TITLE OF THE INVENTION

HIV INTEGRASE INHIBITORS

This application claims the benefit of U.S. Provisional Application Nos. 60/551,625 (filed March 9, 2004) and 60/633,134 (filed December 3, 2004), the disclosures of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The present invention is directed hydroxy tetrahydro-2,6-naphthyridine dione and hydroxy hexahydro-2,6-naphthyridine dione compounds and pharmaceutically acceptable salts thereof, their synthesis, and their use as inhibitors of the HIV integrase enzyme. The compounds and pharmaceutically acceptable salts thereof of the present invention are useful for preventing or treating infection by HIV and for preventing or treating or delaying the onset of AIDS.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV), particularly the strains known as HIV type-1 (HIV-1) virus and type-2 (HIV-2) virus, is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the insertion by virally-encoded integrase of +proviral DNA into the host cell genome, a required step in HIV replication in human T-lymphoid and monocytoid cells. Integration is believed to be mediated by integrase in three steps: assembly of a stable nucleoprotein complex with viral DNA sequences; cleavage of two nucleotides from the 3' termini of the linear proviral DNA; covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The fourth step in the process, repair synthesis of the resultant gap, may be accomplished by cellular enzymes.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, integrase and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al., Science, 231, 1567 (1986); Pearl, L.H. et al., Nature, 329, 351 (1987)]. All three enzymes have been shown to be essential for the replication of HIV.

It is known that some antiviral compounds which act as inhibitors of HIV replication are effective agents in the treatment of AIDS and similar diseases, including reverse transcriptase inhibitors such as azidothymidine (AZT) and efavirenz and protease inhbitors such as indinavir and nelfinavir. The

compounds of this invention are inhibitors of HIV integrase and inhibitors of HIV replication. The inhibition of integrase in vitro and HIV replication in cells is a direct result of inhibiting the strand transfer reaction catalyzed by the recombinant integrase in vitro in HIV infected cells. The particular advantage of the present invention is highly specific inhibition of HIV integrase and HIV replication.

The following references are of interest as background:

US 6380249, US 6306891, and US 6262055 disclose 2,4-dioxobutyric acids and acid esters useful as HIV integrase inhibitors.

WO 01/00578 discloses 1-(aromatic- or heteroaromatic-substituted)-3-(heteroaromatic substituted)-1,3-propanediones useful as HIV integrase inhibitors.

US 2003/0055071 (corresponding to WO 02/30930), WO 02/30426, and WO 02/55079 each disclose certain 8-hydroxy-1,6-naphthyridine-7-carboxamides as HIV integrase inhibitors.

WO 02/036734 discloses certain aza- and polyaza-naphthalenyl ketones to be HIV integrase inhibitors.

WO 03/016275 discloses certain compounds having integrase inhibitory activity.

WO 03/35076 discloses certain 5,6-dihydroxypyrimidine-4-carboxamides as HIV integrase inhibitors, and WO 03/35077 discloses certain N-substituted 5-hydroxy-6-oxo-1,6-dihydropyrimidine-4-carboxamides as HIV integrase inhibitors.

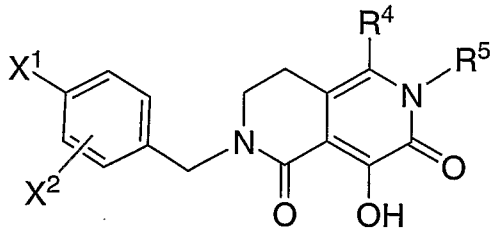
WO 03/062204 discloses certain hydroxynaphthyridinone carboxamides that are useful as HIV integrase inhibitors.

WO 04/004657 discloses certain hydroxypyrrole derivatives that are HIV integrase inhibitors.

WO 2005/016927 discloses certain nitrogenous condensed ring compounds that are HIV integrase inhibitors.

SUMMARY OF THE INVENTION

The present invention is directed to hydroxy polyhydro-2,6-naphthyridine dione compounds. These compounds are useful in the inhibition of HIV integrase, the prevention of infection by HIV, the treatment of infection by HIV and in the prevention, treatment, and delay in the onset of AIDS and/or ARC, either as compounds or their pharmaceutically acceptable salts or hydrates (when appropriate), or as pharmaceutical composition ingredients, whether or not in combination with other HIV/AIDS antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. More particularly, the present invention includes compounds of Formula I, and pharmaceutically acceptable salts thereof:



(I)

wherein:

X^1 is:

(1) -H,
(2) bromo,
(3) chloro,
(4) fluoro, or
(5) methoxy;

X^2 is:

(1) -H,
(2) bromo,
(3) chloro,
(4) fluoro,
(5) methoxy,
(6) -C_{1-4} alkyl,
(7) -CF_3,
(8) -OCF_3,
(9) -CN, or
(10) -SO_2(C_{1-4} alkyl);

R^4 is:

(1) -CO_2H,
(2) -C(=O)-O-C_{1-4} alkyl,
(3) -C(=O)NH_2,
(4) -C(=O)NH-C_{1-4} alkyl,
(5) -C(=O)N(C_{1-4} alkyl)$_2$,
(6) -C(=O)-NH-$(CH_2)_{2-3}$-O-C_{1-4} alkyl,
(7) -C(=O)-N(C_{1-4} alkyl)-$(CH_2)_{2-3}$-O-C_{1-4} alkyl,

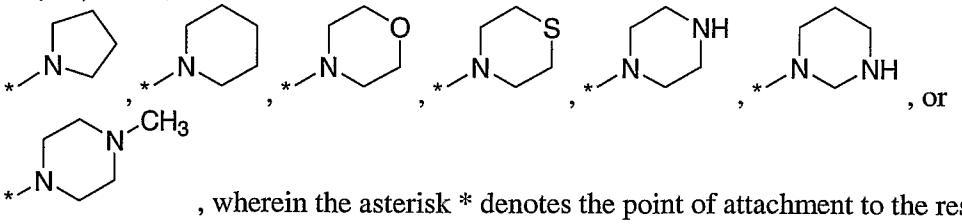
(8) -NHC(=O)-C_{1-4} alkyl,

(9) -N(C_{1-4} alkyl)C(=O)-C_{1-4} alkyl,

(10) -NHSO_2-C_{1-4} alkyl,

(11) -N(C_{1-4} alkyl)SO_2-C_{1-4} alkyl,

(12) -C(=O)-HetK, wherein HetK is:



, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(13) -C(=O)NH-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl),

(14) -C(=O)N(C_{1-4} alkyl)-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl),

(15) -C(=O)NH-CH_2-phenyl, or

(16) -C(=O)N(C_{1-4} alkyl)-CH_2-phenyl; and

R^5 is:

(1) -H,

(2) -C_{1-4} alkyl,

(3) cyclopropyl,

(4) cyclobutyl,

(5) -CH_2-cyclopropyl,

(6) -CH_2-cyclobutyl, or

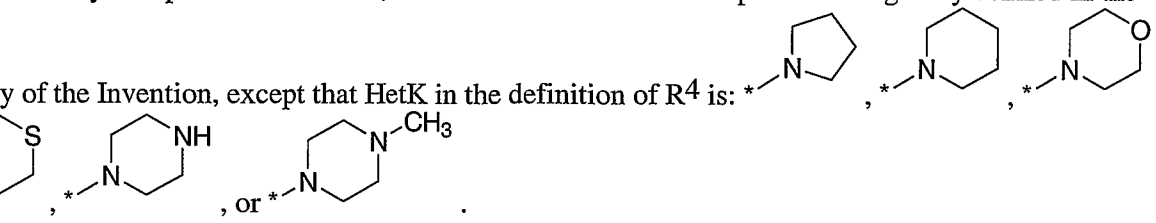
(7) -CH_2-phenyl.

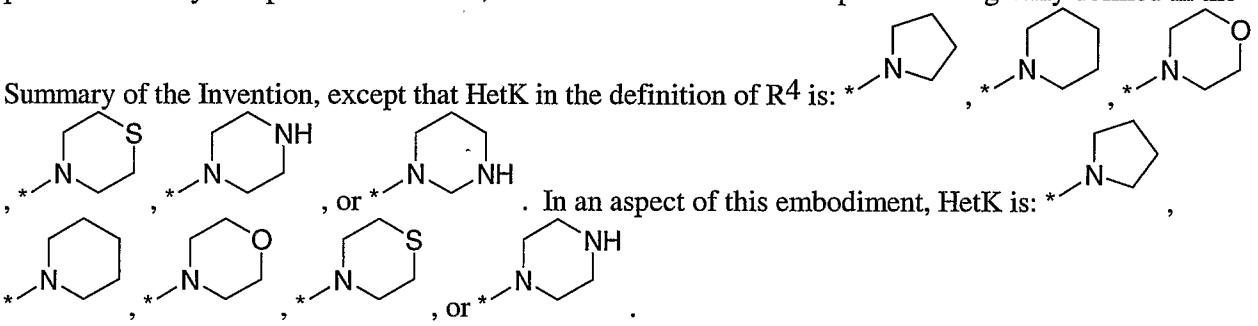
The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating AIDS, methods of delaying the onset of AIDS, methods of preventing AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV.

Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes compounds of Formula I above, and pharmaceutically acceptable salts thereof. These compounds and their pharmaceutically acceptable salts are HIV integrase inhibitors (e.g., HIV-1 integrase inhibitors).

A first embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, which is identical to the compound as originally defined in the Summary of the Invention, except that HetK in the definition of R^4 is: .

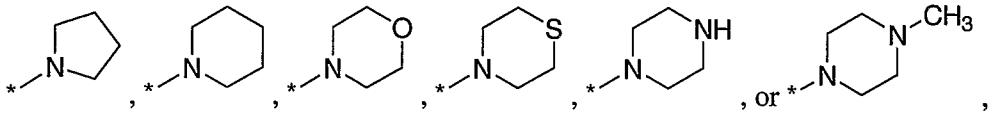
A second embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, which is identical to the compound as originally defined in the Summary of the Invention, except that HetK in the definition of R^4 is: . In an aspect of this embodiment, HetK is: .

A third embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein:

X^1 is fluoro;

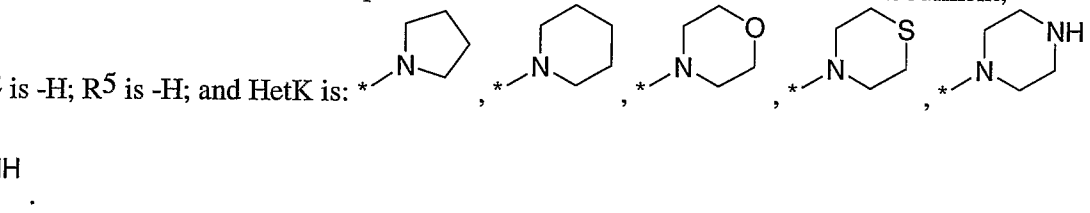
X^2 is -H or chloro;

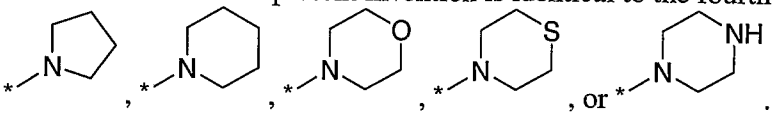
R^4 is: (1) -C(=O)-O-C_{1-3} alkyl, (2) -C(=O)NH-C_{1-3} alkyl, (3) -C(=O)N(C_{1-3} alkyl)$_2$, (4) -C(=O)-N(C_{1-3} alkyl)-$(CH_2)_2$-O-C_{1-3} alkyl, (5) -N(C_{1-3} alkyl)C(=O)-C_{1-3} alkyl, (6) -N(C_{1-3} alkyl)SO_2-C_{1-3} alkyl, (7) -C(=O)-HetK, wherein HetK is:

,

wherein the asterisk * denotes the point of attachment to the rest of the compound, (8) -C(=O)NH-$(CH_2)_{0-1}$-(cyclopropyl), (9) -C(=O)NH-$(CH_2)_{0-1}$-(cyclobutyl), (10) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclopropyl, (11) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclobutyl, (12) -C(=O)NH-CH_2-phenyl, or (13) -C(=O)N(C_{1-3} alkyl)-CH_2-phenyl; and

R^5 is -H or C_{1-4} alkyl.

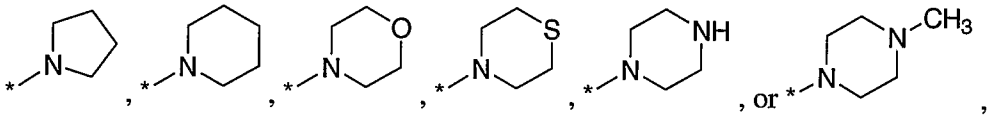
A fourth embodiment of the present invention is identical to the third embodiment, except that X^2 is -H; R^5 is -H; and HetK is:  .

A fifth embodiment of the present invention is identical to the fourth embodiment, except that HetK is:  .

A sixth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein X^1 is fluoro; X^2 is -H or chloro; R^4 is:

(1) -C(=O)N(C_{1-3} alkyl)$_2$,

(2) -C(=O)-HetK, wherein HetK is:



wherein the asterisk * denotes the point of attachment to the rest of the compound,

(3) -C(=O)N(C_{1-3} alkyl)-(CH_2)$_{0-1}$-cyclopropyl, or

(4) -C(=O)N(C_{1-3} alkyl)-(CH_2)$_{0-1}$-cyclobutyl; and

R^5 is -C_{1-4} alkyl.

A seventh embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is is -C(=O)N(C_{1-3} alkyl)$_2$; and all other variables are as defined in the sixth embodiment.

An eighth embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^4 is is -C(=O)N(CH_3)$_2$; and all other variables are as defined in the sixth embodiment.

Another embodiment of the present invention is a compound, or a pharmaceutically acceptable salt thereof, selected from the group consisting of the compounds set forth in Examples 1 to 20 below. An aspect of this embodiment is a compound, or a pharmaceutically acceptable salt thereof, which is the compound set forth in Example 11, 13, or 14. Another aspect of this embodiment is a compound, or a pharmaceutically acceptable salt thereof, which is the compound set forth in Example 11 or Example 13. Another aspect of this embodiment is a compound, or a pharmaceutically acceptable salt thereof, which is the compound set forth in Example 11 (i.e., 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide). Another aspect of this embodiment is a compound, or a pharmaceutically acceptable salt thereof, which is the compound set

forth in Example 13 (i.e., 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-isopropyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide).

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a compound of Formula I and a pharmaceutically acceptable carrier.

(b) A pharmaceutical composition which comprises the product prepared by combining (e.g., mixing) an effective amount of a compound of Formula I and a pharmaceutically acceptable carrier.

(c) The pharmaceutical composition of (a) or (b), further comprising an effective amount of an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

(d) The pharmaceutical composition of (c), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(e) A pharmaceutical combination which is (i) a compound of Formula I and (ii) an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents; wherein the compound of Formula I and the HIV infection/AIDS treatment agent are each employed in an amount that renders the combination effective for inhibiting HIV integrase, for treating or preventing infection by HIV, or for preventing, treating or delaying the onset of AIDS.

(f) The combination of (e), wherein the HIV infection/AIDS treatment agent is an antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors and nucleoside HIV reverse transcriptase inhibitors.

(g) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I.

(h) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I.

(i) The method of (h), wherein the compound of Formula I is administered in combination with an effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors.

(j) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject an effective amount of a compound of Formula I.

(k) The method of (j), wherein the compound is administered in combination with an effective amount of at least one antiviral selected from the group consisting of HIV protease inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, and nucleoside HIV reverse transcriptase inhibitors

(l) A method of inhibiting HIV integrase in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(m) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(n) A method of preventing, treating or delaying the onset of AIDS in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

The present invention also includes a compound of the present invention (i) for use in, (ii) for use as a medicament for, or (iii) for use in the preparation of a medicament for: (a) inhibiting HIV integrase, (b) preventing or treating infection by HIV, or (c) preventing, treating or delaying the onset of AIDS. In these uses, the compounds of the present invention can optionally be employed in combination with one or more HIV/AIDS treatment agents selected from HIV/AIDS antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(n) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt.

As used herein, the term "alkyl" refers to any linear or branched chain alkyl group having a number of carbon atoms in the specified range. Thus, for example, "C_{1-6} alkyl" (or "C_1-C_6 alkyl") refers to all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. As another example, "C_{1-4} alkyl" refers to n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl.

The terms "cycloalkyl" refers to any cyclic ring of an alkane having a number of carbon atoms in the specified range. Thus, for example, "C_{3-8} cycloalkyl" (or "C_3-C_8 cycloalkyl") refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo).

When any variable occurs more than one time in any constituent or in Formula I or in any other formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic or prophylactic administration to a subject).

As would be recognized by one of ordinary skill in the art, certain of the compounds of the present invention can exist as tautomers. The present invention includes tautomers of compounds of Formula I, singly and in mixtures.

Certain of the compounds of the present invention can exhibit a chirality resulting from the presence of bulky substituents that hinder the otherwise free rotation about a bond. These rotational enantiomers are named atropisomers, and the interconversion can be sufficiently slow to allow for their separation and characterization. See, e.g., J. March, Advanced Organic Chemistry, 4th Edition, John Wiley & Sons, 1992, pp. 101-102; and Ahmed et al., *Tetrahedron* 1998, 13277. For example, certain of the compounds of the present invention in which R^4 is -C(=O)N(C_{1-4} alkyl)$_2$ or -C(=O)NH-C_{1-4} alkyl can have sufficiently hindered rotation along the bond linking R^4 to the bicyclic core of the molecule when R^5 is other than H (e.g., R^5 = alkyl, cycloalkyl, or aryl) to permit separation of the enantiomers using, e.g., column chromatography on a chiral stationary phase. The present invention includes atropisomers of compounds embraced by Formula I, singly and in mixtures.

The compounds of the present inventions are useful in the inhibition of HIV integrase (e.g., HIV-1 integrase), the prevention or treatment of infection by human immunodeficiency virus (HIV) and the prevention, treatment or the delay in the onset of consequent pathological conditions such as AIDS. Preventing AIDS, treating AIDS, delaying the onset of AIDS, or preventing or treating infection by HIV is defined as including, but not limited to, treatment of a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by such means as blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of

other antivirals to HIV integrase, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which possesses the effectiveness of the parent compound and which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts which may, for example, be formed by mixing a solution of the compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. Many of the compounds of the invention carry an acidic moiety, in which case suitable pharmaceutically acceptable salts thereof can include alkali metal salts (e.g., sodium or potassium salts), alkaline earth metal salts (e.g., calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention mean providing the compound or a prodrug of the compound to the individual in need of treatment. When a compound of the invention or a prodrug thereof is provided in combination with one or more other active agents (e.g., antiviral agents useful for treating HIV infection or AIDS), "administration" and its variants are each understood to include concurrent and sequential provision of the compound or prodrug and other agents.

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

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

The term "subject" (alternatively referred to herein as "patient") as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. In one embodiment, the effective amount is a "therapeutically effective amount" for the alleviation of the symptoms of the disease or condition being treated. In another embodiment, the effective amount is a "prophylactically effective amount" for prophylaxis of the symptoms of the disease or condition being

prevented. The term also includes herein the amount of active compound sufficient to inhibit HIV integrase and thereby elicit the response being sought (i.e., an "inhibition effective amount"). When the active compound (i.e., active ingredient) is administered as the salt, references to the amount of active ingredient are to the free acid or free base form of the compound.

For the purpose of inhibiting HIV integrase, preventing or treating HIV infection or preventing, treating or delaying the onset of AIDS, the compounds of the present invention, optionally in the form of a salt, can be administered by any means that produces contact of the active agent with the agent's site of action. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing an effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. Liquid preparations suitable for oral administration (e.g., suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water, glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (e.g., powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as a solubility aid. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions of the present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990.

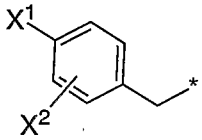
The compounds of this invention can be administered orally in a dosage range of about 0.001 to about 1000 mg/kg of mammal (e.g., human) body weight per day in a single dose or in divided doses. One preferred dosage range is about 0.01 to about 500 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is about 0.1 to about 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or capsules containing about 1.0 to about 500 milligrams of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 milligrams of

the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy. As an example, the title compound of Example 12 below can be administered to adult humans in the form of an amorphous Na salt in a neat drug-filled capsule in an amount of from about 5 mg to about 800 mg (e.g., 400 mg) twice/day. As another example, the crystalline compound of Example 13 or an amorphous Na salt thereof can be administered to adult humans in the same fashion.

As noted above, the present invention is also directed to use of the HIV integrase inhibitor compounds of the present invention with one or more agents useful in the treatment of HIV infection or AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of one or more HIV/AIDS antivirals, imunomodulators, antiinfectives, or vaccines useful for treating HIV infection or AIDS, such as those disclosed in Table 1 of WO 01/38332 or in the Table in WO 02/30930. Suitable HIV/AIDS antivirals for use in combination with the compounds of the present invention include, for example, HIV protease inhibitors (e.g., indinavir, atazanavir, lopinavir optionally with ritonavir, saquinavir, or nelfinavir), nucleoside HIV reverse transcriptase inhibitors (e.g., abacavir, lamivudine (3TC), zidovudine (AZT), or tenofovir), and non-nucleoside HIV reverse transcriptase inhibitors (e.g., efavirenz or nevirapine). It will be understood that the scope of combinations of the compounds of this invention with HIV/AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the foregoing substances or to the list in the above-referenced Tables in WO 01/38332 and WO 02/30930, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS. The HIV/AIDS antivirals and other agents will typically be employed in these combinations in their conventional dosage ranges and regimens as reported in the art, including, for example, the dosages described in the Physicians' Desk Reference, 57th edition, Thomson PDR, 2003. The dosage ranges for a compound of the invention in these combinations are the same as those set forth above.

