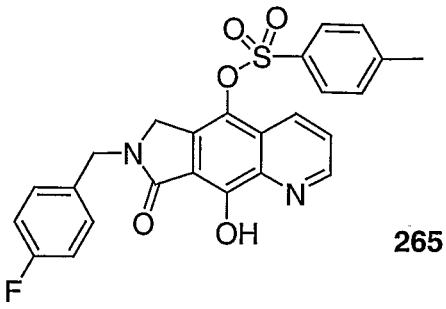
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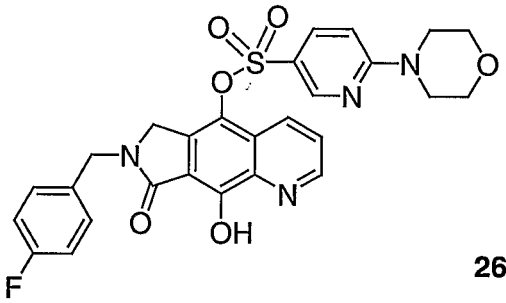
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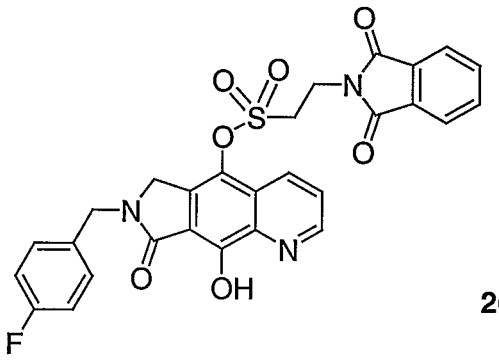
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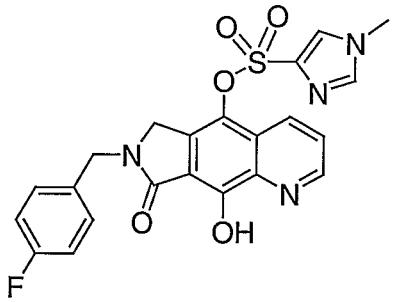
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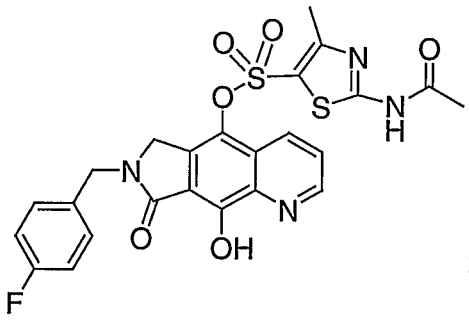
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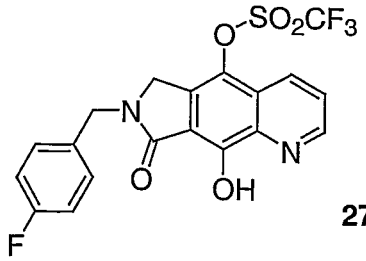
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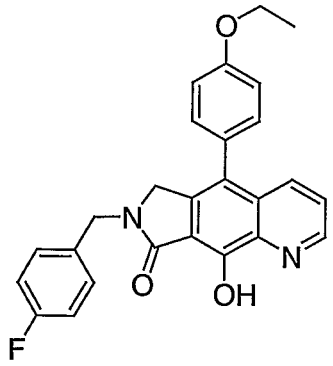
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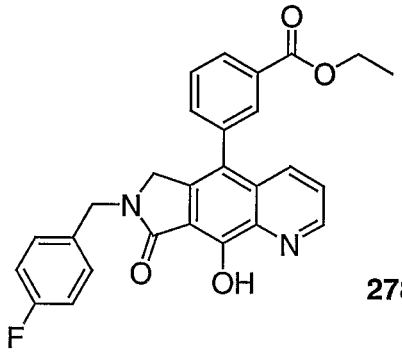
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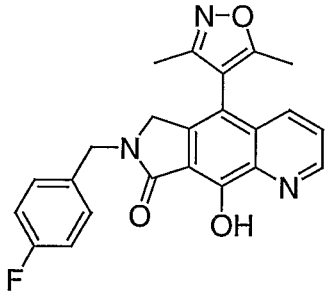
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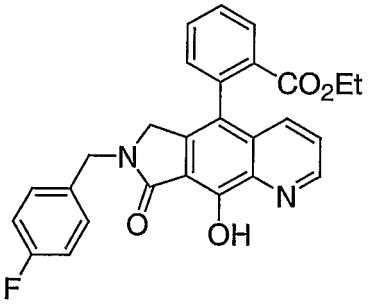
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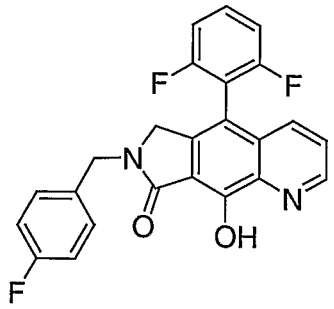
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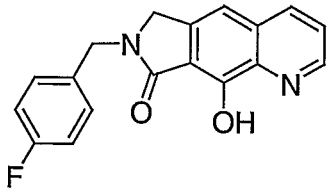
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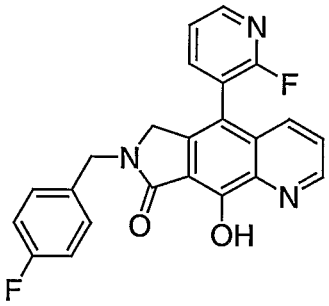
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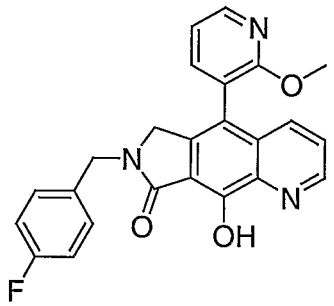
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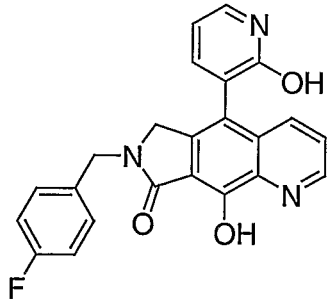
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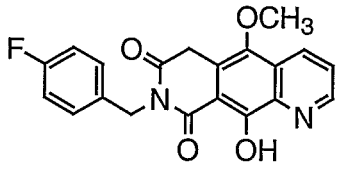


