TITLE OF THE INVENTION

TETRAHYDRO-4H-PYRIDO[1,2-a]PYRIMIDINES AND RELATED COMPOUNDS USEFUL AS HIV INTEGRASE INHIBITORS

FIELD OF THE INVENTION

The present invention is directed to tetrahydro-4H-pyrido[1,2-a]pyrimidines, related 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 treating or delaying the onset of AIDS.

BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) 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.

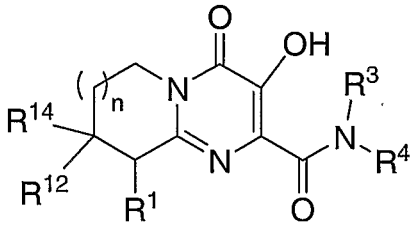
Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, integrase and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); 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.

SUMMARY OF THE INVENTION

The present invention is directed to novel pyridopyrimidine derivatives and related 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:

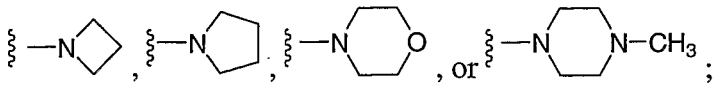

(I);

R^1 is H or NR^2R^5;

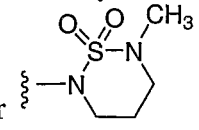
R^2 is CH_3;

R^5 is

1) $C(O)CH_2SO_2CH_3$,
2) $C(O)C(O)N(CH_3)_2$,
3) $SO_2N(CH_3)_2$, or
4) SO_2R^{20}, wherein R^{20} is:



or alternatively R^2 and R^5 together with the nitrogen atom to which they are attached form

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R^3 is hydrogen;

R^4 is:

1) p-fluorobenzyl,
2) 4-fluoro-3-methylbenzyl,
3) 3-chlorobenzyl, or
4) 3-chloro-4-methylbenzyl;

R^{12} and R^{14} are both H, except that when R^5 is $C(O)C(O)N(CH_3)_2$ and R^4 is p-fluorobenzyl and n is 1, then R^{12} and R^{14} are either both H or both CH_3; and

n is an integer equal to zero, 1 or 2.

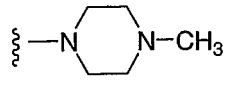
The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating AIDS, methods of delaying the onset of AIDS, methods of preventing AIDS,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

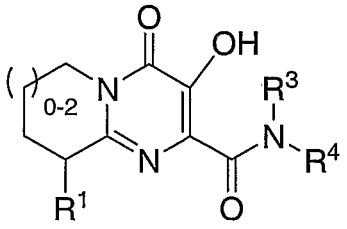
The present invention includes compounds of Formula I above, and pharmaceutically acceptable salts thereof. These compounds and pharmaceutically acceptable salts thereof are HIV integrase inhibitors.

An embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is NR^2R^5; n is an integer equal to 1 or 2; and all other variables are as originally defined above.

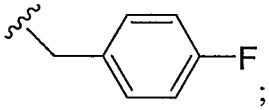
Another embodiment of the present invention is a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein R^1 is NR^2R^5; R^2 is CH_3; R^5 is 1) $C(O)C(O)N(CH_3)_2$ or 2) SO_2R^{20}, wherein R^{20} is ; R^3 is hydrogen; R^4 is p-fluorobenzyl or 4-fluoro-3-methylbenzyl; R^{12} and R^{14} are both H, except that when R^5 is

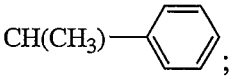
$C(O)C(O)N(CH_3)_2$ and R^4 is p-fluorobenzyl and n is 1, then R^{12} and R^{14} are either both H or both CH_3; and n is an integer equal to 1 or 2.

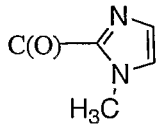
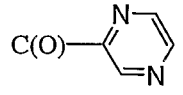
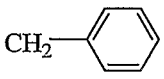
The present invention also includes a compound of Formula II, or a pharmaceutically acceptable salt thereof:



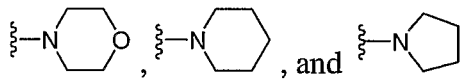
(II);

wherein R^1 is hydrogen, NR^2R^5, OR^2, SR^2, SOR^2, SO_2R^2, $SO_2NR^2R^5$, or $OC(O)NR^2R^5$; R^3 is hydrogen; R^4 is ;

R^2 is 1) hydrogen, 2) CH_3, or 3) ; and

R^5 is 1) $C(O)CH_3$, 2) $C(O)CH_2SO_2CH_3$, 3) CH_3, 4) $C(O)C(O)N(CH_3)_2$, 5) SO_2CH_3, 6) $SO_2N(CH_3)_2$, 7) $C(O)CH_2N(CH_3)_2$, 8) $SO_2CH_2SO_2CH_3$, 9) $C(O)CF_3$, 10) , 11) , or 12) ;

or R^2 and R^5, together with the nitrogen atom to which they are attached, form a heterocyclic ring selected from the group consisting of



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 Table 1 below.

Still other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising 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 a therapeutically 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 combination useful for inhibiting HIV integrase, for treating or preventing infection by HIV, or for preventing, treating or delaying the onset of AIDS, which is a therapeutically effective amount of a compound of Formula I and a therapeutically effective amount of an HIV infection/AIDS treatment agent selected from the group consisting of HIV/AIDS antiviral agents, immunomodulators, and anti-infective agents.

(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 a therapeutically 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 a therapeutically effective amount of a compound of Formula I.

(i) The method of (h), wherein the compound of Formula (I) is administered in combination with a therapeutically 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 a therapeutically effective amount of a compound of Formula I.

(k) The method of (j), wherein the compound is administered in combination with a therapeutically 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).

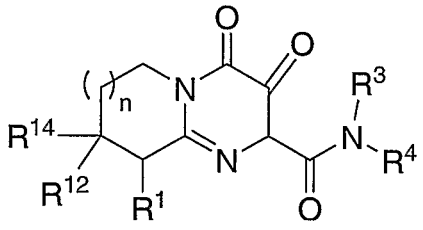
(m) A method of preventing or treating infection by HIV in a subject in need thereof which comprises administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

(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.

The compounds of the present invention may have asymmetric centers and may occur, except when specifically noted, as mixtures of stereoisomers or as individual diastereomers, or enantiomers, with all isomeric forms being included in the present invention.

The N-substituted hydroxypyrimidinone compounds of the present invention may also occur as tautomers thereof, such as the following tautomer of a compound of Formula I:



It is understood that the present invention includes all tautomers of the hydroxypyrimidinone compounds of Formula I (or II), both singly and in mixtures.

The compounds of the present inventions are useful in the inhibition of HIV 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.

Compounds representative of the present invention have been tested for inhibition in an assay for the strand transfer activity of integrase. The assay is conducted in the manner described in WO 02/30930. The assay is also in accordance with Wolfe, A.L. et al., *J. Virol.* 1996, 70: 1424-1432, for recombinant integrase, except that: (i) the assay uses preassembled integrase strand transfer complexes; (ii) the strand transfer reaction is performed in the presence of inhibitor in 2.5 mM $MgCl_2$ using 0.5 to 5 nM of a 3' FITC labeled target DNA substrate, and (iii) strand transfer products are detected using an alkaline phosphatase conjugated anti-FITC antibody and a chemiluminescent alkaline phosphatase substrate. Representative compounds of the present invention exhibit inhibition of strand transfer activity in this assay. For example, the compounds set forth in Table 1 below were tested in the integrase assay and demonstrated IC_{50}'s of about 5 micromolar or less. Further description on conducting the assay using preassembled complexes is found in 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.

Certain compounds representative of the present invention have also been tested in an assay for inhibition of acute HIV infection of T-lymphoid cells, conducted in accordance with Vacca, J.P. et al., *Proc. Natl. Acad. Sci. USA* 1994, 91: 4096. These compounds -- including the compounds set forth below in Table 1 -- demonstrated IC_{95}'s of about 20 micromolar or less.

The compounds of the present invention can also act as inhibitors of HIV ribonuclease H (RNase H). The human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) catalyzes the conversion of genomic RNA into double-stranded proviral DNA after cell entry, utilizing the RNA- and DNA-dependent polymerase and RNase H activities of the enzyme. HIV-1 RT is an asymmetric dimer consisting of p66 and p51 polypeptides. The catalytic activities of RT are conducted at discrete sites in the p66 subunit; i.e., the N terminus of p66 catalyzes the RNA- and DNA-dependent DNA polymerase activity, and the p15 domain at the C terminus catalyzes RNase H activity. RNase H is required to cleave the RNA strand of the RNA:DNA heteroduplex intermediates in reverse transcription. The compounds of the present invention can selectively bind to and inhibit the RNase H domain of HIV-1 RT. The RNase H inhibition activity of the compounds can be measured using suitable assays known in the art, such as the assay described in Shaw-Reid et al., *J. Biol. Chem.* 2003, 278 (5): 2777-2780. Accordingly, the present invention includes a method of inhibiting HIV RNase H in a subject in need of such inhibition which comprises administering to the subject an effective amount of a

compound of the invention. The present invention further 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 inhibiting HIV RNase H.

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. When the compounds of the invention carry an acidic moiety, 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.

For the purpose of inhibiting HIV integrase or HIV RNase H, preventing or treating HIV infection or preventing, treating or delaying the onset of AIDS, the compounds of the present invention may 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 a therapeutically effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

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 in the specified amounts, as well as any product which results, directly or indirectly, from combining the specified ingredients in the specified amounts.

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 "therapeutically 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, which includes alleviation or prophylaxis of the symptoms of the disease or condition being treated or prevented. The term also includes herein the amount of active compound sufficient to inhibit HIV integrase and/or RNase H and thereby elicit the response being sought. 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.

The pharmaceutical compositions may be in the form of orally-administrable suspensions or tablets or capsules, nasal sprays, sterile injectible preparations, for example, as sterile injectible aqueous or oleagenous suspensions or suppositories. These compositions can be prepared by methods and contain excipients which are well known in the art. Suitable methods and ingredients are described in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990, which is herein incorporated by reference in its entirety.

The compounds of this invention can be administered orally in a dosage range of 0.001 to 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 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another preferred dosage range is 0.1 to 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 1.0 to 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 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, both documents being herein incorporated by reference in their entireties. 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 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 Schemes and Examples, include the following: AIDS = acquired immunodeficiency syndrome, ARC = AIDS related complex, Bn = benzyl, CBZ (or Cbz) = benzyloxycarbonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAD = dimethylacetylenedicarboxylate, DMF = N,N-dimethylformamide, DMSO = dimethylsulfoxide, EtOAc = ethyl acetate, FIA-MS = flow injection analysis mass spectrometry, h = hour(s), HIV = human immunodeficiency virus, HPLC = high performance liquid chromatography, IPA = isopropanol, LDA = lithium diisopropylamide, Me = methyl, MeOH = methanol, NMP = N-methyl pyrrolidinone, NMR = nuclear magnetic resonance, Pd/C = palladium on carbon catalyst, RP-HPLC = reversed phase HPLC, 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 and reagents. In the reactions shown below, 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 defined, the variables listed in Schemes 1, A, B, C and D have the following meanings:

P^ is hydrogen or a protective group, e.g., an ester such as, but not limited to, benzoate and pivalate, or an ether such as, but not limited to, a benzyl ether, that is normally removed under the conditions employed to convert the methyl ester to the amide or is removed in a different step. The protective group is typically used for synthetic and/or purification reasons.

R^ is hydrogen or C_{1-6} alkyl.

Y is hydrogen or $NR^{sa}R^{sb}$.

R^{sa} is C_{1-6} alkyl, $C(O)R^{sc}$, $C(O)C(O)NR^{sc}R^{sd}$, SO_2R^{sc}, $SO_2NR^{sc}R^{sd}$, $C(O)CH_2SO_2R^{sc}$, $C(O)CH_2NR^{sc}R^{sd}$, $SO_2CH_2SO_2R^{sc}$, or $CH(CH_3)R^{sc}$, or R^{sa} and R^{sb}, together with the nitrogen atom to which they are attached, form a heterocyclic ring containing 1 or 2 heteroatoms.

R^{sb} is hydrogen, C_{1-6} alkyl, or $C(O)CF_3$, or R^{sa} and R^{sb}, together with the nitrogen atom to which they are attached, form a heterocyclic ring containing 1 or 2 heteroatoms.

R^{sc} is C_{1-6} alkyl, aryl, a 5- or 6-membered heteroaryl ring which is unsubstituted or substituted with C_{1-6} alkyl, $C(O)CH_2SO_2C_{1-6}$ alkyl, or $(CH_2)_{1-6}$ aryl.

R^{sd} is C_{1-6} alkyl.

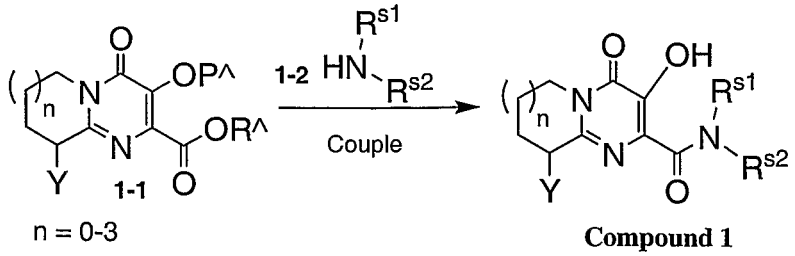
R^{s5} is R^{sc}, $C(O)NR^{sc}R^{sd}$, $CH_2SO_2R^{sc}$, $CH_2NR^{sc}R^{sd}$, $NR^{sc}R^{sd}$, or $CH_2SO_2R^{sc}$.

R^{s1} is hydrogen.

R^{s2} is CH_2R^{se}, wherein R^{se} is unsubstituted aryl or aryl substituted with halogen.

The compounds of the present invention can be prepared by coupling the appropriate amines with suitable substituted alkyl 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a] pyrimidine -2-carboxylate (or carboxylic acids or halides) or alkyl 3-hydroxy-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]pyrimidine-2-carboxylate (or carboxylic acids or halides) or alkyl 3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepine-2-carboxylate (or carboxylic acids or halides) or alkyl 3-hydroxy-4-oxo-6,7,8,9,10,11-hexahydro-4*H*-pyrimido[1,2-*a*]azepine-2-carboxylate (or carboxylic acids or halides), as represented by Scheme 1.