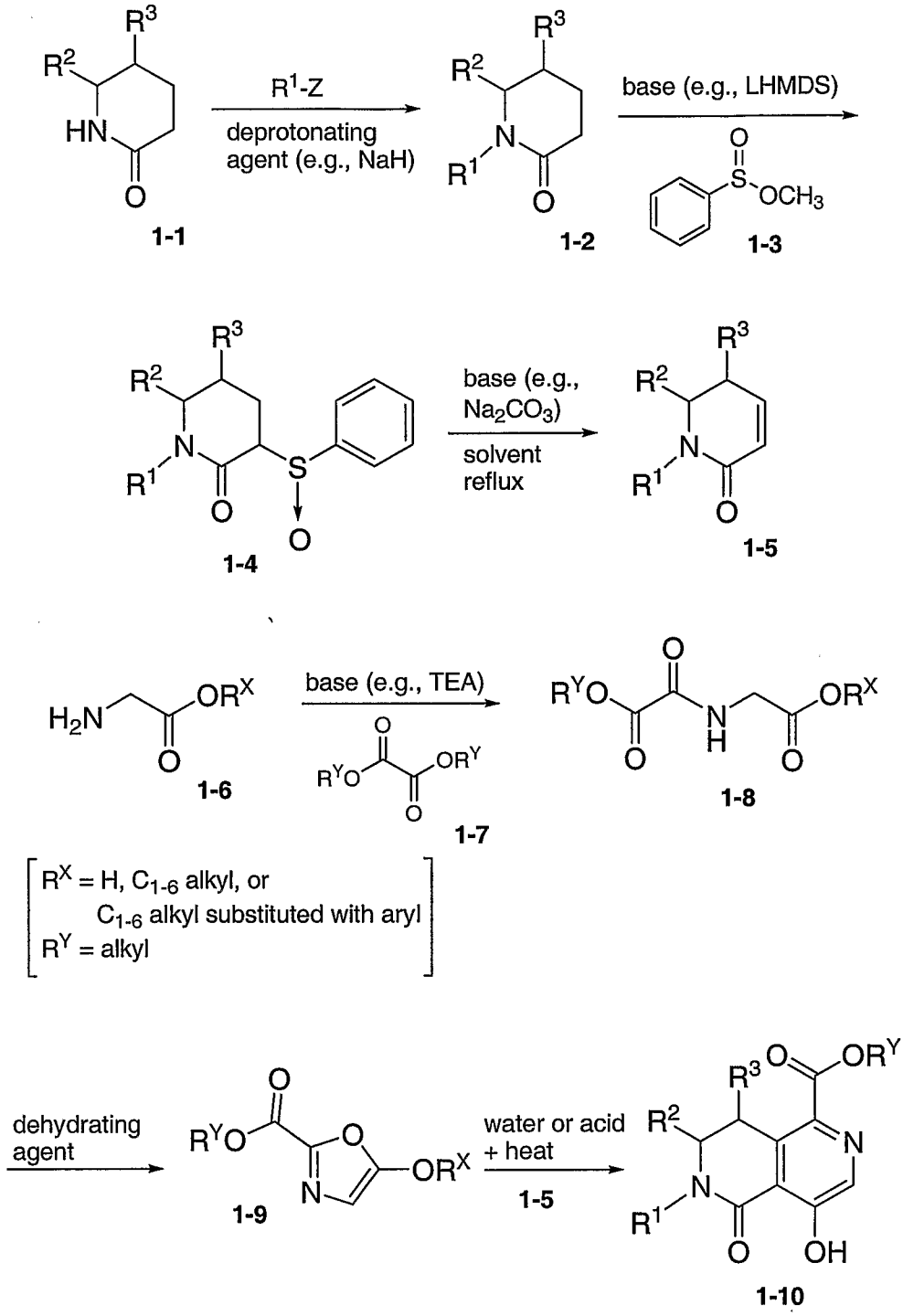
Abbreviations used in the instant specification, particularly the in the Schemes and Examples, include the following: Ac = acetyl; AIDS = acquired immunodeficiency syndrome; AIBN = 2,2-azobisisobutyronitrile; ARC = AIDS related complex; BOC or Boc = t-butyloxycarbonyl; BOP = benzotriazol-1-yloxytris-(dimethylamino)phosphonium; DABCO = 1,4-diazabicyclo[2.2.2]octene; DCM = dichloromethane; DMF = N,N-dimethylformamide; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-

pyrimidinone (or N,N'-dimethylpropyleneurea); DMSO = dimethylsulfoxide; ES MS = electrospray mass spectroscopy; EtOAc = ethyl acetate; HIV = human immunodeficiency virus; HOAc = acetic acid; HOAT = 1-hydroxy-7-azabenzotriazole; HPLC = high performance liquid chromatography; HMPA = hexamethylphosphoramide; IPAc = isopropyl acetate; LC = liquid chromatography; LHMDS = lithium hexamethyldisilazide; mCPBA = meta-chloroperbenzoic acid; Me = methyl; MeOH = methanol; MTBE = methyl tert-butyl ether; NBS = N-bromosuccinimide; NMR = nuclear magnetic resonance; TEA = triethylamine; TFA = trifluoroacetic acid; THF = tetrahydrofuran.

The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above. In the schemes, R^2 and R^3 are both H; and R^1 is  wherein X^1 and X^2 are as defined above and the asterisk * denotes the point of attachment to the rest of the compound; and R^a and R^b are each independently H or C_{1-4} alkyl..

Scheme 1 depicts a method for preparing 5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate intermediates useful for making compounds of the present invention. In the scheme, lactam **1-1** can be alkylated with an appropriate alkyl halide to give **1-2**, using methods as described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 377-379. Piperidin-2-one **1-2** can be converted to the corresponding dihydropyridinone compound **1-5** following the two step procedure set forth in Meyers et al., *Tett. Lett.* 1995, 36: 7051-7054, wherein the lactam can be treated with base and methyl benzene sulfinate to give intermediate **1-4**, which can then be treated by heating in a high boiling solvent (e.g., toluene) and optionally in the presence of base to effect the elimination to **1-5**. Separately, oxazoles of the type **1-9** can readily be prepared by acylating amino acid ester **1-6** with an oxylate ester **1-7** in the presence of base to afford acylated compound **1-8**, which can then be cyclized and dehydrated (using, e.g., P_2O_5) in the manner described in Krapcho et al. *J. Heterocyclic Chem.* 1995, 32, 1693-1702 to afford oxazole **1-9**. Diels-Alder reaction of **1-9** and **1-5**, optionally in the presence of water or an acid (preferably in the presence of water), will then provide the desired napthyridine intermediate **1-10**.

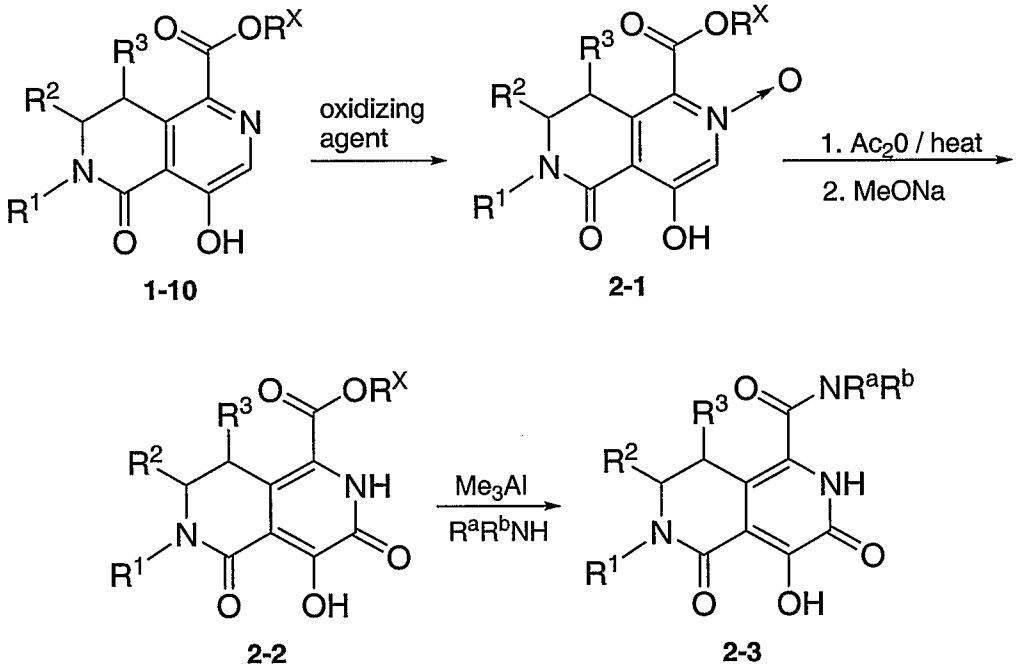
SCHEME 1



Scheme 2 depicts a method for preparing naphthyridine carboxylates and carboxamides embraced by the present invention from naphthyridine intermediate **1-10**, wherein the intermediate **1-10**

is contacted with a suitable oxidizing agent (e.g., hydrogen peroxide or mCPBA) to obtain N-oxide **2-1**, which can then be treated as described Suzuki et al. *J.Med. Chem.* 1992, 35, 4045-4053 with acetic anhydride to effect the rearrangement to the O-acylated intermediate, and then treated with a nucleophile (e.g., an alkoxide such as NaOMe) to afford the desired dioxohexahydro-2,6-naphthyridine-1-carboxylate **2-2**. The alkyl carboxylate **2-2** can then be further treated with an appropriate amine and trimethylaluminum in the manner described in Evans et al., *J. Am. Chem. Soc.* 1990, 112: 7001 to give the desired alkyl carboxamide **2-3**.

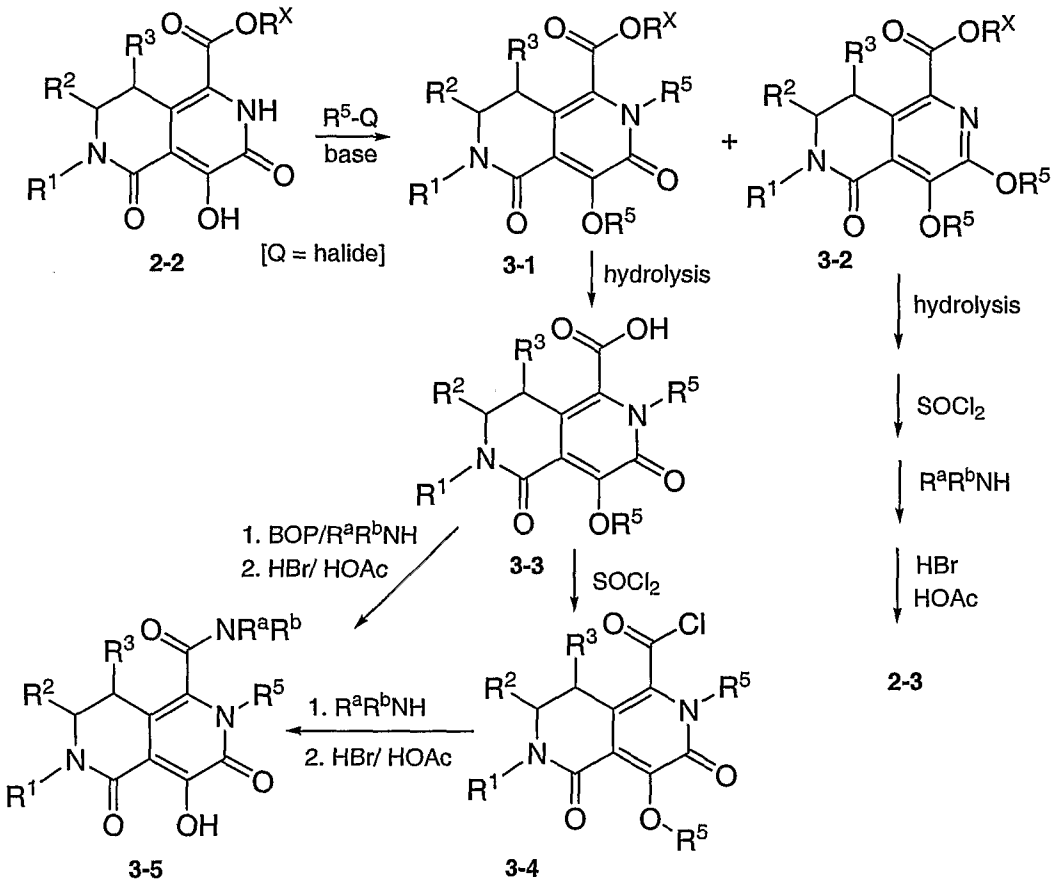
SCHEME 2



Scheme 3 depicts an alternative method for preparing naphthyridine carboxamides **2-3** and analogs in which the R^5 substituent is other than H. The intermediate **2-2** can be alkylated with an alkylating agent (e.g., an alkyl halide or an alkyl sulfate such as dimethyl sulfate) using a suitable base (e.g., (i) an alkali metal carbonate such as K_2CO_3 or Cs_2CO_3, (ii) an alkali metal hydride such as NaH, (iii) a metal alkoxide such as $Mg(OMe)_2$, or (iv) the combination of (i) and (iii) in successive steps) to give a mixture of N- and O-alkylated products **3-1** and **3-2**. A similar method using alkali metal carbonates is described in T. Ukita et.al., *Chem. Pharm. Bull.* 2000, 48 (4): 589-591. Analogs possessing a non-H R^5 substituent can also be prepared by hydrolysis of the N-alkylated product **3-1** with a nucleophile such as hydroxide to afford the acid **3-3**, followed by conversion to the acid chloride **3-4** using a suitable agent like thionyl chloride or oxalyl chloride/catalytic DMF, similar to the method

described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 388. The acid **3-3** can be coupled with an amine using a peptide coupling reagent such as BOP, or, alternatively, the acid chloride **3-4** can be treated directly with an amine to give the amide. The O-alkylated groups can then be removed under acidic conditions (e.g., using a strong acid like HBr in a suitable solvent like acetic or propionic acid, or using p-toluene sulfonic acid, or a reagent like BBr_3) to give **3-5**, similar to the method described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 384. A similar sequence of hydrolysis, acid chloride formation, coupling and de-protection, starting from the bis-O-alkylated compound **3-2**, can allow the preparation of compounds **2-3**.

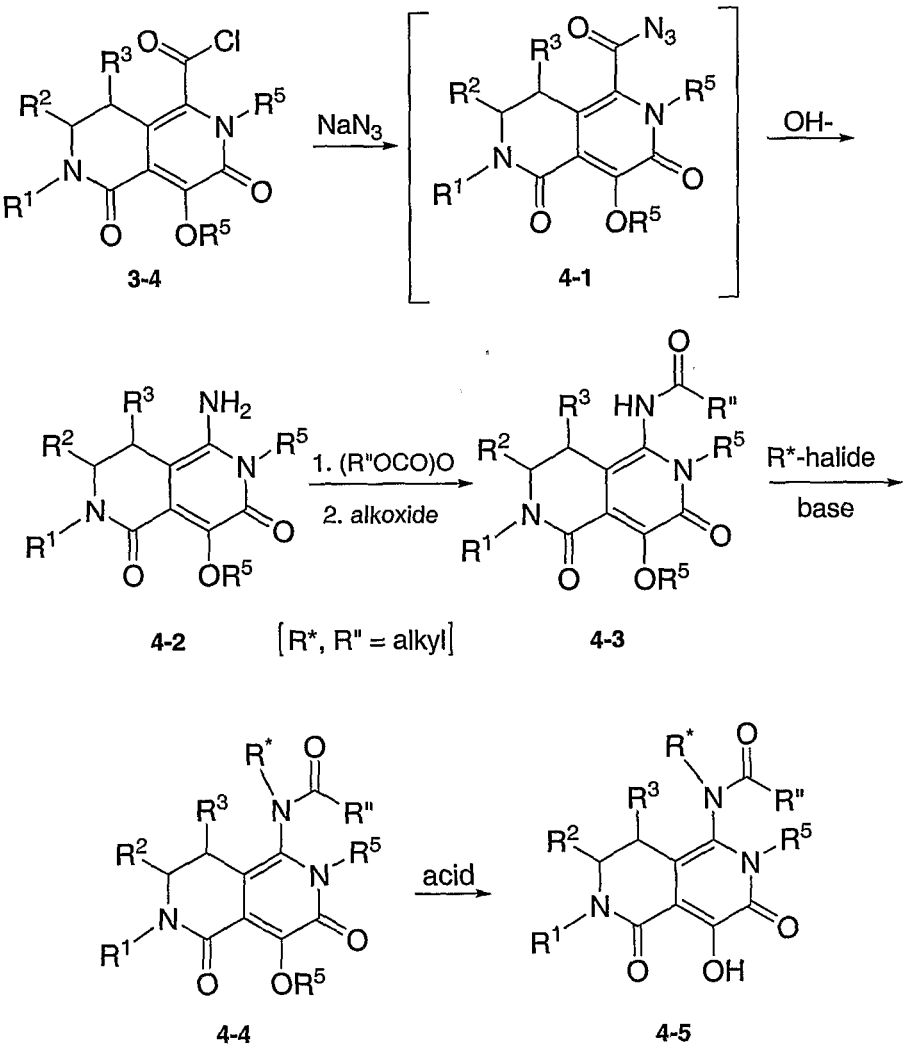
SCHEME 3



Scheme 4 depicts a method for preparing compounds of the invention in which the R^4 group is linked to the parent template via a nitrogen-carbon bond. Acid chloride 3-4 can be treated with sodium azide to give the acyl azide, which will undergo Curtius rearrangement followed by hydrolysis to the amine **4-2**, similar to the method described in R.J. Borchis et.al. *J. Med. Chem.* (1981), 24, 1518-

1521. The amine may then be acylated or sulfonylated with the appropriate agent like an acyl or sulfonyl anhydride or acyl or sulfonyl chloride to give the mono or bis N-acyl or N-sulfonylated intermediate, which can then be converted to product **4-3** by using a suitable nucleophile like sodium methoxide or sodium hydroxide. The amine can further be modified by alkylation with a suitable alkyl halide under the influence of a base (e.g., Cs_2CO_3 or K_2CO_3, using a method similar to that described in A. Nadin, et.al. *J. Org. Chem.* (2003), 68(7), 2844-2852, to give compounds **4-4**. The O-alkyl group can then be removed with a strong acid like HBr to give **4-5**.

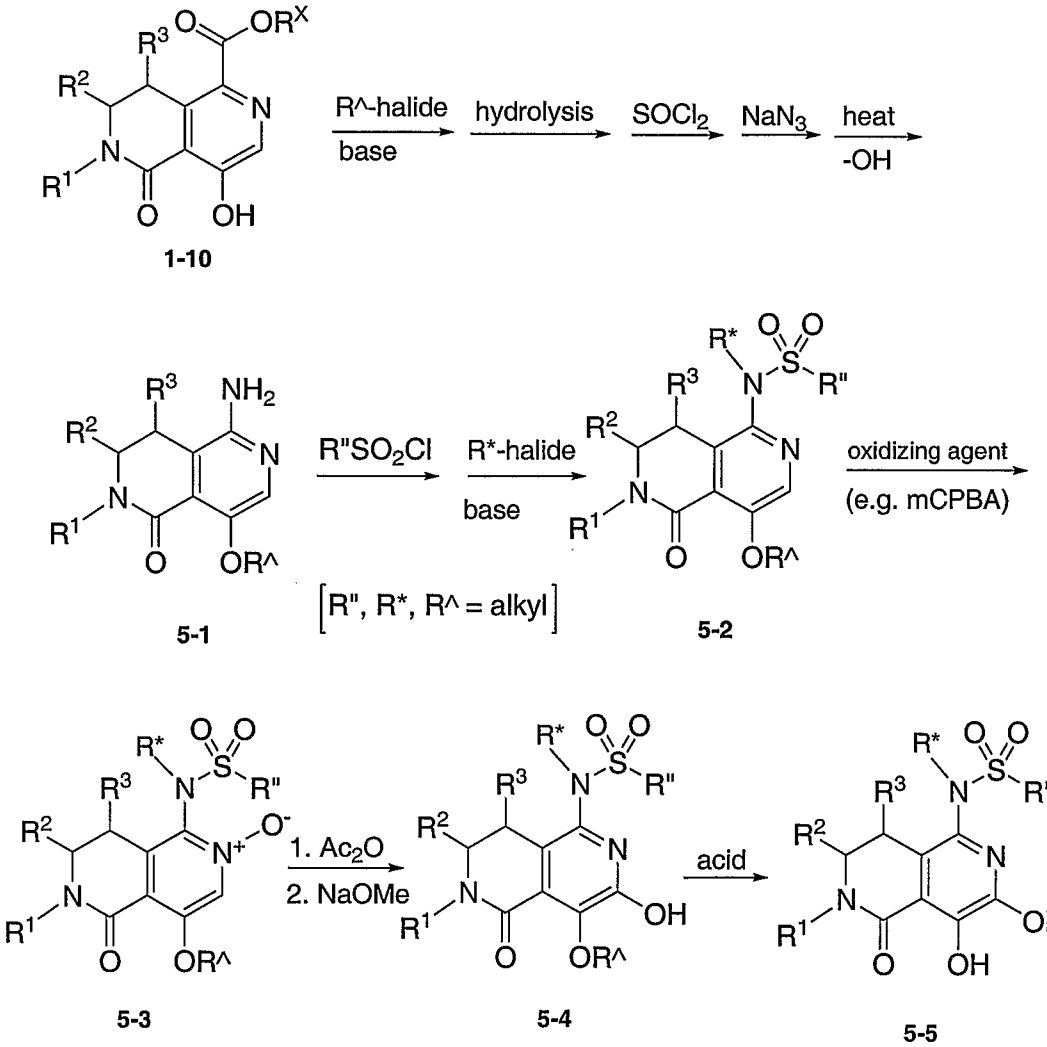
SCHEME 4



Scheme 5 depicts an alternative sequence of transformations similar to those described in the above schemes. Starting with the intermediate **1-10**, O-alkylation, hydrolysis of the ester to the acid,

acid chloride formation, acyl azide formation, Curtius rearrangement and hydrolysis give the intermediate **5-1**, which can be derivatized with various acyl or sulfonyl halides, and then alkylated to give **5-2**. N-oxide formation, similar to that described in M. Adamczyk, *Tetrahedron* (2002) 58, 6951-6963, followed by rearrangement in acetic anhydride and hydrolysis will give **5-4**, and cleavage of the O-alkyl group in acid will afford **5-5**.

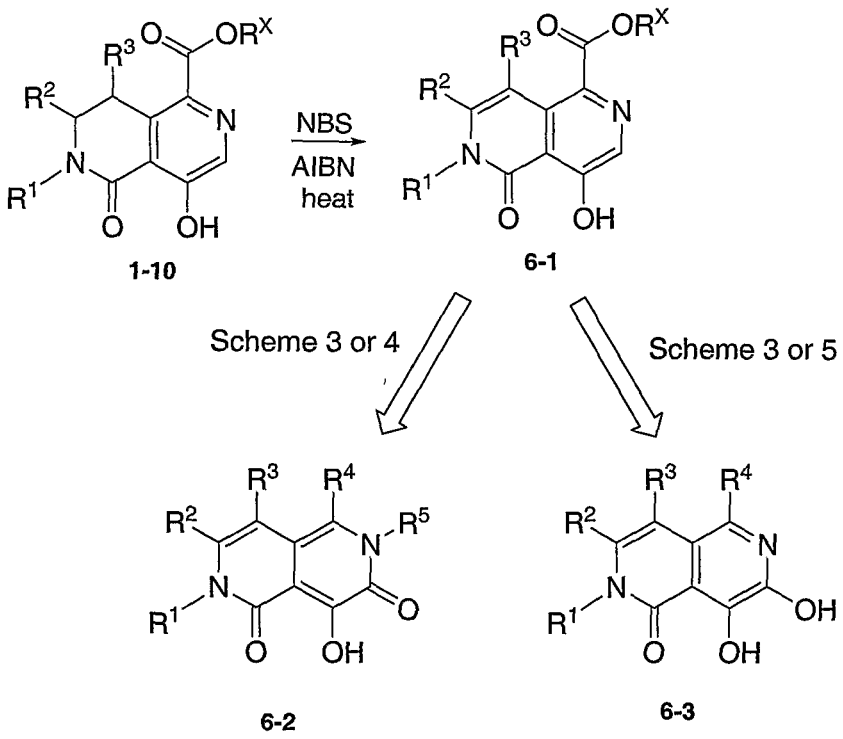
SCHEME 5



Scheme 6 depicts a route to compounds containing a double bond in the "a" position. These analogs can be prepared from treatment of an intermediate like **1-10** with a brominating agent (e.g., NBS) followed by elimination to give the double bond, similar to the method described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 914. The intermediate

6-1 can then be taken through a series of transformations as previously outlined to give products **6-2** and **6-3**.

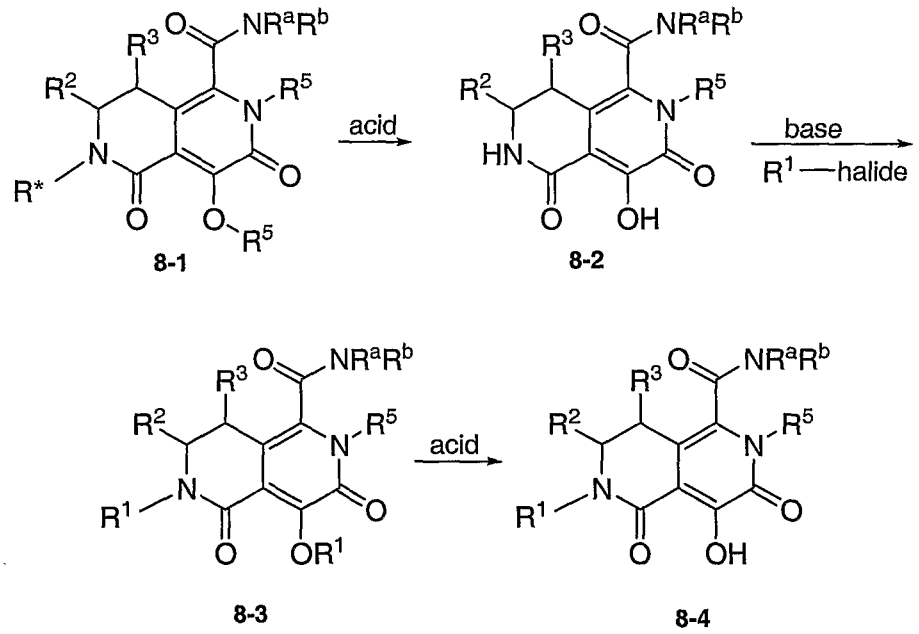
SCHEME 6



There is no Scheme 7.