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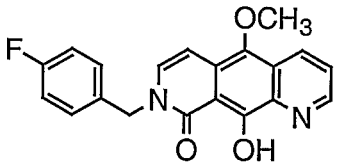


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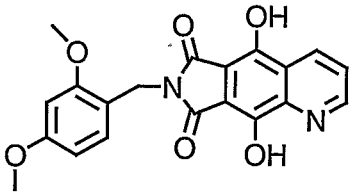
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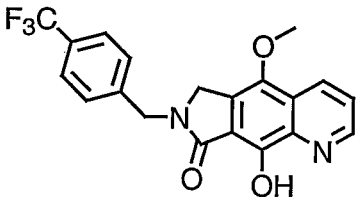
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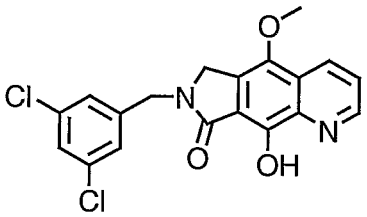
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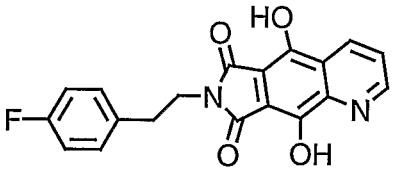
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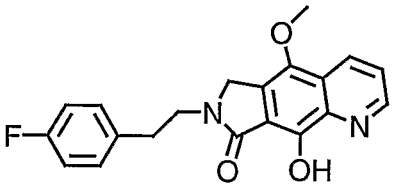
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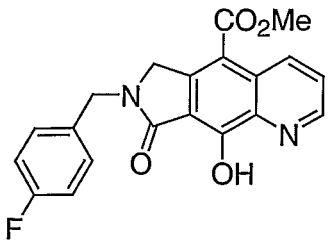
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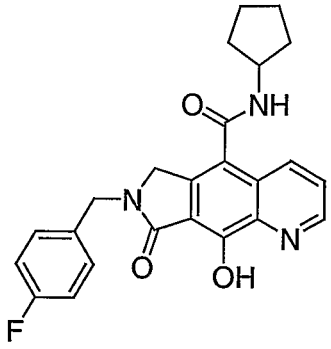
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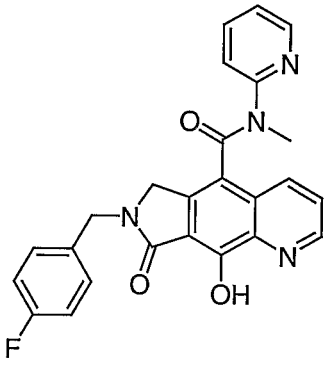
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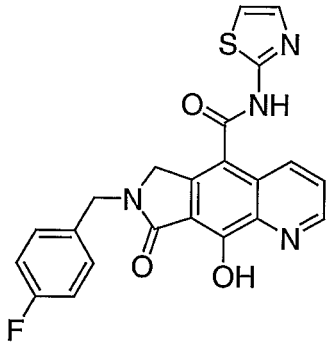
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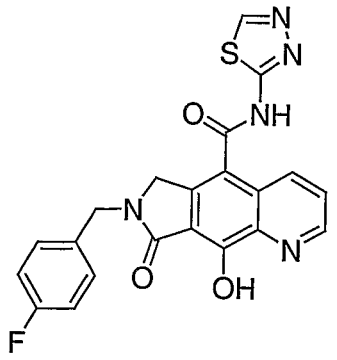
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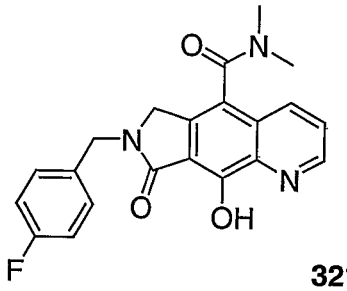
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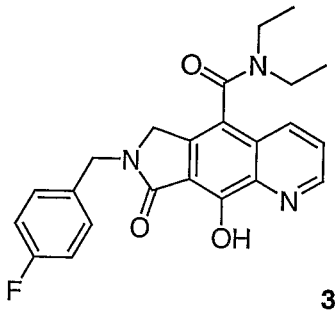