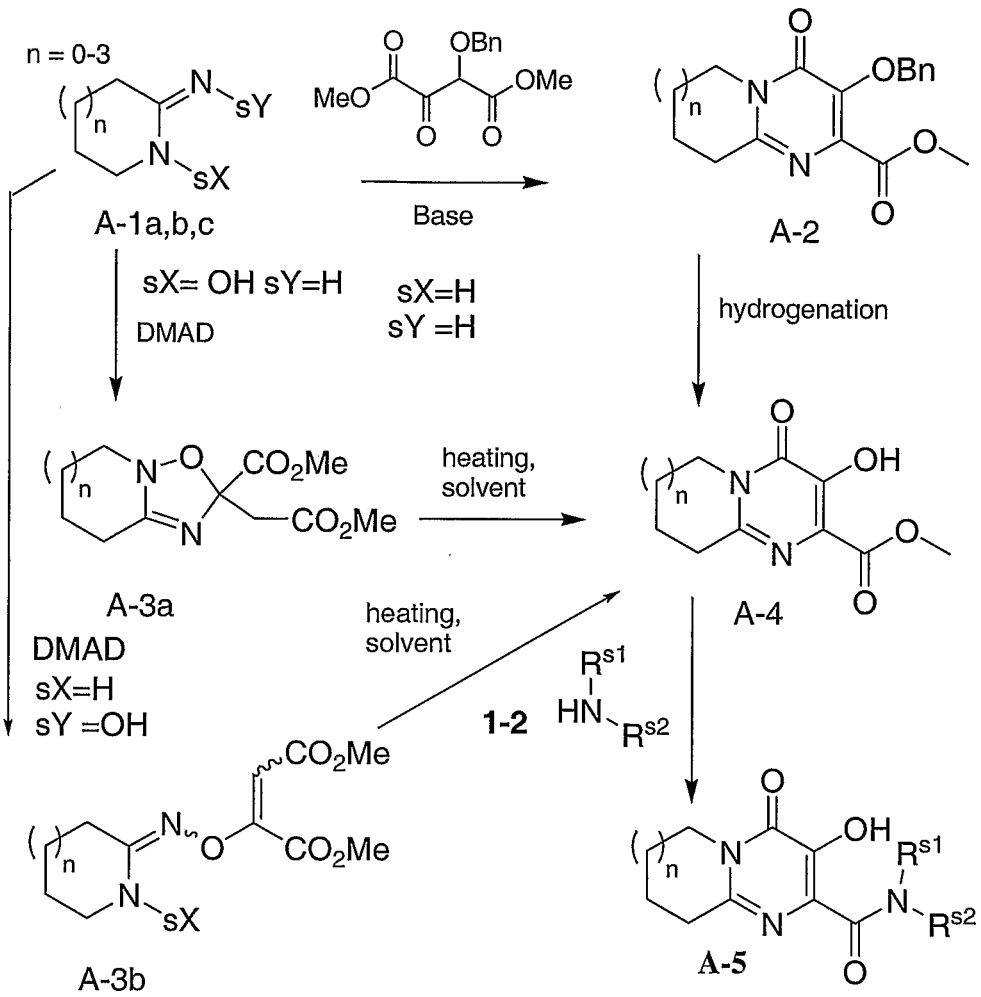
Scheme 1



Methods for coupling carboxylic acid derivatives with amines to form carboxamides are well known in the art. Suitable methods are described, for example, in Jerry March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, 1985, pp. 370-376. Amines of formula **1-2** can be prepared using the methods described in Richard Larock, Comprehensive Organic Transformations, VCH Publishers Inc, 1989, pp 385-438, or routine variations thereof.

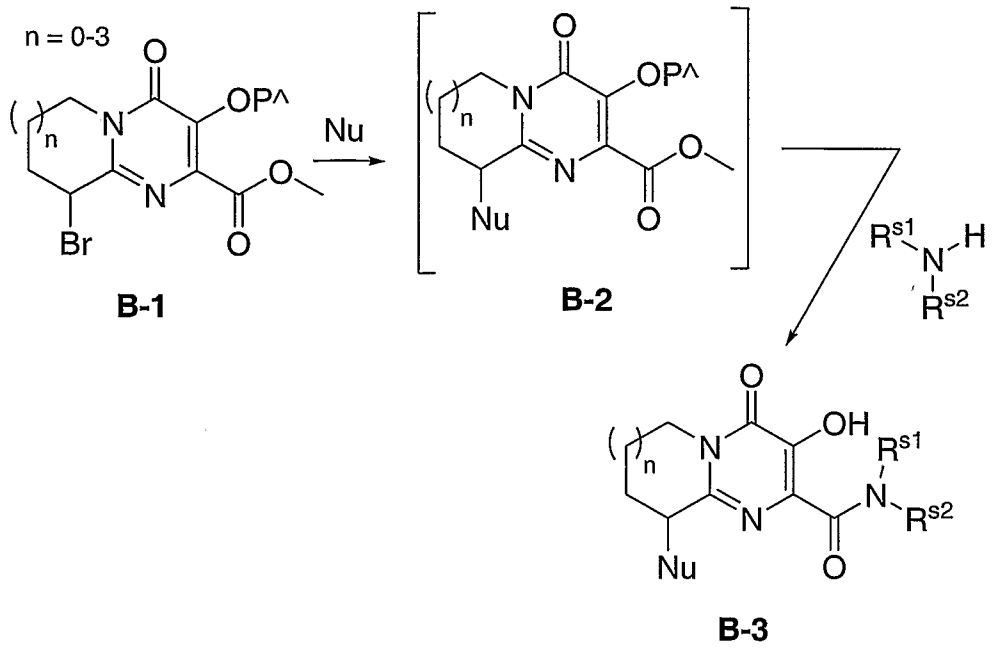
Scheme A depicts a general synthesis of carboxamides **A-5**. The methyl ester **A-4** can be reacted with an amine **1-2** in solvents like DMF, methanol, ethanol, toluene, NMP at the appropriate temperature (e.g., from 20 to 150°C) to give the final compound **A-5**. Methyl ester **A-4** can be synthesized by one of three synthetic routes. In the first route, amidine hydrochloride **A-1a** (sX=H; sY=H) can be reacted with dimethyl 2-(benzyloxy)-3-oxosuccinate in the presence of a base to afford the protected methyl ester intermediate **A-2**, which can be readily deprotected to afford the methyl ester **A-4** . In a second route, amidoxine **A-1b** (sX=OH; sY=H), obtained in three steps from tert-butyl benzyloxycarbamate, can be reacted with DMAD to afford the cyclic intermediate **A-3a**, which can be rearranged by heating in an appropriate solvent (e.g., xylene) to afford the methyl ester **A-5**. In a third route, amidoxyme **A-1c** (sX=H;sY=OH) can be reacted with DMAD in an appropriate solvent (e.g., acetonitrile) to afford the intermediate **A3-b**, which can be rearranged to the methyl ester **A-4** by heating in an appropriate solvent (e.g., xylene). All three of these routes can be applied to amidines and amidoxymes containing ring substituents. Scheme A is exemplified in Example 1.

Scheme A



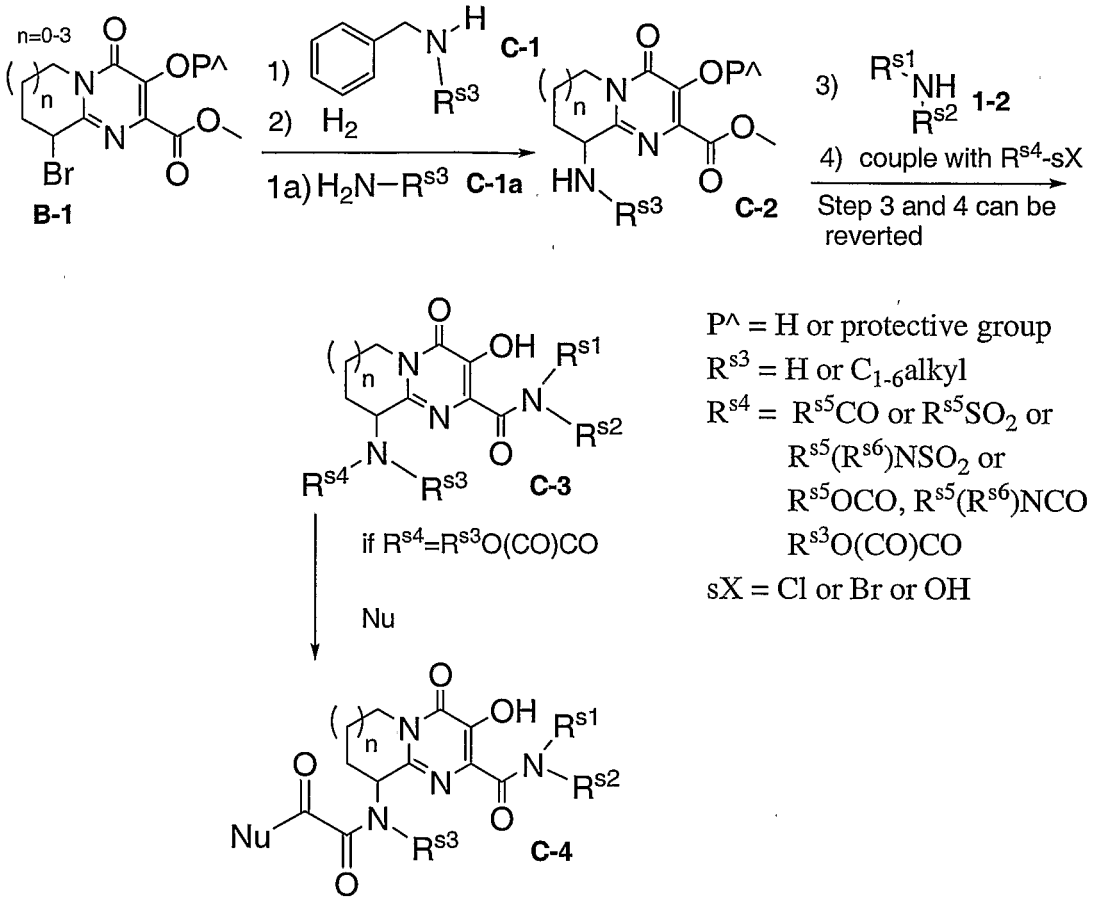
Scheme B shows a method for preparing compounds of the present invention that contain an amine, ether, thioether, sulfoxide or sulfone group at the 9-position of the 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide core. The bromo derivative **B-1** can be obtained from methyl ester **A-4** by first protecting the hydroxy group on **A-4** with a suitable protective group (e.g., conversion to a benzoate or pivalate or to benzyloxy) and then contacting the protected **A-4** with a brominating agent (e.g., NBS). The bromo derivative **B-1** can then be treated with a nucleophile ("Nu"; e.g. an amine, thiol or alcoholate) to afford with or without isolation the methyl ester intermediate **B-2**, that is reacted with the desired amine to give the final product **B-3**. If the nucleophile is a thiol or contains an oxidizable sulfur, an oxidation step to obtain the sulfoxide or sulfone can be included in the scheme. If the nucleophile contains an ester, the ester can be converted to an amide by routine chemistry after the synthesis of **B-3**. Scheme B is exemplified in Example 2.

Scheme B



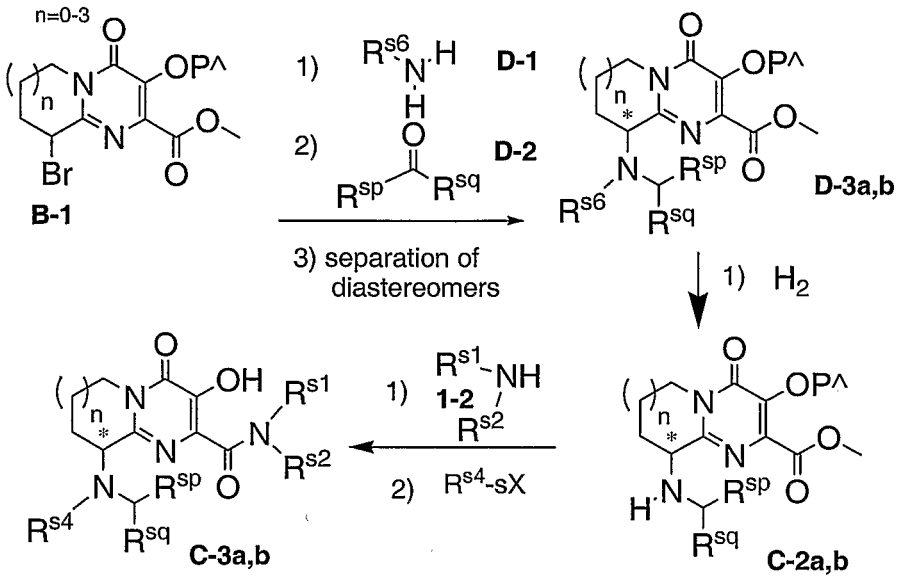
Scheme C depicts a general synthesis of derivatives **C-3** or **C-4** containing an aliphatic ring substituent such as amide, sulfonamide, sulfonylurea, carbamate, or urea. The bromo derivative **B-1** can be treated with benzylamine **C-1** and then hydrogenated or reacted directly with amine **C-1a** to give intermediate **C-2**, which can then be treated with amine **1-2**, with or without isolation, and then coupled with a carboxylic acid or reacted with a carbonyl chloride (or sulfonyl chloride or sulfamoyl chloride) or isocyanate to afford the final product **C-3**. If **C-3** contains $R^{s4} = R^{s3}O(CO)CO$, it can be further reacted with a nucleophile such as an amine to afford the product **C-4**. Scheme C is exemplified in Examples 3, 4 and 6. The last two steps can be reversed.

Scheme C



Scheme D shows the synthesis of homochiral compounds **C-3**, **C3a,b**, and **C-4**. The bromo derivative **B-1** is displaced with chiral amines **D-1** to give a mixture of diastereoisomers, with subsequent or simultaneous removal of the protecting group. The amino group at the 9-position is reductively alkylated with aldehydes or ketones **D-2** to afford the intermediate **D-3**. The mixture of diastereoisomers can be separated by crystallization or chromatography to give the single diastereoisomers **D-3a,b**. R^{s6} can be removed by hydrogenation to afford the homochiral **C-2a,b** intermediate. A subsequent reaction with amine **1-2** and coupling with carboxylic acid or treatment with carbonyl chloride (or sulfonyl chloride or sulfamoyl chloride) or isocyanate affords the final homochiral product **C-3a,b**. As in the case of the racemic compounds **C-3** in Scheme C, an additional step can be performed to produce homochiral **C-4** compounds. Scheme D is exemplified in Examples 5 and 7.

Scheme D



P^ = H or protective group
R^{s6} = chiral alkyl residue (e.g. (S)-a-methylbenzyl)
R^{sp}, R^{sq} = H or C_{1-6}alkyl
R^{s4} = $R^{s5}CO$ or $R^{s5}SO_2$ or $R^{s5}(R^{s6})NSO_2$ or $R^{s5}OCO$, $R^{s3}O(CO)CO$ $R^{s5}(R^{s6})NCO$
sX = Cl or Br or OH

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.

EXAMPLE 1

N-(4-Fluorobenzyl)-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxamide

Step 1a: *Tert*-butyl benzyloxy(4-cyanobutyl)carbamate (Bergeron, R. J., McManis, J. S., Tetrahedron *45* (16), 4939-4944 (1989).

To a solution of tert-butyl benzyloxycarbamate in anhydrous dimethylformamide were added 5 mol% of sodium iodide and portionwise 1.36 eq. of sodium hydride (60 % dispersion in mineral oil). The mixture was stirred at room temperature for 15 min. before 1.05 eq. of 4-chlorovaleronitrile were added. The mixture was heated to 85 °C and stirred for 3.5 h. After cooling to room temperature the mixture was quenched with water and extracted with diethyl ether. The combined organic phases were concentrated and washed with half saturated aq. sodium thiosulfate, water and brine. The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The oily residue was washed with petroleum

ether and dried under high vacuum to yield Tert-butyl benzyloxy(4-cyanobutyl)carbamate as a light yellow oil.
1H-NMR (400 MHz, CDCl3) δ: 7.38 (m, 5H), 4.84 (s, 2H), 3.45 (t, J = 6.4 Hz, 2H), 2.34 (t, J = 6.8 Hz, 2H), 1.70 (m, 4H), 1.52 (s, 9H). MS m/z: 271 (M+H)+.