Scheme 8 depicts a method for preparing analogs with R^1 substituents from starting substrate **8-1** with a removable R^* group. Substrate **8-1**, containing an R^* functional group (i.e., a group which is readily removable from an amide moiety, such as p-methoxybenzyl, 3,4- or 2,4-bismethoxybenzyl, allyl, or tosyl), can be prepared by coupling a suitable acid **3-3** or acid chloride **3-4** with an amine (see Scheme 3), and can be de-protected with a strong acid like p-toluene sulfonic acid in a manner similar to the method described in W.M. Kan et.al., *Tetrahedron* 2000, 44: 1039-1041 to give intermediate **8-2**. Deprotected compound **8-2** can then be bis-alkylated with a suitable alkyl halide using a base (e.g., NaH) to give the N,O-alkylated intermediate **8-3**. Removal of the O-alkyl group with strong acid (e.g., HBR in a solvent such as acetic or propionic acid) will then afford the product **8-4**.

SCHEME 8



8-1 8-2 8-3 8-4

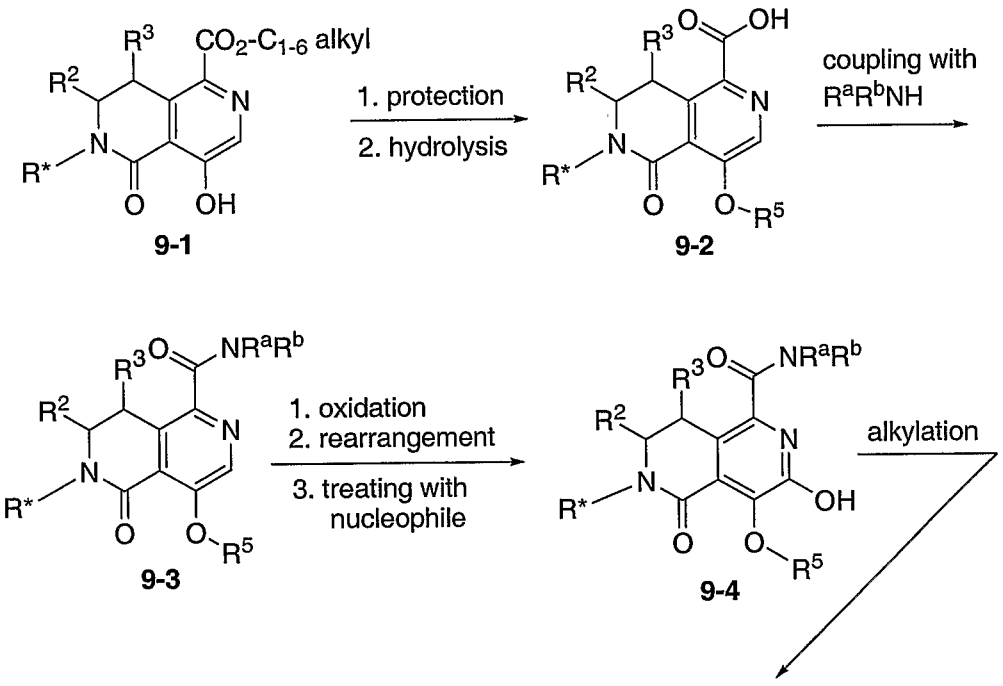
Scheme 9 depicts an alternative method for preparing naphthyridine carboxamide analog intermediate **8-1** embraced by the present invention in which the amide substituent is incorporated early in the reaction scheme, and in which the R^* substituent (defined in Scheme 8) is used to allow variation of R^1 at a late stage in the synthesis. Starting material **9-1** can be prepared in a manner similar to that used for **1-10**, incorporating the removable group in the initial alkylation step as described for **1-2**. The phenolic group in **9-1** can be protected with a suitable alkyl protecting group (e.g., an R^5 group as defined herein other than H) followed by hydrolysis with a nucleophile such as hydroxide to afford **9-2**. Protection can be accomplished, for example, by treatment with a diazomethane reagent (e.g., TMS diazomethane) in solvent (e.g., chloroform) or by alkylation with an alkylating agent (e.g., by contact with an alkyl halide or an alkyl sulfate such as dimethyl sulfate) in the presence of a suitable base (e.g., an alkali metal carbonate such as K_2CO_3 or Cs_2CO_3 or an alkali metal hydride such as NaH) in a solvent such as DMSO or methylene chloride. The acid **9-2** can be coupled with an amine using a peptide coupling reagent such as EDC to obtain **9-3**. The intermediate **9-3** can then be treated with a suitable oxidizing agent (e.g., mCPBA or peracetic acid) to obtain the N-oxide, which can then be treated as described Suzuki et al. *J. Med. Chem.* 1992, 35, 4045-4053 with acetic anhydride to effect the rearrangement to the O-acylated intermediate, and then treated with a nucleophile (e.g., an alkoxide such as NaOMe) to afford the dioxohexahydro-2,6-naphthyridine-1-carboxylate **9-4**. Intermediate **9-4** can be alkylated with an alkylating agent (e.g., an alkyl halide or an alkyl sulfate such as dimethyl sulfate) using a suitable base (e.g., an alkali metal carbonate such as K_2CO_3 or Cs_2CO_3, an alkali metal hydride such

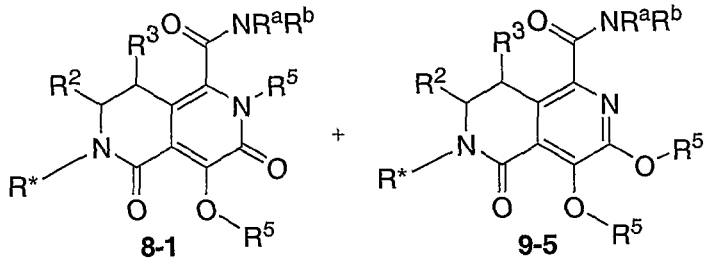
as NaH, or a metal alkoxide such as $Mg(OMe)_2$) in a solvent like DMSO to give a mixture of N- and O-alkylated products **8-1** and **9-5**. A similar use of alkali metal carbonates is described in T. Ukita, et.al. *Chem. Pharm. Bull.* 2000, 48 (4) 589-591.

When R* is a benzyl analog containing a chloro in the benzyl ring the chloro can be removed via catalytic dechlorination (e.g., in the presence of 10% palladium on charcoal in methanol) under an atmosphere of hydrogen using conditions similar to those described in M. Freifelder, Catalytic Hydrogenation in Organic Synthesis Procedures and Commentary, John Wiley& Sons, 1978, pp. 121. See, e.g., Examples 69 and 70.

When R* is a benzyl analog, the benzyl can be iodinated with a suitable iodinating reagent (e.g., N-iodosuccinimide) in the presence of an acid (e.g., trifluoromethanesulfonic acid or TFA) in a manner similar to that described in Olah et al., *J Org. Chem.* 1999, 3194, or Castanet et al., *Tetrahedron. Lett.* 2002, 5047. See, e.g., Examples 71 and 72.

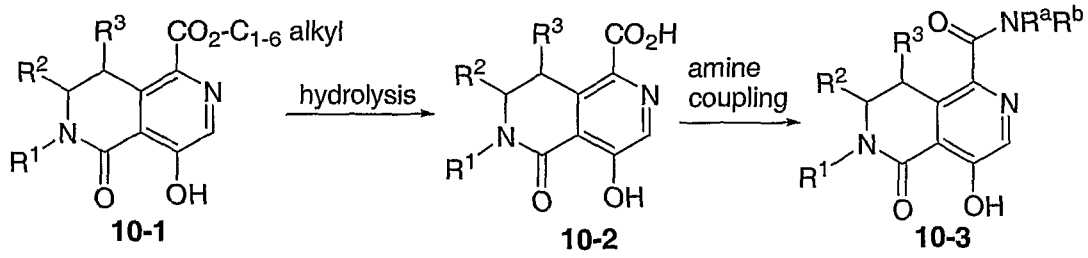
SCHEME 9

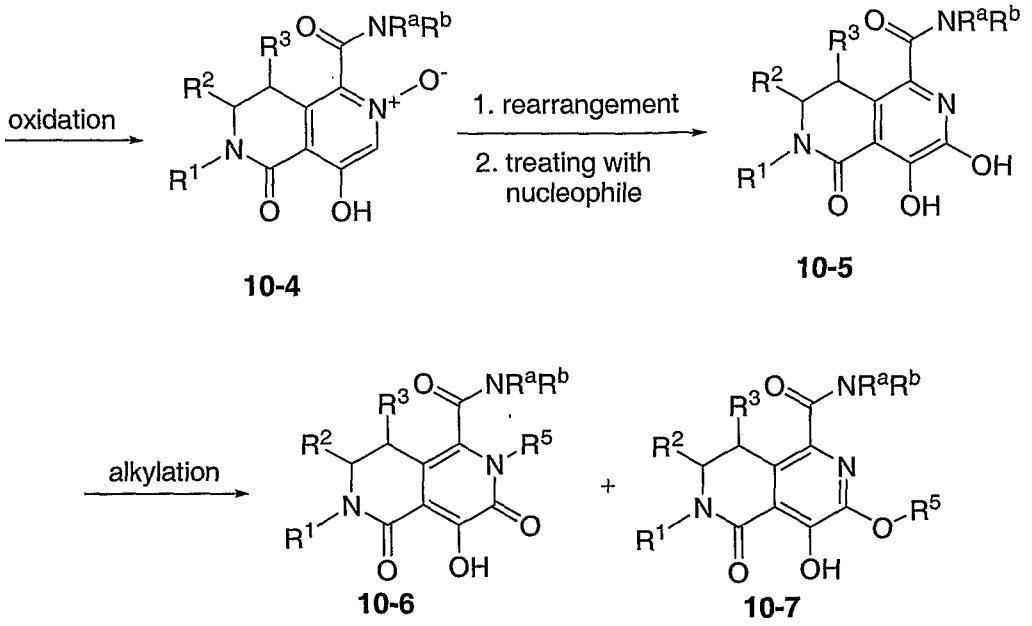




Scheme 10 depicts an alternative method for preparing naphthyridine carboxamide analogs embraced by the present invention in which the R^5 substituent is other than H, starting from naphthyridine intermediate **10-1**. Hydrolysis of the pyridine **10-1** with a nucleophile such as hydroxide can afford the acid **10-2**, which can be coupled with an amine using a peptide coupling reagent such as BOP to afford amide **10-3**. Alternatively, **10-2** can be converted to the acid chloride using a suitable agent like thionyl chloride or oxalyl chloride/catalytic DMF, similar to the method described in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 388, and the acid chloride treated directly with an amine to give the amide **10-3**. The intermediate **10-3** can then be treated with a suitable oxidizing agent (e.g., mCPBA or peracetic acid) to obtain the N-oxide **10-4**, which can then be treated as described Suzuki et al. *J. Med. Chem.* 1992, 35, 4045-4053 with acetic anhydride to effect the rearrangement to the O-acylated intermediate, and then treated with a nucleophile (e.g., an alkoxide such as NaOMe) to afford the desired dioxohexahydro-2,6-naphthyridine-1-carboxylate **10-5**. Intermediate **10-5** can be alkylated with an alkylating agent (e.g., an alkyl halide or an alkyl sulfate such as dimethyl sulfate) using a suitable base (e.g., an alkali metal carbonate such as K_2CO_3 or Cs_2CO_3, an alkali metal hydride such as NaH, or a metal alkoxide such as $Mg(OMe)_2$)) in a solvent like DMSO to give a mixture of N- and O-alkylated products **10-6** and **10-7**. A similar use of alkali metal carbonates is described in T. Ukita, et.al. *Chem. Pharm. Bull.* 2000, 48 (4) 589-591.

SCHEME 10

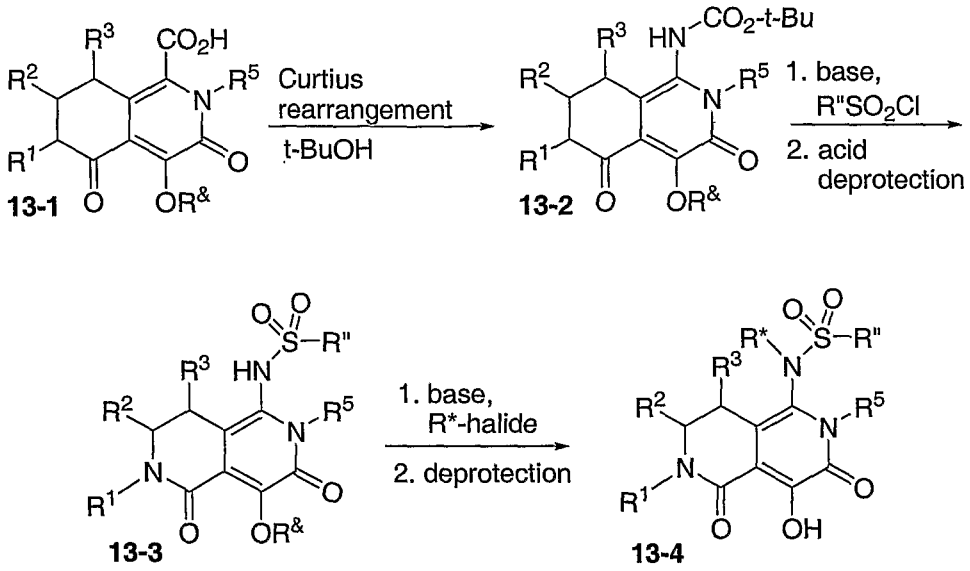




There are no Schemes 11 and 12.

Scheme 13 depicts a method for preparation of napthyridine sulfonamides. The carboxylic group in intermediate **13-1**, which can be prepared as described in Scheme 3, can be converted to the corresponding tert-butyl carbamate **13-2** via a Curtius rearrangement in the manner described in J. March, Advanced Organic Chemistry, 3rd edition, John Wiley& Sons, 1992, p. 1091 (e.g., acid **13-1** can be treated with diphenylphosphoryl azide in the presence of anhydrous tert-butanol to afford carbamate **13-2**). Carbamate **13-2** can then be treated with base (e.g., as sodium hydride or sodium bis(trimethyl)silylamide), followed by contact with a sulfonylation reagent (e.g., an alkane sulfonyl chloride) to proivde an intermediate sulfonylated carbamate, which can be transformed to the corresponding sulfonamide **13-3** by treatment with acid (e.g., TFA) in a manner similar to the conditions described in T. W. Greene & P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley& Sons, 1999, p. 520. Treatment of **13-3** with a base (e.g., sodium hydride or sodium bis(trimethyl)silyl-amide), followed by alkylation with a suitable reagent (e.g., an alkyl halide such as methyl iodide) and then by removal of the ether protecting group (see Schemes 2 and 11) to afford the desired **13-4**.

Scheme 13

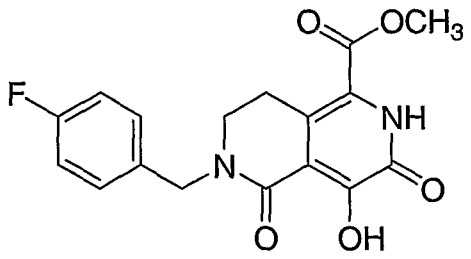


Unless a contrary meaning is clear from the context, a reference herein to "equivalent" or "equivalents" means molar equivalent(s).

The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention. In the following examples "MS (M+1)" refers to the mass of the molecular ion plus 1 of the subject compound as determined by mass spectroscopy.

EXAMPLE 1

Methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate



Step 1: 1-(4-Fluorobenzyl)piperidine-2-one

To a suspension of sodium hydride (2.4 g, 0.1 mol) in anhydrous THF (400 mL) was added piperidine-2-one (9.0 g, 90 mmol) in anhydrous THF (20 mL) over 10 minutes. After 20 minutes, the resultant thick slurry was treated with 4-fluorobenzyl bromide (18.9 g, 99.9 mmol). The reaction mixture was refluxed overnight. The resultant mixture was cooled to 0 °C and treated with H_2O (10 mL)

cautiously. The mixture was stirred for 10 minutes and concentrated under vacuum. The residue was partitioned between ethyl acetate (300 mL) and H_2O. The organic extract was washed with brine, dried with $MgSO_4$, filtered, and concentrated under vacuum. The residual oil was subjected to column chromatography on silica gel eluting with 50 % - 70 % ethyl acetate in hexanes. The appropriate fractions were combined and concentrated to afford the benzylated piperidinone as a white solid. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.23 (dd, *J*= 8.7 Hz, 5.4 Hz, 2H), 7.00 (t, *J*=8.7 Hz, 2H), 4.56 (s, 2H), 3.18 (t, *J*=6 Hz, 2H), 2.46 (t, *J*=6 Hz, 2H), 1.79 (m, 4H).

Step 2: 1-(4-fluorobenzyl)-3-(phenylsulfinyl)piperidin-2-one

To a cooled (0 °C) solution of 1-(4-fluorobenzyl)piperidine (5.0g, 24.1 mmol) in anhydrous THF (100 mL) was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 53 mL, 53 mmol) dropwise, and the solution was stirred for one half hour. The solution was treated with methyl benzene sulfinate (5.65g, 36.1 mmol) in anhydrous THF (3 mL) dropwise. After 30 minutes at 0 °C, the resultant mixture was quenched with water and partitioned between 10% $KHSO_4$ and $CHCl_3$, the layers separated and the aqueous extracted several more times with $CHCl_3$. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to afford 1-(4-fluorobenzyl)-3-(phenylsulfinyl)piperidin-2-one as a waxy solid that was taken on to the next step. ES MS M+1 = 332

Step 3: 1-(4-Fluorobenzyl)-5,6-dihydropyridin-2-(1*H*)-one

To a solution of 1-(4-fluorobenzyl)-3-(phenylsulfinyl)piperidin-2-one (0.37 g, 1.11 mmol) in toluene (15 mL) was added solid Na_2CO_3 (2g, 18.8 mmol). The reaction mixture was refluxed for about 6 hours. The resultant solution was filtered and concentrated under vacuum and the residue chromatographed on silica eluting with a gradient of 0-40% EtOAc/Hexanes to give the product as colorless glass.

^{1}HNMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.01 (m, 2H), 6.56 (dt, *J*=9.9 Hz, 4.2 Hz, 1H), 6.00 (dt, *J*=9.7 Hz, 1.8 Hz, 1H), 4.59 (s, 2H), 3.32 (t, *J*=7.2 Hz, 2H), 2.33 (m, 2H).

Step 4: Methyl[(2-methoxy-2-oxoethyl)amino](oxo)acetate

To a cooled (0 °C) solution of the glycine methyl ester HCl salt (30.0 g, 0.24 mol) in methylene chloride (500 mL) was added triethylamine (50.8 g, 0.50 mol). Methyl oxalyl chloride (29.3 g, 0.24 mol) was carefully added dropwise. The reaction solution warmed to room temperature and stirred overnight. The product mixture was partitioned between H_2O and methylene chloride. The organic extract was dried with Na_2SO_4 and concentrated under vacuum to afford the title compound as a brown oil.

^{1}HNMR (400 MHz, $CDCl_3$) δ 7.59 (br, 1H), 4.14 (d, *J*=5.6 Hz, 2H), 3.93 (s, 3H), 3.79 (s, 3H). ES MS M+1 = 176

Step 5: Methyl 5-methoxy-1, 3-oxazole-2-carboxylate

To a warm (35 - 40 °C) suspension of phosphorous pentoxide (77.7 g, 109 mmol) in anhydrous acetonitrile (200 mL) was added methyl[(2-methoxy-2-oxoethyl)amino](oxo)acetate (19.19 g, 109.6 mmol). The reaction mixture was heated to 65 °C, then stirred overnight at room temperature. The product mixture was cooled to 0 °C and carefully quenched with ice and brine keeping the reaction from generating an unsuitable exotherm. The resultant mixture was extracted with ethyl acetate (600 mL). The organic extract was washed with brine, dried with Na_2SO_4, then concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 100 % CH_2Cl_2. The appropriate fractions were combined and concentrated to afford the title compound as a light yellow solid that was used without further purification.
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (s, 1H), 4.01 (s, 3H), 3.96 (s, 3H). ES MS M+1 =158

Step 6: Methyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

In a sealed tube, 1-(4-fluorobenzyl)-5,6-dihydropyridin-2-(1*H*)-one (3.84 g, 18.7 mmol), and methyl 5-methoxy-1,3-oxazole-2-carboxylate prepared in Step 5 (2.94 g, 18.7 mmol), were combined. The reaction mixture was heated at 120 °C. After 24 hours, the resultant mixture was cooled and methanol saturated with HCl (2 mL) was added. The product mixture stirred at room temperature for 40 minutes, then was concentrated under vacuum. The residual crude material was diluted with DMSO (6.0 mL) and filtered to give the title compound.
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (br, 1H), 8.39 (s, 1H), 7.31 (m, 2H), 7.06 (t, *J*=8.5 Hz, 2H), 4.72 (s, 2H), 3.94 (s, 3H), 3.50 (m, 4H). ES MS M+1 =331

Step 7: Methyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide

To a solution of methyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (0.509 g, 1.541 mmol) in acetic acid (2 mL) was added hydrogen peroxide (35 % wt % in H_2O, 0.262 g, 7.705 mmol). The reaction mixture was heated to 100 °C for 1 hour. The product mixture was concentrated under vacuum and purified by reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound as a yellow solid.

^{1}HNMR (400 MHz, CD_3OD) δ 7.95 (s, 1H), 7.38 (dd, *J*=5.3 Hz, 8.6 Hz, 2H), 7.08 (t, *J*=8.8 Hz, 2H), 4.71 (s, 2H), 3.93 (s, 3H), 3.56 (t, *J*=6.7 Hz, 2H), 2.89 (t, *J*=6.7 Hz, 2H). ES MS M+1 = 347

Step 8: Methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

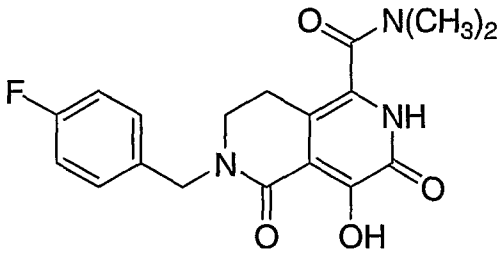
To methyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide (0.178 g, 0.514 mmol) was added acetic anhydride (0.157 g, 1.542 mmol) and refluxed. After 1 hour, the reaction mixture was concentrated under vacuum, then sodium methoxide (30 wt. % in methanol, 0.083 g, 1.540 mmol) was added. After stirring at room temperature for 1 hour, the product mixture was concentrated under vacuum. The residue was purified by reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound as a pale yellow solid.

^{1}HNMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J*=5.3 Hz, 8.4 Hz, 2h), 7.06 (t, *J*=8.5 Hz, 2H), 4.71 (s, 2H), 3.93 (s, 3H), 3.46 (t, *J*=6.5 Hz, 2H), 3.32 (t, *J*=6.5 Hz, 2H).