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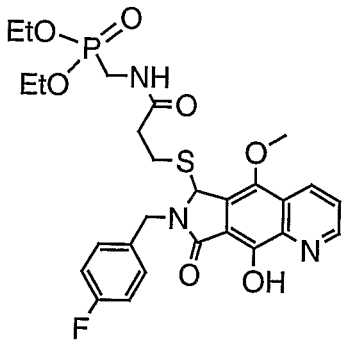
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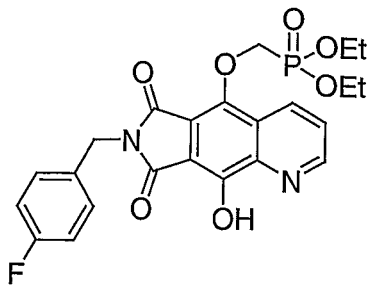


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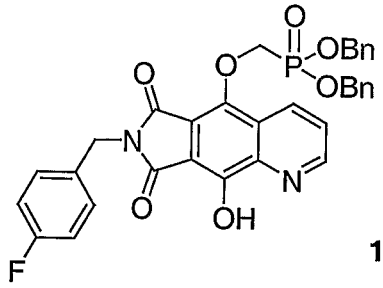
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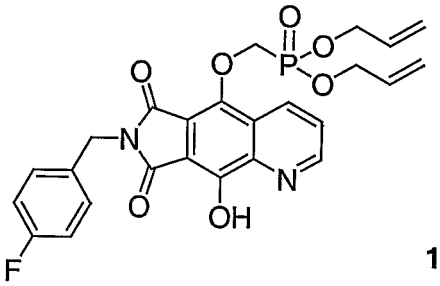
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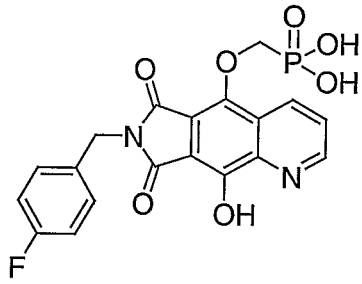
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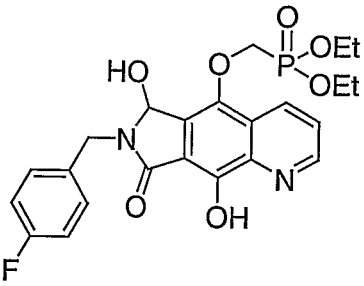
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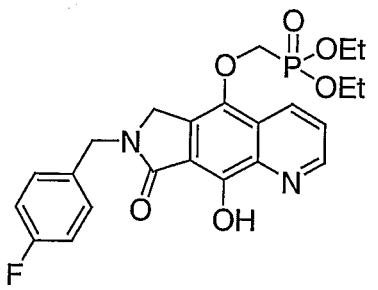
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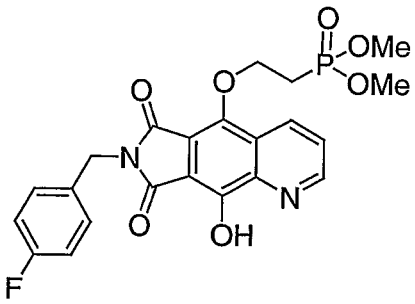
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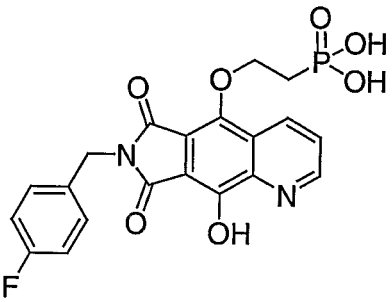