Step 2a: 1-(Benzyloxy)piperidin-2-imine hydrochloride

Tert-butyl benzyloxy(4-cyanobutyl)carbamate was dissolved in a solution of 4 M HCl in 1,4-dioxane and the mixture was stirred for 18 h at room temperature. The solvent was removed under reduced pressure and the residue was treated with ethyl acetate and diethyl ether. A solid formed which was washed with diethyl ether, filtered and dried under high vacuum to give 1-(benzyloxy)piperidin-2-imine hydrochloride as a pale yellow solid.
1H-NMR (400 MHz, DMSO-d6) δ: 9.53 (s, 1H), 8.97 (s, 1H), 7.57-7.41 (m, 5H), 5.05 (s, 2H), 3.67 (t, J=6.0 Hz, 2H), 2.64 (t, J=6.4 Hz, 2H), 1.90-1.84 (m, 2H), 1.69-1.63 (m, 2H). MS m/z: 205 $(M+H)^+$.

Step 3a: 2-Iminopiperidin-1-ol hydrochloride

A solution of 1-(benzyloxy)piperidin-2-imine hydrochloride in methanol, containing palladium on charcoal (10 %, w/w) was stirred under hydrogen at atmospheric pressure for 3 h. The catalyst was filtered off and the solution was concentrated to dryness under reduced pressure. The residue was triturated with diethyl ether, filtered and dried under high vacuum to afford 2-iminopiperidin-1-ol hydrochloride as a pale yellow solid.
1H-NMR (400 MHz, DMSO-d6) δ: 11.76 (s, 1H), 8.82 (s, 1H), 8.49 (s, 1H), 3.63 (t, J=6.0 Hz, 2H), 2.63 (t, J=6.0 Hz, 2H), 1.87 (m, 2H), 1.66 (m, 2H). 13C-NMR (150 MHz, DMSO-d6) δ: 159.06, 50.92, 25.76, 22.01, 17.22.
MS m/z: 115 (M+H)+.

Step 4a: Methyl 2-(2-methoxy-2-oxoethyl)-5,6,7,8-tetrahydro-2*H*-[1,2,4]oxadiazolo[2,3-a]pyridine-2-carboxylate

To a solution of 2-iminopiperidin-1-ol hydrochloride in chloroform was added triethylamine. The mixture was stirred for 5 min. at room temperature, then cooled to 0 °C and 1.2 eq. of dimethyl acetylenedicarboxylate were added dropwise under stirring. The cooling bath was removed and the mixture was stirred at room temperature for one hour. The solvent was removed under reduced pressure and the solution was partitioned between ethyl acetate and half saturated aq. ammonium chloride. The aqueous phase was further extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and filtered through silica gel. The

solvent was removed under vacuum to afford methyl 2-(2-methoxy-2-oxoethyl)-5,6,7,8-tetrahydro-2*H*-[1,2,4]oxadiazolo[2,3-*a*]pyridine-2-carboxylate as a light yellow oil.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.82 (s, 3H), 3.70 (s, 3H), 3.51 (m, 1H), 3.36 (m, 1H), 3.31 (d, J = 16.6 Hz, 1H), 2.98 (d, J = 16.6 Hz, 1H), 2.53 (m, 2H), 1.94 (m, 2H), 1.74 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.15, 168.88, 164.97, 103.27, 55.71, 52.97, 51.84, 42.26, 26.06, 23.49, 22.83.
MS *m/z*: 257 $(M+H)^+$.

Step 5a: Methyl 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate

A solution of methyl 2-(2-methoxy-2-oxoethyl)-5,6,7,8-tetrahydro-2H-[1,2,4]oxadiazolo [2,3-a]pyridine-2-carboxylate in anhydrous o-xylene was placed in a double necked round bottom flask. The flask was equipped was a thermometer and closed with a septum. The mixture was heated to 148-150 °C for 5 h. The heating bath was removed and the mixture was left standing at room temperature for 16 h. To the mixture containing a precipitate was added diethyl ether. After 5 min. the precipitate was filtered off, washed with diethyl ether and dried under vacuum. Product methyl 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate was obtained as a pale brown solid.
1H-NMR (400 MHz, DMSO-d6) δ: 10.03 (s, 1H), 3.86 (t, J = 6.0 Hz, 2H), 3.80 (s, 3H), 2.75 (t, J = 6.8 Hz, 2H), 1.90-1.70 (m, 4H). 13C-NMR (150 MHz, DMSO-d6) δ:165.81, 158.65, 148.60, 143.10, 127.07, 51.98, 42.87, 30.32, 20.91, 18.40.
MS m/z: 225 (M+H)+.

The following procedure is an alternative route for the synthesis of methyl 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate

Step 1b: Dimethyl 2-(benzyloxy)-3-oxosuccinate

A solution of methyl(benzyloxy)acetate (1 eq) and dimethyl oxalate (1.2 eq) in dry THF was cooled to –78°C and LDA (2M in THF-heptane, 1.2 eq) was added dropwise. After stirring for an hour the cold bath was removed, and stirring was continued for an additional hour. The reaction was quenched at 0°C by pouring into cold 1N aq HCl, and the aqueous phase was extracted with EtOAc; the organic layer was washed with brine, dried and concentrated to give a crude that was used without further purification.

Step 2b: Methyl 3-(benzyloxy)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate

Commercially available 2-iminopiperidine hydrochloride (1.5 eq) was added at room temperature to a solution of oxosuccinate prepared in Step 1b (1 eq) in MeOH. After dropwise addition of neat DBU (4.5 eq), the reaction mixture was stirred for 2 days. Evaporation of the solvent gave a residue that was taken into EtOAc and washed with 1N HCl and brine; the organic layer was dried on Na_2SO_4 and the solvent removed. The crude was used without further purification.

An analytical sample of this product was purified by flash chromatography (Petroleum ether / EtOAc 1:2 to 1:5), and has the following spectroscopical data:

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.49-7.30 (m, 5H), 5.25 (s, 2H), 4.00 (t, *J*=6.2 Hz, 2H), 3.86 (s, 3H), 2.94 (t, *J*=6.6 Hz, 2H), 2.01- 1.95 (m, 2H), 1.92-1.87 (m, 2H) .

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 164.1, 159.3, 154.1, 141.1, 140.6, 136.0, 128.1, 127.8, 127.7, 73.8, 52.2, 42.7, 30.9, 21.0, 18.4.

MS *m/z*: 315 $(M+H)^+$.

Step 3b: Methyl 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate

Intermediate methyl 3-(benzyloxy)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2a]pyrimidine-2-carboxylate prepared in Step 2b was dissolved in MeOH and catalytic 10% Pd/C was added at room temperature. The mixture was stirred under H_2 atmosphere for 3.5 hours. Filtration of the catalyst and evaporation of methanol gave a residue to which diethyl ether was added; filtration afforded methyl 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate as a pale brown solid with the spectroscopical properties identical to the compound described in Step 5a.

Step 6: *N*-(4-Fluorobenzyl)-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxamide

A solution of methyl 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate obtained in Step 3b or Step 5a and 4-fluoro-benzylamine (2 eq.) in methanol was stirred and heated to 65°C for 22 h. The solvent was removed under reduced pressure and the title product was obtained by preparative RP-HPLC, using water (0.1 % TFA) and acetonitrile (0.1 % TFA) as eluents (column: C18). The pooled product fractions were lyophilized to afford the title compound as a fluffy white material.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.12 (s, 1H), 9.35 (m, 1H), 7.36 (m, 2H), 7.15 (m, 2H), 4.44 (m, 2H), 3.84 (t, J=6.4Hz, 2H), 2.80 (t, J=6.8Hz, 2H), 1.90-1.73 (m, 4H). MS *m/z*: 318 $(M+H)^+$.

EXAMPLE 2

N-(4-Fluorobenzyl)-3-hydroxy-9-morpholin-4-yl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxamide hydrochloride

Step 1: Methyl 3-(benzoyloxy)-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate

To a solution of methyl 3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate (obtained following Example 1) in pyridine was added benzoic anhydride (1.55 eq.). The mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and 0.5 M aq. HCl. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with 0.5 M aq. HCl, water and brine. The organic phase was dried over sodium sulfate, filtered and concentrated to dryness under vacuum. Title compound was obtained after flash chromatography (eluent petroleum ether/ethyl acetate, 1:2) as a colorless solid.
^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.07 (m, 2H), 7.78 (m, 1H), 7.62 (m, 2H), 3.86 (t, J = 6.0 Hz, 2H), 3.74 (s, 3H), 2.92 (t, J = 6.4 Hz, 2H), 1.93-1.81 (m, 4H). MS *m/z*: 329 $(M+H)^+$.

Step 2: Methyl 3-(benzoyloxy)-9-bromo-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate

A mixture of methyl 3-(benzoyloxy)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate , N-bromo-succinimide (1.2 eq.) and dibenzoylperoxide (70 %, 0.13 eq.) in carbon tetrachloride was stirred under reflux for one hour. The mixture was cooled to room temperature, the succinimide was filtered off and the solvent was removed under reduced pressure. Methyl 3-(benzoyloxy)-9-bromo-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate was obtained after flash chromatography (eluent petroleum ether/ethyl acetate, 1:1) as a pale yellow oil.
^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.08 (m, 2H), 7.79 (m, 1H), 7.63 (m, 2H), 5.58 (m, 1H), 4.24 (m, 1H), 3.77 (s, 3H), 3.72 (m, 1H), 2.43-2.35 (m, 1H), 2.30-2.05 (m, 3H). MS m/z: 409/407 $(M+H)^+$.

Step 3: N-(4-Fluorobenzyl)-3-hydroxy-9-morpholin-4-yl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide.

To a solution of methyl 3-(benzoyloxy)-9-bromo-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate in DMF was added morpholine (3 eq.) and the mixture was stirred at room temperature for 1h. The solvent was removed under reduced pressure and the residue was triturated with diethyl ether. The crude material was dissolved in methanol, 4-fluorobenzylamine (3 eq.) was added and the mixture was stirred for 1.5 h at 65°C . The solvent was removed under reduced pressure and the product was purified by preparative RP-HPLC, using water (0.1 % TFA) and acetonitrile (0.1 % TFA) as eluents (column: C18). The pooled product fractions were lyophilized and redissolved in 1N HCl. The solvent was removed under reduced pressure and the residue was lyophilized from water/ acetonitrile to afford the hydrochloride salt of *N*-(4-fluorobenzyl)-3-hydroxy-9-morpholin-4-yl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxamide as a slightly pink fluffy material.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.34 (s, 1H), 10.99 (s, 1H), 10.47 (s, 1H), 7.44 (m, 2H), 7.16 (m, 2H), 4.85 (m, 1H),4.60-4.40 (m, 3H), 4.10-3.85 (m, 4H), 3.60-3.05 (m, 5H obscured by water signal), 2.35-2.15 (m, 2H), 2.03-1.80 (m, 2H). MS *m/z*: 403 $(M+H)^+$.

EXAMPLE 3

(+/-)-9-[[(Dimethylamino)sulfonyl](methyl)amino]-N-(4-fluorobenzyl)-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide C-3

Step 1: Methyl 9-[benzyl(methyl)amino]-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate hydrochloride

To a stirred solution of the bromo derivative methyl 3-(benzoyloxy)-9-bromo-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate (obtained in Example 2, Step 2) in anhydrous dimethylformamide was added N-benzyl-N-methylamine (3 eq.). The mixture was stirred for 1.5 h at room temperature before diethyl ether and 2 M HCl in diethyl ether were added. The mixture was stirred for 5 min., the formed precipitate was filtered off and washed with diethyl ether. The precipitate was dissolved in anhydrous methanol and the solution was concentrated to dryness under reduced pressure. The title crude product obtained as a pale yellow oil, which contained an excess of N-benzyl-N-methylamine hydrochloride, was used without further purification.

MS m/z: 344 $(M+H)^+$.

Step 2: Methyl 3-hydroxy-9-(methylamino)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxylate

A solution of crude obtained in Step 1 in methanol, containing palladium on charcoal (10 % w/w) was stirred under hydrogen at atmospheric pressure for 3 h. The catalyst

was filtered off and the solution was concentrated to dryness under reduced pressure. The residue was triturated with diethyl ether, filtered and dried under high vacuum to afford the crude product as a yellow solid, which was used in the next step without further purification.
MS m/z: 254 (M+H)+.

Step 3: *N*-(4-Fluorobenzyl)-3-hydroxy-9-(methylamino)-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxamide

To a solution of the crude obtained in Step 2 in dry methanol were added an excess of triethylamine. The solvent was removed under reduced pressure and then under high vacuum. The oily residue was dissolved in anhydrous methanol and 4-fluoro-benzylamine was added (3.1 eq. th.). The mixture was stirred and heated to 60 °C overnight. After cooling to room temperature the solvent was removed under reduced pressure. The residue was triturated with diethyl ether and left under high vacuum for 15 min. The title crude product was obtained as a yellow solid, which contained an excess of 4-fluoro-benzylamine (ca. 3.5 eq.) and was used without further purification.
MS m/z: 347 $(M+H)^+$.

Step 4: (+/-)-9-[[(Dimethylamino)sulfonyl](methyl)amino]-*N*-(4-fluorobenzyl)-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxamide

To a solution of crude compound obtained in Step 3 in a 2:1 mixture of tetrahydrofuran and 2 M aq. sodium hydroxide was added *N,N*-dimethylsulfamoyl chloride (4.6 eq.). The mixture was stirred at roomtemperature for 16 h. The mixture was concentrated under reduced pressure and the product was isolated by preparative RP-HPLC, using water (0.1 % TFA) and acetonitrile (0.1 % TFA) as eluents (column: C18). The pooled product fractions were lyophilized to afford the title compound as a fluffy, slightly pink material.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 11.95 (s, 1H), 9.13 (m, 1H), 7.38 (m, 2H), 7.04 (m, 2H), 4.98 (m, 1H), 4.56 (m, 2H), 4.36 (m, 1H), 3.62 (m, 1H), 2.84 (s, 6H), 2.57 (s, 3H), 2.38-1.85 (m, 4H).
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.53, 162.55, 160.11, 157.74, 145.76 144.11, 132.70, 128.89, 128.81, 124.82, 114.60, 114.39, 58.06, 42.93, 41.53, 37.00, 29.03, 23.89, 20.09.
MS *m/z*: 454 $(M+H)^+$.

EXAMPLE 4

(+/-)-N^1-(2-{[(4-Fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl)-N^1,N^2,N^2-trimethylethanediamide

Step 1: (+/-)-N^1-(2-{[(4-Fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N^1,N^2,N^2-trimethylethanediamide

To a stirred solution of crude N-(4-fluorobenzyl)-3-hydroxy-9-(methylamino)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide (synthesized as described in Example 3, Step 3) in dichloromethane were added 6 eq. of triethylamine and 6 eq. of methyl chlorooxoacetate. The mixture was stirred at room temperature for 2 h, the solvent was removed under reduced pressure and the residue was dissolved in a solution of dimethylamine (2 M) in tetrahydrofuran. The mixture was stirred at 57 °C overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the product was isolated by preparative RP-HPLC, using water (0.1 % TFA) and acetonitrile (0.1 % TFA) as eluents (column: C18). The pooled product fractions were lyophilized to afford the title compound as a fluffy, slightly pink material. The product was a mixture of rotamers by NMR.