ES MS M+1 = 347

EXAMPLE 2

6-(4-Fluorobenzyl)-4-hydroxy-*N*,*N*-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



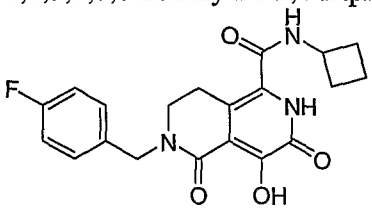
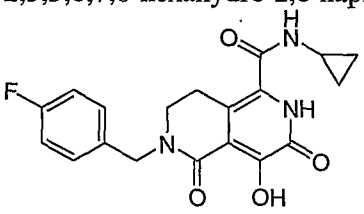
To a cooled (-10 °C) solution of dimethylamine (2M in THF, 0.002 g, 0.035 mmol) was slowly added trimethylaluminum (2M in toluene, 0.002 g, 0.035 mmol) and stirred for 30 minutes at room temperature. The reaction mixture was cooled to -10 °C and methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (0.004 g, 0.012 mmol, Example 1, Step 8) in THF (5 mL) was added. The reaction stirred at room temperature for 2 hours, then transferred via syringe to a solution of 1:1 CH_2Cl_2:0.5 N aq. HCl at 0 °C and stirred for 1 hour. The product mixture was separated, and the aqueous was extracted three times with CH_2Cl_2. The aqueous layer was treated with saturated Na_2CO_3 solution to pH 5 and extracted three times with CH_2Cl_2 again. The organic combined extracts were dried with Na_2SO_4 and concentrated under vacuum. The residue was

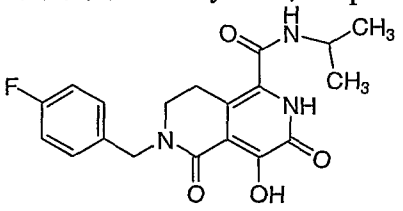
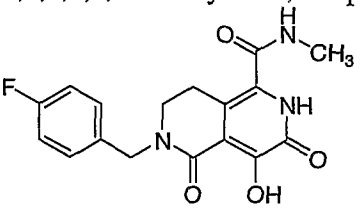
purified by reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound as a light yellow solid.

^1H NMR (400 MHz, CD_3OD) δ 7.39 (dd, *J*= 5.3 Hz, 8.6 Hz, 2H), 7.09 (t, *J*=8.8 Hz, 2H), 4.74 (s, 2H), 3.50 (t, *J*=6.4 Hz, 2H), 3.05 (s, 3H), 2.96 (s, 3H), 2.67 (t, *J*=6.4 Hz, 2H) ppm. ES MS M+1 = 360

EXAMPLES 3 - 6

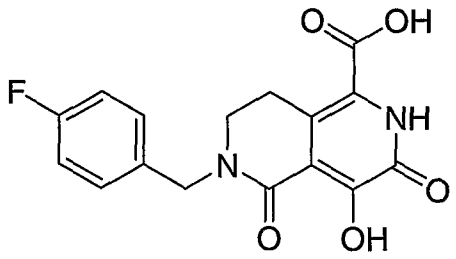
The compounds in the following table were prepared in accordance with the procedure set forth in Example 2 using the appropriate analogous starting materials.

Example	Compound	Data
3	*N*-Cyclobutyl-6-(4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide 	^{1}HNMR (400 MHz, CD_3OD) δ 7.39 (dd, *J*=5.6 Hz, 8.7 Hz, 2H), 7.09 (t, *J*=8.7 Hz, 2H), 4.74 (s, 2H), 4.39 (p, *J*=7.9 Hz, 1H), 3.49 (t, *J*=6.1 Hz, 2H), 3.06 (t, *J*=6.1 Hz, 2H), 2.32 (m, 2H), 2.04 (m, 2H), 1.78 (m, 2H) ppm. ES MS M+1 = 386
4	*N*-Cyclopropyl-6-(4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide 	^{1}HNMR (400 MHz, $CDCl_3$) δ 13.53 (br, 1H), 7.63 (br, 1H), 7.30 (dd, *J*=5.6 Hz, 8.5 Hz, 2H), 7.06 (t, *J*=8.5 Hz, 2H), 4.71 (s, 2H), 3.51 (m, 2H), 3.46 (m, 2H), 2.86 (m, 1H), 1.88 (br, 1H), 0.83 (q, *J*=5.9 Hz, 2H), 0.71 (m, 2H) ppm. ES MS M+1 = 372

5	6-(4-Fluorobenzyl)-4-hydroxy-*N*-isopropyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide 	^{1}HNMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J*=5.7 Hz, 8.8 Hz, 2H), 7.06 (t, *J*=8.8 Hz, 2H), 6.89 (d, *J*=7.3 Hz, 1H), 4.82 (br, 1H), 4.71 (s, 2H), 4.17 (m, 1H), 3.47 (t, *J*=6.3 Hz, 2H), 3.35 (t, *J*=6.3 Hz, 2H), 1.26 (d, *J*=6.1 Hz, 6H) ppm. ES MS M+1 = 374
6	6-(4-fluorobenzyl)-4-hydroxy-N-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide 	^{1}H NMR (400 MHz, CD_3OD) δ 7.38 (m, 2H), 7.08 (m, 2H), 4.73 (s, 2H), 3.48 (t, J = 6.6 Hz, 2H), 3.08 (t, J = 6.5 Hz, 2H), 2.85 (s, 3H) ppm. MS m/z 346.3 (M +1).

EXAMPLE 7

6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid

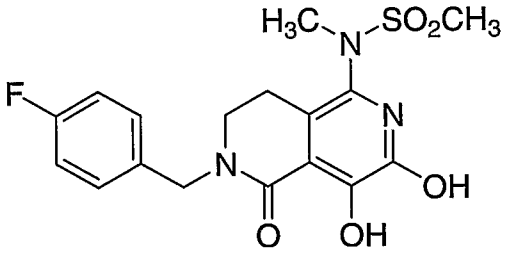


To methyl 6-(4-fluorobenzyl)-4-hydroxy-3,5-dioxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (0.178 g, 0.514 mmol) in wet methanol was added N,N-dimethylamine in MeOH (4.0 eq.). The reaction mixture was put in a microwave reactor where it was heated at 130 °C for 1.5 hours, after which the reaction mixture was concentrated under vacuum. The residue was purified by reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound as a solid. . Alternatively, the starting material can be treated with LiOH in 1:1:1 THF/MeOH/H_2O to give the product.

^{1}HNMR (400 MHz, CD_3OD) δ 7.38 (m, 2H), 7.06 (m, 2H), 4.74 (s, 2H), 3.48 (m, 2H), 3.32 (m, 2H). ES MS M+1 = 333

EXAMPLE 8

N-[6-(4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide



Step 1: 1-(glycyloxy)butane chloride

To a suspension of glycine hydrochloride (10g, 89.6 mmol) in 250 mL butanol under nitrogen was added thionyl chloride (45.7 mL, 627 mmol) dropwise. After the addition was complete, the solution was heated at 70 °C overnight. The volatile components were removed on the roto-evaporator and the residue was suspended and evaporated from toluene three times. The resulting crude gum was dissolved in an equal weight of toluene for easy transfer and was used as is in the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.5 (bs, 3H), 4.18 (t, *J*=6.7 Hz, 2H), 4.0 (bs, 2H), 1.62 (m, 2H), 1.38 (m, 2H), 0.92 (t, *J*=7.4 Hz, 3H) ppm. ES MS M+1 = 132.

Step 2: Butyl N-[ethoxy(oxo)acetyl]glycinate

A 1:1 by weight solution of 1-(glycyloxy)butane chloride (10g, 59.6 mmol) in toluene (10g) was treated with EtOH ((100 mL), then Triethylamine (10 mL, 71.6 mmol) and diethyloxalate (16.2 mL, 119.3 mmol) and heated to 50 °C for three hours. . The volatile components were removed on the roto-evaporator and the residue was dissolved in $CHCl_3$, washed two times with 10% $KHSO_4$, the aqueous layer was washed two times with $CHCl_3$, the organic layers were combined, dried over Na_2SO_4, filtered and evaporated to give the crude oil, which was chromatographed on silica eluting first with 20% EtOAc/hexanes and then with 50% EtOAc/hexanes to give clean product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (bs, 1H), 4.37 (q, *J*=7.2 Hz, 2H), 4.2 (t, , *J*=6.6 Hz, 2H), 4.12 (d, *J*=5.5 Hz, 2H), 1.64 (p, *J*=6.8 Hz, 2H), 1.39 (t, *J*=7.15 Hz, 3H), 1.37 (m, buried, 2H), 0.94 (t, , *J*=7.4 Hz, 3H) ppm. ES MS M+1 = 232

Step 3: Ethyl 5-butoxy-1,3-oxazole-2-carboxylate

A suspension of P_2O_5 (22g, 155.6 mmol) in CH_3CN (50 mL) under nitrogen was warmed to 50 °C and treated with butyl N-[ethoxy(oxo)acetyl]glycinate (6g, 25.9 mmol) dissolved in 10 mL CH_3CN. The mixture was heated to 65 °C for 1.5 hours, then cooled in an ice bath. Ice and brine were added to the reaction mixture, then EtOAc was added and the mixture transferred to a separatory funnel. $CHCl_3$ was added to dissolve solids and the organic layer was isolated. The aqueous layer was washed repeatedly with $CHCl_3$ and EtOAc, the organic layers were combined and dried with Na_2SO_4, then concentrated. The residue was chromatographed on silica eluting with a gradient of 0-30% EtOAc/Hexanes to give the product as a clear, colorless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 4.42 (q, *J*=7.15 Hz, 2H), 4.18 (t, *J*=6.4 Hz, 2H), 1.8 (p, *J*=6.4 Hz, 2H), 1.47 (p, *J*=7.4 Hz, 2H), 1.41 (t, *J*=7.15 Hz, 3H), 0.97 (t, *J*=7.4 Hz, 3H) ppm. ES MS M+1 = 214.

Step 4: Ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

In a heavy walled round bottom flask with screw top were combined ethyl 5-butoxy-1,3-oxazole-2-carboxylate (2.53g, 11.88mmol) and 1-(4-fluorobenzyl)-5,6-dihydropyridin-2-(1*H*)-one (1.22g, 5.94 mmol; see Example 1, Step 3) and trifluoroacetic acid (0.46 mL, 5.94 mmol). The vessel was sealed and placed in an oil bath heated to 130 °C. The reaction mixture was stirred for 3 days. The dark brown reaction mixture was cooled and a crystalline precipitate formed. The mixture was diluted with ether and the solids collected by filtration and washed with ether to give the product as tan shiny plates. Further product can be obtained by evaporating the mother liquor, adding more trifluoroacetic acid and re-heating the mixture.

^1H NMR (400 MHz, $CDCl_3$) δ 12.9 (s, 1H), 8.42 (s, 1H), 7.31 (dd, *J*=5.3, 8.8 Hz, 2H), 7.06 (t, *J*=8.6 Hz, 2H), 4.72 (s, 2H), 4.41 (q, *J*=7.15 Hz, 2H), 3.50 (m, 4H), 1.41 (t, *J*=7.15 Hz, 3H) ppm. ES MS M+1 = 345.

Step 5: Ethyl 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

To a solution of chloroform (10 mL) and methanol (10 mL) was added trimethylsilyl diazomethane (2.0 M in hexanes, 5 mL, 0.01 mole). After stirring for 10 minutes at room temperature, ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (1.6 g, 3.5 mmol) in chloroform was added. After 7 hours, methanol (5 mL) and trimethylsilyl diazomethane (2.5 mL, 0.005 mole) was added to the reaction mixture. After 1 hour, glacial acetic acid (3 mL) was added

with gas evolution observed. The solution was stirred for 0.5 hour. The product mixture was concentrated under vacuum. The residual material was subjected to column chromatography on silica gel eluting with 0-100 % ethyl acetate in hexanes. The appropriate fractions were combined and concentrated to afford the title compound as a foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.32 (dd, *J*=5.3, 8.5 Hz, 2H), 7.03 (t, *J*=8.6 Hz, 2H), 4.73 (s, 2H), 4.45 (q, *J*=7.14 Hz, 2H), 4.11 (s, 3H), 3.43 (t, *J*=6 Hz, 2H), 3.29 (t, *J*=6 Hz, 2H), 1.42 (t, *J*=7.2 Hz, 3H) ppm. ES MS M+1 = 359

Step 6: 6-(4-Fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carboxylic acid

To a solution of ethyl 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (1.21 g, 3.38 mmol) in methanol (5 mL) and water (5 mL) and THF (5 mL) was added lithium hydroxide (0.425 g, 10.13 mmol). After 5 minutes, 1N HCl (3 equiv.) was added to the product mixture, which was then dried under vacuum to provide the crude title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (br, 1H), 8.35 (s, 1H), 7.27 (m, 2H), 7.03 (m, 2H), 4.73 (s, 2H), 4.15 (s, 3H), 3.55 (m, 4H) ppm. ES MS M+1 = 331

Step 7: 6-(4-Fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carbonyl chloride

A solution of 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carboxylic acid (1.11 g, 3.36 mmol) in thionyl chloride (0.4 g, 3.36 mmol) was heated to 110 °C. After 0.5 hours, the product mixture was concentrated under vacuum. The residue was suspended in toluene, evaporated, then suspended in chloroform and evaporated to give the title compound. The product was assayed by quenching in methanol solution to produce the methyl ester. ES MS M+1 = 345 (methyl ester forms after quench in methanol)

Step 8: 5-Amino-2-(4-fluorobenzyl)-8-methoxy-3,4-dihydro-2,6-naphthyridin-1(2H)-one

To a solution of sodium azide (0.24 g, 3.69 mmol) in water (2.5 mL) was added 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carbonyl chloride (1.17 g, 3.36 mmol) in acetone (15 mL). After 20 minutes, the product mixture was concentrated under vacuum to provide 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridine-1-carbonyl azide. The crude azide (1.19 g, 3.35 mmol) in DMF (20 mL) was heated to 110 °C. After 20 minutes, the product mixture was cooled for 10 minutes, then 1N NaOH (3.3 mL) was added. After 20 minutes, the mixture was concentrated under vacuum, re-dissolved in toluene and $CHCl_3$ and evaporated. The

residue was partitioned between $CHCl_3$ and saturated sodium bicarbonate. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound.
^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.32 (m, 2H), 7.03 (t, *J*=9 Hz, 2H), 4.71 (s, 2H), 4.17 (s, 2H), 3.94 (s, 3H), 3.47 (t, *J*=6 Hz, 2H), 2.58 (t, *J*=6 Hz, 2H) ppm. ES MS (M+1) = 302.

Step 9: *N*-[6-(4-Fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]methanesulfonamide

To a solution of 5-amino-2-(4-fluorobenzyl)-8-methoxy-3,4-dihydro-2,6-naphthyridin-1(2H)-one (0.889 g, 2.95 mmol) in pyridine (5 mL) was added dropwise methanesulfonyl chloride (0.575 g, 5.016 mmol). After stirring for an hour at room temperature, the product mixture was quenched with pH 7 buffer, then concentrated under vacuum. The residue was dissolved in $CHCl_3$ and pH 7 buffer, the pH of the aqueous layer was adjusted to pH 5 with 1N NaOH and the layers separated. Several more extractions with $CHCl_3$ were performed. The organic extracts were dried with Na_2SO_4, filtered, and concentrated under vacuum, then dissolved in toluene and $CHCl_3$ and evaporated to provide the title compound.
^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.04 (t, *J*=9 Hz, 2H), 4.70 (s, 2H), 4.03 (s, 3H), 3.44 (t, *J*=6.5 Hz, 2H), 3.21 (s, 3H), 2.89 (t, *J*=6.4 Hz, 2H) ppm. ES MS (M+1) = 380.

Step 10: *N*-[6-(4-Fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide

To a solution of *N*-[6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]methanesulfonamide (0.097 g, 0.256 mmol) in DMF (2 mL) was added Cs_2CO_3 (0.083 g, 0.256 mmol) and MeI (0.04 g, 0.28 mmol, dissolved in DMF). After stirring for 2 hours, additional MeI (0.02 g, 0.14 mmol) was added. The product mixture was concentrated. The residue was partitioned between $CHCl_3$ and pH 7 buffer. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound.
^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.26 (m, 2H), 7.04 (t, *J*=9 Hz, 2H), 4.70 (s, 2H), 4.06 (s, 3H), 3.43 (t, *J*=7 Hz, 2H), 3.21 (s, 3H), 3.03 (m, 5H) ppm. ES MS (M+1) = 394.

Step 11: *N*-[6-(4-Fluorobenzyl)-4-methoxy-2-oxido-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide

To a solution of *N*-[6-(4-fluorobenzyl)-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide (0.35 g, 0.89 mmol) in CH_2Cl_2 (10 mL) was added mCPBA (1.08 g, 6.23 mmol) in portions. After stirring for 3.5 hours at reflux, the product mixture was

cooled to room temperature, 1 mL of ethanol was added, and the solution was concentrated. The residue was partitioned between $CHCl_3$ and saturated Na_2SO_3. The organic layer was extracted repeatedly with saturated sodium bicarbonate. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the crude title compound.

^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.30(m, 2H), 7.03 (t, *J*=7 Hz, 2H), 4.72 (d, *J*= 14.6 Hz, 1H), 4.65 (d, J = 14.6 Hz, 1H), 4.01 (s, 3H), 3.45 (m, 2H), 3.29 (s, 3H), 3.20 (s, 3H), 3.18 (m, 1H), 2.87 (m, 1H) ppm. ES MS (M+1) = 410.

Step 12: *N*-[6-(4-Fluorobenzyl)-3-hydroxy-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide

A solution of *N*-[6-(4-fluorobenzyl)-4-methoxy-2-oxido-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide (0.36 g, 0.889 mmol) in acetic anhydride (10 mL) was heated to 110 °C for 3 hours, then evaporated to dryness to give the intermediate 6-(4-fluorobenzyl)-4-methoxy-1-[methyl(methylsulfonyl)amino]-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-3-yl acetate (ES MS (M+1) = 452). The crude material was dissolved in methanol (6 mL) and treated with sodium methoxide (30 % by weight in methanol, 0.5 mL, 2.6 mmol). After 1 hour, the product mixture was neutralized with 6 N HCl, then concentrated. The residue was partitioned between $CHCl_3$ and 10% $KHSO_4$. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound.

^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.03 (t, *J*=9 Hz, 2H), 4.71 (bs, 2H), 4.06 (s, 3H), 3.41 (t, *J*=6 Hz, 2H), 3.28 (s, 3H), 3.11 (s, 3H), 2.8 (m, 2H) ppm. ES MS (M+1) = 410.

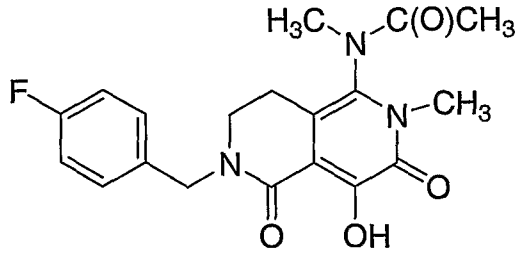
Step 13: N-[6-(4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide

To a solution of *N*-[6-(4-fluorobenzyl)-3-hydroxy-4-methoxy-5-oxo-5, 6, 7, 8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide (0.0207 g, 0.506 mmol) in CH_2Cl_2 (6 mL) was added 30% by weight HBr in propionic acid (0.196 g HBr, 2.42 mmol). Alternatively, 30% HBr in acetic acid can be used. After 1.5 hours, the product mixture was evaporated and the residue partitioned between $CHCl_3$ and 10% $KHSO_4$. The organic extract was dried with Na_2SO_4, filtered, and concentrated under vacuum. The residual material was purified using reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound.

^1H NMR (400 MHz, $CDCl_3$) δ 12.97 (br, 1H), 7.28 (m, 2H), 7.04 (t, *J*=9 Hz, 2H), 4.69 (s, 2H), 3.46 (t, *J*=7 Hz, 2H), 3.24 (s, 3H), 3.09 (s, 3H), 2.98 (m, 2H) ppm. ES MS (M+1) = 396.

EXAMPLE 9

N-[6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-methylacetamide



Step 1: Ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide

To ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (0.5 gm, 1.09 mmol; see Example 8, Step 4) in glacial acetic acid (25 mL) at room temperature under nitrogen was added, with stirring, aqueous peroxide (30% by wt) (1.24 mL, 10.9 mmol). The reaction was warmed to 100 °C and stirred for 1.5 hours. The reaction was allowed to cool, ethanol (1 mL) was added and volatile components were removed under reduced pressure. The resulting oil was placed under high vacuum for 16 hours, then used as is. Alternatively, after cooling, water can be added and the volatile components removed under reduced pressure. The residue can be partitioned between $CHCl_3$ and saturated Na_2SO_3. The organic extract can be dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound.

^1H NMR (400 MHz, $CDCl_3$) δ 12.8 (br, 1H), 7.90 (s, 1H), 7.28 (dd, J = 5.3, 8.5 Hz, 2H), 7.04 (t, J = 8.6 Hz, 2H), 4.69 (s, 2H), 4.43 (q, J = 7.14 Hz, 2H), 3.50 (t, J = 6.8 Hz, 2H), 2.87 (t, J = 6.8 Hz, 2H), 1.37 (t, J = 7.14 Hz, 3H) ppm. ES MS (M+1) = 361.

Step 2: Sodium 1-(ethoxycarbonyl)-6-(4-fluorobenzyl)-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-4-olate

To ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide (2.3 gm, 6.38 mmol) in neat acetic anhydride (24 mL) was stirred under nitrogen at 100 °C for 1 hour. The reaction was concentrated to an oil under reduced pressure and dry methanol (20 mL) was added followed by a methanolic sodium methoxide solution (30% by wt) (4.54 mL, 25.2 mmol). The reaction was stirred at room temperature for 1 hour. The reaction was then concentrated to an oil under reduced pressure and crystallized from a small amount of methanol (~5 mL). The crystals were collected by filtration, washed an additional 10 mL of methanol and dried in vacuo to give the desired product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (br, 1H), 7.30 (m, 2H), 7.06 (t, *J*=9 Hz, 2H), 4.71 (s, 2H), 4.36 (q, *J*=7 Hz, 2H), 3.44 (t, *J*=6 Hz, 2H), 3.33 (t, *J*=6 Hz, 2H), 1.38 (t, *J*=7 Hz, 3H) ppm. ES MS M+1 = 361.

Step 3: Ethyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

To a solution of sodium 1-(ethoxycarbonyl)-6-(4-fluorobenzyl)-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-4-olate (1.45 g, 3.79 mmol) in DMF (20 mL) was added cesium carbonate (4.94 g, 15.1 mmol). After 5 minutes, methyl iodide (2.15 g, 15.1 mmol) was added. The reaction mixture was stirred at room temperature. After 24 hours, the product mixture was concentrated under vacuum. The residual material was subjected to column chromatography on silica gel eluting with 0-3 % methanol in CH_2Cl_2. The appropriate fractions were combined and concentrated to afford the *N*- and *O*-methylated compounds separately.

N-methylated compound: Ethyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.02 (t, *J*=9 Hz, 2H), 4.69 (s, 2H), 4.39 (q, *J*=7 Hz, 2H), 4.13 (s, 3H), 3.51 (s, 3H), 3.53 (t, *J*=6 Hz, 2H), 2.59 (t, *J*=6 Hz, 2H), 1.38 (t, *J*=7 Hz, 3H) ppm. ES MS M+1 = 389.

O-methylated compound: Ethyl 6-(4-fluorobenzyl)-3,4-dimethoxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.03 (t, *J*=9 Hz, 2H), 4.73 (s, 2H), 4.37 (q, *J*=7 Hz, 2H), 4.05 (m, 6H), 3.38 (t, *J*=6 Hz, 2H), 3.14 (t, *J*=6 Hz, 2H), 1.39 (t, *J*=7 Hz, 3H) ppm. ES MS M+1 = 389.

Step 4: 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid

To a solution of ethyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (1.15 g, 2.96 mmol) in 1:1:1 MeOH/H_2O/THF (15 mL) was added LiOH (0.37g, 8.88 mmol) and the solution was stirred for 2 hours. A solution of 1 N HCl (8.9 mL) was added, the solution was concentrated and $CHCl_3$ and 10% $KHSO_4$ were added. The layers were separated and the aqueous was extracted repeatedly. The combined organic layers were filtered and the solid collected. The remaining organic was dried over Na_2SO_4, filtered, combined with the collected solid and evaporated to give the crude product.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32 (dd, *J*=5.6, 8.6 Hz, 2H), 7.16 (t, *J*=8.8 Hz, 2H), 4.64 (s, 2H), 3.84 (s, 3H), 3.42 (s, 3H), 3.4 (t, *J*=6 Hz, 2H), 2.6 (t, *J*=6 Hz, 2H) ppm. ES MS M+1 = 361.

Step 5: 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carbonyl chloride

To 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid (0.213g, 0.6 mmol) was added thionyl chloride (5 mL) and the mixture was heated to reflux for 2 hours, then evaporated to dryness, suspended in toluene and evaporated three times to give the crude product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J*=5.3, 8.6 Hz, 2H), 7.03 (t, *J*=8.8 Hz, 2H), 4.7 (s, 2H), 4.18 (s, 3H), 3.58 (s, 3H), 3.39 (t, *J*=6 Hz, 2H), 2.65 (t, *J*=6 Hz, 2H)ppm.
ES MS M+1 = 379.