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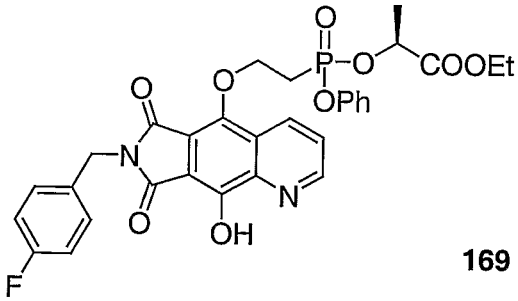
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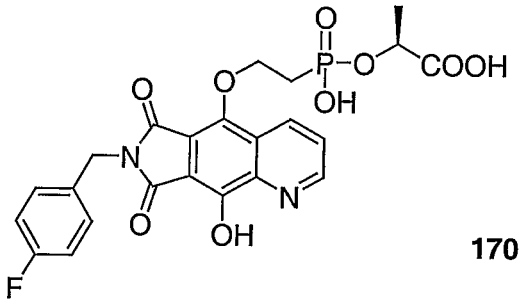
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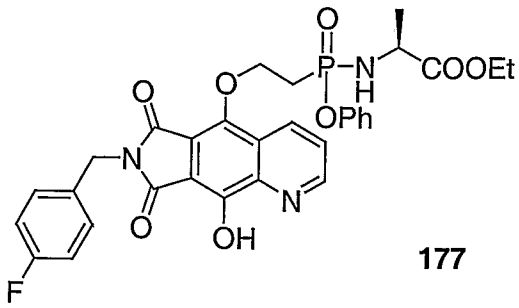
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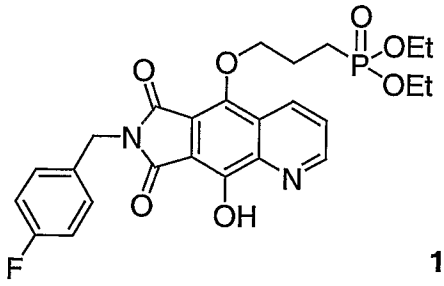
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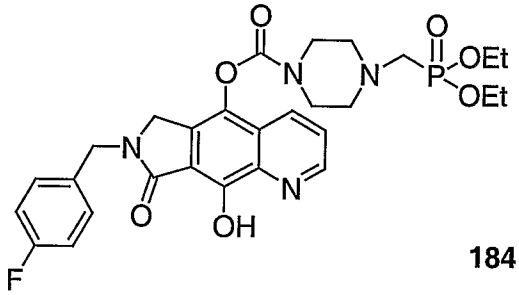
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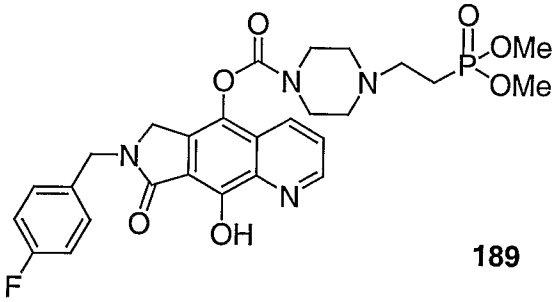
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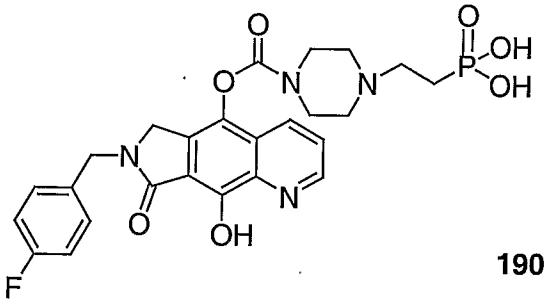
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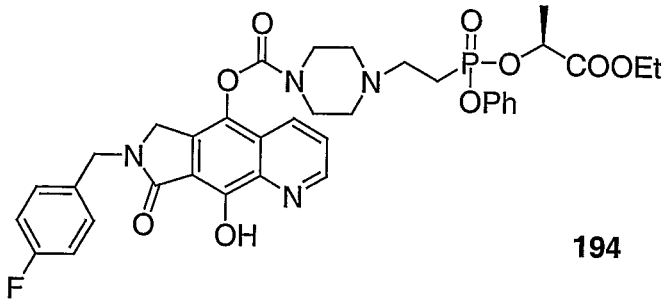
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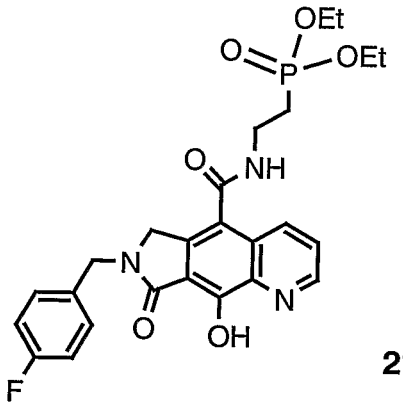