^{1}H-NMR (400 MHz, DMSO-d6) δ: 12.05 (s, 0.2H), 11.89 (s, 0.8H), 9.21 (m, 0.8H), 8.74 (m, 0.2H), 7.40-7.28 (m, 2H), 7.20-7.10 (m, 2H), 5.17 (m, 0.8H), 4.63-4.35 (m, 2.2H), 4.13-4.00 (m, 1H), 3.65-3.53 (m, in part overlaid by water signal), 2.95-2.75 (m, 9H), 2.15-1.80 (m, 4H). ^{13}C-NMR (100 MHz, DMSO-d6) δ: 167.87, 167.73, 165.92, 165.46, 164.51, 164.30, 162.42, 160.01, 157.50, 157.41, 146.27, 146.18, 145.76, 145.49, 134.44, 129.43, 129.35, 129.08, 129.00, 125.17, 125.05, 115.07, 114.85, 57.47, 53.60, 43.14, 41.37, 36.49, 35.95, 32.92, 32.64, 32.36, 28.19, 23.88, 22.12, 19.67, 19.35.

MS m/z: 446 $(M+H)^+$.

EXAMPLE 5

(+)-N^1-(2-{[(4-Fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N^1,N^2,N^2-trimethylethanediamide

Step 1: (+)3-Hydroxy-2-(methoxycarbonyl)-*N*-methyl-4-oxo-*N*-[(1*S*)-1-phenylethyl]-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-ammonium trifluoroacetate

To a 7:3 mixture (v/v) of methanol and water at –30°C, containing (1*S*)-1-phenylethylamine (4.5 eq.) was added bromo derivative methyl 3-(benzoyloxy)-9-bromo-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-2-carboxylate (synthesized as reported in Example 2, Step 2) (1.0 eq.). The mixture was stirred vigorously for 1.5 h at –30 °C. The cooling bath was removed and stirring was continued for 1 h at room temperature. The pH was adjusted to ca. 5 with acetic acid before 37 % aqueous formaldehyde (11.5 eq.) and sodium cyanoborohydride (3.25 eq.) were added. After stirring at room temperature for 20 min. the volume was reduced to ca. 1/4 under reduced pressure. A formed white precipitate was filtered off and the filtrate was acidified to pH 2-3 with trifluoroacetic acid. The solution was applied on

cation-exchange resin cartridges (Varian MEGA BOND ELUTE SCX), the cartridges washed with methanol and the crude product was eluted with 2 M ammonia in methanol. The pooled eluents were concentrated to dryness under reduced pressure and the oily residue was dissolved in methanol and neutralized with trifluoroacetic acid. After removal of the solvent an oily residue was obtained. The resulting diasteroisomers in 1:3 ratio were separated by preparative RP-HPLC-purification (column: C18) eluents water (0.1 % TFA), acetonitrile (0.1 % TFA). The major diasteroisomer was eluted as second peak and after lyophilization the title compound was obtained as a slightly pink solid.

^{1}H-NMR (500 MHz, pyridine-d_5) δ: 7.53 (m, 2H), 7.39 (m, 2H), 7.29 (m, 1H), 4.45 (m, 1H), 4.38 (m, 1H), 4.14 (m, 1H), 3.91 (s, 3H), 3.80 (m, 1H), 2.13 (s, 3H), 1.95-1.82 (m, 3H), 1.70-1.60 (m, 1H), 1.49 (d, J=6.4 Hz, 3H).

MS *m/z*: 358 $(M+H)^+$.

Step 2: (-)-3-Hydroxy-2-(methoxycarbonyl)-*N*-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-ammonium trifluoroacetate

A solution of (+)3-hydroxy-2-(methoxycarbonyl)-*N*-methyl-4-oxo-*N*-[(1*S*)-1-phenylethyl]-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-ammonium trifluoroacetate in methanol, containing palladium on charcoal (10 %, w/w) was stirred under hydrogen at atmospheric pressure for 1.5 h. The catalyst was filtered off and the solution was concentrated to dryness under reduced pressure to afford the title compound as a slightly pink oil.

^{1}H-NMR (400 MHz, CD_3OD) δ: 4.41 (m, 1H), 4.14 (m, 1H), 3.99 (s, 3H), 3.91 (m, 1H), 2.86 (s, 3H), 2.50 (m, 1H), 2.26 (m, 1H), 2.08 (m, 1H), 1.86 (m, 1H).

MS *m/z*: 254 $(M+H)^+$.

Step 3: (+)-N^1-(2-{[(4-Fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl)-N^1,N^2,N^2-trimethylethanediamide

A solution of (-)-3-Hydroxy-2-(methoxycarbonyl)-*N*-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-ammonium trifluoroacetate, p-fluoro-benzylamine (2.2 eq.) and triethylamine (1.3 eq.) in methanol was stirred and heated to 65 °C for 3 h. The solvent was removed under vacuum and the residue was dissolved in anhydrous dichloromethane. Methyl chlorooxoacetate (5 eq.) and triethylamine (5 eq.) were added and the mixture was stirred at room temperature for 50 min. The solvent was removed under reduced pressure and the residue was dissolved in a 2 M solution of dimethylamine in tetrahydrofuran. The mixture was stirred at 57 °C overnight. After cooling to room temperature the solvent was removed under reduced pressure and the product was isolated by preparative RP-HPLC, using

water (0.1 % TFA) and acetonitrile (0.1 % TFA) as eluents (column: C18). The pooled product fractions were lyophilized to afford the title product as a fluffy white material (ee 94.4 %).

The compound was dissolved in ethylacetate/heptane (3:2.5 (v/v) mixture) and left standing at room temperature for four days. The supernatant from the formed precipitate was taken off, concentrated under reduced pressure and the residue was lyophilized from water/acetonitrile to afford enantiopure title product e.e.100 %(e.e. determined by Chiral HPLC Chiralpak AS, mobile phase 0.2% TFA n-Hex/IPA) with spectroscopical properties identical to the compound described in Example 4, Step 1.

$[\alpha]^{20}_{D} = +36.5 \pm 2.5°$ (C = 0.63 in ethanol).

EXAMPLE 6

(+/-)-*N*-(2-{[(4-fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepin-10-yl)-*N*,*N*',*N*'-trimethylethanediamide

The title compound was prepared according to the synthetic sequence described in EXAMPLE 4, with the following variations:

Step 1: 1-(Benzyloxy)azepan-2-imine

T*ert*-butyl-(benzyloxy)-(5-cyanopentyl)-carbamate (synthesized following the procedure described in EXAMPLE 1 – Step 1a starting from 6-bromohexanenitrile) was dissolved in a saturated solution of HCl in EtOH and the mixture was stirred for 45 minutes. Nitrogen was bubbled into the solution to remove HCl in excess. The solvent was removed under reduced pressure and the residue, dissolved in 1,4-dioxane, was treated with triethylamine to adjust pH at 10. Ethanol was removed and the title compound containing an excess of triethylammonium chloride and ethyl 6-[(benzyloxy)amino]hexanoate was used without further purification. The analytical sample was purified by preparative RP-HPLC, using water (0.1% TFA) and acetonitrile (0.1% TFA) as eluents (column C_{18}). The pooled product fractions were lyophilized.

^{1}H-NMR (400 MHz, DMSO-d_6, 300K) δ: 9.39 (s, 1H), 8.81 (s, 1H), 7.61-7.52 (m, 2H), 7.48-7.38 (m, 3H), 5.03 (s, 2H), 4.02-3.93 (m, 2H), 2.70-2.59 (m, 2H), 1.69-1.54 (m, 6H).

MS *m/z*: 219 $(M+H)^+$.

Step 2: (+/-)-*N*-(2-{[(4-Fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4-6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepin-10-yl)-*N*,*N*',*N*'-trimethylethanediamide

To a stirred solution of crude N-(4-fluorobenzyl)-3-hydroxy-10-(methylamino)-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepine-2-carboxamide (synthesized starting from 1-

(benzyloxy)azepan-2-imine according to the procedure used in the analogous 6-membered series (EXAMPLE 3 – Step 3) in dichloromethane were added 3 eq. of triethylamine, 2 eq of potassium (dimethylamino)(oxo)acetate, 2.2 eq. of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 2.2 eq. of 1-hydroxybenzotriazole. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and 1 M aq. HCl. The aqueous phase was extracted with ethyl acetate and the combined organic phases were dried over sodium sulfate, filtered and concentrated to dryness under vacuum. The title product was isolated by preparative RP-HPLC, using water (0.1 % TFA) and acetonitrile (0.1 % TFA) as eluents (column: C18). The pooled product fractions were lyophilized to afford the title compound as a fluffy, white material. The product is a mixture of rotamers by ^{1}H NMR.

^{1}H-NMR (400 MHz, DMSO-d_6, 300K) δ: 12.29 (bs, 0.1H), 11.95 (bs, 0.9H), 9.30 (bs, 0.9H), 8.45 (bt, 0.1H), 7.38 (dd, J = 8.33, 5.5 Hz, 1.8H), 7.33 (dd, J = 8.33, 5.5 Hz, 0.2H), 7.15 (t, J = 9.0 Hz, 2H), 5.45-5.25 (m, 0.9H), 4.94 (dd, J = 14, 5.7 Hz, 1.0H), 4.84-4.79 (m, 0.1H), 4.57-4.43 (m, 2H), 3.54 (dd, J = 14, 11 Hz, 0.9H), 3.28-3.18 (m, 0.1H), 3.05 (s, 0.3H), 2.92 (s, 2.7H), 2.90 (s, 5.4H), 2.81 (s, 0.3H), 2.76 (s, 0.3H), 2.19-1.78 (m, 5H), 1.41-1.27 (m, 1H).

MS *m/z*: 460 $(M+H)^+$.

EXAMPLE 7

(-)-*N*-(2-{[(4-fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepin-10-yl)-*N*,*N*',*N*'-trimethylethanediamide

Step 1: Dimethyl (2*E*)-2-[(azepan-2-ylideneamino)oxy]but-2-enedioate and dimethyl (2*Z*)-2-[(azepan-2-ylideneamino)oxy]but-2-enedioate

To a suspension of azepan-2-one oxime in acetonitrile 1.1 eq. of dimethyl acetylenedicarboxylate were added dropwise under stirring. The mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure to afford a mixture 8/1 of dimethyl (2*E*)-2-[(azepan-2-ylideneamino)oxy]but-2-enedioate and dimethyl (2*Z*)-2-[(azepan-2-ylideneamino)oxy]but-2-enedioate as a yellow oil. To better characterize the title compounds a small amount of the crude was purified by preparative RP-HPLC, using water (0.1% TFA) and acetonitrile (0.1% TFA) as eluents (column C_{18}). The pooled product fractions were lyophilized.

Isomer E: ^{1}H-NMR (400 MHz, DMSO-d_6, 300K) δ: 7.08 (bs, 1H), 5.63 (s, 1H), 3.77 (s, 3H), 3.59 (s, 3H), 3.19-3.11 (m, 2H), 2.29-2.21 (m, 2H), 1.66-1.42 (m, 6H).

^{13}C-NMR (125 MHz, DMSO-d_6, 300 K) δ: 166.20, 162.81, 161.90, 161.61, 92.38, 52.42, 50.92, 42.28, 29.84, 29.32, 28.81, 25.40.

MS *m/z*: 271 $(M+H)^+$.

Isomer Z: ^{1}H-NMR (400 MHz, DMSO-d6, 300K): 6.66 (bs, 1H), 5.63 (s, 1H), 3.74 (s, 3H), 3.61 (s, 3H), 3.24-3.16 (m, 2H), 2.20-2.12 (m, 2H), 1.65-1.44 (m, 6H).

^{13}C-NMR (125 MHz, DMSO-d6, 300 K) δ: 165.01, 163.01, 161.45, 154.11, 101.09, 52.32, 51.05, 42.24, 29.93, 29.31, 28.45, 25.14.

MS *m/z* :271 $(M+H)^+$.

Step 2: Methyl 3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxylate

A mixture of dimethyl (2*E*)-2-[(azepan-2-ylideneamino)oxy]but-2-enedioate and dimethyl (2*Z*)-2-[(azepan-2-ylideneamino)oxy]but-2-enedioate in ratio 8/1 was dissolved in o-xylene and refluxed. After 16 h the solvent was removed under reduced pressure and the residue, dissolved in ethyl acetate, was extracted with a saturated solution of $NaHCO_3$ in water. The pH of the aqueous phase was adjusted to about 3 adding 6M HCl aq. and the solution was extracted with dichloromethane. The organic phase was dried over sodium sulphate and concentrated.

^{1}H-NMR (400 MHz, DMSO-d_6, 300 K) δ: 10.12 (s, 1H), 4.29-4.16 (m, 2H), 3.80 (s, 3H), 2.95-2.78 (m, 2H), 1.79-1.41 (m, 6H).

^{13}C-NMR (100 MHz, DMSO-d_6, 300K) δ: 165.79, 158.54, 153.41, 143.55, 126.61, 52.04, 43.02, 35.75, 28.76, 26.94, 24.58.

MS *m/z*: 239 $(M+H)^+$.

Step 3: Methyl 3-(benzoyloxy)-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxylate

To a solution of methyl 3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxylate in pyridine, benzoic anhydride (1.1 eq.) and a catalytic amount of dimethylaminopyridine were added. The mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue partitioned between dichloromethane and 1 M aq. HCl. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed with 1 M aq. HCl and brine. The organic phase was dried over sodium sulfate, filtered and concentrated to dryness under vacuum. Title compound was obtained after flash chromatography (eluents petroleum ether/ethyl acetate, 6:4) as a brown solid.

^{1}H-NMR (400 MHz, DMSO-d_6, 300 K) δ: 8.07 (dd, J = 8.6, 1.3 Hz, 2H), 7.78 (t, J = 7.5 Hz, 1H), 7.62 (t, J = 7.9 Hz, 2H), 4.31-4.29 (m, 2H), 3.74 (s, 3H), 3.06-3.04 (m, 2H), 1.82-1.65 (m, 6H).

^{13}C-NMR (75 MHz, DMSO-d_6, 300K) δ: 162.78, 162.65, 162.43, 157.01, 140.29, 135.23, 134.18, 129.63, 128.86, 127.59, 52.46, 43.13, 36.07, 28.47, 26.12, 23.68.
MS *m/z*: 343 $(M+H)^+$.

Step 4: Methyl 3-(benzoyloxy)-10-bromo-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxylate

A mixture of methyl 3-(benzoyloxy)-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxylate , N-bromo-succinimide (2 eq.) and α,α'-azoisobutyronitrile (0.45 eq.) in carbon tetrachloride was stirred under reflux for 14 hour. The mixture was cooled to room temperature, the succinimide was filtered off and the solvent was removed under reduced pressure. Methyl 3-(benzoyloxy)-10-bromo-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxylate was obtained after flash chromatography (eluents petroleum ether/ethyl acetate, 8:2) as a pale yellow solid.
^{1}H-NMR (400 MHz, DMSO-d_6, 300 K) δ: 8.07 (dd, J = 8.3, 0.9 Hz, 2H), 7.79 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.9 Hz, 2H), 5.63 (dd, J = 5.9, 2.2 Hz, 1H), 4.98 (dd, J = 14.3, 6.1 Hz, 1H), 3.97 (dd, J = 14.3, 11.0 Hz, 1H), 3.76 (s, 3H), 2.31-2.13 (m, 2H), 2.10-1.79 (m, 3H), 1.-1.61-1.48 (m, 1H).
^{13}C-NMR (75 MHz, DMSO-d_6, 300 K) δ: 162.65, 162.14, 157.22, 157.10, 139.45, 136.59, 134.37, 129.72, 128.94, 127.36, 53.56, 52.67, 42.37, 31.52, 25.78, 24.40.
MS m/z: 423/421 $(M+H)^+$.