Step 6: 5-amino-2-(4-fluorobenzyl)-8-methoxy-6-methyl-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione

To a solution of sodium azide (0.091g, 1.4 mmol) in 2 mL water cooled to 0 °C was add 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carbonyl chloride (0.48g, 1.28 mmol) in acetone (8 mL). The solution was stirred for 30 minutes, then evaporated. The residue was partitioned between $CHCl_3$ and saturated Na bicarbonate, dried with Na_2SO_4, filtered and evaporated to give the crude product, which was chromatographed on silica eluting with 5% MeOH/$CHCl_3$ saturated with NH_3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J*=5.5, 8.4 Hz, 2H), 7.01 (t, *J*=8.6 Hz, 2H), 4.7 (s, 2H), 4.05 (bs, 2H), 3.96 (s, 3H), 3.56 (s, 3H), 3.37 (t, *J*=6 Hz, 2H), 2.42 (t, *J*=6 Hz, 2H) ppm. ES MS M+1 = 332.

Step 7: N-acetyl-N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]acetamide

To 5-amino-2-(4-fluorobenzyl)-8-methoxy-6-methyl-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione (0.119mg, 0.36 mmol) in a sealable microwave tube was added acetic anhydride (3.5 mL) and the solution was heated to 150 °C for 25 minutes in a microwave. The solution was evaporated to dryness to give the crude product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2H), 7.02 (t, *J*=8.6 Hz, 2H), 4.69 (s, 2H), 4.14 (s, 3H), 3.37 (s, 3H), 3.35 (t, *J*=6 Hz, 2H), 2.37 (t, *J*=6 Hz, 2H), 2.32 (s, 6H)ppm.
ES MS M+1 = 416.

Step 8: N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]acetamide

To N-acetyl-N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]acetamide (0.149g, 0.36 mmol) in MeOH (5 mL) cooled to 0 °C was added 30% weight solution NaOMe in MeOH (0.2 mL, 1.07 mmol). The reaction was warmed to room temperature for 40 minutes, then 1 N HCl was added (1.07 mL) and the reaction was concentrated, and $CHCl_3$ and 10% $KHSO_4$ were added. The layers were separated and the aqueous was extracted repeatedly. The organic layer was dried over Na_2SO_4, filtered, combined with the collected solid and evaporated to give the crude product.

^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (bs, 1H), 7.26 (m, 2H), 7.01 (t, *J*=8.6 Hz, 2H), 4.65 (bs, 2H), 3.96 (s, 3H), 3.39 (s, 3H), 3.33 (t, *J*=6 Hz, 2H), 2.45 (bs, 2H), 2.23 (s, 3H)ppm. ES MS M+1 = 374.

Step 9: N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-methylacetamide

To N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]acetamide (0.073g, 0.196 mmol) in 2 mL DMF was added Cs_2CO_3 (0.084g, 0.25 mmol) and methyl iodide (0.044 mL, 0.7 mmole) and the reaction was stirred overnight at room temperature. The solvent was removed and the residue was partitioned between $CHCl_3$ and 10% $KHSO_4$, the organic was dried with Na_2SO_4, filtered and evaporated to give the crude product.

^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J*=5.4, 8.5 Hz, 2H), 7.03 (t, , *J*=8.6 Hz, 2H), 4.70 (s, 2H), 4.14 (s, 3H), 3.43 (s, 3H), 3.37 (m, 2H), 3.08 (s, 3H), 2.48 (m, 2H), 1.87 (s, 3H) ppm. ES MS M+1 = 388.

Step 10: N-[6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-methylacetamide

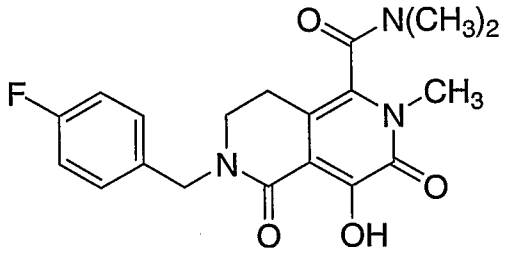
To N-[6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-methylacetamide (0.070g, 0.181 mmol) was dissolved in 1 mL glacial acetic acid and 0.75 mL 30% by weight HBr in acetic acid solution was added. The reaction was stirred for 1.5 hours, water was added and the reaction evaporated to dryness under vacuum. The residue was purified on reverse phase and the fractions collected and evaporated. The residue was dissolved in dioxane, from which crystals formed and were collected. The crystals were dried under vacuum with heat to give the product.

^1H NMR (400 MHz, $CDCl_3$) δ 13.17 (s, 1H), 7.30 (dd, *J*=5.3, 8.7 Hz, 2H), 7.03 (t, , *J*=8.7 Hz, 2H), 4.73 (d, *J*=14.6 Hz, 1H), 4.66 (d, *J*=14.6 Hz, 1H), 3.44 (s, 3H), 3.41 (m, 2H), 3.08 (s, 3H), 2.61 (m, 2H), 1.86 (s, 3H) ppm.

ES MS M+1 = 374.

EXAMPLE 10

6-(4-Fluorobenzyl)-4-hydroxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



Step 1: Methyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

To a solution of methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (0.28 g, 0.81 mmol) in DMF (3.0 mL) was added Cs_2CO_3 (0.81 g, 2.47 mmol) at room temperature. After 10 minutes, CH_3I (0.597 g, 4.21 mmol) was added and the warmed to 40 °C. After 2.5 hours, the product mixture was partitioned between EtOAc and 1 N HCl. The organic extract was washed with brine, dried with Na_2SO_4, filtered, and concentrated under vacuum to give a mixture of N,O- and O,O-alkylated products. The residual material was subjected to column chromatography on silica gel eluting with 0-3 % methanol in CH_2Cl_2. The appropriate fractions were combined and concentrated to afford the title compound.

^{1}HNMR (400 MHz, $CDCl_3$) δ 7.29 (m, 2h), 7.02 (t, *J*=9 Hz, 2H), 4.68 (s, 2H), 4.12 (s, 3H), 3.91 (s, 3H), 3.48 (s, 3H), 3.32 (t, *J*=6 Hz, 2H), 2.56 (t, *J*=6.5 Hz, 2H) ppm. ES MS M+1 = 375.

Step 2: 6-(4-Fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid

To a solution of methyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (0.575 g, 1.536 mmol) in methanol was added LiOH (0.11 g, 4.61 mmol) in water. The reaction mixture was heated to reflux. After 0.5 hours, the product mixture cooled to room temperature and concentrated under vacuum. The residual material was partitioned between EtOAc and 1 N HCl. The organic extract was washed with brine, dried with Na_2SO_4, filtered, and concentrated under vacuum to provide the title compound.

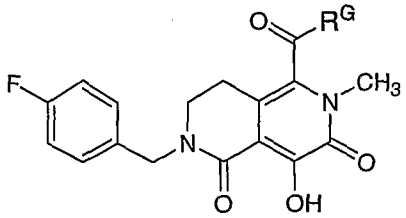
^{1}HNMR (400 MHz, $CDCl_3$) δ 7.27 (m, 2h), 7.03 (t, *J*=9 Hz, 2H), 4.66 (s, 2H), 3.95 (s, 3H), 3.49 (s, 3H), 3.35 (t, *J*=6 Hz, 2H), 2.68 (t, *J*=6 Hz, 2H) ppm. ES MS M+1 = 361.

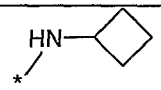
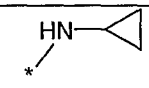
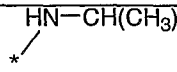
Step 3: 6-(4-Fluorobenzyl)-4-hydroxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

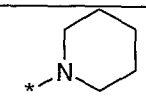
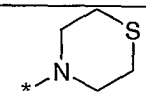
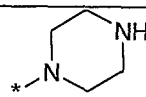
To a solution of 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid (0.14 g, 0.40 mol) in DMF was added BOP (0.515 g, 1.167 mmol) and the dimethylamine (2.0 M in THF) (0.035 g, 0.778 mmol). After 24 hours, the product mixture was concentrated under vacuum. The residual material was purified using reverse phase HPLC eluting with 5-95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to give 6-(4-fluorobenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (ES MS M+1= 388) . A solution of this product (0.1 g, 0.3 mmol) in CH_2Cl_2 was treated with HBr (30 wt % in acetic acid) (0.104 g, 1.29 mmol) and after stirring at room temperature for 24 hours, concentrated under vacuum. The residual material was purified using reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA) to afford the title compound.

^{1}HNMR (400 MHz, CD_3OD) δ 7.38 (m, 2H), 7.04 (t, *J*=9 Hz, 2H), 4.81 (d, *J* = 14.8 Hz, 1H), 4.56 (d, *J* = 14.8 Hz, 1H), 3.49 (t, *J*=6 Hz, 2H), 3.43 (s, 3H), 3.08 (s, 3H), 2.93 (s, 3H), 2.59 (t, *J*=6 Hz, 2H) ppm. ES MS M+1 = 374.

The compounds in the following table were prepared in accordance with the procedure set forth in Example 10, using the appropriate amine in place of the dimethylamine employed in Step 3 of Example 10. When the compound was prepared as a salt, the identity of the salt is included in parentheses following the compound name for the free base.



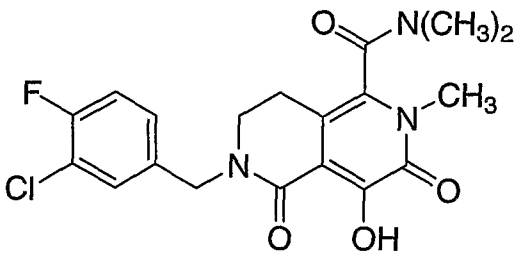
Example	R^G	Name	ES MS (M+1)
10-2		N-cyclobutyl-6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide	400.2
10-3		N-cyclopropyl-6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide	386.1
10-4		6-(4-fluorobenzyl)-4-hydroxy-N-isopropyl-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide	388.1

10-8		2-(4-fluorobenzyl)-8-hydroxy-6-methyl-5-(piperidin-1-ylcarbonyl)-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione	414.1
10-10		2-(4-fluorobenzyl)-8-hydroxy-5-(thiomorpholin-4-ylcarbonyl)-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione	418.3
10-11		2-(4-fluorobenzyl)-8-hydroxy-5-(piperazin-1-ylcarbonyl)-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione (TFA salt)	401.1

There are no Examples 10-5, 10-6, 10-7, or 10-9.

EXAMPLE 11

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



Step 1: 6-(4-methoxybenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

In a manner similar to that described for 6-(4-fluorobenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (Example 10, Step 3), 6-(4-methoxybenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide was prepared starting from p-methoxybenzyl chloride, and the material was purified using reverse phase HPLC eluting with 5 % - 95 % acetonitrile (0.1 % TFA) in H_2O (0.1 % TFA). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J*=8.6 Hz, 2H), 6.84 (d, *J*=8.6 Hz, 2H), 4.82 (d, *J*=14.5 Hz, 1H), 4.46 (d, *J*=14.5 Hz, 1H), 4.07 (s, 3H), 3.78 (s, 3H), 3.45 (s, 3H), 3.40 (m, 1H), 3.30 (m, 1H), 3.09 (s, 3H), 2.90 (s, 3H), 2.51 (m, 1H), 2.35 (m, 1H) ppm. (ES MS M+1= 400.1)

Step 2: 4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

A solution of 6-(4-methoxybenzyl)-4-methoxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (0.18g, 0.45 mmol) in toluene (about 3 mL) was treated with p-toluene sulfonic acid (0.34g, 1.8 mmol). The mixture was heated to 110 °C for 4 hours, then cooled and concentrated under vacuum. The residue was partitioned between water and EtOAc, the

aqueous layer concentrated,and the residue purified by reverse phase chromatography to give the title product.

^{1}HNMR (400 MHz, CD_3OD) δ 3.44 (m, 5H), 3.10 (s, 3H), 2.97 (s, 3H), 2.60 (t, *J*= 6.6 Hz, 2H) ppm. (ES MS M+1= 266.2)

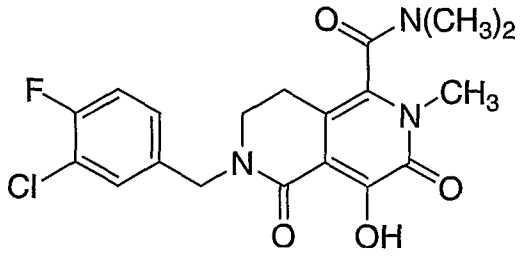
Step 3: 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

A solution of 4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (0.018g, 0.068 mmol) in DMF (2 mL) was treated with Cs_2CO_3 (0.066g, 0.2 mmol) and 3-chloro-4-fluoro benzyl bromide (0.045g, 0.2 mmol) and heated to 40 °C. The reaction mixture was then cooled to 0 degrees C, a suspension of NaH (95% dispersion in oil, 0.2 mmol) was added and the reaction was warmed to room temperature. After 1 hr the reaction was partitioned between ice water and EtOAc, the organic layer was dried with brine and Na_2SO_4, filtered and evaporated to give 6-(3-chloro-4-fluorobenzyl)-4-[(3-chloro-4-fluorobenzyl)oxy]-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (ES MS M+1= 549.9) . This material was then dissolved in CH_2Cl_2 (3 mL) and treated with 4 drops of a 30% by weight solution of HBr in propionic acid at room temperature. After 20 minutes the solution was concentrated and purified by reverse phase chromatography to give the product.

^{1}HNMR (400 MHz, CD_3OD) δ 7.48 (m, 1H), 7.32 (m, 1H), 7.22 (t, *J*=8.5 Hz, 1H), 4.76 (d, *J*=14.8 Hz, 1H), 4.63 (d, *J*=14.8 Hz, 1H), 3.50 (t, *J*=6.4 Hz, 2H), 3.44 (s, 3H), 3.08 (s, 3H), 2.95 (s, 3H), 2.61 (t, *J*=6.2 Hz, 2H) ppm. (ES MS M+1= 407.9)

EXAMPLE 12

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



Step 1: 1-(3-Chloro-4-fluorobenzyl)piperidin-2-one

Valerolactam (153.3 g, 1.54 mol) was dissolved in NMP (3.5 L) and cooled to 0 °C. NaH (67.7g, 1.69 mol, 60% dispersion in oil) was added in portions over 5 minutes keeping the

temperature at 0 °C. The reaction was stirred for 30 minutes, and 3-chloro-4-fluorobenzylbromide (345.5 g, 1.54 mol) dissolved in 200 mL NMP was added over 30 minutes, again keeping the internal temperature at 0 °C. The reaction was aged for 1 hour at 0 °C, and allowed to warm to room temperature overnight. LCMS showed the reaction complete. The reaction mixture was quenched with 5L distilled H_2O, extracted with 3 portions of CH_2Cl_2 (2L, 1L, 1L) and the organic layers combined and washed with three 4L portions of water. The organic layer was concentrated and was found to contain NMP. The residual oil was dissolved in EtOAc (4 L), and extracted with three 2L portions of water. The organic layer was concentrated to give the product that solidified upon standing.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 2H), 7.0 (m, 2H), 7.1 (m, 1H), 4.56 (s, 2H), 3.19 (t, J = 4.9, 2H), 2.46 (t, J = 6.4, 2H), 1.8-1.75 (m, 4H) ppm.

Step 2: 1-(3-Chloro-4-fluorobenzyl)-5,6-dihydropyridin-2(1H)-one

1-(3-Chloro-4-fluorobenzyl)piperidin-2-one (340g, 1.41 mol) was dissolved in THF (5 L) and cooled to -20 °C under nitrogen. LHMDS (3.09L, 3.09 mol, 1M in THF) was added over 40 minutes keeping the temperature at -20 °C and aged for 1 hr at -20 °C. The methyl benzene sulfonate (231 mL, 1.69 mol) was added over 30 minutes, again keeping the internal temperature at -20 °C. The reaction was aged for 30 minutes at -20 °C and LCMS showed the reaction complete. The reaction mixture was diluted with 4L EtOAc and washed with four 2L portions of distilled H_2O. The organic layer was concentrated and the residue was dissolved in 4L toluene. Na_2CO_3 (500g) was added and the reaction heated to 100 °C for 1 hour. LCMS showed the reaction complete. The residue was diluted with 4 L EtOAc and washed with four 2L portions of distilled water. The organic layer was concentrated and the residue purified by flash chromatography on silica eluting with a gradient of 0-60% EtOAc/heptane. The product was isolated as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 (m, 1H), 7.15 (m, 1H), 7.1 (t, 1H), 6.6 (m, 1H), 6.0 (m, 1H), 4.55 (s, 2H), 3.33 (t, 2H), 1.38 (m, 2H) ppm. (ES MS M+1 = 240.13)

Step 3: 2-Butoxy-2-oxoethanaminium chloride

Glycine hydrochloride (400g, 3.58 mol) was suspended in 8 L of n-butanol and thionyl chloride (1.37L, 18.84 mol) was added slowly dropwise (exotherm). After addition was complete, the reaction was heated to 70 °C overnight. The reaction could be followed by spotting directly on TLC, pumping off the volatiles, eluting with 10% MeOH/$CHCl_3$ saturated with NH_3, and staining in ninhydrin. The next day the reaction was stripped to dryness under vacuum and the residue was triturated with heptane/EtOAc to give the product as a white solid after drying on a filter under Nitrogen.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.5 (bs, 3H), 4.18 (t, J = 6.7 Hz, 2H), 4.0 (bs, 2H), 1.62 (m, 2H), 1.38 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H) ppm. ES MS M+1 = 132.

Step 4: Butyl N-[ethoxy(oxo)acetyl]glycinate

2-Butoxy-2-oxoethanaminium chloride (573.5g, 3.42 mol) was suspended in 7 L of ethanol and triethylamine (415g, 4.1 mol) was added. Diethyloxalate (1.0Kg, 6.8 mol) was added and the reaction warmed to 50 °C for 3 hours. The reaction was cooled, the volatiles were removed under vacuum and the residue was dissolved in methylene chloride and washed with two 4L portions of water and dried over $MgSO_4$. The next day the reaction was filtered, evaporated to give ~1.2 Kg of an oil that was chromatographed on silica eluting with Heptane/EtOAc to give product.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (bs, 1H), 4.37 (q, J = 7.2 Hz, 2H), 4.2 (t, J = 6.6 Hz, 2H), 4.12 (d, J = 5.5 Hz, 2H), 1.64 (p, J = 6.8 Hz, 2H), 1.39 (t, J = 7.15 Hz, 3H), 1.37 (m, buried, 2H), 0.94 (t, J = 7.4 Hz, 3H) ppm. ES MS M+1 = 232.

Step 5: Ethyl 5-butoxy-1,3-oxazole-2-carboxylate

Butyl N-[ethoxy(oxo)acetyl]glycinate (783g, 3.38 mol) was dissolved in 8 L of acetonitrile in a 50L Chemglass reactor with overhead stirrer and P_2O_5 (415g, 2.92 mol) was added in large portions, watching for exotherm. The reaction was heated to 60 °C for 1 hour and LCMS showed the reaction done. After cooling, water (8L) was added at 20 °C and the reaction was transferred to a 50L flask. Methylene chloride (8L) was added, the layers split and the aqueous layer was extracted with three 2L volumes of methylene chloride. The combined organic layers were washed with two 4L portions of saturated aqueous $NaHCO_3$, then dried with $MgSO_4$ and evaporated to give an oil that was purified on silica eluting with 0-30% EtOAc/heptane to give the product as an oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 4.42 (q, J = 7.15 Hz, 2H), 4.18 (t, J = 6.4 Hz, 2H), 1.8 (p, J = 6.4 Hz, 2H), 1.47 (p, J = 7.4 Hz, 2H), 1.41 (t, J = 7.15 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H) ppm. ES MS M+1 = 214.

Step 6: Ethyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

Ethyl 5-butoxy-1,3-oxazole-2-carboxylate (44.5g, 208.6 mmol) and 1-(3-chloro-4-fluorobenzyl)-5,6-dihydropyridin-2(1H)-one (25g, 104.3 mmol) were placed in a heavy walled round bottom flask equipped with a screw top and acid resistant O-ring and a stir bar. The mixture was stirred and water (2.82 mL, 156.7 mmol) was added. The reaction was sealed and placed in an oil bath pre-heated to 130 °C. The reaction was aged for 72 hours, when LCMS showed much of the lactam had been

consumed. The reaction was allowed to cool and sit until the mass had solidified. The mass was taken up in ether and the solids collected by filtration to give the product as a tan solid. The product was further purified by crystallization from EtOAc.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.79 (s, 1H), 8.42 (s, 1H), 7.4 (dd, J = 2, 7Hz, 1H), 7.2 (m, 1H), 7.15 (t, J = 8.6 Hz, 1H), 4.7 (s, 2H), 4.4 (q, J = 7 Hz, 2H), 3.5 (m, 4H), 1.4 (t, J = 7 Hz, 3H) ppm. (ES MS M+1 = 379.0)

Step 7: Ethyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide

Ethyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (22g, 58 mmol) was dissolved in 500 mL glacial acetic acid and H_2O_2 (30% by weight in water, 65.8 mL) was added. The reaction was warmed to 100 °C and aged for four hours at which time LCMS showed the reaction done. The solution was cooled in an ice bath to 25 °C and treated with saturated Na_2SO_3 solution, keeping the temperature below 40 °C. When starch paper test showed no peroxides present, the solution was concentrated by 1/3, the pH was adjusted to ~3 with aqueous HCl and the solution extracted with CH_2Cl_2 several times. The organic layers were dried over Na_2SO_4, filtered and evaporated to give product as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.65 (s, 1H), 7.9 (s, 1H), 7.38 (dd, J = 2, 7Hz, 1H), 7.27-7.1 (m, 2H), 4.66 (s, 2H), 4.44 (q, J = 7 Hz, 2H), 3.52 (t, J = 7Hz, 2H), 2.90 (t, J = 7Hz, 2H), 1.38 (t, J = 7 Hz, 3H) ppm. (ES MS M+1 = 395.0)

Step 8: Ethyl 3,4-bis(acetyloxy)-6-(3-chloro-4-fluorobenzyl)-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

Ethyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate 2-oxide (23g, 58 mmol) was dissolved in 400 mL acetic anhydride and heated with stirring under nitrogen to 100 °C for 1 hour. By LCMS, the starting material and product are very close in retention time. To check that the reaction was done, an aliquot was treated with NaOMe in water and CH_3CN. The resulting hydrolyzed product elutes at an earlier retention time and allows distinguishing between remaining N-oxide and rearranged product. The reaction was evaporated to give the crude product as an oily residue that was taken on to the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 1H), 7.2-7.1 (m, 1H), 7.12 (t, J = 8Hz, 1H), 4.68 (bs, 2H), 4.4 (q, J = 7 Hz, 2H), 3.48 (m, 2H), 3.35 (m, 2H), 2.38 (bs, 6H), 1.4 (t, J = 7 Hz, 3H) ppm. (ES MS M+1 = 394.9)

Step 9: Methyl 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

Ethyl 3,4-bis(acetyloxy)-6-(3-chloro-4-fluorobenzyl)-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (27.8g, 58 mmol) was dissolved in 300 mL MeOH and treated with a 30% by weight solution of NaOMe in MeOH (41.8 mL, 232 mmol, 4 equivalents was sufficient to get the pH of the reaction to 9) for 5 hours at 40 °C. LCMS showed the cleavage of the acetate groups was complete, a little transesterification was observed as well. The volume was reduced by half under vacuum and the mixture was diluted with THF (400 mL) and an additional 33mL of NaOMe was added. The reaction was stirred at room temperature overnight and then warmed to 50°C for four hours, when LCMS showed transesterification completed. The reaction was neutralized with 1N HCl and allowed to sit at room temperature overnight, then later acidified to pH 3 and extracted with $CHCl_3$ several times. The organic layer was dried over Na_2SO_4 and evaporated to give a black oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0-8.2 (bs, 1H), 7.38 (dd, J = 6.8. 2Hz, 1H), 7.2 (m, 1H), 7.13 (t, J = 8.4 Hz, 1H), 4.68 (s, 2H), 3.92 (s, 3H), 3.46 (t, J = 6.4 Hz, 2H), 3.34 (t, J = 6.4 Hz, 2H) ppm. (ES MS M+1 = 380.9)

Step 10: Methyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

To a solution of methyl 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (18.00 g, 47 mmol) in DMF (200 mL) was added magnesium methylate (96.08 mL, 95 mmol), and the reaction was warmed for 1 hour and cooled. The reaction was treated with iodomethane (17.66 mL, 283 mmol) and stirred at 45 °C overnight. At this time, LCMS showed the reaction incomplete, and an additional equivalent of iodomethane (2.95 mL, 48 mmol) was added. The reaction was again stirred for 4 hours. The solvent was removed *in vacuo*, and the resulting oil was partitioned between chloroform and 1N HCl. The aqueous layer was washed twice more with chloroform. The organic fractions were extracted with 10% sodium bisulfite, and the bisulfite layer was washed twice with chloroform. The combined organic layers were washed with 5% aqueous HCl and brine, dried over sodium sulfate and concentrated *in vacuo* to afford the product as a black oil. This material appears quite clean by NMR and HPLC, but is highly colored.