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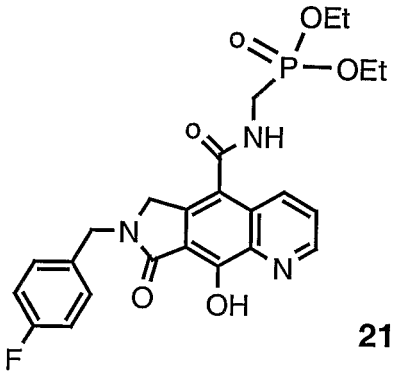
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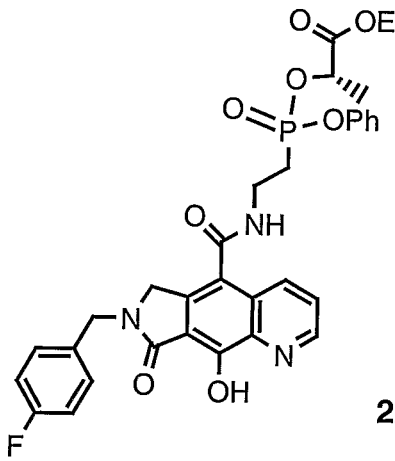
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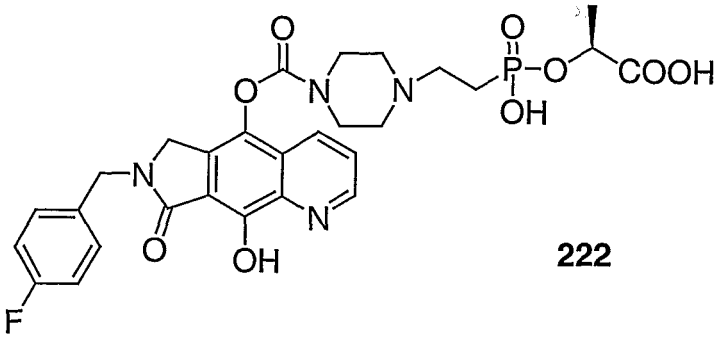
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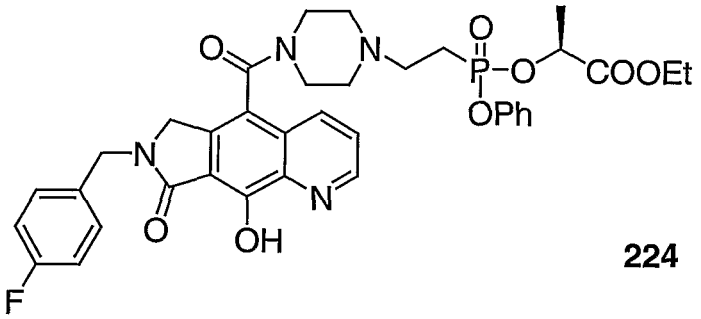
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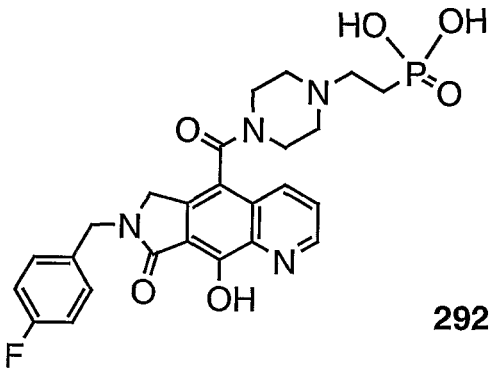
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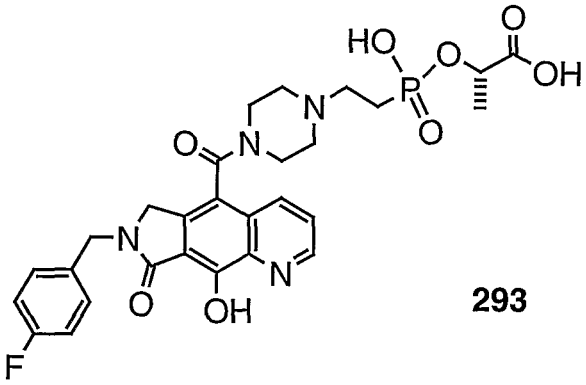
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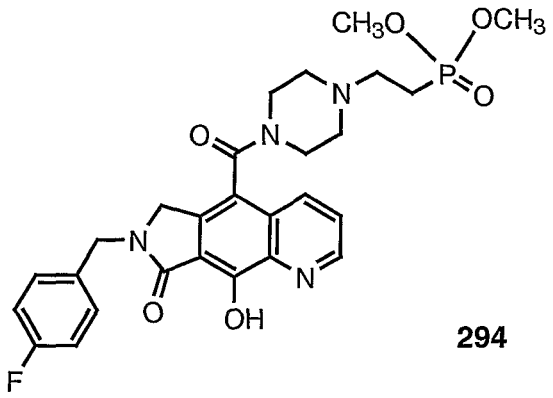
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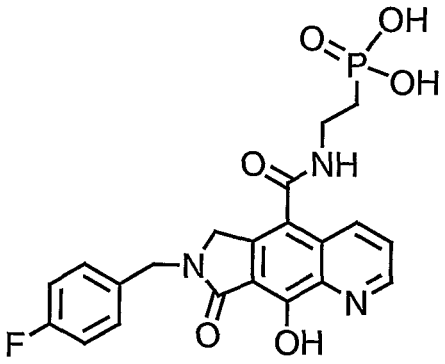
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293

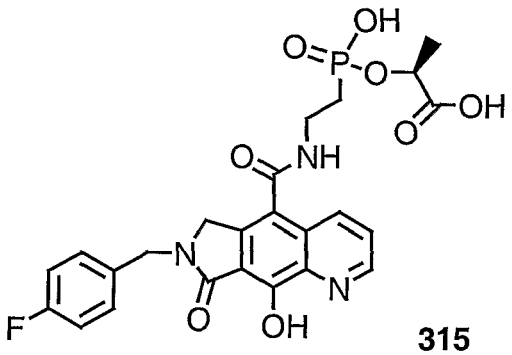


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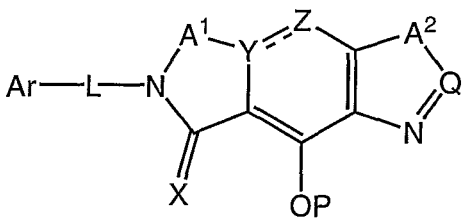
314

and



315

49. A compound having the structure:

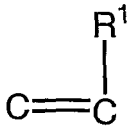
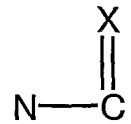
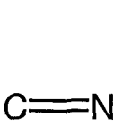


or a salt thereof;

wherein:

A^1 and A^2 are independently selected from O, S, NR, $C(R^2)_2$, CR^2OR, $CR^2OC(=O)R$, C(=O), C(=S), CR^2SR, C(=NR), $C(R^2)_2$–$C(R^3)_2$, $C(R^2)$=$C(R^3)$, 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  ,  , or  ;

L is selected from a bond, O, S, S–S, S(=O), $S(=O)_2$, $S(=O)_2NR$, 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, 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;

X is selected from O, S, NH, NR, N–OR, $N–NR_2$, $N–CR_2OR$ and $N–CR_2NR_2$;

Ar is selected from 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;

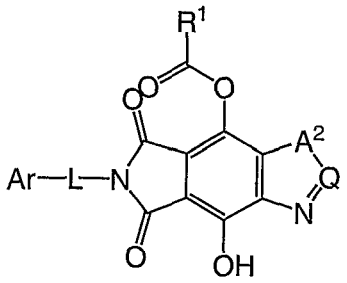
R^1, R^2, R^3 and R^4 are each independently selected from H, F, Cl, Br, I, OH, $–NH_2$, $–NH_3^+$, –NHR, $–NR_2$, $–NR_3^+$, C_1–C_8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, C_1–C_8 alkylsulfonate, C_1–C_8 alkylamino, 4-dialkylaminopyridinium, C_1–C_8 alkylhydroxyl, 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;

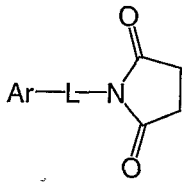
R is independently selected from H, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl, polyethyleneoxy, phosphonate, phosphate, and a prodrug; and

P is a protecting group selected from benzyhydryl ($CHPh_2$), trialkylsilyl (R_3Si), 2-trimethylsiloxyethyl, alkoxymethyl (CH_2OR), and ester (C(=O)R).

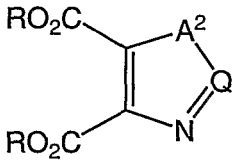
50. A process for preparation of a compound having the structure:



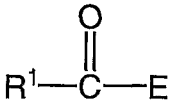
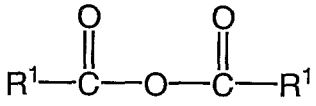
comprising reacting a succinimide compound having the structure:



with a heterocyclic compound having the structure:



and reaction with an acylation reagent comprising a formula selected from:

 and 

wherein:

A^2 is selected from O, S, NR, $C(R^2)_2$, CR^2OR, $CR^2OC(=O)R$, C(=O), C(=S), CR^2SR, C(=NR), $C(R^2)_2$–$C(R^3)_2$, $C(R^2)$=$C(R^3)$, 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;

L is selected from a bond, O, S, NR, N–OR, C_1–C_{12} alkyldiyl, C_1–C_{12} substituted alkyldiyl, C(=O)NH, C(=O), S(=O), $S(=O)_2$, $C(=O)NH(CH_2)_n$, and $(CH_2CH_2O)_n$, where n ranges from 1 to 6;

Ar is selected from C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl;

R^1 is selected from R, OR, NR_2, NHR, $NHSO_2R$, and $NRSO_2R$;

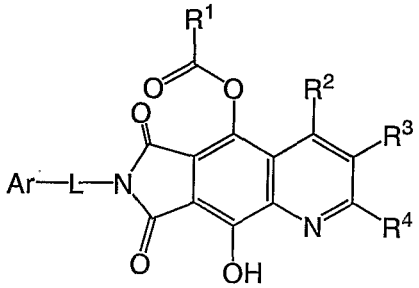
E is selected from Cl, imidazole, and hydroxybenzotriazole;

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,

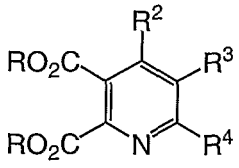
5-7 membered ring sultam, C_1–C_8 alkylsulfonate, C_1–C_8 alkylamino, 4-dialkylaminopyridinium, C_1–C_8 alkylhydroxyl, C_1–C_8 alkylthiol, $-SO_2R$, $-SO_2Ar$, $-SOAr$, $-SAr$, $-SO_2NR_2$, $-SOR$, $-CO_2R$, $-C(=O)NR_2$, 5-7 membered ring lactam, 5-7 membered ring lactone, $-CN$, $-N_3$, $-NO_2$, C_1–C_8 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; and

R is selected from 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} heteroaryl, C_2–C_{20} substituted heteroaryl, polyethyleneoxy, phosphonate, phosphate, and a prodrug moiety.

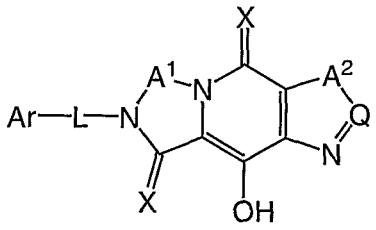
51. The process of claim 50 for preparation of a compound having the structure:



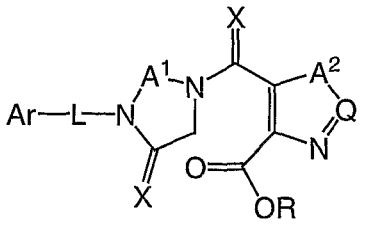
wherein the heterocyclic compound has the structure:



52. A process for preparation of a compound having the structure:



comprising reacting a compound having the structure:



with a basic reagent comprising hydroxide, an alkoxide or an amine;

wherein:

A^1 and A^2 are independently selected from O, S, NR, $C(R^2)_2$, CR^2OR, $CR^2OC(=O)R$, C(=O), C(=S), CR^2SR, C(=NR), $C(R^2)_2$–$C(R^3)_2$, $C(R^2)$=$C(R^3)$, 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;

X is selected from O, S, NH, NR, N–OR, N–NR_2, N–CR_2OR and N–CR_2NR_2;

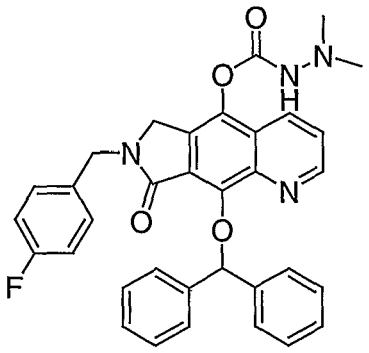
L is selected from a bond, O, S, NR, N–OR, C_1–C_{12} alkyldiyl, C_1–C_{12} substituted alkyldiyl, C(=O)NH, C(=O), S(=O), $S(=O)_2$, $C(=O)NH(CH_2)_n$, and $(CH_2CH_2O)_n$, where n ranges from 1 to 6;

Ar is selected from C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl;

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; and

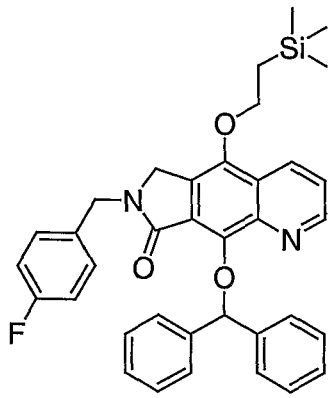
R is selected from C_1–C_6 alkyl, C_1–C_6 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, C_2–C_{20} substituted heteroaryl, polyethyleneoxy, phosphonate, phosphate, and a prodrug moiety.

53. A process for preparation of a compound having structure 115:



115

comprising reacting a compound having the structure 44:



44

with tetrabutylammonium fluoride to form a desilylated intermediate; and reacting the desilylated intermediate with triphosgene (bis(trichloromethyl) carbonate), followed by dimethylhydrazine to form structure 115.

54. A compound of claim 1 comprising a phosphonate prodrug and capable of accumulating in human PBMC.

55. The compound of claim 54 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.

56. The compound of claim 54 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.

57. The compound of claim 56 wherein the half-life is improved by at least about 50%.

58. The compound of claim 56 wherein the half-life is improved by at least about 100%.

59. The compound of claim 54 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.

60. The compound of claim 59 wherein the half-life is improved by at least about 50%.

61. The compound of claim 59 wherein the half-life is improved by at least about 100%.

62. The compound of claim 59 wherein the half-life is improved by greater than 100%.

63. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

64. The pharmaceutical composition of claim 62 further comprising a therapeutically effective amount of an AIDS treatment agent selected from an HIV inhibitor agent, an anti-infective agent, and an immunomodulator.

65. The pharmaceutical composition of claim 64 wherein the HIV inhibitor agent is an HIV-protease inhibitor.

66. The composition of claim 64 wherein the HIV inhibitor agent is a nucleoside reverse transcriptase inhibitor.

67. The composition of claim 64 wherein the HIV inhibitor agent is a non-nucleoside reverse transcriptase inhibitor.

68. A process for making a pharmaceutical composition comprising combining a compound of claim 1 and a pharmaceutically acceptable carrier.

69. A method of inhibiting HIV integrase, comprising the administration to a mammal in need of such treatment of a therapeutically effective amount of a compound of claim 1.

70. 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 a compound of claim 1.

71. Method of treating a disorder affecting white blood cells, comprising:

administering a compound of claim 1 comprising phosphonate prodrug to a patient in need of white-blood-cell targeting.

72. Method of targeting a compound to white blood cells, comprising:

selecting a compound of claim 1 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.

73. A method of manufacturing an HIV 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.

74. The method of claim 73, 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.

75. The method of claim 73, wherein said first molecule is synthesized by a series of chemical reactions that never includes a molecule of said second structure.

76. 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.

77. The method of claim 75 wherein said sample is a patient.

78. The method of claim 73, wherein said compound has a chemical structure A-B, wherein (a) a compound having structure A-H has HIV integrase inhibitor activity and (b) substructure B comprises a phosphonate group or a precursor phosphonate group.

79. Method of increasing half-life of an HIV integrase inhibitor compound, comprising:

replacing at least one hydrogen atom or organic radical of a compound of claim 1 by an organic substituent comprising a phosphonate group or incipient phosphonate.