Step 5: Methyl 3-hydroxy-4-oxo-10-{[(1*R*)-1-phenylethyl]amino}-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxylate

Methyl 3-(benzoyloxy)-10-bromo-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxylate (1.0 eq.) was added to a solution of (1*R*)-1-phenylethylamine (2.2 eq.) and triethylamine (1 eq) dissolved in N,N-dimethylformamide. The mixture was stirred vigorously for 2 hours at room temperature and then at 50° C for 30 minutes. The solvent was removed under reduced pressure and the title crude product (a mixture 1:1 of diasteroiesomers) for use without further purification. In an alternative procedure (Step 5A), solid methyl 3-(benzoyloxy)-10-bromo-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxylate (1.0 eq.) was added to a solution of (1*R*)-1-phenylethylamine (4.5 eq.) dissolved in a 7:3 methanol/ water mixture at -30°C. The reaction was carried out over night, then the temperature was raised to room temperature and the solvent concentrated to obtain a white solid that was filtered off and discarded. The title compound (as a mixture 7:3 of diasteroisomers) was extracted in dichloromethane from the mother liquid for use in the next step without further purification.
MS *m/z*: 358 $(M+H)^+$.

Step 6: *N*-(4-fluorobenzyl)-3-hydroxy-4-oxo-10-{[(1*R*)-1-phenylethyl]amino}-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxamide

p-Fluorobenzylamine (3 eq.) was added to the methyl 3-hydroxy-4-oxo-10-{[(1*R*)-1-phenylethyl]amino}-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxylate (prepared as described in Step 5 or Step 5A) dissolved in methanol. The mixture was stirred at 70° C overnight, then cooled to room temperature for use directly in Step 7. In an alternative procedure (Step 6A), the solvent was removed and the crude product crystallized from acetonitrile several times to obtain a single diasteroisomer of the title compound as the 4-fluorobenzylammonium salt with d.e.>95%

Step 7: (+) *N*-(4-fluorobenzyl)-3-hydroxy-10-{methyl[(1*R*)-1-phenylethyl]amino}-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxamide

N-(4-Fluorobenzyl)-3-hydroxy-4-oxo-10-{[(1*R*)-1-phenylethyl]amino}-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepine-2-carboxamide obtained in Step 6 was dissolved in methanol and the pH was adjusted to circa 5 with acetic acid before 37 % aqueous formaldehyde (6 eq.) and sodium cyanoborohydride (6.25 eq.) were added. The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue, dissolved in the minimum amount of methanol, was acidified to pH 2-3 with trifluoroacetic acid. The solution was applied on cation-exchange resin cartridges (Varian MEGA BOND ELUTE SCX), the cartridges washed with methanol and the crude product was eluted with 2 M ammonia in methanol. The pooled eluents were concentrated to dryness under reduced pressure to get an oily residue. The product, a mixture of diasteroisomers, was separated by preparative RP-HPLC-purification (column: C18) eluants water (0.1 % TFA), acetonitrile (0.1 % TFA). The title diasteroisomer was eluted as the first peak, and after lyophilization the title compound was obtained as a white solid (TFA salt).

In an alternative procedure (Step 7A), the product of Step 6A was reacted in the same manner as the product of Step 6 to obtain a single diastereomer without separation by HPLC.

^{1}H-NMR (300 MHz, DMSO-d_6-TFA, 300 K) δ: 9.42 (t, J = 6.2 Hz, 1H), 9.20 (bs, 1H), 7.60 (bd, J = 7.3 Hz, 2H), 7.51-7.29 (m, 5H), 7.21 (t, J = 8.9 Hz, 2H), 4.98-4.75 (m, 3H), 4.69 (dd, J = 15.5, 6.9 Hz, 1H), 4.47 (dd, J = 15.5, 5.5 Hz, 1H), 3.66 (t, J = 12.8 Hz, 1H), 2.94-2.81 (m, 3H), 1.97-1.81 (bm, 2H), 1.79-1.33 (m, 7H) .

MS m/z: 465 $(M+H)^+$.

$[\alpha]^{20}_D = +62 \pm 2$ (C = 0.1 in chloroform).

Step 8: (-)2-{[(4-fluorobenzyl)amino]carbonyl}-3-hydroxy-*N*-methyl-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepin-10-ammonium trifluoroacetate

A solution of the TFA salt of the product of Step 7 (or 7A) in methanol, containing palladium on charcoal (10%, w/w) was stirred under hydrogen at atmospheric pressure for 4 h. The catalyst was filtered off and the solution was concentrated to dryness under reduced pressure to afford the title compound.

^{1}H-NMR (300 MHz, DMSO-d$_6$- TFA, 300 K) δ: 9.88 (bs, 1H), 9.56 (bs, 1H), 9.14 (bs, 1H), 7.41 (dd, J = 8.6, 5.7 Hz, 2H), 7.17 (t, J = 8.8 Hz, 2H), 4.92 (dd, J = 14.6, 4.6 Hz, 1H), 4.72 (bm, 1H), 4.58-4.44 (m, 2H), 3.51 (dd, J = 13.9, 11.7 Hz, 1H), 2.66 (t, J = 4.9 Hz, 3H), 2.29 (d, J = 13.3 Hz, 1H), 2.02-1.57 (m, 4H), 1.45- 1.27 (m, 1H) .

MS m/z: 361 $(M+H)^+$.

$[\alpha]^{20}_D = -4 \pm 2$ (C = 0.4 in methanol).

Step 9: (-)*N*-(-{[(4-Fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepin-10-yl)-*N*,*N*',*N*'-trimethylethanediamide

Methyl chlorooxoacetate (2-6 eq.) and N-ethyldiisopropylamine (4 eq.) were added to a solution of the ammonium trifluoroacetate compound of Step 8 in chloroform. The mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure and the residue dissolved in a 2 M solution of dimethylamine in methanol was stirred at room temperature for 6 hours. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane was washed with 1 M HCl in water. The organic phase was dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The title product was isolated by preparative RP-HPLC, using water (0.1% TFA) and acetonitrile (0.1% TFA) as eluents (column: C18). The pooled product fractions were lyophilized to afford the title product with an enantiomeric excess of 99.5% (e.e. determined by Chiral HPLC Chiralpak AD, mobile phase 0.2% TFA n-Hex/0.2% TFA ethanol with 3% methanol). An amorphous potassium salt of the title compound was obtained by treating the compound dissolved in acetonitrile with aqueous KOH and then freeze drying.

^{1}H-NMR spectra was identical to the compound described in Example 6.

^{13}C-NMR (100 MHz, DMSO-d$_6$, 300 K) δ: 168.01, 165.80, 165.03, 161.30 (d, J_{C-F} = 243 Hz), 157.68, 149.67, 145.94, 134.59, 129.56 (d, J_{C-F} = 8.5 Hz), 124.72, 115.10 (d, J_{C-F} = 21 Hz), 55.88, 42.42, 41.56, 36.24, 32.79, 32.34, 28.83, 27.10, 26.15.

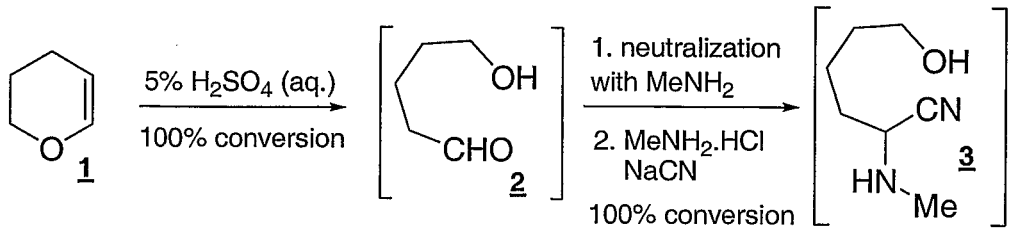
MS m/z: 460 $(M+H)^+$.

$[\alpha]^{20}_D = -72 \pm 2$ (C = 0.1 in chloroform).

EXAMPLE 8

Racemic *N*-(2-{[(4-fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepin-10-yl)-*N*,*N*',*N*'-trimethylethanediamide

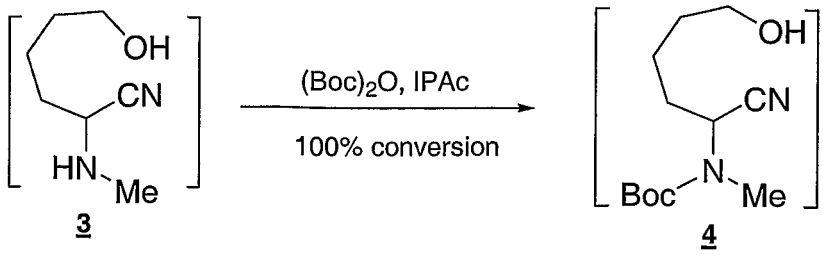
Step 1: Preparation of ω-Hydroxy N-Methyl aminonitrile **3**



Materials	MW	Equiv.	Moles	Wt. (g)	Vol. (mL)	Density
DHP	84.12	1	0.2500	21.10	22.93	0.92
5% H_2SO_4	98.08	0.122	0.0305		60 mL	
40% $MeNH_2$	31.06	0.244	0.0610	4.74	5.3	0.902
$MeNH_2$.HCl	67.51	5	1.250	84.4		
NaCN	49.01	1	0.2500	12.25		
IPAc					900	

To a 5% H_2SO_4 aqueous solution was added 3,4-dihydro-2H-pyran (DHP; 21.1 g) at 20-35 °C. The resulting solution was aged at 20-35 °C for 1 h. The reaction mixture was cooled to 0-5 °C, and neutralized to pH = 6-7 by 40% aqueous methylamine. Methylamine hydrochloride and sodium cyanide were added respectively to the reaction mixture. The resulting solution was aged at room temperature for 36 h. The reaction mixture was extracted by IPAc (6 x 150 mL). The combined organic layers were concentrated to a total volume about 150 mL (assay yield about 91%) and was used in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.81 (m, 1 H), 3.45 (m, 2 H), 2.47 (s, 3 H), 1.90-1.40 (m, 6 H).

Step 2: Preparation of ω-Hydroxy N-Methyl N-Boc-aminonitrile **4**

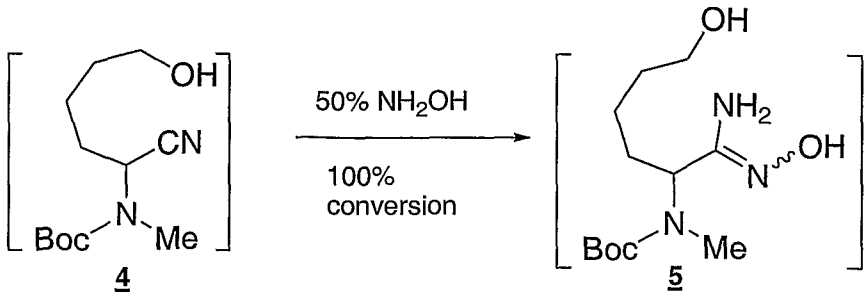


3 **4**

Materials	MW	Equiv.	Moles	Wt. (g)	Vol. (mL)
Aminonitrile **3**	142.20	1	0.2106	29.95	
$(Boc)_2°$	218.25	1.05	0.2211	48.3	
5% NH_2OH/ 10%NH_4Cl					35
IPAc					80

To a solution of ω-hydroxy *N*-methyl aminonitrile **3** (0.2106 moles) in IPAc (from Step 1) was added $(Boc)_2O$ (48.3 g) at room temperature. The resulting solution was aged at 30-35 °C for 2 h (100% conversion by ^1H NMR). The reaction mixture was cooled to 0-5 °C and 5%NH_2OH/10%NH_4Cl (35 mL) was added. The resulting mixture was aged at 10-20 °C for 3 h. After a phase cut, the aqueous layer was extracted with IPAc (80 mL), the combined organic layers were washed with brine (50 mL), and then concentrated and solvent-switched to IPA (total volume 230 mL), which was used for next step. ^1H NMR ($CDCl_3$, 400 MHz) δ: 5.18 (m, 1 H), 3.64 (q, J = 5.7 Hz, 2 H), 2.88 (s, 3 H), 1.88-1.75 (m, 3 H). 1.65-1.61 (m, 2 H), 1.49-1.46 (m, 1 H), 1.18 (s, 9 H).

Step 3: Preparation of Hydroxyamidine **5**

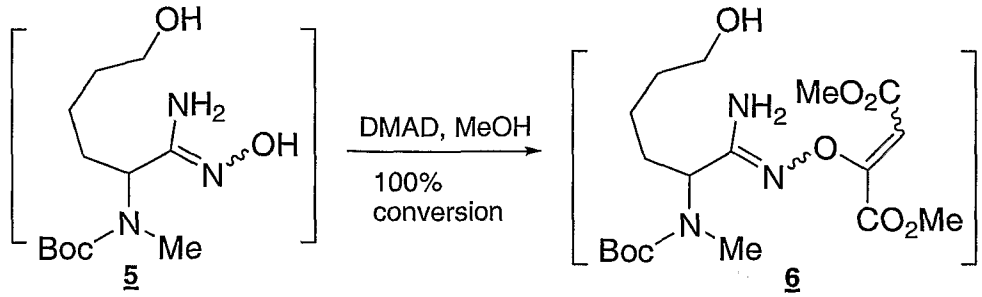


Materials	MW	Equiv.	Moles	Wt. (g)	Vol. (mL)	Density
N-Boc-amino-nitrile **4**	242.31	1	0.2106	51.03		
50% NH_2OH	33.03	1.25	0.2633	17.40	16.20	1.078
IPA					180	
MeOH					600	

To a solution of *N*-Boc-aminonitrile **4** (0.2106 moles) in IPA (total volume 230 mL) was added 50% hydroxylamine (16.2 mL) at ambient temperature. The resulting solution was aged at 60 °C for 3 h. The reaction mixture was then concentrated and solvent-switched to methanol solution (total volume 230 mL), which was used in the next step. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.53 (br s, 1 H), 4.84 (br s, 2 H), 4.64 (t, J = 7.1 Hz, 1 H), 3.71-3.62 (m, 2 H), 2.72 (s, 3 H), 2.00 (br s, 1 H), 1.92-1.82 (m, 1 H), 1.76 (1.55 (m, 3 H), 1.49 (s, 9 H), 1.42-1.23 (m, 2 H).