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.37 (s, 1H), 7.35 (dd, J = 2.4, 6.9 Hz, 1H), 7.22-7.18 (m, 1H), 7.13 (t, J = 8.4 Hz, 1H), 4.67 (s, 2H), 3.92 (s, 3H), 3.54 (s, 3H), 3.43 (t, J = 6.4 Hz, 2H), 2.81 (t, J = 6.4 Hz, 2H) ppm. (ES MS M+1 = 395.0)

Step 11: Methyl 6-(3-chloro-4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

To a solution of methyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (7.25 g, 18 mmol) in anhydrous DMF (75 mL) was added cesium carbonate (5.98 g, 18 mmol) and iodomethane (2.86 mL, 46 mmol). The reaction was stirred at room temperature overnight, and LCMS showed 70% completion. The reaction was heated to 50 °C for 7 hours and then allowed to stir at room temperature again overnight. LCMS indicated completion. The reaction was concentrated to dryness, and the resulting residue was dissolved in chloroform. The solution was extracted twice with saturated Na_2SO_3 solution, dried over sodium sulfate, filtered, and evaporated to afford a dark brown oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 2.1, 7.0 Hz, 1H), 7.19 (m, 1H), 7.11 (m, 1H), 4.65 (s, 2H), 4.12 (s, 3H), 3.92 (s, 3H), 3.49 (s, 3H), 3.34 (m, 2H), 2.59 (m, 2H) ppm. (ES MS M+1 = 409.0)

Step 12: 6-(3-Chloro-4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid

To a solution of methyl 6-(3-chloro-4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (14.3 g, 35 mmol) in THF (150mL) and MeOH (150 mL) was added LiOH (2.74g, 114 mmol) dissolved in 114 mL water and the reaction was heated to 50 °C for 45 minutes. HPLC showed completion. The reaction was neutralized with 1N HCl and cooled to room temperature. THF was removed *in vacuo*, and the resulting slurry was partitioned between $CHCl_3$ and 5% aqueous HCl. The aqueous was washed with additional $CHCl_3$. The combined organics were dried over sodium sulfate, filtered, and concentrated to dryness to afford the desired product as a pale yellow foam. The material was crystallized from ethyl acetate to give a light yellow solid.
^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (dd, J = 2.0, 6.8 Hz, 1H), 7.34-7.30 (m, 1H), 7.25-7.20 (m, 1H), 4.71 (s, 2H), 3.98 (s, 3H), 3.58 (s, 3H), 3.50 (m, 2H), 2.77-2.74 (m, 2H) ppm. (ES MS M+1 = 395.0)

Step 13: 6-(3-Chloro-4-fluorobenzyl)-4-methoxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

To a suspension of 6-(3-chloro-4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid (8.50 g, 22 mmol) in methylene chloride (300 mL) at 0 °C was added oxalyl chloride (2.25 mL, 26 mmol) and 1 drop of anhydrous DMF. The reaction was stirred at 0 °C for 15 minutes during which time no bubbling was observed. The reaction was then allowed to warm to room temperature and stirred for 40 minutes. At this time bubbling had ceased, and all material was in solution. An aliquot of the solution was quenched with dimethylamine and checked

by LCMS to confirm completion. To the solution of the acid chloride starting material at 0 °C was added dimethylamine in THF (43.56 mL, 87 mmol, 2.0 M). The green/yellow reaction was allowed to stir at room temperature overnight although the reaction appeared to proceed immediately by LCMS. The solvent was removed *in vacuo*, and the resulting residue was dissolved in chloroform. The solution was washed with water and 5% aqueous HCl solution and back extracted to recover the product. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting iridescent green/yellow residue was examined in several TLC solvent systems (95:5 CH_2Cl_2:MeOH, 2:1 acetone:hexanes, 1:1 EtOAc:hexanes) with the most efficient separation of some early running impurities achieved in the CH_2Cl_2:MeOH system. The material was purified by silica gel flash column chromatography, loaded as a solution in methylene chloride onto a 330 g RediSep column. Gradient elution consisted of 1.5 L each of neat CH_2Cl_2, 1% MeOH:CH_2Cl_2, 2% MeOH:CH_2Cl_2, 3% MeOH:CH_2Cl_2, 4% MeOH:CH_2Cl_2, and 5% MeOH:CH_2Cl_2, in sequential order. The desired material began to elute with 3% and was pushed off the column with 4% and 5%, yielding two sets of fraction. The earlier set afforded of the desired product plus a fluorescent green contaminant. The later set afforded clean material.

^1H NMR (400 MHz, CD_3OD) δ 7.49 (dd, J = 2.0, 7.2 Hz, 1H), 7.34-7.31 (m, 1H), 7.22 (t, J = 8.8 Hz, 1H), 4.77 (d, J = 15.2 Hz, 1H), 4.65 (d, J = 15.2 Hz, 1H), 3.97 (s, 3H), 3.52-3.48 (m, 2H), 3.45 (s, 3H), 3.11 (s, 3H), 2.97 (s, 3H), 2.57-2.54 (m, 2H) ppm. (ES MS M+1 = 422.0)

Step 14: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

To 6-(3-chloro-4-fluorobenzyl)-4-methoxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (5.43 g, 13 mmol) was added 33% HBr in acetic acid (20 mL, 129 mmol), and the mixture was heated to 50 °C for 15 minutes to give a thick, pale brown/orange solution. By LCMS, the reaction was complete, and the acetic acid was removed *in vacuo*. The resulting residue was partitioned between chloroform and water, and the organic layer was then washed with aqueous sodium sulfite solution and brine. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a pale yellow foam. The foam was dissolved in hot isopropanol and crystallized quickly, and the crystals were collected by filtration. The material was then taken up in hot acetone which did not afford a complete solution, so the mixture was hot filtered. The resulting filtrate was allowed to cool causing crystals to form. The insoluble material from the hot acetone filtration was dissolved in hot ethanol and re-filtered. This resulting filtrate also produced large, slowly grown crystals over the course of one day. The crystals compound free base from both filtrates were collected, combined, dried for 4 hours, milled, and re-dried overnight without heat to give product.

^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (dd, J = 2.1, 7.2 Hz, 1H), 7.36-7.33 (m, 1H), 7.23 (t, J = 8.9 Hz, 1H), 4.79 (d, J = 14.8 Hz, 1H), 4.65 (d, J = 14.8 Hz, 1H), 3.52 (t, J = 6.8 Hz, 2H), 3.46 (s, 3H), 3.10 (s, 3H), 2.97 (s, 3H), 2.64 (t, J = 6.8 Hz, 2H) ppm. (ES MS exact mass = 408.1113)

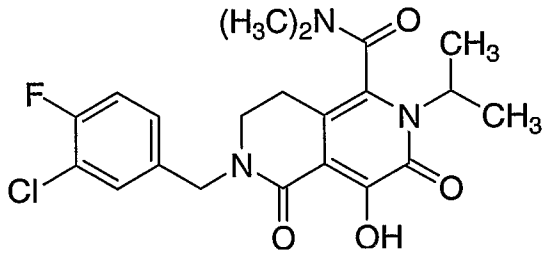
Step 15: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide sodium salt

To 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (1.08g, 2.65 mmol) in a freeze drying flask was added acetonitrile (5 mL) at room temperature. The flask was placed in an ultrasonic bath at room temp for 1 minute. Some crystals remained. Water was added (5 mL) followed by the 1 N NaOH (2.65 mL, 2.65 mmol). The total was placed in the ultrasonic bath for 1 minute. An additional 1 mL of acetonitrile was added and placed in the ultrasonic bath for an additional minute. All material was now dissolved. More water (30 mL) was added to the flask and all stayed soluble. The contents of the flask were frozen with spinning in a -78 °C acetone /dry ice bath and placed on the freeze drier for 40 hours to give the product as a dry fluffy solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (dd, J = 2.2, 7.14 Hz, 1H), 7.33-7.29 (m, 1H), 7.17 (t, J = 9.0 Hz, 1H), 4.72 (d, J = 14.8 Hz, 1H), 4.65 (d, J = 14.8 Hz, 1H), 3.35 (s, 3H), 3.33-3.96 (m, 2H), 3.07 (s, 3H), 2.97 (s, 3H), 2.47 (dd, J = 5.68,11.36 Hz, 2H) ppm. (ES MS M+1 = 408.0)

EXAMPLE 13

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-2-isopropyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



Step 1: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylic acid

To a solution of ethyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (27.0 g, 71 mmol) in THF (333mL) and MeOH (166 mL) was added LiOH (5.21g, 214 mmol) dissolved in enough water to make a 1N solution (total volume 213 mL) and the

reaction was heated to 60 °C overnight. HPLC showed completion. A white precipitate was observed. The reaction was neutralized with 1N HCl and the more volatile solvents removed, leaving the water solution. 300 mL water was added the solution was acidified to pH 1 with 1 N HCl. A large amount of solids had precipitated. The resulting slurry was stirred vigorously with 100 mL $CHCl_3$. Most of the solid had precipitated from the partitioning and the entire mix was filtered and dried over the weekend to give product. Additional less pure product was recovered from extraction of the filtrate.
^1H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1H), 7.53(dd, J = 2.2, 6.9 Hz, 1H), 7.36 (m, 1H), 7.23 (t, J = 8.9 Hz, 1H), 4.74 (s, 2H), 3.61(bt, J = 6.4 Hz, 1H), 3.50(bt, J = 6.4 Hz, 1H) ppm. (ES MS M+1 = 351.0)

Step 2: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide

To a suspension of 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylic acid (25.0 g, 71.3 mmol) in methylene chloride (1000 mL) at 0 °C was added oxalyl chloride (12.4 mL, 143 mmol) and 8 drops of anhydrous DMF. The reaction was stirred at 0 °C for 15 minutes. during which time no bubbling was observed. The reaction was then allowed to warm to room temperature and stirred for 40 minutes. At this time bubbling had ceased. An aliquot of the solution was quenched with dimethylamine and checked by LCMS. The reaction was incomplete. An additional 0.5 equivalent of oxalyl chloride was added and the reaction stirred an additional 40 minutes. The reaction never attained complete solution but was complete by LCMS. To the suspension of the acid chloride cooled to 0 °C was slowly added 2M dimethylamine in THF (140.8 mL, 281 mmol). The rate of addition was adjusted to avoid a large exotherm. The pH of the solution was found to be about 9. The yellow reaction was allowed to stir at room temperature overnight although the reaction appeared to proceed immediately by LCMS. The solvent was removed *in vacuo*, and the resulting residue was dissolved in chloroform. The solution was washed with water and 5% aqueous HCl solution and the aqueous layer back extracted to recover the product. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give a brown/yellow waxy solid. The initial NMR shows an excessive number of methyl group peaks, perhaps as a result of oxalyl chloride reacting with dimethylamine. A small sample was purified by reverse phase chromatography eluting with 95:5-5:95 water/acetonitrile 0.1% TFA to give clean material for NMR.
^1H NMR (400 MHz, $CDCl_3$) δ 12.35 (bs, 1H), 10.9 (bs, 1H), 8.32 (s, 1H), 7.38 (dd, J = 2.0, 6.7 Hz, 1H), 7.22 (m, 1H), 7.14 (t, J = 8.5 Hz, 1H), 4.69 (s, 2H), 3.54 (t, J = 6.8 Hz, 2H), 3.14 (s, 3H), 3.05 (t, J = 6.8 Hz, 2H), 2.95 (s, 3H) ppm. (ES MS M+1 = 378.1)

Step 3: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide 2-oxide

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide (24g, 63.5 mmol) was dissolved in 1000 mL glacial acetic acid and per-acetic acid (32% by weight in acetic acid, 151 mL, 635 mmol) and sodium acetate (2.6g, 31.7 mmol) was added. The reaction was warmed to 50 °C and aged overnight at which time LCMS showed the reaction done. The solution reduced in volume to 1/3 on the rotoevaporator, cooled in an ice bath and quenched slowly with 10% Na_2SO_3 solution until no peroxide was detected by a starch paper test. The reaction was transferred to a separatory funnel and water (500mL) and chloroform was added. The layers were separated and the water extracted with $CHCl_3$ several times. The combined organic layers were washed with slightly acidic water, brine and dried over Na_2SO_4, filtered and evaporated to give the product as an oil. The initial NMR shows an excessive number of methyl group peaks, perhaps as a result of oxalyl chloride reacting with dimethylamine in the second step and this impurity being carried through. A small sample was purified by reverse phase chromatography eluting with 95:5-5:95 water/acetonitrile 0.1% TFA to give clean material for NMR.

^1H NMR (400 MHz, $CDCl_3$) δ 12.75 (bs, 1H), 8.4 (bs, 2H), 8.1 (s, 1 H), 7.37 (dd, J = 1.9, 6.9 Hz, 1H), 7.20 (m, 1H), 7.15 (t, J = 8.5 Hz, 1H), 4.84 (d, J = 14.7 Hz, 1H), 4.51 (d, J = 14.7 Hz, 1H), 3.61 (m, 1H), 3.59 (m, 1H), 3.15 (s, 3H), 3.05 (m, 1H)), 2.93 (s, 3H), 2.74 (m, 1H) ppm. (ES MS M+1 = 394.1)

Step 4: 6-(3-Chloro-4-fluorobenzyl)-1-[(dimethylamino)carbonyl]-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-3,4-diyl diacetate

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide 2-oxide (25g, 63.5 mmol) was dissolved in 24 mL acetic anhydride and heated with stirring under nitrogen to 100°C for 16 hours. By LCMS, the starting material and product are close in retention time and appear as the same molecular weight. To check that the reaction was done, an aliquot was treated with NaOMe in water and CH_3CN. The resulting hydrolyzed product elutes at an earlier retention time and allows distinguishing between remaining N-oxide and rearranged product. The reaction was evaporated and the residue was partitioned between chloroform and water and the water layer was back-extracted with more chloroform. The aqueous layer was checked by LCMS for product and no longer contained any. The organic layers were combined, dried over Na_2SO_4, filtered and evaporated to give an oil. (ES MS M+1 of NaOMe treated aliquot= 394.0)

Step 5: 6-(3-Chloro-4-fluorobenzyl)-3,4-dihydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide

6-(3-Chloro-4-fluorobenzyl)-1-[(dimethylamino)carbonyl]-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-3,4-diyl diacetate (30g, 62.7 mmol) was dissolved in 500 mL MeOH and treated with a 30% by weight solution of NaOMe in MeOH (45.2 mL, 251 mmol 4 equivalents was sufficient to get the pH of the reaction to 9) for 1 hour at 40 °C. LCMS showed the cleavage of the acetate groups was complete. The reaction was neutralized with 1N HCl and the volume reduced to remove the MeOH and the residue was diluted with water and acidified to pH 3. The cloudy aqueous layer was diluted with an equal volume (800 mL) of chloroform. After shaking, the product began to crystallize out of the solutions and gathered at the miniscus. The total contents of the funnel were filtered and the collected solids were washed with water until no more salts appeared to remain. The solid was dried *in vacuo* for 16 hours to give a cinnamon colored solid. The organic layer from the filtered extraction was collected, washed with water and dried over Na_2SO_4, filtered and evaporated. The residue was crystallized from methanol to give product. The crude material was quite insoluble but was crystallized from DMF, then boiled in MeOH, filtered and dried under vacuum to give product.

^{1}H NMR (400 MHz, DMSO) δ 13.0 (s, 1H), 11.9 (s, 1H), 7.58 (d, J = 6.9 Hz, 1H), 7.38 (m, 2H), 4.69 (bs, 2H), 3.49 (m, 2H), 2.91 (s, 3H), 2.84 (s, 3H), 2.56 (bs, 2H), ppm. (ES MS M+1 = 394.0)

Step 6: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-2-isopropyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

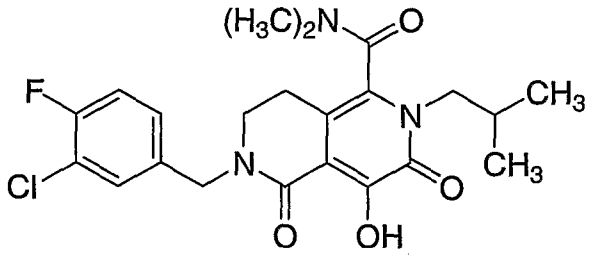
To a solution of 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide (3.00 g, 7.62 mmol) in DMSO (86 mL) was added magnesium methylate (42.75 mL of a 6-10% methanol solution, 24.4 mmol), and the reaction was heated to 60 °C for 0.75 hour. The reaction mixture was reduced on a rotoevaporator to remove all of the MeOH over 45 minutes. The heat gun was used to drive all MeOH from the bump bulb. The reaction was treated with 2-iodopropane (2.84 mL, 38.1 mmol) and allowed to stir at 60 °C for 3 hours. LCMS showed 11% starting material remaining and over 70% conversion to N- and O-alkylated products (typically 2:1). The reaction was diluted with 350mL EtOAc to which 125 mL 1N HCl was added, and the phases were separated. The aqueous layer was washed once with methylene chloride (100 mL). The combined organic layers were washed with 1N HCl twice more and the organic layer was isolated. The organic layer was washed with 10% aqueous solution of $NaHSO_3$ (3x 100 mL) followed by brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to afford a yellow-orange foam residue. The solid combined with additional crude material from other reactions, dissolved in DMSO and Methanol and purified via reverse phase chromatography using a Biotage 75L canister and a Varian Metaflash 75L C-18 column, eluting with a gradient of 70:30 to 35:65 A:B where A= 0.05% TFA in water and B = 0.05% TFA in acetonitrile (flowrate = 300 mL/minute, detection at 214 and 254 nM).

Evaporation of the fractions afforded pure oil by HPLC/LCMS and NMR. Crystallization from EtOAc:hexane afforded white, analytically pure product.

^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (dd, J = 1.9, 7.2 Hz, 1H), 7.32 (m, 1H), 7.22 (t, J = 8.8 Hz, 1H), 4.78 (d, J = 14.9 Hz, 1H), 4.63 (d, J = 14.9 Hz, 1H), 4.02 (m, 1H), 3.50 (t, J = 6.4 Hz, 2H), 3.09 (s, 3H), 3.00 (s, 3H), 2.59 (t, J = 6.4 Hz, 2H), 1.64 (d, J = 6.8 Hz, 3H), 1.57 (d, J = 6.7 Hz, 3H) ppm. (ES MS exact mass M+1 = 436.144)

EXAMPLE 14

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-2-isobutyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



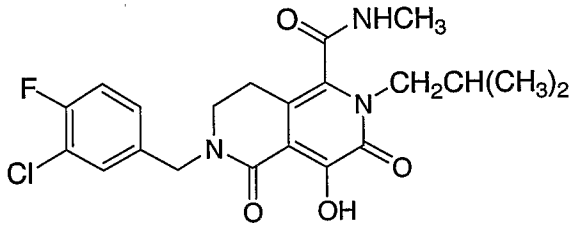
Step 1: 4-Amino-6-(3-chloro-4-fluorobenzyl)-2-isobutyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

To a solution of 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide (0.5 g, 1.27 mmol) in DMSO (10 mL) was added magnesium methylate (5.48 mL of a 6-10% methanol solution, 30.8 mmol), and the reaction was heated to 60 °C for 0.5 hour. The reaction mixture was rotavapped to remove all of the MeOH. The heat gun was used to drive all MeOH from the bump bulb. The reaction was treated with 1-iodo-2-methylpropane (0.73 mL, 6.35 mmol) and allowed to stir at 60 °C for 40 minutes. LCMS showed trace starting material remaining and mostly N-alklated product formed (O-alkylated products ~ 3%). The reaction was diluted with 1 mL MeOH then 1 N HCl was added until a precipitate began to form. A 10 mL portion of 10% sodium bisulfite was added and the brown mixture turned green. Water was added and the mixture stirred for 1 hr, then the liquid was decanted off the solids. The solids were partitioned with chloroform 20 mL and 1 N HCl 20 mL. The organic layer was washed 2 times more with 1 N HCl and then with brine, dried over Na_2SO_4, filtered and evaporated to an oil that smelled strongly of alkylating agent. The residue was diluted with toluene and evaporated and pumped on for 4 hours. The residue would not crystallize from ethyl acetate and methanol. The residue was passed through a Gilson reverse phase column eluting from 95:5 to 5:95 to give an oil after concentration. Crystallization from EtOAc:hexane afforded white, analytically pure product.

^{1}H NMR (400 MHz, DMSO) δ 13.0 (s, 1H), 7.60 (d, J = 4.8 Hz, 1H), 7.40 (t, J = 8.6 Hz, 1H), 7.38 (m, 1H), 4.77 (d, J = 14.7 Hz, 1H), 4.58 (d, J = 14.7 Hz, 1H), 3.90 (dd, J = 7.7, 13.2 Hz, 1H), 3.50 (m, 3H), 2.97 (s, 3H), 2.04 (s, 3H), 2.54 (m, buried), 2.02 (m, 1H), 0.81 (t, J = 6.22 Hz, 6H), ppm. (ES MS exact mass M+1 = 450.151)

EXAMPLE 14-2

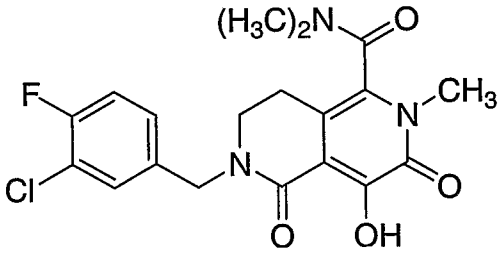
6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-isobutyl-N-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



The title compound was prepared in accordance with the procedure set forth in Example 14, using the appropriate naphthyridine carboxamide penultimate. MS (M+1) = 436.1.

EXAMPLE 15

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



Step 1: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

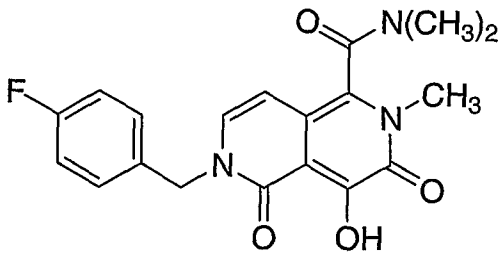
To a solution of 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide (0.1 g, 0.254 mmol) in dry DMSO (5 mL) was added magnesium methylate (1.097 mL of a 6-10% methanol solution, 0.792 mmol), and the reaction was heated to 60 °C for 0.5 hour. The reaction mixture was rotavapped to remove all of the MeOH. The heat gun was used to drive all MeOH from the bump bulb. The reaction was treated with methyl iodide (0.079 mL, 6.35 mmol) and allowed to stir at 60 °C overnight. LCMS showed trace starting material remaining

and mostly N-alklated product formed (O-alkylated products minor). The reaction was diluted with 0.5 mL MeOH then 1 N HCl was added until a precipitate began to form. A 5 mL portion of 10% sodium bisulfite was added and the brown mixture turned green. Water was added and the mixture stirred for 1 hr, then the mixture was partitioned with chloroform 20 mL and 1 N HCl 20 mL. The organic layer was washed 2 times more with 1 N HCl and then with brine, dried over Na_2SO_4, filtered and evaporated to an oil. The residue was passed through a Gilson reverse phase column eluting from 95:5 to 5:95 to give an oil after concentration.