HPLC conditions: Column: Zorbax, Rx C8 250 x 4.6 mm; Temperature: 30 ° C; Detection at 210 nm; Mobile Phase: 0.1% aq H_3PO_4 (A)/MeCN (B); Gradient: 90:10 (A)/(B) to 10:90 over 15 min, 10:90 hold for 5 min, 10:90 to 90:10 (A)/(B) over 10 seconds; Flow Rate: 1 mL/min. Retention time: amidoxime - 6.152 minutes and 6.256 minutes (two isomers)

Step 4: Preparation of O-Alkene Amidoxime **6**



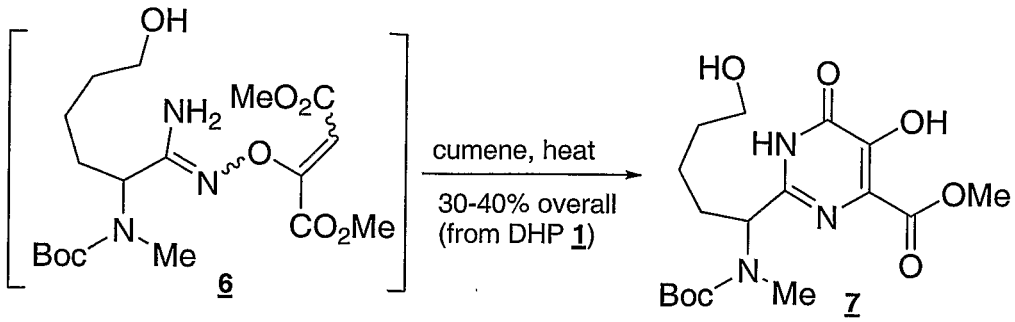
Materials	MW	Equiv.	Moles	Wt. (g)	Vol. (mL)	Density
Hydroxyamidine **5**	275.35	1	0.2106	57.93		
DMAD	142.11	1.05	0.2211	31.42	27.10	1.16
MeOH						
Cumene					500	

To a solution of hydroxyamidine **5** (about 0.2106 mole) in methanol (total volume 230 mL) was added dimethyl acetylenedicarboxylate (27.10 mL) at room temperature. The resulting solution was aged at room temperature for 16 h. The reaction mixture was concentrated and solvent-switched to cumene at 40-60 °C (total volume 430 mL). The solution was used in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.82 (s, 0.28 H), 5.73 (s, 0.72 H), 5.44 (br s, 1.77 H), 5.25 (br s, 0.56 H), 4.61 (m, 1 H), 3.89 (s, 0.84 H), 3.84 (s, 2.16 H), 3.72 (s, 2.16 H), 3.68 (s, 0.84 H), 3.65-3.58 (m, 2 H), 2.73 (s, 0.84 H), 2.71 (s, 2.16 H), 1.90-1.52 (m, 4 H), 1.47 (s, 9 H), 1.43-1.30 (m, 2 H).

HPLC conditions: Column: Zorbax, Rx C8 250 x 4.6 mm; Temperature: 30 ° C; Detection at 210 nm; Mobile Phase: 0.1% aq H_3PO_4 (A)/MeCN (B); Gradient: 90:10 (A)/(B) to 10:90 over 15 min, 10:90 hold for 5 min, 10:90 to 90:10 (A)/(B) over 10 seconds; Flow Rate: 1 mL/min.

Retention time: amidoxime **6**- 12.051 minutes, 12.315 minutes, ratio *ca* 3.6: 1.

Step 5: Preparation of Pyrimidine 7

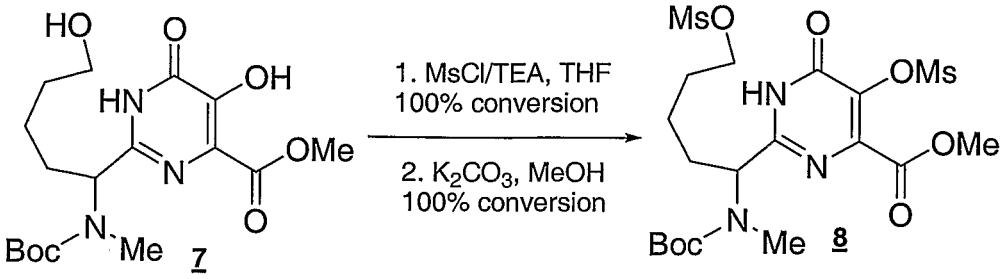


Materials	MW	Equiv.	Moles	Wt. (g)	Vol. (mL)	Density
O-Alkene amidoxime **6**	417.45	1	0.2106	87.91		
Cumene					430 (total)	
5% $NaHCO_3$	84.1	1.44	0.3032		510	
EtOAc					750	
Brine					150	
THF						

A solution of O-alkene amidoxime **6** (about 0.2106 moles) in cumene (total volume 430 mL) was heated at 120 °C (inside temperature) for 12 h. The reaction mixture was then cooled to about 60 °C, concentrated to a total volume 250 mL, then diluted with EtOAc (250 mL), and cooled to 25-35 °C. 5% Sodium bicarbonate (330 mL, about 1 equiv.) was then slowly added, and the resulting solution was aged at 25-35 °C for 0.5 h. After a phase cut, the organic layer was extracted with 5% sodium bicarbonate (180 mL) again. The combined aqueous extracts were acidified by 5 N HCl to pH = 2-3, and extracted by EtOAc (3 x 250 mL). The combined organic layers were washed with brine (150 mL). The organic solution was concentrated and solvent-switched to THF (about 30-40% yield overall, KF about 100-150 ppm). ^1H NMR ($CDCl_3$, 400 MHz) δ: 10.66 (br s, 2 H), 4.77 (m, 1 H), 4.01 (s, 3 H), 3.72-3.67 (m, 2 H), 2.77 (s, 3 H), 2.20-1.55 (m, 5 H), 1.48 (s, 9 H), 1.43-1.35 (m, 1 H).

HPLC conditions: Column: Zorbax, Rx C8 250 x 4.6 mm; Temperature: 30 ° C; Detection at 210 nm; Mobile Phase: 0.1% aq H_3PO_4 (A)/MeCN (B); Gradient: 90:10 (A)/(B) to 10:90 over 15 min, 10:90 hold for 5 min, 10:90 to 90:10 (A)/(B) over 10 seconds; Flow Rate: 1 mL/min. Retention time: pyrimidine **7** - 9.905 minutes

Step 6: Preparation of Bismesyl-Pyrimidine **8**



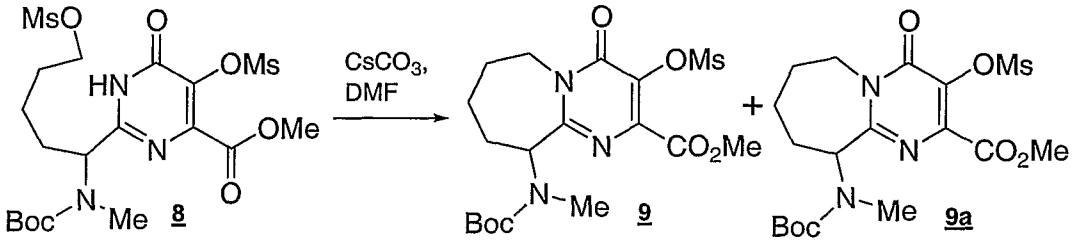
Materials	MW	Equiv.	Moles	Wt. (g)	Vol. (mL)	Density
Pyrimidine 7	385.41	1	0.09029	43.5 (80%)		
TEA	101.19	3	0.2709	27.4	37.8	0.726
MsCl	114.55	3	0.2709	31.0	21.0	1.480
THF					575	
K_2CO_3	138.21	1	0.09029	12.5		
MeOH					200	
EtOAc					400	

To a solution of pyrimidine 7 (43.5 g, about 80% pure, 0.09029 moles) in THF (275 m L) was slowly added TEA (37.8 mL) and MsCl (21.0 mL) at the same time at 0-5 °C over 1 h. The resulting solution was aged at the same temperature for 4 h. The solid was filtered off, washed with THF (3 x 100 mL). The combined filtrations were concentrated and solvent-switched to methanol (total volume 200 mL). To the trimesyl-pyrimidine in methanol solution was added potassium carbonate (12.5 g, 0.09029 moles) at 10-20 °C. The resulting solution was aged at the same temperature for 6-10 h (monitored by HPLC). The reaction mixture was neutralized to pH = 6-7 by 5 N HCl, and concentrated to a total volume about 100 mL. 16% brine (100 mL) was added, and the resulting solution was extracted by EtOAc (3 x100 mL). The combined organic layers were washed with brine (50 mL), concentrated and solvent-switched to DMF. The by-product ($MeSO_3Me$), which was generated in 1 equiv from the selectively hydrolysis of the trimesyl-pyrimidine, was removed by azeotrope with DMF at 60-65 °C (monitored by ^{1}H NMR until <10 mole%). The concentration of bismesyl-pyrimidine **8** in DMF was about 0.3 M (total volume 300 mL). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.00 (br s, 1 H), 4.78 (d, J = 7.8 Hz, 1 H), 4.24-4.15 (m, 2 H), 3.95 (s, 3 H), 3.50 (s, 3 H), 2.99 (s, 3 H), 2.81 (s, 3 H), 2.12-2.11 (m, 1 H), 1.90-1.76 (m, 2 H), 1.46 (s, 9 H), 1.43-1.35 (m, 2 H).

HPLC conditions: Column: Zorbax, Rx C8 250 x 4.6 mm; Temperature: 30 ° C; Detection at 210 nm; Mobile Phase: 0.1% aq H_3PO_4 (A)/MeCN (B); Gradient: 90:10 (A)/(B) to 10:90 over 15

min, 10:90 hold for 5 min, 10:90 to 90:10 (A)/(B) over 10 seconds; Flow Rate: 1 mL/min. Retention time: trimesyl-pyrimidine - 14.140 minutes; bismesyl-pyrimidine - 12.760 minutes.

Step 7: Preparation of Seven-Membered Ring-Pyrimidine Mesylate **9**



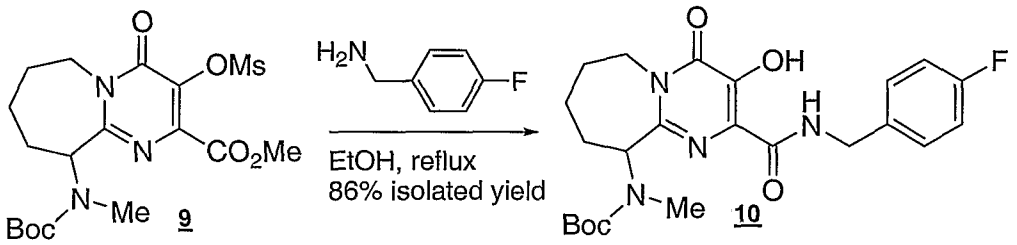
Materials	MW	Equiv.	Moles	Wt. (g)	Vol. (mL)
Bismesyl-pyrimidine **8**	541.59	1	0.09029	48.90	
Cs2CO3	325.82	1.2	0.1083	35.30	
DMF					

To a solution of bismesyl-pyrimidine **8** (0.09029 moles) in DMF (total volume 300 mL) was added cesium carbonate (35.30 g) at room temperature. The resulting slurry was aged at 55 °C for 2-3 h (76% conversion by HPLC). After being neutralized to pH = 7, the reaction mixture was diluted with 250 mL of water, extracted with IPAc (2 x 250 mL). The combined organic layers were washed with brine (2 x 200 mL). The organic layer was concentrated to give crude product. Half of the crude product was purified by passing a short column (silica gel, hexane: EtOAc 2: 1) to afford desired product **9** (6.00 g, 98A% pure), and **9a** (2.3 g, 40A% pure). The overall yield from DHP to cyclized product is about 13% after correction.

^{1}H NMR ($CDCl_3$, 400 MHz) For compound **9**: δ: 5.34 (m, 1 H), 5.22 (m, 1 H), 3.93 (s, 3 H), 3.51 (s, 3 H), 3.47 (m, 1 H), 2.97 (s, 3 H), 2.20-2.05 (m, 3 H), 1.90-1.65 (m, 2 H), 1.44 (s, 9 H), 1.24 (m, 1 H). For compound **9a**: 11.86 (br s, 1 H), 7.90-7.55 (br s, 1 H), 7.31 (dd, J = 8.5, 5.4 Hz, 2 H), 7.06 (t, J = 8.5 Hz, 2 H), 5.40-4.90 (m, 2 H), 4.53-4.40 (m, 2 H), 3.45-3.23 (m, 1 H), 2.23-2.05 (m, 3 H), 1.86-1.76 (m, 1 H); 1.74-1.64 (m, 1 H), 1.47-1.37 (m, 1 H), 1.30 (s, 9 H). HPLC conditions: Column: Zorbax, Rx C8 250 x 4.6 mm; Temperature: 30 ° C; Detection at 210 nm; Mobile Phase: 0.1% aq H_3PO_4 (A)/MeCN (B); Gradient: 90:10 (A)/(B) to 10:90 over 15 min, 10:90 hold for 5 min, 10:90 to 90:10 (A)/(B) over 10 seconds; Flow Rate: 1 mL/min. Retention time: the seven-membered ring-pyrimidine mesylate **9**: 13.969 minutes; the seven-membered ring-pyrimidine **9a**: 13.141 minutes.

Alternative procedure using LiH was also employed: To a solution of bismesyl-pyrimidine **8** (65 mg) in dioxane (1 mL) was added LiH powder at room temperature. The resulting mixture was aged at 65 ° C for 4 h. The reaction mixture was then cooled to room temperature and 1 N HCl was added to quenched the excess LiH. The solution was extracted with EtOAc (2 x 5 mL). The combined organic layer was washed with brine, and then concentrated. The residue was purified by flash chromatography (silica gel, hexane:EtOAc = 2:1) to afford seven-membered ring-pyrimidine mesylate **9** (45.6 mg, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.34 (m, 1 H), 5.22 (m, 1 H), 3.93 (s, 3 H), 3.51 (s, 3 H), 3.47 (m, 1 H), 2.97 (s, 3 H), 2.20-2.05 (m, 3 H), 1.90-1.65 (m, 2 H), 1.44 (s, 9 H), 1.24 (m, 1 H).

Step 8: Preparation of Seven-Membered Ring-Pyrimidine Amide **10**



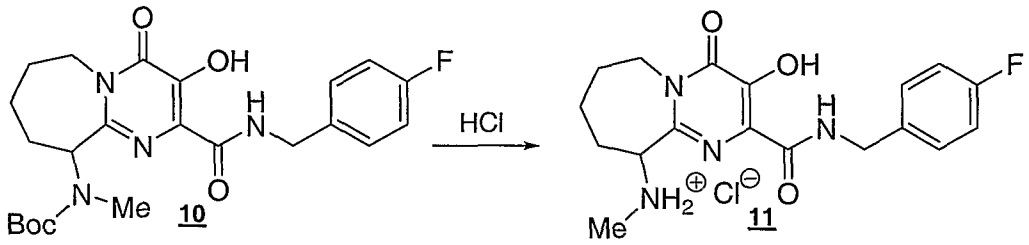
Materials	MW	Equiv.	Moles	Wt. (g)	Vol. (mL)	Density
Seven-membered ring-pyrimidine **9**	445.49	1	0.01347	6.000		
4-fluorobenzylamine	125.15	3	0.04041	5.060	5.22	1.09
EtOH					80	

To a solution of seven-membered ring-pyrimidine mesylate **9** (6 g) in EtOH (80 mL) was added 4-fluorobenzylamine (5.060 g). The resulting solution was reflux for 8 h. (100% conversion by HPLC). The reaction mixture was concentrated to about 20 mL total volume, and 80 mL of EtOAc was added. To the resulting solution was added 20% brine (15 mL), 4 N HCl (15 mL), and water 10 mL). After a phase cut, the aqueous layer was back-extracted with EtOAc (25 mL). The combined organic layers were washed with 4 N HCl : 20% brine (1: 1, 3 x 15 mL), brine (15 mL). The organic solution was concentrated to a total volume about 30 mL. Hexane (70 mL) was slowly added to the solution over 1 h. The resulting slurry was aged at 0-5 ° C for 1 h. The crystalline solid was filtered off, washed with hexane:EtOAc (4:1, 50 mL), dried under vacuum with nitrogen sweep to afford seven-membered ring-pyrimidine amide **10** (5.30 g, 86%, HPLC >97A%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.85 (br s, 1 H), 7.84 (br s, 0.5 H), 7.68 (br s,

0.5 H), 7.31 (m, 2 H), 7.04 (m, 2 H), 5.40-4.90 (m, 2 H), 4.53 (m, 2 H), 3.38 (m, 1 H), 2.87 (s, 3 H), 2.20-2.15 (m, 3 H), 1.90-1.40 (m, 3 H), 1.37 (s, 9 H).

HPLC conditions: Column: Zorbax, Rx C8 250 x 4.6 mm; Temperature: 30 ° C; Detection at 210 nm; Mobile Phase: 0.1% aq H_3PO_4 (A)/MeCN (B); Gradient: 90:10 (A)/(B) to 10:90 over 15 min, 10:90 hold for 5 min, 10:90 to 90:10 (A)/(B) over 10 seconds; Flow Rate: 1 mL/min. Retention time: the seven-membered ring-pyrimidine **10** - 15.467 minutes.

Step 9: Preparation of Seven-Membered Ring-Pyrimidine Amide Hydrochloride Salt **11**



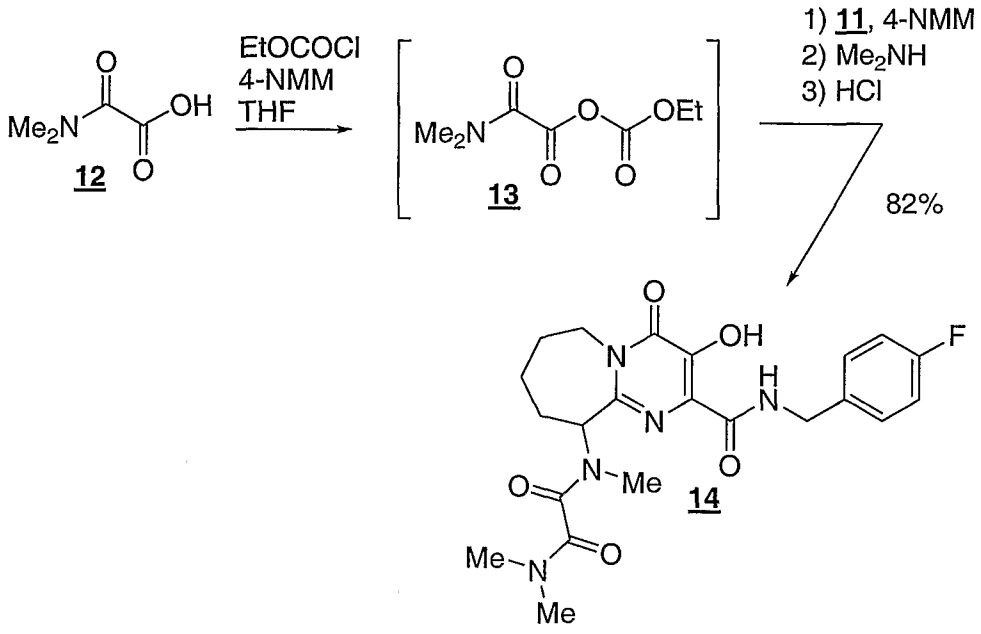
Materials	MW	Equiv.	Moles	g	mL	Density
Seven-membered pyrimidine amide **10**	460.50	1	0.001846	0.8500		
HCl (gas)	36.46	8	0.01478	0.5389		
EtOAc					3.5	

To a solution of ethyl acetate (3.5 mL) was bubbled HCl gas (0.5389 g), at -30 to -20 °C. N-Boc-seven-membered ring pyrimidine amide **10** (crystalline solid) was charged to the HCl-EtOAc solution at -30 to -20 °C. The resulting solution was slowly warmed to room temperature over 2.5 h, and aged at room temperature for 0.5 h (100% conversion by HPLC). The reaction mixture was diluted by EtOAc (7 mL). The resulting slurry was aged at 0-5 °C for 1 h. The crystalline solid was filtered off, washed with EtOAc, hexane, dried under vacuum with nitrogen sweep to afford desired product **11** (98% isolated yield, >97A % pure). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 12.35 (s, 1 H), 9.96 (t, J = 6.3 Hz, 1 H), 9.51 (br s, 1 H), 9.19 (br s, 1 H), 7.42 (dd, J = 8.5, 5.6 hz, 2 H), 7.19 (t, J = 8.5 Hz, 2 H), 4.92 (dd, J = 14.5, 5.1 Hz, 1 H), 4.71 (m, 1 H), 4.57-4.45 (m, 2 H), 3.52 (t, J = 14.5 Hz), 2.65 (t, J = 5.0 HZ, 3 H), 2.30 (br d, J = 12.6 Hz, 1 H), 1.99-1.92 (m, 1 H), 1.90-1.75 (m, 2 H), 1.68-1.60 (m, 1 H), 1.41-1.33 (m, 1 H).

HPLC conditions: Column: Zorbax, Rx C8 250 x 4.6 mm; Temperature: 30 ° C; Detection at 210 nm; Mobile Phase: 0.1% aq H_3PO_4 (A)/MeCN (B); Gradient: 90:10 (A)/(B) to 10:90 over 15

min, 10:90 hold for 5 min, 10:90 to 90:10 (A)/(B) over 10 seconds; Flow Rate: 1 mL/min. Retention time: the seven-membered ring-pyrimidine hydrochloride salt **11** - 8.118 minutes.

Step 10: Preparation of Racemic *N*-(2-{[(4-fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-*a*]azepin-10-yl)-*N,N',N'*-trimethylethanediamide **14**



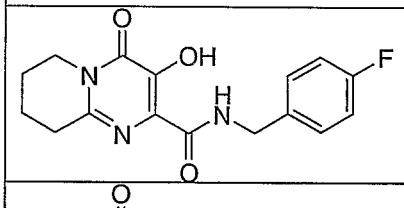
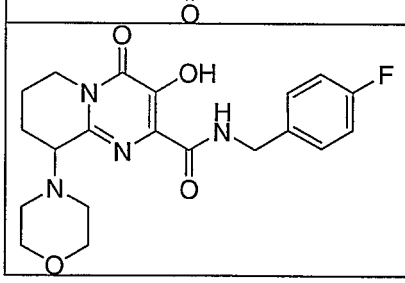
Materials	MW	Equiv.	mmoles	Wt. (g)	Vol. (mL)	Density
Acid **12** (96% pure)	117.10	5	1.000	0.122		
Ethyl chloroformate	125.15	4.8	0.960	0.104	0.092	1.135
4-NMM	101.15	4.8	0.960	0.0971	0.106	0.9200
THF					3	
pyrimidine hydrochloride salt **11**	396.84	1	0.200	0.0794		
40% dimethylamine 2 N HCl	45.07	6.25	1.250	0.141	0.158	0.8900

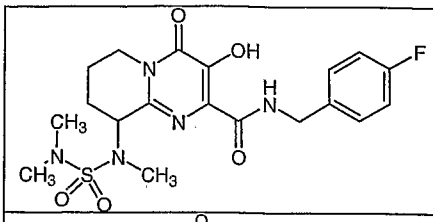
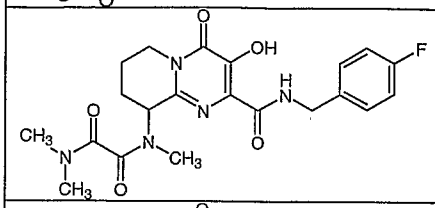
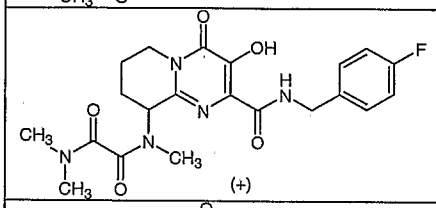
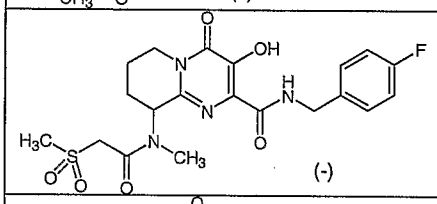
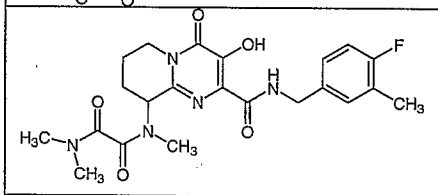
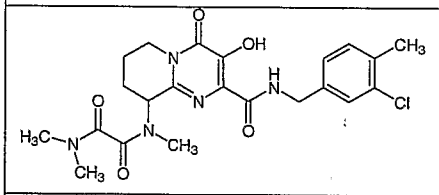
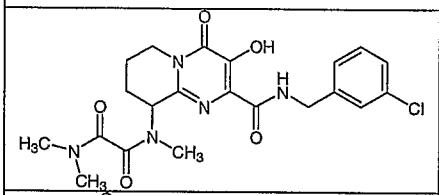
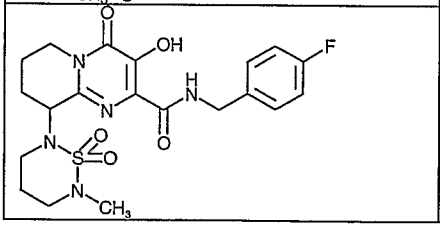
To a solution of acid **12** (122 mg) in THF (3 mL) was added ethyl chloroformate (92 µl) at 0-5 °C. Then, 4-NMM (106 µl) was slowly added to the reaction mixture at 0-5 °C. The reaction mixture was aged at the same temperature for 2 h. The pyrimidine hydrochloride salt **11** (79.4 mg) was added as a solid to the mixed-anhydride solution at 0-5 °C, and aged at the same temperature for 5 h, and then at 5-10 °C for another 2 h (100% conversion by HPLC).

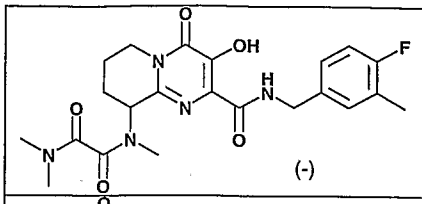
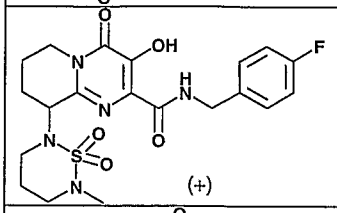
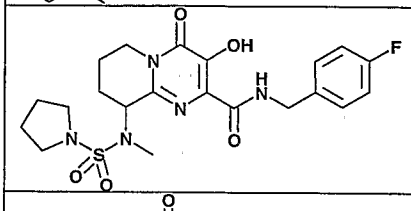
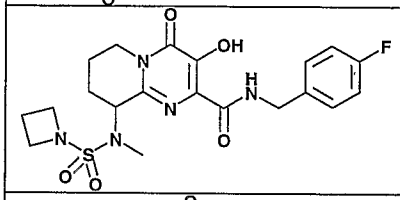
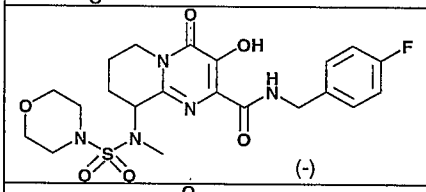
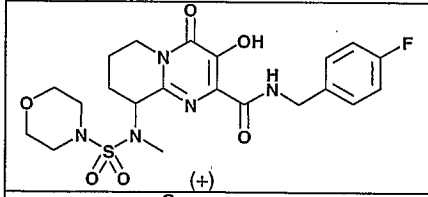
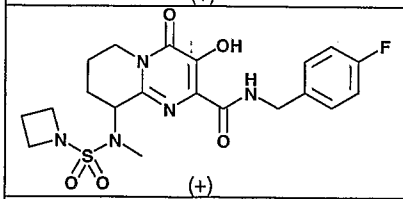
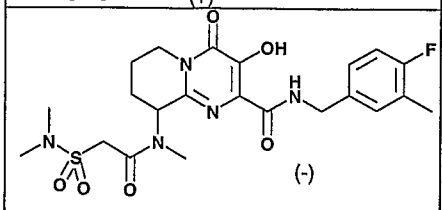
Dimethylamine aqueous (40%, 158 μl) was added to the reaction mixture, and the mixture aged at 10-15 °C for 1 h, wherein the reaction was monitored by HLPC to assure complete conversion. The reaction mixture was acidified by 2 N HCl to adjust to pH = 3-4 at 5-15 °C. EtOAc (6 mL) and brine (2 mL) were added, respectively. After phase cut, the organic layer was washed with 1 N HCl (2 mL), brine (2 x 2 mL). The organic layer was concentrated to a total volume of 1 mL. Hexane (5 mL) was slowly added over 0.5 h. The resulting slurry was aged at 0-5 °C for 1 h. The crystalline solid was filtered off, washed with hexane/EtOAc (5: 1), MTBE, dried under vacuum with nitrogen sweep to give the title compound **14** (75.6 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 12.13 (s, 1 H), 9.41 (br s, 1 H), 7.38 (dd, J = 8.5, 5.4 Hz, 2 H), 7.00 (t, J = 8.5 Hz, 2 H), 5.40 (br s, 1 H), 5.29 (dd, J = 14.5, 6.0 Hz, 1 H), 4.60 (dd, J = 14.5, 6.6 Hz, 1 H), 4.52 (dd, J = 14.5, 6.3 Hz, 1 H), 3.35 (dd, J = 14.5, 11.6 Hz, 1 H), 3.04 (s, 3 H), 3.01 (s, 3 H), 2.98 (s, 3 H), 2.23-2.12 (m, 3 H), 1.95-1.81 (m, 2 H), 1.58-1.49 (m, 1 H).