^{1}H NMR (400 MHz, CD_3OD) δ 7.5 (dd, J = 2.0, 7.1 Hz, 1H), 7.34 (m, 1H), 7.22 (t, J = 8.8 Hz, 1H), 4.78 (d, J = 14.8 Hz, 1H), 4.64 (d, J = 14.8 Hz, 1H), 3.52 (t, J = 6.5 Hz, 2H), 3.45 (s, 3H), 3.10 (s, 3H), 2.97 (s, 3H), 2.64 (t, J = 6.4 Hz, 2H) ppm.

EXAMPLE 16

6-(4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6-tetrahydro-2,6-naphthyridine-1-carboxamide



Step 1: Ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-2,3,5,6-tetrahydro-2,6-naphthyridine-1-carboxamide

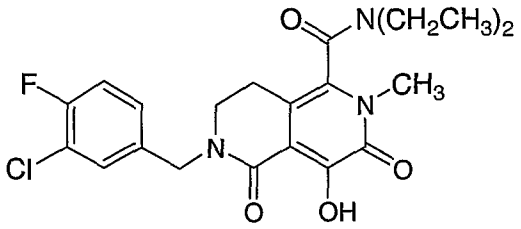
To solution of 5-(ethoxycarbonyl)-2-(4-fluorobenzyl)-8-hydroxy-1-oxo-1,2,3,4-tetrahydro-2,6-naphthyridin-6-ium trifluoroacetate (0.020g, 0.045 mmol; see Example 8, Step 4) in CCl_4 (2 mL) is added N-bromo succinimide (0.017g, 0.095 mmol) and AIBN(catalytic). The reaction is heated to 80 °C for 1 hour, then concentrated and chromatographed on reverse phase to give the product.

Step 2: 6-(4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6-tetrahydro-2,6-naphthyridine-1-carboxamide

The title compound can be prepared using a sequence of transformations similar to those described for Examples 9 and 10.

EXAMPLE 17

6-(3-chloro-4-fluorobenzyl)-N,N-diethyl-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



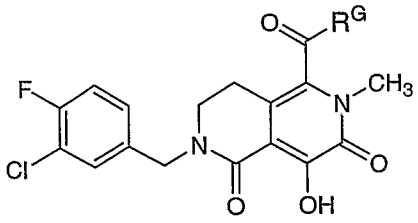
Step 1: Methyl 6-(3-chloro-4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

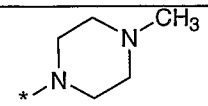
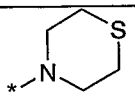
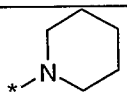
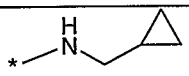
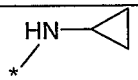
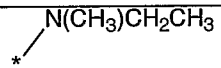
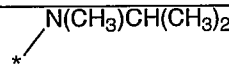
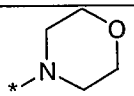
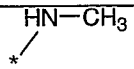
Methyl 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate which was prepared as described in Example 12, Steps 1-9 was converted in a manner similar to Example 10, Step 1 for methyl 6-(4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate to obtain the title compound from preparative silica gel chromatography eluting with 0-3% methanol in methylene chloride.

Step 2: 6-(3-chloro-4-fluorobenzyl)-N,N-diethyl-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

The title compound was prepared from methyl 6-(3-chloro-4-fluorobenzyl)-4-methoxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate in a manner similar to that described in Example 12, Steps 12, 13 and 14, using diethyl amine in place of dimethylamine in the step corresponding to Step 13 of Example 12.
^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (dd, J = 2.1, 7.1 Hz, 1H), 7.36-7.32 (m, 1H), 7.23 (t, J = 8.7 Hz, 1H), 4.75 (d, J = 14.8 Hz, 1H), 4.67 (d, J = 14.6 Hz, 1H), 3.60-3.55 (m, 2H), 3.54-3.51 (m, 2H), 3.46 (s, 3H), 3.36-3.33 (m, 2H), 2.68-2.61 (m, 2H), 1.25 (t, J = 6.7 Hz, 3H), 1.13 (t, J = 6.7 Hz, 3H) ppm.
ES MS M+1 = 436.0

The compounds in the following table were prepared in accordance with the procedure set forth in Example 17, using the appropriate amine in place of the diethylamine employed in Step 2 of Example 17. When the compound was prepared as a salt, the identity of the salt is included in parentheses following the compound name for the free base.

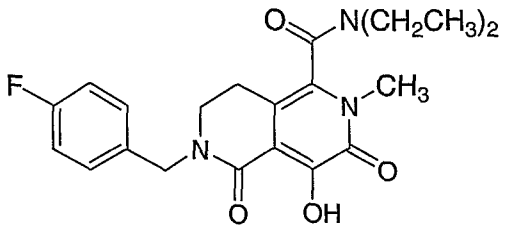


Example	R^G	Name	ES MS (M+1)
17-2		2-(3-chloro-4-fluorobenzyl)-8-hydroxy-6-methyl-5-[(4-methylpiperazin-4-yl)carbonyl]-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione (TFA salt)	463.0
17-3		2-(3-chloro-4-fluorobenzyl)-8-hydroxy-6-methyl-5-(thiomorpholin-4-ylcarbonyl)-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione	465.9
17-4		2-(3-chloro-4-fluorobenzyl)-8-hydroxy-6-methyl-5-(piperidin-1-ylcarbonyl)-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione	448.1
17-5		6-(3-chloro-4-fluorobenzyl)-N-(cyclopropylmethyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide	434.1
17-6		6-(3-chloro-4-fluorobenzyl)-N-cyclopropyl-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide	420.1
17-7		6-(3-chloro-4-fluorobenzyl)-N-ethyl-4-hydroxy-N,2-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide	422.1
17-8		6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N-isopropyl-N,2-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide	436.1
17-10		2-(3-chloro-4-fluorobenzyl)-8-hydroxy-6-methyl-5-(morpholin-4-ylcarbonyl)-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione	450.1
17-11		6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,2-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide	394.1

There is no Example 17-9.

EXAMPLE 18

N,N-diethyl-6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



Step 1: Ethyl 6-(4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

The title compound was prepared using the procedure described in Steps 1-4 of Example 8.

Step 2: Methyl 6-(4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

The title compound was be prepared in a manner similar to that described for methyl 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate shown in Example 12, Steps 7, 8, 9.

Step 3: Methyl 6-(4-fluorobenzyl)-3,4-dimethoxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

The title compound was prepared in the manner described in Example 10, Step 1, where the desired compound, the N-methyl O-methoxy analog, was isolated as the second major product from the mixture of N,O- and O,O-alkylated products via silica gel chromatography eluting with 0-3% methanol in methylene chloride.

Step 4: 6-(4-Fluorobenzyl)-3,4-dimethoxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylic acid

The title compound was prepared in a similar manner to that described in Example 10, Step 2.

Step 5: N,N-diethyl-6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

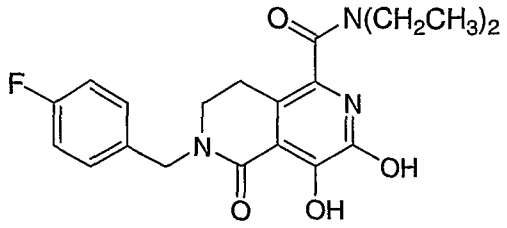
The title compound was prepared in a manner similar to that described in Example 12, Steps 13 and 14.

^{1}HNMR (400 MHz, CD_3OD) δ 7.41-7.37 (m, 2H), 7.10-7.06 (m, 2H), 4.76 (d, *J* = 14.6 Hz, 1H), 4..72 (d, *J* = 14.6 Hz, 1H), 3.57 (q, *J*= 7.14 Hz, 2H), 3.50 (m, 2H), 3.45 (s, 3H), 3.37 (m, 2H)2.64 (m, 2H), 1.27-1.23 (m, 3H), 1.15-1.11 (m, 3H) ppm.

ES MS M+1 = 402.2

EXAMPLE 19

N,N-diethyl-6-(4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide

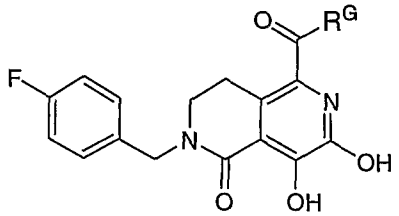


The title compound was prepared using the procedure set forth above in Example 18, except that in the methylation step the O,O alkylated product was isolated and used (first major product eluted off with 0-3% methanol/ CH_2Cl_2).

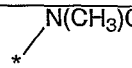
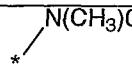
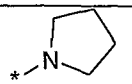
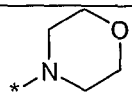
^{1}H NMR (400 MHz, CD_3OD) δ 7.38 (m, 2H), 7.09 (m, 2H), 4.73 (bs, 2H), 3.62 (m, 2H), 3.50 (m, 2H), 3.41 (m, 2H), 2.64 (bs, 2H), 1.22 (m, 3H), 1.14 (m, 3H), ppm.

ES MS M+1 = 388.2

The compounds in the following table were prepared in accordance with the procedure set forth in Example 19, using the appropriate amine in place of the diethylamine.



Example	R^G	Name	ES MS (M+1)
19-2		6-(4-fluorobenzyl)-3,4-dihydroxy-N-isobutyl-N-methyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide	402.2
19-3		N-ethyl-6-(4-fluorobenzyl)-3,4-dihydroxy-N-methyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide	374.2

19-4		6-(4-fluorobenzyl)-3,4-dihydroxy-N-methyl-5-oxo-N-propyl-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide	388.2
19-5		6-(4-fluorobenzyl)-3,4-dihydroxy-N-isopropyl-N-methyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide	388.2
19-6		2-(4-fluorobenzyl)-7,8-dihydroxy-5-(pyrrolidin-1-ylcarbonyl)-3,4-dihydro-2,6-naphthyridin-1(2H)-one	386.2
19-7		2-(4-fluorobenzyl)-7,8-dihydroxy-5-(morpholin-4-ylcarbonyl)-3,4-dihydro-2,6-naphthyridin-1(2H)-one	402.2

EXAMPLE 20

6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

Step 1: Ethyl 4-hydroxy-6-(4-methoxybenzyl)-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

Ethyl 4-hydroxy-6-(4-methoxybenzyl)-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate was prepared in a manner similar to that described in Example 8, Steps 1-4 starting with 4-methoxybenzyl chloride instead of 4-fluorobenzyl bromide, and also in a manner similar to that described in Example 12, Steps 1-6, starting with 4-methoxybenzyl chloride or 3-chloro-4-fluorobenzyl bromide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39-1.42 (m, *J*=7.1 Hz, 3H), 3.42-3.52 (m, 4H), 3.8 (s, 3H), 4.37-4.43 (q, *J*=7.1 Hz, 2H), 4.69 (s, 2H), 6.88-6.90 (dd, *J*= 2, 6.8 Hz, 2H), 7.24-7.26 (m, 2H), 8.42 (s, 1H), 13.05 (br s, 1H) ppm.

LRMS (M+1) = 357.0

Step 2: Ethyl 4-methoxy-6-(4-methoxybenzyl)-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

The title product was prepared by treating ethyl 4-hydroxy-6-(4-methoxybenzyl)-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate with TMS-diazomethane, using a method set forth in Step 5 of Example 8 for the preparation of ethyl 6-(4-fluorobenzyl)-4-methoxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate, except that after quenching with HOAc the reaction was concentrated in vacuo and partitioned between sat aq $NaHCO_3$ and $CHCl_3$. LRMS (M+1) = 371.0

Step 3: 4-methoxy-6-(4-methoxybenzyl)-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylic acid

To a solution of ethyl 4-methoxy-6-(4-methoxybenzyl)-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (15.2 g) in THF (150mL) was added LiOH monohydrate (5.16g) and sufficient water to dissolve the solids. The reaction was allowed to stir at room temperature for 1.5 hours. The reaction was neutralized with 125 mL of 1N HCl and the THF was removed *in vacuo*. The resulting slurry was partitioned between $CHCl_3$ and 10% aqueous $KHSO_4$. The combined organics were dried over sodium sulfate, filtered, and concentrated to dryness to afford the desired product as a pale tan foam. LRMS (M+1) = 343.0

Step 4: 4-methoxy-6-(4-methoxybenzyl)-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide

A 250mL THF suspension of 4-methoxy-6-(4-methoxybenzyl)-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylic acid (11.0 g), 8.0g EDC, 5.7g HOAT, and 11.2mL TEA was stirred at room temperature for 20 minutes, followed by addition of 45mL of a 2M THF solution of dimethylamine and then stirring for 1.5 hours. The reaction was quenched with 200mL of 1N aq HCl and stirred vigorously for 30 minutes. After concentrating *in vacuo* until an oil formed on the water layer, 200mL chloroform was added. The water layer was washed again with chloroform then the combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to pure product by HPLC/MS and NMR.

HPLC/MS (M+1) = 370.1

Step 5: 4-methoxy-6-(4-methoxybenzyl)-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide 2-oxide

A 100ml CH_2Cl_2 solution of 12 g 4-methoxy-6-(4-methoxybenzyl)-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide and 16.8 g mCPBA (maximum 77% purity) was allowed to stir at room temperature until the starting material was consumed (5 hours). The reaction was washed four times with 100 mL sat aqueous $NaHCO_3$ then the organic layer was concentrated. The crude reaction was dissolved in 250mL CH_2Cl_2 and the excess mCPBA was then quenched by vigorous stirring with a sat aq sodium sulfite solution for 30 minutes (both organic and aqueous layers were cloudy initially but then turned transparent). The layers were separated and the organic washed twice with sat aqueous $NaHCO_3$. The organic layer was dried over sodium sulfate and concentrated to pure product by HPLC/MS and NMR.

HPLC/MS (M+1) = 386.2

Step 6: 1-[(dimethylamino)carbonyl]-4-methoxy-6-(4-methoxybenzyl)-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-3-yl acetate

4-methoxy-6-(4-methoxybenzyl)-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide 2-oxide (10.3g) was dissolved in 30ml acetic anhydride and transferred to a 50mL heavy walled pressure flask and sealed. The reaction was heated in a 100°C oil bath overnight. The reaction was concentrated *in vacuo*. The remaining oil was dissolved in 5mL EtOAc and purified on an Isco automated system affixed with a Biotage Flash 40(L) (120g silica) cartridge eluted with 0-10% MeOH in EtOAc over 20 minutes and hold at 10% for 40 minutes. The product eluted pure by HPLC/MS and NMR.

LRMS (M+1) = 428.3

Step 7: 3-hydroxy-4-methoxy-6-(4-methoxybenzyl)-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide

1-[(dimethylamino)carbonyl]-4-methoxy-6-(4-methoxybenzyl)-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-3-yl acetate (7.55g) was dissolved in 50 mL MeOH and treated with 6.65mL of a 30% by weight solution of NaOMe in MeOH at room temperature for 30 minutes. The reaction was concentrated and the remaining solid partitioned between 10% $KHSO_4$ and chloroform. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated to pure product by HPLC/MS and NMR.

LRMS (M+1) = 386.3

Step 8: 4-methoxy-6-(4-methoxybenzyl)-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

To a solution of 3-hydroxy-4-methoxy-6-(4-methoxybenzyl)-N,N-dimethyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide (5.00 g) in DMF (50 mL) was added magnesium methylate (14.3 mL of a 6-10% methanol solution), and the reaction was heated to 50°C for 1 hour. The reaction was treated with iodomethane (17.66 mL) and allowed to stir at 50 degrees for 1.5 hours. The reaction was quenched with 150mL 10% aq $KHSO_4$ and concentrated *in vacuo* to remove the methanol. The mixture was diluted with 300mL chloroform and the phases were separated. The aqueous layer was washed twice more with chloroform. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The remaining solid was purified on an Isco automated system affixed with a Biotage Flash 40(L) (120g) cartridge eluted with 0-10% MeOH in EtOAc over 20 minutes and hold at 10% MeOH for 45 minutes. The product eluted last, pure by HPLC/MS and NMR.

LRMS (M+1) = 400.3

Step 9: 4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

In a 50mL heavy walled glass pressure flask 4-methoxy-6-(4-methoxybenzyl)-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (3.9g) and 15ml of (commercial) 33% HBr in HOAc were mixed. The flask was sealed, heated to 75^{0}C and allowed to stir overnight. The solvent was removed in vacuo. The remaining oil was dissolved in CH_3CN and purified by reverse phase on a Biotage KPCM 250 compression module containing a 10cm x 60cm Kiloprep cartridge. The product elutes at 13% CH_3CN in water containing 0.1% TFA.

LRMS (M+1) = 266.2.

Step 10: 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

4-Hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (0.43g, 0.0016 mol) was dissolved in 10mL dry DMF and 100mg NaH was added. The mixture was allowed to stir until the bubbles ceased, then 3-chloro-4-fluoro benzyl bromide (0.362g, 0.0016mole) was added. The reaction was quenched with 30mL of a 10% aq $KHSO_4$ solution and diluted with 100mL chloroform. The reaction was further diluted with 100mL brine and allowed to stir vigorously for 30 minutes. The layers were separated and the aqueous layer was washed with chloroform. The organic fractions were combined and dried over $NaSO_4$, filtered and concentrated under high vacuum to remove the DMF (yield 0.5g, 75%). HPLC analysis showed 85% purity. The solid product was crystallized first from isopropanol, then from ethanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49-2.57 (m, 1H), 2.67-2.74 (m, 1H), 2.9 (s, 3H), 3.1 (s, 3H), 3.34-3.46 (m, 1H), 3.47 (s, 1H), 3.48-3.53 (m, 1H), 4.48-4.52 (d, J=15, 1H), 4.79-4.83 (d, J=15, 1H), 7.11-7.21 (m, 2H), 7.34-7.36 (m, 1H), 12.94 (s, 1H).

LRMS (M+ 1) 408.2.

EXAMPLE 21

Oral Compositions

As a specific embodiment of an oral composition of a compound of this invention, 50 mg of compound of Example 1 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule. Encapsulated oral compositions containing any one of the compounds disclosed in the other examples can be similarly prepared.

EXAMPLE 22

HIV Integrase Assay: Strand Transfer Catalyzed by Recombinant Integrase

Assays for the strand transfer activity of integrase were conducted in accordance with WO 02/30930 for recombinant integrase. Representative compounds of the present invention exhibit inhibition of strand transfer activity in this assay. For example, the compounds in Examples 1-15, and 17-20 were tested in the integrase assay and were found to have IC_{50}'s less than about 1 micromolar.

Further description on conducting the assay using preassembled complexes is found in Wolfe, A.L. et al., *J. Virol.* 1996, 70: 1424-1432, Hazuda et al., *J. Virol.* 1997, 71: 7005-7011; Hazuda et al., *Drug Design and Discovery* 1997, 15: 17-24; and Hazuda et al., *Science* 2000, 287: 646-650.

EXAMPLE 22

Assay for inhibition of HIV replication

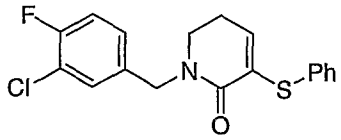
Assays for the inhibition of acute HIV infection of T-lymphoid cells were conducted in accordance with Vacca, J.P. et al., *Proc. Natl. Acad. Sci. USA* 1994, 91: 4096. Representative compounds of the present invention exhibit inhibition of HIV replication in this assay. For example, the compounds in Examples 1-15 and 17-20 were found to have IC_{95}'s equal to or less than about 10 micromolar in the present assay.

EXAMPLE 23

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

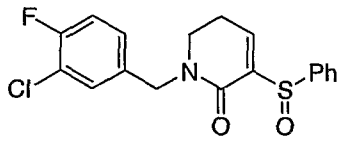
Step 1: 1-(3-Chloro-4-fluorobenzyl)piperidin-2-one

Valerolactam (60 g) was dissolved in MTBE (1.5L) at room temperature. To this solution was added Bu_4NSO_4 (4.9 g) as a phase transfer catalyst. The cloudy solution was stirred at room temperature for 5 minutes. Then, NaOH (50 wt%;300 mL) was slowly added as to keep the internal temperature below 30°C. 3-Chloro-4-fluorobenzyl bromide (108.3 g) was then added slowly to this biphasic mixture, again as to keep the internal temperature under control. The reaction was then aged for 4 hours at room temperature. At this time LC showed the reaction to be complete. Water (500 mL) was then added. After phase cut, the organic layer was washed with brine (300 mL), dried under $MgSO_4$ followed by solvent switch to heptane (400 mL). The slurry obtained was stirred at room temperature. for 1 hour and then filtered to afford the title product.



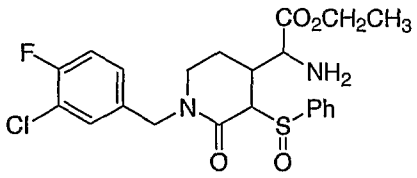
Step 2: Preparation of an unsaturated sulfide of formula 1:

1-(3-Chloro-4-fluorobenzyl)piperidin-2-one (25g) was dissolved in THF (250 mL) and cooled to -20 degrees C under nitrogen atmosphere. LHMDS (204 mL, 1M in THF) was added over 40 minutes at -20 to -30°C and aged for 1 hour at -20°C. Methyl benzene sulfinate (17.78 g) was added over 30 minutes, again keeping the internal temperature at -20°C. The reaction was aged for 30 minutes at -20°C at which time LC showed the reaction to be complete. The reaction mixture was then quenched with water (100 mL) and diluted with EtOAc (300 mL). After phase cut, the organic layer was washed with HCl 2N (2 x 100 mL). The organic layer was then washed with brine (2 x 100 mL), dried under $MgSO_4$ followed by solvent switch to DCM (600 mL; final volume 400 mL). To this solution was added acetic anhydride (11.6 mL) and $MeSO_3H$ (3.07 mL). The solution was then aged at room temperature overnight. The reaction was quenched with water (300 mL) and cooled to 0°C. The slurry obtained was then carefully basified to pH=8 with solid Na_2CO_3. The organic layer obtained after phase cut was then washed with brine and dried under $MgSO_4$. After evaporation of solvents, the title unsaturated sulfide 1 was obtained as an oil which solidified on standing. The title sulfide 1 can be crystallized from MeOH.



Step 3: Preparation of a vinyl sulfoxide of formula 2:

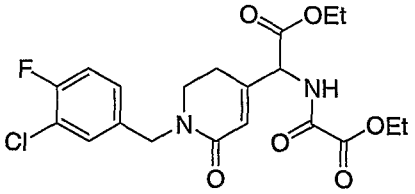
Unsaturated sulfide 1 (35.47 g) was dissolved in MeOH (200 mL) and water was added (50 mL) followed by the addition of solid $NaIO_4$ (39.82 g). The slurry obtained was stirred at room temperature for 3 days. The slurry was then filtered and the solid obtained was washed with EtOAc (200 mL). The filtrate was then evaporated until almost dryness and diluted with EtOAc (350 mL) and washed with H_2O (200 mL). The organic layer was then washed with brine (200 mL) and dried under $MgSO_4$. The organic solvents were then removed to completion. The oil obtained was crystallized with a IPAc:Hexane (1: 1.2) mixture and seeding to afford the title sulfoxide 2.



Step 4: Preparation of a Michael adduct of formula 3:

To a solution of vinyl sulfoxide 2 (5g, 13.74 mmoles) in THF (70 mL) at 0°C was added diphenylketimine glycine ethyl ester (4g, 15.mmoles) followed by t-BuOLi (0.2g, 2.5 mmoles). The mixture was stirred for 20 minutes at 0°C then, HCl 2N (80 mL) was added. The resulting mixture was

stirred at 20°C for 20 minutes and MTBE (160 mL) was added. After phase separation, the aqueous layer was basified to pH=8-9 by addition of solid Na_2CO_3. The resulting aqueous layer was extracted twice with EtOAc (2x100 mL) and the solvent evaporated under reduced pressure to give the title adduct **3** as an oil.