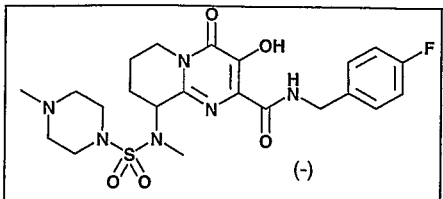
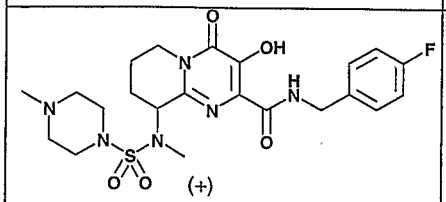
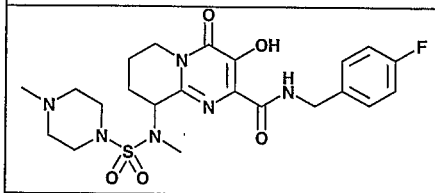
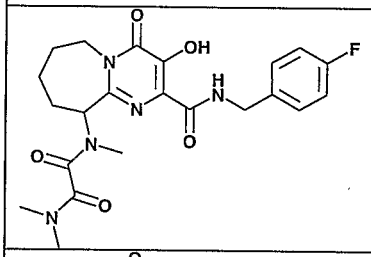
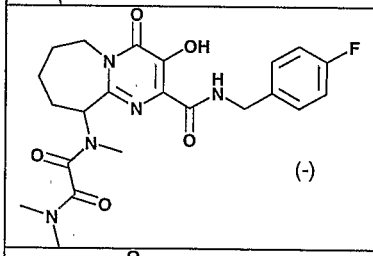
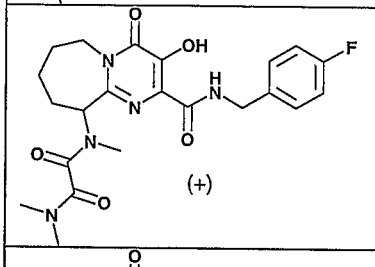
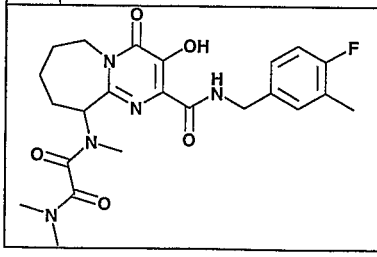
HPLC conditions: Column: Zorbax, Rx C8 250 x 4.6 mm; Temperature: 30 ° C; Detection at 210 nm; Mobile Phase: 0.1% aq H_3PO_4 (A)/MeCN (B); Gradient: 90:10 (A)/(B) to 10:90 over 15 min, 10:90 hold for 5 min, 10:90 to 90:10 (A)/(B) over 10 seconds; Flow Rate: 1 mL/min. Retention time: the title compound **14** - 12.191 minutes.

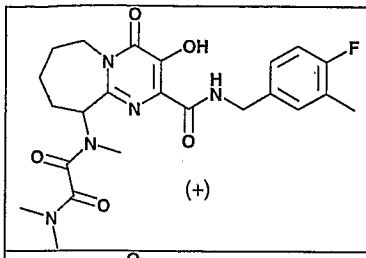
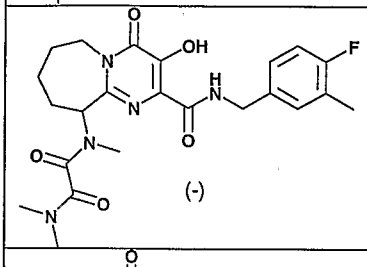
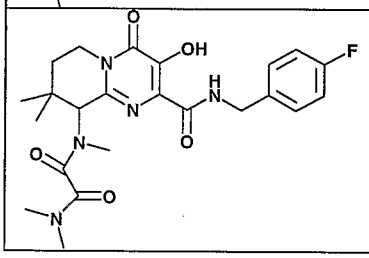
Table 1 below lists compounds of the present invention which have been prepared. The table provides the structure and name of each compound, the mass of its molecular ion plus 1 (M^+) or molecular ion minus 1 (M^-) as determined via FIA-MS, and the synthetic scheme employed to prepare the compound.

Structure	Name	M+	Scheme
	N-(4-fluorobenzyl)-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	318	A (Ex. 1)
	N-(4-fluorobenzyl)-3-hydroxy-9-morpholin-4-yl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	403	B (Ex. 2)

	9-[[(dimethylamino)sulfonyl]-(methyl)amino]-N-(4-fluorobenzyl)-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	454	C (Ex. 3)
	(+/-)-N1-(2-{[(4-fluorobenzyl)amino]-carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N1,N2,N2-trimethylethanediamide	446	C (Ex. 4)
	(+)N1-(2-{[(4-fluorobenzyl)amino]-carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N1,N2,N2-trimethylethanediamide	446	D (Ex. 5)
	(-)-N-(4-fluorobenzyl)-3-hydroxy-9-{methyl[(methylsulfonyl)acetyl]amino}-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	467	D
	N-(2-{[(4-fluoro-3-methylbenzyl)-amino]carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N,N',N'-trimethylethanediamide	460	C
	N-(2-{[(3-chloro-4-methylbenzyl)-amino]carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N,N',N'-trimethylethanediamide	476	C
	N-(2-{[(3-chlorobenzyl)amino]-carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N,N',N'-trimethylethanediamide	462	C
	N-(4-fluorobenzyl)-3-hydroxy-9-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	466	B

 (-)	(-)-N-(2-{[(4-fluoro-3-methylbenzyl)-amino]carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N,N',N'-trimethylethanediamide	460	D
 (+)	(+)-N-(4-fluorobenzyl)-3-hydroxy-9-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	466	D
	N-(4-fluorobenzyl)-3-hydroxy-9-[methyl(pyrrolidin-1-ylsulfonyl)amino]-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	480	C
	9-[(azetidin-1-ylsulfonyl)(methyl)-amino]-N-(4-fluorobenzyl)-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	466	C
 (-)	(-)-N-(4-fluorobenzyl)-3-hydroxy-9-[methyl(morpholin-4-ylsulfonyl)-amino]-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	496	D
 (+)	(+)-N-(4-fluorobenzyl)-3-hydroxy-9-[methyl(morpholin-4-ylsulfonyl)-amino]-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	496	D
 (+)	(+)-9-[(azetidin-1-ylsulfonyl)(methyl)-amino]-N-(4-fluorobenzyl)-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	466	D
 (-)	(-)-9-[{[(dimethylamino)sulfonyl]-acetyl}(methyl)amino]-N-(4-fluoro-3-methylbenzyl)-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	510	D

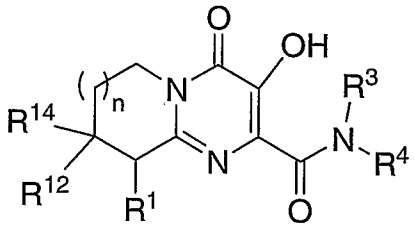
 (-)	(-)-N-(4-fluorobenzyl)-3-hydroxy-9-{methyl[(4-methylpiperazin-1-yl)sulfonyl]amino}-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	509	D
 (+)	(+)-N-(4-fluorobenzyl)-3-hydroxy-9-{methyl[(4-methylpiperazin-1-yl)sulfonyl]amino}-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	509	D
	N-(4-fluorobenzyl)-3-hydroxy-9-{methyl[(4-methylpiperazin-1-yl)sulfonyl]amino}-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide	509	D
	N-(2-{[(4-fluorobenzyl)amino]-carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide	460	C (Ex. 6)
 (-)	(-)N-(2-{[(4-fluorobenzyl)amino]-carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide	460	D (Ex. 7)
 (+)	(+)N-(2-{[(4-fluorobenzyl)amino]-carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide	460	D
	N-(2-{[(4-fluoro-3-methylbenzyl)-amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide	474	C

 (+)	(+)-N-(2-{[(4-fluoro-3-methylbenzyl)-amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide	474	D
 (-)	(-)-N-(2-{[(4-fluoro-3-methylbenzyl)-amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide	474	D
	N-(2-{[(4-fluorobenzyl)amino]-carbonyl}-3-hydroxy-8,8-dimethyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N,N',N'-trimethylethanediamide	474	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:



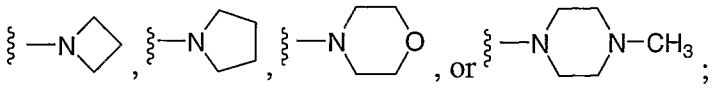
(I);

R^1 is H or NR^2R^5;

R^2 is CH_3;

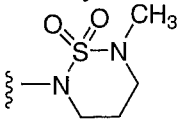
R^5 is

1) $C(O)CH_2SO_2CH_3$,
2) $C(O)C(O)N(CH_3)_2$,
3) $SO_2N(CH_3)_2$, or
4) SO_2R^{20}, wherein R^{20} is:



;

or alternatively R^2 and R^5 together with the nitrogen atom to which they are attached form

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R^3 is hydrogen;

R^4 is:

1) p-fluorobenzyl,
2) 4-fluoro-3-methylbenzyl,
3) 3-chlorobenzyl, or
4) 3-chloro-4-methylbenzyl;

R^{12} and R^{14} are both H, except that when R^5 is $C(O)C(O)N(CH_3)_2$ and R^4 is p-fluorobenzyl and n is 1, then R^{12} and R^{14} are either both H or both CH_3; and

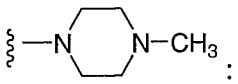
n is an integer equal to zero, 1 or 2.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is NR^2R^5; and n is 1 or 2.

3. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

R^1 is NR^2R^5;

R^2 is CH_3;

R^5 is $C(O)C(O)N(CH_3)_2$, or SO_2R^{20}, wherein R^{20} is ;

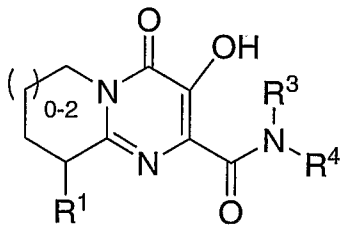
R^3 is hydrogen;

R^4 is p-fluorobenzyl or 4-fluoro-3-methylbenzyl;

R^{12} and R^{14} are both H, except that when R^5 is $C(O)C(O)N(CH_3)_2$ and R^4 is p-fluorobenzyl and n is 1, then R^{12} and R^{14} are either both H or both CH_3; and

n is an integer equal to 1 or 2.

4. A compound of Formula II, or a pharmaceutically acceptable salt thereof:

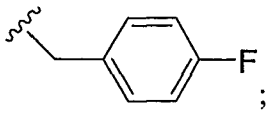

(II);

wherein

R^1 is hydrogen, NR^2R^5, OR^2, SR^2, SOR^2, SO_2R^2, $SO_2NR^2R^5$, or $OC(O)NR^2R^5$;

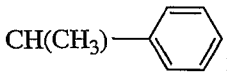
R^3 is hydrogen;

R^4 is

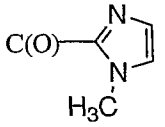
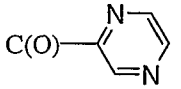
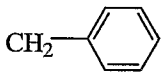


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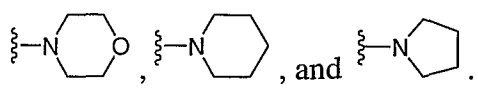
R^2 is

1) hydrogen,
2) CH_3, or
3)  ; and

R^5 is

1) $C(O)CH_3$,
2) $C(O)CH_2SO_2CH_3$,
3) CH_3,
4) $C(O)C(O)N(CH_3)_2$
5) SO_2CH_3,
6) $SO_2N(CH_3)_2$,
7) $C(O)CH_2N(CH_3)_2$,
8) $SO_2CH_2SO_2CH_3$,
9) $C(O)CF_3$,
10) ,
11) , or
12) ;

or R^2 and R^5, together with the nitrogen atom to which they are attached, form a heterocyclic ring selected from the group consisting of



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

N-(4-fluorobenzyl)-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-(4-fluorobenzyl)-3-hydroxy-9-morpholin-4-yl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

9-[[(dimethylamino)sulfonyl]-(methyl)amino]-N-(4-fluorobenzyl)-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N1-(2-{[(4-fluorobenzyl)amino]-carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N1,N2,N2-trimethylethanediamide;

(+)-N1-(2-{[(4-fluorobenzyl)amino]-carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N1,N2,N2-trimethylethanediamide;

(-)-N-(4-fluorobenzyl)-3-hydroxy-9-{methyl[(methylsulfonyl)acetyl]amino}-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-(2-{[(4-fluoro-3-methylbenzyl)amino]carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N,N',N'-trimethylethanediamide;

N-(2-{[(3-chloro-4-methylbenzyl)amino]carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N,N',N'-trimethylethanediamide;

N-(2-{[(3-chlorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N,N',N'-trimethylethanediamide;

N-(4-fluorobenzyl)-3-hydroxy-9-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

(-)-N-(2-{[(4-fluoro-3-methylbenzyl)amino]carbonyl}-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl)-N,N',N'-trimethylethanediamide;

(+)-N-(4-fluorobenzyl)-3-hydroxy-9-(6-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl)-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-(4-fluorobenzyl)-3-hydroxy-9-[methyl(pyrrolidin-1-ylsulfonyl)amino]-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

9-[(azetidin-1-ylsulfonyl)(methyl)amino]-N-(4-fluorobenzyl)-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

(-)-N-(4-fluorobenzyl)-3-hydroxy-9-[methyl(morpholin-4-ylsulfonyl)amino]-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

(+)-N-(4-fluorobenzyl)-3-hydroxy-9-[methyl(morpholin-4-ylsulfonyl)amino]-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

(+)-9-[(azetidin-1-ylsulfonyl)(methyl)amino]-N-(4-fluorobenzyl)-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

(-)-9-[{[(dimethylamino)sulfonyl]acetyl}(methyl)amino]-N-(4-fluoro-3-methylbenzyl)-3-hydroxy-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

(-)-N-(4-fluorobenzyl)-3-hydroxy-9-{methyl[(4-methylpiperazin-1-yl)sulfonyl]amino}-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

(+)-N-(4-fluorobenzyl)-3-hydroxy-9-{methyl[(4-methylpiperazin-1-yl)sulfonyl]amino}-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-(4-fluorobenzyl)-3-hydroxy-9-{methyl[(4-methylpiperazin-1-yl)sulfonyl]amino}-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-(2-{[(4-fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide;

(-)N-(2-{[(4-fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide;

(+)N-(2-{[(4-fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide;

N-(2-{[(4-fluoro-3-methylbenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide;

(+)-N-(2-{[(4-fluoro-3-methylbenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide;

(-)-N-(2-{[(4-fluoro-3-methylbenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide;

N-(2-{[(4-fluorobenzyl)amino]carbonyl}-3-hydroxy-8,8-dimethyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl)-*N*,*N*',*N*'-trimethylethanediamide;

6. A compound according to claim 5, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

N-(2-{[(4-fluoro-3-methylbenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide;

(+)-N-(2-{[(4-fluoro-3-methylbenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide;

(-)-N-(2-{[(4-fluoro-3-methylbenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide;

(-)-N-(4-fluorobenzyl)-3-hydroxy-9-{methyl[(4-methylpiperazin-1-yl)sulfonyl]amino}-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

(+)-N-(4-fluorobenzyl)-3-hydroxy-9-{methyl[(4-methylpiperazin-1-yl)sulfonyl]amino}-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-(4-fluorobenzyl)-3-hydroxy-9-{methyl[(4-methylpiperazin-1-yl)sulfonyl]amino}-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidine-2-carboxamide;

N-(2-{[(4-fluorobenzyl)amino]carbonyl}-3-hydroxy-8,8-dimethyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl)-*N*,*N*',*N*'-trimethylethanediamide.

N-(2-{[(4-fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide;

(-)N-(2-{[(4-fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide;

(+)N-(2-{[(4-fluorobenzyl)amino]carbonyl}-3-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrimido[1,2-a]azepin-10-yl)-N,N',N'-trimethylethanediamide;

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

8. Use of a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, for inhibiting HIV integrase in a subject in need thereof.

9. A compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for inhibiting HIV integrase in a subject in need thereof.

10. A compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for preventing or treating infection by HIV or for preventing, treating or delaying the onset of AIDS in a subject in need thereof.