Step 5: Preparation of an oxamate of formula **4**:

To a solution of adduct **3** (6.2g, 13.28 mmoles) in THF (70 mL) at 0°C was added triethylamine (2 mL, 14.6 mmoles) followed by dropwise addition of ethyloxalyl chloride (1.55 mL, 13.94 mmoles). The resulting slurry was stirred for 20 minutes at 0°C, then water (50 mL) was added. The mixture was extracted with EtOAc (2x100 mL), then solvent switched to toluene (final volume: 80 mL). The toluene solution was heated to 90°C for 30-45 minutes then passed through a plug of silica gel (50g) using EtOAc/hexanes 1:1 (200 mL), then EtOAc as eluent. After evaporation of the solvents, the title oxamate **4** was obtained.

Step 6: Ethyl 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

To a solution of oxamate **4** (2g, 4.5 mmoles) in THF (35 mL) was added LiBr (1.2g, 18.1 mmoles) followed by DABCO (0.76g, 6.8 mmoles). The mixture was stiired for 18 hours at 20°C, then HCl 2N (50 mL) was added and the mixture was extracted with EtOAc (50 mL). Solvents were evaporated under reduced pressure to give the title compound as a pale yellow solid.

Alternative Route:

Ethyl 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate

To a stirred solution of ethyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (5.0 g; see Example 12, Step 6) and sodium acetate (0.89 g) in acetic acid (90 mL) was added peracetic acid (28 mL). The mixture was then heated at 50°C overnight. The mixture was cooled to 5°C and saturated $NaHSO_4$ (17 mL) added, keeping the temperature at less than 25°C. The mixture was concentrated to 50% original volume and partitioned between tert-butyl methyl ether (100 mL) and water (50 mL). The organic phase collected and the volatiles evaporated. The residue was dissolved in toluene (50 mL) and volatiles evaporated, the residue

dissolved in toluene (50 mL) and evaporation repeated. Finally the residue was dissolved in toluene (20 mL). Acetic anhydride (3.9 mL) was added and the mixture heated at reflux until complete by HPLC analysis. The mixture cooled to ambient temperature and sodium ethoxide in ethanol (20 mL) was added. The reaction mixture stirred overnight. 2N HCl (31 mL) was added and the title product isolated by filtration.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.6-9.5 (bs, 1H), 7.4 (dd, *J* = 6.8. 2.4Hz, 1H), 7.2 (m, 1H), 7.15 (t, *J* = 8.4 Hz, 1H), 4.7 (s, 2H), 4.35 (q, *J* =7.2Hz, 2H), 3.45 (t, *J* = 6.4 Hz, 2H), 3.35 (t, *J* = 6.4 Hz, 2H), 1.4 (t, J = 7.2 Hz, 3H) ppm.

Step 7: Methyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate

To a stirred suspension of ethyl 6-(3-chloro-4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxylate (40g) in DMF (200 mL) was added magnesium methoxide in methanol (100 mL). The mixture heated at 40-50°C for 3 hours. The excess methanol distilled off, and methyl tosylate (18 mL) was added. The reaction mixture was heated at 50°C overnight, then cooled to 25°C, and then quenched into 1N HCl (100 mL). The suspension stirred for 1 hour at ambient temperature. The product was isolated by filtration, and the filter cake washed with water (2 x 100 mL) and then dried on the filter under an atmosphere of nitrogen. The crude product was suspended in methanol (460 mL), heated at reflux temperature for 1 hour, and then allowed to cool to ambient temperature. The product was isolated by filtration and the filter cake washed with cold methanol (2x 40 mL) and dried to give the title product.

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.37 (s, 1H), 7.35 (dd, *J* = 2.4, 6.9 Hz, 1H), 7.22-7.18 (m, 1H), 7.13 (t, *J* = 8.4 Hz, 1H), 4.67 (s, 2H), 3.92 (s, 3H), 3.54 (s, 3H), 3.43 (t, *J* = 6.4 Hz, 2H), 2.81 (t, *J* = 6.4 Hz, 2H) ppm. (ES MS M+1 = 395.0)

Step 8: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

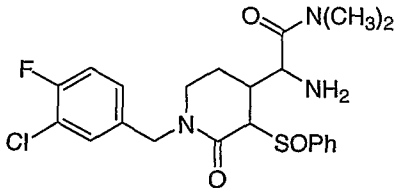
To THF (80mL) cooled to -10°C was added iPrMgCl (2M in THF, 60 mL). Dimethylamine (2M in THF) was then added at -10 to 0°C, the mixture then stirred for 1 hour at -5 to -10°C. The resulting suspension of $ClMgNMe_2$ at -10°C was allowed to warm to 0°C, and a solution of methyl 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate (10.0 g) in dichloromethane (100 mL) was added over 20 minutes at 0°C. The mixture was then stirred until reaction was complete by HPLC. The reaction mixture was quenched with 1N HCl (335 mL). The organic layer was collected and the aqueous layer extracted with CH_2Cl_2

(35 mL). The organic phases were then combined and washed with brine (35 mL). Volatiles were evaporated to give the title product as an amorphous solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (dd, J = 2.2, 7.14 Hz, 1H), 7.33-7.29 (m, 1H), 7.17 (t, J = 9.0 Hz, 1H), 4.72 (d, J = 14.8 Hz, 1H), 4.65 (d, J = 14.8 Hz, 1H), 3.35 (s, 3H), 3.33-3.96 (m, 2H), 3.07 (s, 3H), 2.97 (s, 3H), 2.47 (dd, J = 5.68,11.36 Hz, 2H) ppm. (ES MS M+1 = 408.0)

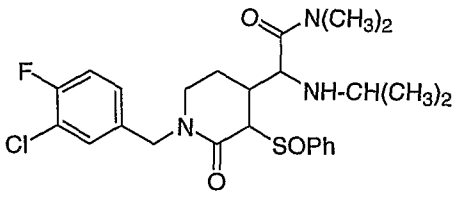
EXAMPLE 24

6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-2-isopropyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide



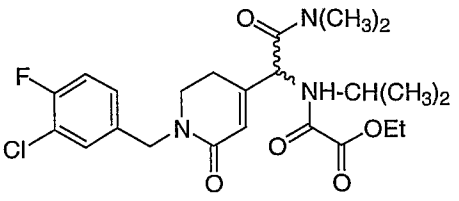
Step 1: Preparation of a Michael adduct of formula **5**:

To a solution of vinyl sulfoxide **2** (5g, 13.74 mmoles; Example 91, Step 3) in THF (70 mL) at 0°C was added diphenylketimine glycine dimethyl amide (4g, 15.mmoles) followed by t-BuOLi (0.2g, 2.5 mmoles). The mixture was stirred for 20 minutes at 0°C, and then HCl 2N (80 mL) was added. The resulting mixture was stirred at 20°C for 20 minutes and MTBE (160 mL) was added. After phase separation, the aqueous layer was basified to pH=8-9 by addition of solid Na_2CO_3. The resulting aqueous layer was extracted twice with EtOAc (2x100 mL) and the solvent evaporated under reduced pressure to give the title adduct as an oil.



Step 2: Preparation of an isopropyl amine of formula **6**:

To a solution of adduct **5** (2.5g, 5.35 mmoles) in MeOH (30 mL) was added acetone (0.8 mL, 10.7 mmoles) followed sodium triacetoxyborohydride (1.2g, 5.9mmoles). The mixture was stirred for 20 minutes, and then water (10 mL) and $NaHCO_3$ saturated (30mL) were added. The resulting mixture was extracted twice with EtOAc (2x30 mL) and the solvent evaporated under reduced pressure to provide the crude title product.



Step 3: Preparation of an oxamate of formula **7**:

Crude amine **6** (5 mmol) is dissolved in THF (40 mL) at 0°C and triethylamine (1.4 mL, 2.2 eq.) was added followed by dropwise addition of ethyloxalyl chloride (1 mL, 2.1 eq.). The resulting slurry was stirred for 20 minutes at 0°C, then water (30 mL) was added. The mixture was extracted with EtOAc (2x40 mL), then solvent switched to toluene (final volume: 20 mL). The toluene solution was heated at 90°C for 30-45 minutes then passed through a plug of silica gel (20g) using EtOAc/hexanes 1:1 (200 mL), then EtOAc as eluant. The title oxamate **7** was obtained after evaporation of the solvents.

Step 4: 6-(3-Chloro-4-fluorobenzyl)-4-hydroxy-2-isopropyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

To a solution of oxamate **7** (160mg) in THF (3 mL) was added LiBr (110mg, 4eq.) followed by DABCO (56mg, 1.5 eq.). The mixture was stirred for 10 minutes at room temperature, then HCl 2N (5 mL) was added and the mixture was extracted with EtOAc (5 mL). The solvents were evaporated under reduced pressure to give the title compound.

EXAMPLE 25

Crystalline sodium salt of 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-isopropyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide

Part A: Preparation

MeOH (10 mL) and MTBE (50 mL) were added to 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-isopropyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide (6.94 g). NaOH/MeOH (1 N; 15.95 mL) was then charged thereto, and the admixture stirred until the carboxamide dissolved. The solution was filtered and additional MTBE (65 mL) was added to the filtrate. The filtrate was concentrated by removal of MeOH under vacuum (190 mm Hg at 40°C). The resulting concentrate (140 mL) was seeded, heated to 40°C, and aged overnight. The aged concentrate was then cooled to room temperature, and the resulting solids were separated by filtration, washed with 10% MeOH/MTBE, and vacuum dried at room temperature to afford a crystalline sodium salt.

Part B: Characterization

An XRPD pattern of a Na salt prepared in the manner described in Part A was generated on a Philips Analytical X'Pert Pro X-ray powder diffractometer using a continuous scan from 2.5 to 40 degrees 2 Θ. Copper K-Alpha 1 ($K_{\alpha 1}$) and K-Alpha 2 ($K_{\alpha 2}$) radiation was used as the source. The experiment was run under ambient conditions. 2Θ values and the corresponding d-spacings in the XRPD pattern include the following:

Peak No.	d-spacing (Å)	2 Theta
1	15.0	5.9
2	8.1	10.9
3	7.1	12.5
4	6.6	13.3
5	5.7	15.5
6	5.0	17.6
7	4.7	18.7
8	4.2	21.3
9	3.7	23.9

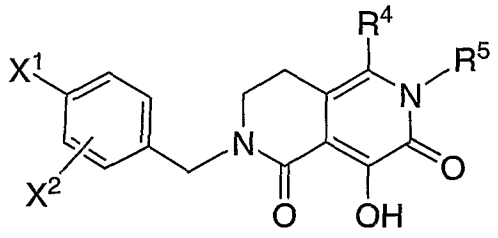
A Na salt prepared in the manner described in Part A was also analyzed by a TA Instruments DSC 2910 differential scanning calorimeter at a heating rate of 10°C/min from room temperature to 250°C in a closed pan in a nitrogen atmosphere. The DSC curve exhibited an endotherm with a peak temperature of 220°C and an associated heat of fusion of 27 J/gm. The endotherm is believed to be due to melting.

A thermogravimetric analysis was performed with a Perkin-Elmer Model TGA 7 under nitrogen at a heating rate of 10°C/min from room temperature to 250 °C. The TG curve showed a 1.1 % weight loss from 20 to 220 °C.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, the practice of the invention encompasses all of the usual variations, adaptations and/or modifications that come within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



(I)

wherein:

X^1 is:

(1) -H,
(2) bromo,
(3) chloro,
(4) fluoro, or
(5) methoxy;

X^2 is:

(1) -H,
(2) bromo,
(3) chloro,
(4) fluoro,
(5) methoxy,
(6) -C_{1-4} alkyl,
(7) -CF_3,
(8) -OCF_3,
(9) -CN, or
(10) -$SO_2(C_{1-4}$ alkyl);

R^4 is:

(1) -CO_2H,
(2) -C(=O)-O-C_{1-4} alkyl,
(3) -$C(=O)NH_2$,

(4) -C(=O)NH-C_{1-4} alkyl,

(5) -C(=O)N(C_{1-4} alkyl)$_2$,

(6) -C(=O)-NH-$(CH_2)_{2-3}$-O-C_{1-4} alkyl,

(7) -C(=O)-N(C_{1-4} alkyl)-$(CH_2)_{2-3}$-O-C_{1-4} alkyl,

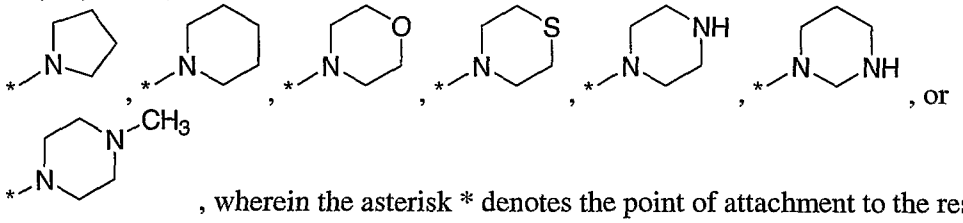
(8) -NHC(=O)-C_{1-4} alkyl,

(9) -N(C_{1-4} alkyl)C(=O)-C_{1-4} alkyl,

(10) -NHSO$_2$-C_{1-4} alkyl,

(11) -N(C_{1-4} alkyl)SO$_2$-C_{1-4} alkyl,

(12) -C(=O)-HetK, wherein HetK is:



, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(13) -C(=O)NH-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl),

(14) -C(=O)N(C_{1-4} alkyl)-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl),

(15) -C(=O)NH-CH_2-phenyl, or

(16) -C(=O)N(C_{1-4} alkyl)-CH_2-phenyl; and

R^5 is:

(1) -H,

(2) -C_{1-4} alkyl,

(3) cyclopropyl,

(4) cyclobutyl,

(5) -CH_2-cyclopropyl,

(6) -CH_2-cyclobutyl, or

(7) -CH_2-phenyl.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^4 is:

(1) -CO_2H,

(2) -C(=O)-O-C_{1-4} alkyl,

(3) -C(=O)NH_2,

(4) -C(=O)NH-C_{1-4} alkyl,

(5) -C(=O)N(C_{1-4} alkyl)$_2$,

(6) -C(=O)-NH-$(CH_2)_{2-3}$-O-C_{1-4} alkyl,

(7) -C(=O)-N(C_{1-4} alkyl)-$(CH_2)_{2-3}$-O-C_{1-4} alkyl,

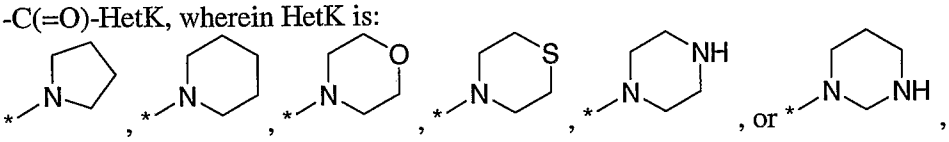
(8) -NHC(=O)-C_{1-4} alkyl,

(9) -N(C_{1-4} alkyl)C(=O)-C_{1-4} alkyl,

(10) -NHSO$_2$-C_{1-4} alkyl,

(11) -N(C_{1-4} alkyl)SO$_2$-C_{1-4} alkyl,

(12) -C(=O)-HetK, wherein HetK is:



, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(13) -C(=O)NH-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl),

(14) -C(=O)N(C_{1-4} alkyl)-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl),

(15) -C(=O)NH-CH_2-phenyl, or

(16) -C(=O)N(C_{1-4} alkyl)-CH_2-phenyl.

3. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^4 is:

(1) -CO_2H,

(2) -C(=O)-O-C_{1-4} alkyl,

(3) -C(=O)NH$_2$,

(4) -C(=O)NH-C_{1-4} alkyl,

(5) -C(=O)N(C_{1-4} alkyl)$_2$,

(6) -C(=O)-NH-$(CH_2)_{2-3}$-O-C_{1-4} alkyl,

(7) -C(=O)-N(C_{1-4} alkyl)-$(CH_2)_{2-3}$-O-C_{1-4} alkyl,

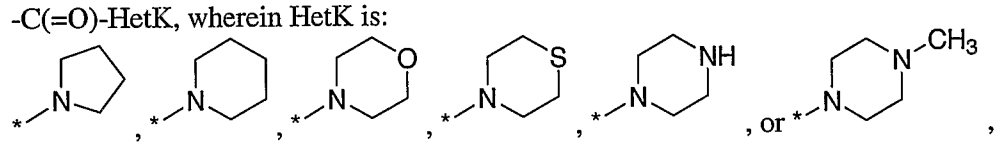
(8) -NHC(=O)-C_{1-4} alkyl,

(9) -N(C_{1-4} alkyl)C(=O)-C_{1-4} alkyl,

(10) -NHSO$_2$-C_{1-4} alkyl,

(11) -N(C_{1-4} alkyl)SO$_2$-C_{1-4} alkyl,

(12) -C(=O)-HetK, wherein HetK is:



, wherein the asterisk * denotes the point of attachment to the rest of the compound,

(13) -C(=O)NH-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl),

(14) -C(=O)N(C_{1-4} alkyl)-$(CH_2)_{0-1}$-(C_{3-6} cycloalkyl),

(15) -C(=O)NH-CH_2-phenyl, or

(16) -C(=O)N(C_{1-4} alkyl)-CH_2-phenyl.

4. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

X^1 is fluoro;

X^2 is -H or chloro;

R^4 is:

(1) -C(=O)-O-C_{1-3} alkyl,

(2) -C(=O)NH-C_{1-3} alkyl,

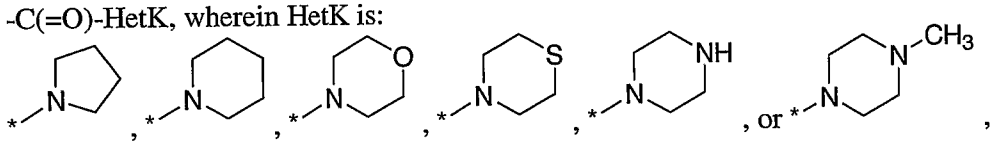
(3) -C(=O)N(C_{1-3} alkyl)$_2$,

(4) -C(=O)-N(C_{1-3} alkyl)-$(CH_2)_2$-O-C_{1-3} alkyl,

(5) -N(C_{1-3} alkyl)C(=O)-C_{1-3} alkyl,

(6) -N(C_{1-3} alkyl)SO_2-C_{1-3} alkyl,

(7) -C(=O)-HetK, wherein HetK is:



wherein the asterisk * denotes the point of attachment to the rest of the compound,

(8) -C(=O)NH-$(CH_2)_{0-1}$-(cyclopropyl),

(9) -C(=O)NH-$(CH_2)_{0-1}$-(cyclobutyl),

(10) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclopropyl,

(11) -C(=O)N(C_{1-3} alkyl)-$(CH_2)_{0-1}$-cyclobutyl,

(12) -C(=O)NH-CH_2-phenyl, or

(13) -C(=O)N(C_{1-3} alkyl)-CH_2-phenyl; and

R^5 is -H or -C_{1-4} alkyl.

5. The compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein

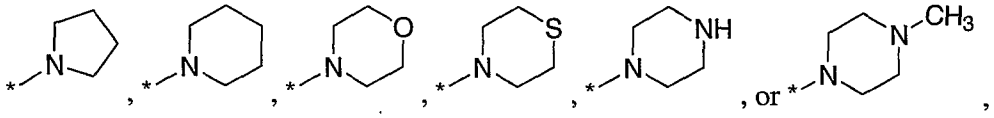
X^1 is fluoro;

X^2 is -H or chloro;

R^4 is:

(1) $-C(=O)N(C_{1-3}\text{ alkyl})_2$,

(2) -C(=O)-HetK, wherein HetK is:



wherein the asterisk * denotes the point of attachment to the rest of the compound,

(3) $-C(=O)N(C_{1-3}\text{ alkyl})-(CH_2)_{0-1}$-cyclopropyl, or

(4) $-C(=O)N(C_{1-3}\text{ alkyl})-(CH_2)_{0-1}$-cyclobutyl; and

R^5 is $-C_{1-4}$ alkyl.

6. The compound according to claim 5, or a pharmaceutically acceptable salt thereof, wherein R^4 is $-C(=O)N(CH_3)_2$.

7. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

methyl 6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylate;

6-(4-fluorobenzyl)-4-hydroxy-*N*,*N*-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

N-cyclobutyl-6-(4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

N-cyclopropyl-6-(4-fluorobenzyl)-4-hydroxy-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(4-fluorobenzyl)-4-hydroxy-*N*-isopropyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(4-fluorobenzyl)-4-hydroxy-N-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(4-fluorobenzyl)-4-hydroxy-3, 5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxylic acid;

N-[6-(4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridin-1-yl]-N-methylmethanesulfonamide;

N-[6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridin-1-yl]-N-methylacetamide;

6-(4-fluorobenzyl)-4-hydroxy-*N*, *N*, 2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-isopropyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-isobutyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

N-cyclobutyl-6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

N-cyclopropyl-6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(4-fluorobenzyl)-4-hydroxy-N-isopropyl-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

2-(4-fluorobenzyl)-8-hydroxy-6-methyl-5-(piperidin-1-ylcarbonyl)-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione;

2-(4-fluorobenzyl)-8-hydroxy-5-(thiomorpholin-4-ylcarbonyl)-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione;

2-(4-fluorobenzyl)-8-hydroxy-5-(piperazin-1-ylcarbonyl)-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione;

6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-isobutyl-N-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(3-chloro-4-fluorobenzyl)-N,N-diethyl-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

2-(3-chloro-4-fluorobenzyl)-8-hydroxy-6-methyl-5-[(4-methylpiperazin-4-yl)carbonyl]-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione;

2-(3-chloro-4-fluorobenzyl)-8-hydroxy-6-methyl-5-(thiomorpholin-4-ylcarbonyl)-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione;

2-(3-chloro-4-fluorobenzyl)-8-hydroxy-6-methyl-5-(piperidin-1-ylcarbonyl)-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione;

6-(3-chloro-4-fluorobenzyl)-N-(cyclopropylmethyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(3-chloro-4-fluorobenzyl)-N-cyclopropyl-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(3-chloro-4-fluorobenzyl)-N-ethyl-4-hydroxy-N,2-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N-isopropyl-N,2-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

2-(3-chloro-4-fluorobenzyl)-8-hydroxy-6-methyl-5-(morpholin-4-ylcarbonyl)-2,3,4,6-tetrahydro-2,6-naphthyridine-1,7-dione;

6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,2-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

N,N-diethyl-6-(4-fluorobenzyl)-4-hydroxy-2-methyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide;

N,N-diethyl-6-(4-fluorobenzyl)-3,4-dihydroxy-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide;

6-(4-fluorobenzyl)-3,4-dihydroxy-N-isobutyl-N-methyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide;

N-ethyl-6-(4-fluorobenzyl)-3,4-dihydroxy-N-methyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide;

6-(4-fluorobenzyl)-3,4-dihydroxy-N-methyl-5-oxo-N-propyl-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide;

6-(4-fluorobenzyl)-3,4-dihydroxy-N-isopropyl-N-methyl-5-oxo-5,6,7,8-tetrahydro-2,6-naphthyridine-1-carboxamide;

2-(4-fluorobenzyl)-7,8-dihydroxy-5-(pyrrolidin-1-ylcarbonyl)-3,4-dihydro-2,6-naphthyridin-1(2H)-one; and

2-(4-fluorobenzyl)-7,8-dihydroxy-5-(morpholin-4-ylcarbonyl)-3,4-dihydro-2,6-naphthyridin-1(2H)-one.

8. The compound according to claim 7, or a pharmaceutically acceptable salt thereof, which is a compound selected from the group consisting of 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-N,N,2-trimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide; 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-isopropyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-

naphthyridine-1-carboxamide; and 6-(3-chloro-4-fluorobenzyl)-4-hydroxy-2-isobutyl-N,N-dimethyl-3,5-dioxo-2,3,5,6,7,8-hexahydro-2,6-naphthyridine-1-carboxamide.

9. A pharmaceutical composition comprising an effective amount of a compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10. A compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for inhibiting HIV integrase in a subject in need thereof or for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof.