(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 March 2007 (29.03.2007)

PCT

(10) International Publication Number
WO 2007/035629 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/US2006/036276

(22) International Filing Date:
15 September 2006 (15.09.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/718,084 16 September 2005 (16.09.2005) US

(71) Applicant *(for all designated States except US)*: **TAKEDA PHARMACEUTICAL COMPANY LIMITED** [JP/JP]; 1-1, Doshmachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0045 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FENG, Jun** [CN/US]; 3536 Corte Yolanda, Carlsbad, CA 92009 (US). **GWALTNEY, Stephen L.** [US/US]; 12246 Dormouse Road, San Diego, CA 92129 (US). **STAFFORD, Jeffrey A.** [US/US]; 12752 Sandy Crest Court, San Diego, CA 92130 (US). **ZHANG, Zhiyuan** [CN/US]; 3775 Carmel View Road, #2, San Diego, CA 92130 (US). **ELDER, Bruce J.** [US/US]; 21 White Tail Circle, Wynantskill, NY 12198 (US). **ISBESTER, Paul K.** [US/US]; 34 Green Avenue, Castleton, NY 12033 (US). **PALMER, Grant J.** [US/US]; 4704 Foxwood Drive South, Clifton Park, NY 12065 (US). **SALSBURY, Jonathon S.** [US/US]; 38 Woodlake Road, Apartment 3, Albany, NY 12203 (US). **ULYSSE, Luckner** [US/US]; 601 Highwood Circle, Albany, NY 12203 (US).

(74) Agents: **BRUSTEIN, Mitchell, R.** et al.; TAKEDA SAN DIEGO, INC., 10410 Science Center Drive, San Diego, CA 92121 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DIPEPTIDYL PEPTIDASE INHIBITORS

(57) Abstract: Methods of making compounds of the formula (I) wherein the variables are as defined herein. Also, methods of making compounds that may be used to inhibit dipeptidyl peptidase.

WO 2007/035629 A2

DIPEPTIDYL PEPTIDASE INHIBITORS

FIELD OF THE INVENTION

[0001] The invention relates to methods of making compounds that may be used to inhibit dipeptidyl peptidases. The invention further relates to methods of making intermediates useful in the production of dipeptidyl peptidase inhibitors.

DESCRIPTION OF RELATED ART

[0002] Dipeptidyl Peptidase IV (IUBMB Enzyme Nomenclature EC.3.4.14.5) is a type II membrane protein that has been referred to in the literature by a wide a variety of names including DPP4, DP4, DAP-IV, FAPβ, adenosine deaminase complexing protein 2, adenosine deaminase binding protein (ADAbp), dipeptidyl aminopeptidase IV; Xaa-Pro-dipeptidyl-aminopeptidase; Gly-Pro naphthylamidase; postproline dipeptidyl aminopeptidase IV; lymphocyte antigen CD26; glycoprotein GP110; dipeptidyl peptidase IV; glycylproline aminopeptidase; glycylproline aminopeptidase; X-prolyl dipeptidyl aminopeptidase; pep X; leukocyte antigen CD26; glycylprolyl dipeptidylaminopeptidase; dipeptidyl-peptide hydrolase; glycylprolyl aminopeptidase; dipeptidyl-aminopeptidase IV; DPP IV/CD26; amino acyl-prolyl dipeptidyl aminopeptidase; T cell triggering molecule Tp103; X-PDAP. Dipeptidyl Peptidase IV is referred to herein as "DPP-IV."

[0003] DPP-IV is a non-classical serine aminodipeptidase that removes Xaa-Pro dipeptides from the amino terminus (N-terminus) of polypeptides and proteins. DPP-IV dependent slow release of dipeptides of the type X-Gly or X-Ser has also been reported for some naturally occurring peptides.

[0004] DPP-IV is constitutively expressed on epithelial and endothelial cells of a variety of different tissues (intestine, liver, lung, kidney and placenta), and is also found in body fluids. DPP-IV is also expressed on circulating T-lymphocytes and has been shown to be synonymous with the cell-surface antigen, CD-26. DPP-IV has been implicated in a number of disease states, some of which are discussed below.

[0005] DPP-IV is responsible for the metabolic cleavage of certain endogenous peptides (GLP-1 (7-36), glucagon) *in vivo* and has demonstrated proteolytic activity against a variety of other peptides (GHRH, NPY, GLP-2, VIP) *in vitro*.

[0006] GLP-1 (7-36) is a 29 amino-acid peptide derived by post-translational processing of proglucagon in the small intestine. GLP-1 (7-36) has multiple actions *in vivo* including the stimulation of insulin secretion, inhibition of glucagon secretion, the promotion of satiety, and the slowing of gastric emptying. Based on its physiological profile, the actions of GLP-1 (7-36) are believed to be beneficial in the prevention and treatment of type II diabetes and potentially obesity. For example, exogenous administration of GLP-1 (7-36) (continuous infusion) in diabetic patients has been found to be efficacious in this patient population. Unfortunately, GLP-1 (7-36) is degraded rapidly *in vivo* and has been shown to have a short half-life *in vivo* ($t_{1/2}$=1.5 minutes).

[0007] Based on a study of genetically bred DPP-IV knock out mice and on *in vivo* / *in vitro* studies with selective DPP-IV inhibitors, DPP-IV has been shown to be the primary degrading enzyme of GLP-1 (7-36) *in vivo*. GLP-1 (7-36) is degraded by DPP-IV efficiently to GLP-1 (9-36), which has been speculated to act as a physiological antagonist to GLP-1 (7-36). Inhibiting DPP-IV *in vivo* is therefore believed to be useful for potentiating endogenous levels of GLP-1 (7-36) and attenuating the formation of its antagonist GLP-1 (9-36). Thus, DPP-IV inhibitors are believed to be useful agents for the prevention, delay of progression, and/or treatment of conditions mediated by DPP-IV, in particular diabetes and more particularly, type 2 diabetes mellitus, diabetic dislipidemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose (IFG), metabolic acidosis, ketosis, appetite regulation and obesity.

[0008] DPP-IV expression is increased in T-cells upon mitogenic or antigenic stimulation (Mattem, T., et al., *Scand. J. Immunol.,* 1991, 33, 737). It has been reported that inhibitors of DPP-IV and antibodies to DPP-IV suppress the proliferation of mitogen-stimulated and antigen-stimulated T-cells in a dose-dependant manner (Schon, E., et al., *Biol. Chem.,* 1991, 372, 305). Various other functions of T-lymphocytes such as cytokine production, IL-2 mediated cell proliferation and B-cell helper activity have been shown to be dependent on DPP-IV activity (Schon, E., et al., *Scand. J. Immunol.,* 1989, 29, 127). DPP-IV inhibitors, based on boroProline, (Flentke, G. R., et al., *Proc. Nat. Acad. Sci. USA,* 1991, 88, 1556) although unstable, were effective at inhibiting antigen-induced lymphocyte proliferation and IL-2 production in murine CD4+ T-helper cells. Such boronic acid inhibitors have been shown to have an effect *in vivo* in mice

causing suppression of antibody production induced by immune challenge (Kubota, T. et al., *Clin. Exp. Immun.*, 1992, 89, 192). The role of DPP-IV in regulating T lymphocyte activation may also be attributed, in part, to its cell-surface association with the transmembrane phosphatase, CD45. DPP-IV inhibitors or non-active site ligands may possibly disrupt the CD45-DPP-IV association. CD45 is known to be an integral component of the T-cell signaling apparatus. It has been reported that DPP-IV is essential for the penetration and infectivity of HIV-1 and HIV-2 viruses in CD4+ T-cells (Wakselman, M., Nguyen, C., Mazaleyrat, J.-P., Callebaut, C., Krust, B., Hovanessian, A. G., Inhibition of HIV-1 infection of CD 26+ but not CD 26-cells by a potent cyclopeptidic inhibitor of the DPP-IV activity of CD 26. Abstract P.44 of the 24.sup.th European Peptide Symposium 1996). Additionally, DPP-IV has been shown to associate with the enzyme adenosine deaminase (ADA) on the surface of T-cells (Kameoka, J., et al., *Science,* 193, 26 466). ADA deficiency causes severe combined immunodeficiency disease (SCID) in humans. This ADA-CD26 interaction may provide clues to the pathophysiology of SCID. It follows that inhibitors of DPP-IV may be useful immunosuppressants (or cytokine release suppressant drugs) for the treatment of among other things: organ transplant rejection; autoimmune diseases such as inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis; and the treatment of AIDS.

[0009] It has been shown that lung endothelial cell DPP-IV is an adhesion molecule for lung-metastatic rat breast and prostate carcinoma cells (Johnson, R. C., et al., *J. Cell. Biol.,* 1993, 121, 1423). DPP-IV is known to bind to fibronectin and some metastatic tumor cells are known to carry large amounts of fibronectin on their surface. Potent DPP-IV inhibitors may be useful as drugs to prevent metastases of, for example, breast and prostrate tumors to the lungs.

[0010] High levels of DPP-IV expression have also been found in human skin fibroblast cells from patients with psoriasis, rheumatoid arthritis (RA) and lichen planus (Raynaud, F., et al., *J. Cell. Physiol.*, 1992, 151, 378). Therefore, DPP-IV inhibitors may be useful as agents to treat dermatological diseases such as psoriasis and lichen planus.

[0011] High DPP-IV activity has been found in tissue homogenates from patients with benign prostate hypertrophy and in prostatosomes. These are prostate derived organelles important for the enhancement of sperm forward motility (Vanhoof, G., et al., *Eur. J.*

Clin. Chem. Clin. Biochem., 1992, 30, 333). DPP-IV inhibitors may also act to suppress sperm motility and therefore act as a male contraceptive agent. Conversely, DPP-IV inhibitors have been implicated as novel for treatment of infertility, and particularly human female infertility due to Polycystic ovary syndrome (PCOS, Stein-Leventhal syndrome) which is a condition characterized by thickening of the ovarian capsule and formation of multiple follicular cysts. It results in infertility and amenorrhea.

[0012] DPP-IV is thought to play a role in the cleavage of various cytokines (stimulating hematopoietic cells), growth factors and neuropeptides.

[0013] Stimulated hematopoietic cells are useful for the treatment of disorders that are characterized by a reduced number of hematopoietic cells or their precursors *in vivo*. Such conditions occur frequently in patients who are immunosuppressed, for example, as a consequence of chemotherapy and/or radiation therapy for cancer. It was discovered that inhibitors of dipeptidyl peptidase type IV are useful for stimulating the growth and differentiation of hematopoietic cells in the absence of exogenously added cytokines or other growth factors or stromal cells. This discovery contradicts the dogma in the field of hematopoietic cell stimulation, which provides that the addition of cytokines or cells that produce cytokines (stromal cells) is an essential element for maintaining and stimulating the growth and differentiation of hematopoietic cells in culture. (See, e.g., PCT Intl. Application No. PCT/US93/017173 published as WO 94/03055).

[0014] DPP-IV in human plasma has been shown to cleave N-terminal Tyr-Ala from growth hormone-releasing factor and cause inactivation of this hormone. Therefore, inhibitors of DPP-IV may be useful in the treatment of short stature due to growth hormone deficiency (Dwarfism) and for promoting GH-dependent tissue growth or re-growth.

[0015] DPP-IV can also cleave neuropeptides and has been shown to modulate the activity of neuroactive peptides substance P, neuropeptide Y and CLIP (Mentlein, R., Dahms, P., Grandt, D., Kruger, R., Proteolytic processing of neuropeptide Y and peptide YY by dipeptidyl peptidase IV, *Regul. Pept.*, 49, 133, 1993; Wetzel, W., Wagner, T., Vogel, D., Demuth, H.-U., Balschun, D., Effects of the CLIP fragment ACTH 20-24 on the duration of REM sleep episodes, *Neuropeptides*, 31, 41, 1997). Thus DPP-IV

inhibitors may also be useful agents for the regulation or normalization of neurological disorders.

[0016] Several compounds have been shown to inhibit DPP-IV. Nonetheless, a need still exists for new DPP-IV inhibitors that have advantageous potency, stability, selectivity, toxicity and/or pharmacodynamics properties. In this regard, synthetic methods are provided that can be used to make a novel class of DPP-IV inhibitors.

Summary Of The Invention

[0017] The present invention relates to methods of making compounds. One use of the methods is for making compounds that have activity for inhibiting DPP-IV. It is noted that these compounds may also have activity for inhibiting other S9 proteases and thus may be used against these other S9 proteases as well as DPP-IV.

[0018] It is noted that unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all possible stereoisomers (e.g., enantiomers or diastereomers depending on the number of chiral centers), independent of whether the compound is present as an individual isomer or a mixture of isomers. Further, unless otherwise specified, recitation of a compound is intended to encompass all possible resonance forms and tautomers. With regard to the claims, the language "compound comprising the formula" is intended to encompass the compound and all pharmaceutically acceptable ionized forms and solvates, all possible stereoisomers, and all possible resonance forms and tautomers unless otherwise specifically specified in the particular claim.

Definitions

[0019] Unless otherwise stated, the following terms used in the specification and claims shall have the following meanings for the purposes of this Application.

[0020] "Alicyclic" means a moiety comprising a non-aromatic ring structure. Alicyclic moieties may be saturated or partially unsaturated with one, two or more double or triple bonds. Alicyclic moieties may also optionally comprise heteroatoms such as nitrogen, oxygen and sulfur. The nitrogen atoms can be optionally quaternerized or oxidized and the sulfur atoms can be optionally oxidized. Examples of alicyclic moieties

include, but are not limited to moieties with C_{3-8} rings such as cyclopropyl, cyclohexane, cyclopentane, cyclopentene, cyclopentadiene, cyclohexane, cyclohexene, cyclohexadiene, cycloheptane, cycloheptene, cycloheptadiene, cyclooctane, cyclooctene, and cyclooctadiene.

[0021] "Aliphatic" means a moiety characterized by a straight or branched chain arrangement of constituent carbon atoms and may be saturated or partially unsaturated with one, two or more double or triple bonds.

[0022] "Alkenyl" represented by itself means a straight or branched, unsaturated, aliphatic radical having a chain of carbon atoms having at least one double bond between adjacent carbon atoms. C_X alkenyl and C_{X-Y} alkenyl are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{2-6} alkenyl includes alkenyls that have a chain of between 2 and 6 carbons.

[0023] "Alkoxy" means an oxygen moiety having a further alkyl substituent. The alkoxy groups of the present invention can be optionally substituted.

[0024] "Alkyl" represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having a chain of carbon atoms, optionally with oxygen (See "oxaalkyl") or nitrogen atoms (See "aminoalkyl") between the carbon atoms. C_X alkyl and C_{X-Y} alkyl are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{1-6} alkyl includes alkyls that have a chain of between 1 and 6 carbons (e.g., methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like). Alkyl represented along with another radical (e.g., as in arylalkyl, heteroarylalkyl) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when no atoms are indicated means a bond (e.g., (C_{6-10})aryl(C_{1-3})alkyl includes, benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-thienylmethyl, 2-pyridinylmethyl and the like).

[0025] "Alkylene", unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical. C_X alkylene and C_{X-Y} alkylene are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{1-6} alkylene includes methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), trimethylene

(-$CH_2CH_2CH_2$-), tetramethylene (-$CH_2CH_2CH_2CH_2$-) 2-butenylene (-CH_2CH=$CHCH_2$-), 2-methyltetramethylene (-$CH_2CH(CH_3)CH_2CH_2$-), pentamethylene (-$CH_2CH_2CH_2CH_2CH_2$-) and the like).

[0026] "Alkylidene" means a straight or branched saturated or unsaturated, aliphatic radical connected to the parent molecule by a double bond. C_X alkylidene and C_{X-Y} alkylidene are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{1-6} alkylidene includes methylene (=CH_2), ethylidene (=$CHCH_3$), isopropylidene (=$C(CH_3)_2$), propylidene (=$CHCH_2CH_3$), allylidene (=CH-CH=CH_2), and the like).

[0027] "Alkynyl" represented by itself means a straight or branched, unsaturated, aliphatic radical having a chain of carbon atoms having at least one triple bond between adjacent carbon atoms. C_X alkynyl and C_{X-Y} alkynyl are typically used where X and Y indicate the number of carbon atoms in the chain. For example, C_{2-6} alkynyl includes alkynyls that have a chain of between 2 and 6 carbons.

[0028] "Amino" means a nitrogen moiety having two further substituents where a hydrogen or carbon atom is attached to the nitrogen. For example, representative amino groups include -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -NHC_{1-3}-alkyl, -$N(C_{1-3}$-alkyl$)_2$ and the like. Unless indicated otherwise, the compounds of the invention containing amino moieties may include protected derivatives thereof. Suitable protecting groups for amino moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like.

[0029] "Aminoalkyl" means an alkyl, as defined above, except where one or more substituted or unsubstituted nitrogen atoms (-N-) are positioned between carbon atoms of the alkyl. For example, an (C_{2-6}) aminoalkyl refers to a chain comprising between 2 and 6 carbons and one or more nitrogen atoms positioned between the carbon atoms.

[0030] "Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (e.g., birds, and the like).

[0031] "Aromatic" means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are sp^2 hybridized and the total number of pi electrons is equal to 4n+2. An aromatic ring may be such that the ring

atoms are only carbon atoms or may include carbon and non-carbon atoms (see Heteroaryl).

[0032] "Aryl" means a monocyclic or polycyclic ring assembly wherein each ring is aromatic or when fused with one or more rings forms an aromatic ring assembly. If one or more ring atoms is not carbon (e.g., N, S), the aryl is a heteroaryl. C_X aryl and C_{X-Y} aryl are typically used where X and Y indicate the number of atoms in the ring. For example, aryl includes phenyl.

[0033] "Bicycloalkyl" means a saturated or partially unsaturated fused bicyclic or bridged polycyclic ring assembly.

[0034] "Bicycloaryl" means a bicyclic ring assembly wherein the rings are linked by a single bond or fused and at least one of the rings comprising the assembly is aromatic. C_X bicycloaryl and C_{X-Y} bicycloaryl are typically used where X and Y indicate the number of carbon atoms in the bicyclic ring assembly and directly attached to the ring.

[0035] "Bridging ring" as used herein refers to a ring that is bonded to another ring to form a compound having a bicyclic structure where two ring atoms that are common to both rings are not directly bound to each other. Non-exclusive examples of common compounds having a bridging ring include borneol, norbornane, 7-oxabicyclo[2.2.1]heptane, and the like. One or both rings of the bicyclic system may also comprise heteroatoms.

[0036] "Carbamoyl" means the radical $-OC(O)NR_aR_b$ where R_a and R_b are each independently two further substituents where a hydrogen or carbon atom is attached to the nitrogen.

[0037] "Carbocycle" means a ring consisting of carbon atoms.

[0038] "Carbocyclic ketone derivative" means a carbocyclic derivative wherein the ring contains a -CO– moiety.

[0039] "Carbonyl" means the radical -CO-. It is noted that the carbonyl radical may be further substituted with a variety of substituents to form different carbonyl groups including acids, acid halides, aldehydes, amides, esters, and ketones.

[0040] "Carboxy" means the radical $–CO_2-$. It is noted that compounds of the invention containing carboxy moieties may include protected derivatives thereof, i.e.,

where the oxygen is substituted with a protecting group. Suitable protecting groups for carboxy moieties include benzyl, *tert*-butyl, and the like.

[0041] "Cyano" means the radical -CN.

[0042] "Cycloalkyl" means a non-aromatic, saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly. C_X cycloalkyl and C_{X-Y} cycloalkyl are typically used where X and Y indicate the number of carbon atoms in the ring assembly. For example, C_{3-10} cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, adamantan-1-yl, decahydronaphthyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, and the like.

[0043] "Cycloalkylene" means a divalent saturated or partially unsaturated, monocyclic or polycyclic ring assembly. C_X cycloalkylene and C_{X-Y} cycloalkylene are typically used where X and Y indicate the number of carbon atoms in the ring assembly.

[0044] "Fused ring" as used herein refers to a ring that is bonded to another ring to form a compound having a bicyclic structure where the ring atoms that are common to both rings are directly bound to each other. Non-exclusive examples of common fused rings include decalin, naphthalene, anthracene, phenanthrene, indole, furan, benzofuran, quinoline, and the like. Compounds having fused ring systems may be saturated, partially saturated, carbocyclics, heterocyclics, aromatics, heteroaromatics, and the like.

[0045] "Halo" means fluoro, chloro, bromo or iodo.

[0046] "Halo-substituted alkyl", as an isolated group or part of a larger group, means "alkyl" substituted by one or more "halo" atoms, as such terms are defined in this Application. Halo-substituted alkyl includes haloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like (e.g. halo-substituted (C_{1-3})alkyl includes chloromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl, 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

[0047] "Heteroatom" refers to an atom that is not a carbon atom. Particular examples of heteroatoms include, but are not limited to nitrogen, oxygen, and sulfur.

[0048] "Heteroatom moiety" includes a moiety where the atom by which the moiety is attached is not a carbon. Examples of heteroatom moieties include -N=, $-NR_c-$, $-N^+(O^-)=$, -O-, -S- or $-S(O)_2-$, wherein R_c is further substituent.

[0049] "Heterobicycloalkyl" means bicycloalkyl, as defined in this Application, provided that one or more of the atoms within the ring is a heteroatom. For example hetero(C_{9-12})bicycloalkyl as used in this application includes, but is not limited to, 3-aza-bicyclo[4.1.0]hept-3-yl, 2-aza-bicyclo[3.1.0]hex-2-yl , 3-aza-bicyclo[3.1.0]hex-3-yl, and the like.

[0050] "Heterocycloalkylene" means cycloalkylene, as defined in this Application, provided that one or more of the ring member carbon atoms is replaced by a heteroatom.

[0051] "Heteroaryl" means a cyclic aromatic group having five or six ring atoms, wherein at least one ring atom is a heteroatom and the remaining ring atoms are carbon. The nitrogen atoms can be optionally quaternerized and the sulfur atoms can be optionally oxidized. Heteroaryl groups of this invention include, but are not limited to, those derived from furan, imidazole, isothiazole, isoxazole, oxadiazole, oxazole, 1,2,3-oxadiazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrroline, thiazole, 1,3,4-thiadiazole, triazole and tetrazole. "Heteroaryl" also includes, but is not limited to, bicyclic or tricyclic rings, wherein the heteroaryl ring is fused to one or two rings independently selected from the group consisting of an aryl ring, a cycloalkyl ring, a cycloalkenyl ring, and another monocyclic heteroaryl or heterocycloalkyl ring. These bicyclic or tricyclic heteroaryls include, but are not limited to, those derived from benzo[b]furan, benzo[b]thiophene, benzimidazole, imidazo[4,5-c]pyridine, quinazoline, thieno[2,3-c]pyridine, thieno[3,2-b]pyridine, thieno[2,3-b]pyridine, indolizine, imidazo[1,2a]pyridine, quinoline, isoquinoline, phthalazine, quinoxaline, naphthyridine, quinolizine, indole, isoindole, indazole, indoline, benzoxazole, benzopyrazole, benzothiazole, imidazo[1,5-a]pyridine, pyrazolo[1,5-a]pyridine, imidazo[1,2-a]pyrimidine, imidazo[1,2-c]pyrimidine, imidazo[1,5-a]pyrimidine, imidazo[1,5-c]pyrimidine, pyrrolo[2,3-b]pyridine, pyrrolo[2,3-c]pyridine, pyrrolo[3,2-c]pyridine, pyrrolo[3,2-b]pyridine, pyrrolo[2,3-d]pyrimidine, pyrrolo[3,2-d]pyrimidine, pyrrolo[2,3-b]pyrazine, pyrazolo[1,5-a]pyridine, pyrrolo[1,2-b]pyridazine, pyrrolo[1,2-c]pyrimidine, pyrrolo[1,2-a]pyrimidine, pyrrolo[1,2-a]pyrazine, triazo[1,5-a]pyridine, pteridine, purine, carbazole, acridine, phenazine, phenothiazene, phenoxazine, 1,2-dihydropyrrolo[3,2,1-*hi*]indole, indolizine, pyrido[1,2-a]indole and 2(1H)-pyridinone. The bicyclic or tricyclic heteroaryl rings can be attached to the parent molecule through either the heteroaryl

group itself or the aryl, cycloalkyl, cycloalkenyl or heterocycloalkyl group to which it is fused. The heteroaryl groups of this invention can be substituted or unsubstituted.

[0052] "Heterobicycloaryl" means bicycloaryl, as defined in this Application, provided that one or more of the atoms within the ring is a heteroatom. For example, hetero(C_{4-10})bicycloaryl as used in this Application includes, but is not limited to, 2-amino-4-oxo-3,4-dihydropteridin-6-yl, tetrahydroisoquinolinyl, and the like.

[0053] "Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more of the atoms forming the ring is a heteroatom selected, independently from N, O, or S. Non-exclusive examples of heterocycloalkyl include piperidyl, 4-morpholyl, 4-piperazinyl, pyrrolidinyl, perhydropyrrolizinyl, 1,4-diazaperhydroepinyl, 1,3-dioxanyl, 1,4-dioxanyl and the like.

[0054] "Hydroxy" means the radical -OH.

[0055] "Iminoketone derivative" means a derivative comprising the moiety -C(NR)-, wherein R comprises a hydrogen or carbon atom attached to the nitrogen.

[0056] "Isomers" mean any compound having an identical molecular formulae but differing in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers." A carbon atom bonded to four nonidentical substituents is termed a "chiral center." A compound with one chiral center has two enantiomeric forms of opposite chirality. A mixture of the two enantiomeric forms is termed a "racemic mixture." A compound that has more than one chiral center has 2^{n-1} enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as ether an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture." When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of

stereochemistry and the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992).

[0057] "Leaving group" means a moiety that can be displaced by another moiety, such as by nucleophilic attack, during a chemical reaction. Leaving groups are well known in the art and include, for example, halides and OSO_2R' where R' is, for example, alkyl, haloalkyl, or aryl optionally substituted by halo, alkyl, alkoxy, amino, and the like. Non-limiting examples of leaving groups include chloro, bromo, iodo, mesylate, tosylate, and other similar groups.

[0058] "Nitro" means the radical $-NO_2$.

[0059] "Oxaalkyl" means an alkyl, as defined above, except where one or more oxygen atoms (-O-) are positioned between carbon atoms of the alkyl. For example, an (C_{2-6})oxaalkyl refers to a chain comprising between 2 and 6 carbons and one or more oxygen atoms positioned between the carbon atoms.

[0060] "Oxoalkyl" means an alkyl, further substituted with a carbonyl group. The carbonyl group may be an aldehyde, ketone, ester, amide, acid or acid chloride.

[0061] "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

[0062] "Pharmaceutically acceptable salts" means salts of inhibitors of the present invention which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid,

4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

[0063] Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

[0064] "Prodrug" means a compound that is convertible *in vivo* metabolically into an inhibitor according to the present invention. The prodrug itself may or may not also have DPP-IV inhibitory activity. For example, an inhibitor comprising a hydroxy group may be administered as an ester that is converted by hydrolysis *in vivo* to the hydroxy compound. Suitable esters that may be converted *in vivo* into hydroxy compounds include acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, cyclohexylsulfamates, quinates, esters of amino acids, and the like. Similarly, an inhibitor comprising an amine group may be administered as an amide that is converted by hydrolysis *in vivo* to the amine compound.

[0065] "Protected derivatives" means derivatives of inhibitors in which a reactive site or sites are blocked with protecting groups. Protected derivatives are useful in the preparation of inhibitors or in themselves may be active as inhibitors. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

[0066] "Reacting" refers to a chemical process or processes in which two or more reactants are allowed to come into contact with each other to effect a chemical change or transformation. "Reacting" is intended to encompass a variety of methods used in the art for directly or indirectly contacting reactants including, but not being limited to, mixing, stirring, sonicating, and the like.

[0067] "Substituted or unsubstituted" means that a given moiety may consist of only hydrogen substituents through available valencies (unsubstituted) or may further comprise one or more non-hydrogen substituents through available valencies (substituted) that are not otherwise specified by the name of the given moiety. For example, isopropyl is an example of an ethylene moiety that is substituted by $-CH_3$. In general, a non-hydrogen substituent may be any substituent that may be bound to an atom of the given moiety that is specified to be substituted. Examples of substituents include, but are not limited to, aldehyde, alicyclic, aliphatic, alkyl, alkylene, alkylidene, amide, amino, aminoalkyl, aromatic, aryl, bicycloalkyl, bicycloaryl, carbamoyl, carbocyclyl, carboxyl, carbonyl group, cyano, cycloalkyl, cycloalkylene, ester, halo, heterobicycloalkyl, heterocycloalkylene, heteroaryl, heterobicycloaryl, heterocycloalkyl, oxo, hydroxy, iminoketone, ketone, nitro, oxaalkyl, and oxoalkyl moieties, each of which may optionally also be substituted or unsubstituted.

[0068] "Sulfinyl" means the radical –SO-. It is noted that the sulfinyl radical may be further substituted with a variety of substituents to form different sulfinyl groups including sulfinic acids, sulfinamides, sulfinyl esters, and sulfoxides.

[0069] "Sulfonyl" means the radical $-SO_2-$. It is noted that the sulfonyl radical may be further substituted with a variety of substituents to form different sulfonyl groups including sulfonic acids, sulfonamides, sulfonate esters, and sulfones.

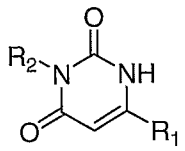
[0070] "Thiocarbonyl" means the radical -CS-. It is noted that the thiocarbonyl radical may be further substituted with a variety of substituents to form different thiocarbonyl groups including thioacids, thioamides, thioesters, and thioketones.

[0071] It is noted in regard to all of the definitions provided herein that the definitions should be interpreted as being open ended in the sense that further substituents beyond those specified may be included. Hence, a C_1 alkyl indicates that there is one carbon atom but does not indicate what are the substituents on the carbon atom. Hence, a C_1 alkyl comprises methyl (i.e., $-CH_3$) as well as $-R_aR_bR_c$ where R_a, R_b, and R_c may each independently be hydrogen or any other substituent where the atom attached to the carbon is a heteroatom or cyano. Hence, CF_3, CH_2OH and CH_2CN, for example, are all C_1 alkyls.

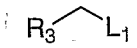
Detailed Description Of The Invention

[0072] The present invention relates to methods of making compounds. One use of the methods provided herein is for making compounds that inhibit dipeptidyl peptidases IV (referred to herein as DPP-IV). The methods may also be used to make intermediates useful in the production of dipeptidyl peptidase inhibitors.

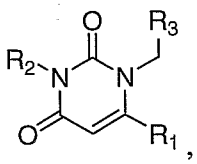
[0073] In one embodiment, the present invention relates to a process comprising reacting a compound of the formula



with a compound of the formula



under conditions that form a reaction product of the formula



wherein

R_1 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted,

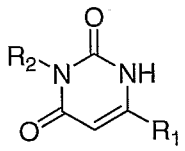
R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl,

thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted,

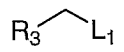
R_3 is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and

L_1 is a leaving group.

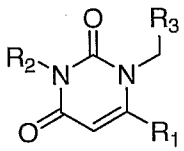
[0074] In another embodiment, the present invention relates to a process comprising reacting a compound of the formula



with a compound of the formula



in dimethylsulfoxide in the presence of K_2CO_3 under conditions that form a reaction product of the formula



wherein

R_1 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl,

heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted,

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted,

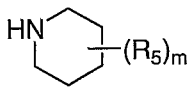
R_3 is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and

L_1 is a leaving group.

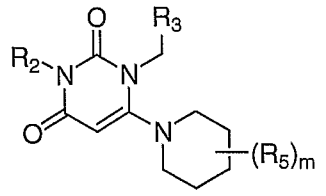
[0075] In one variation of each of the above embodiments, the reacting step is performed at a temperature between 45°C and 75°C. In another variation of each of the above embodiments and variations, the reacting step is performed for at least 1 hr.

[0076] In yet another variation, the process also comprises the step of extracting the reaction product using ethyl acetate. In still another variation, the process further comprises the step of purifying the reaction product. In one particular variation, the reaction product is purified by column chromatography.

[0077] In a further variation of each of the above embodiments and variations, R_1 is a leaving group and the reaction product is further reacted with a piperidine of the formula



under conditions that form a second reaction product of the formula

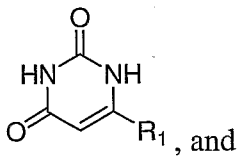


wherein

m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, and

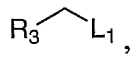
each R_5 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0078] In still another embodiment, the present invention relates to a process comprising forming a mixture of sodium hydride and lithium bromide with a compound of the formula



, and

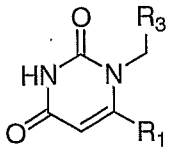
adding to the mixture a compound of the formula



,

wherein

the process is performed under conditions that form a reaction product of the formula



,

R_1 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted,

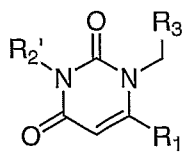
R_3 is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and

L_1 is a leaving group.

[0079] In one variation, at least a portion of the process is conducted at a temperature between -5°C and 5°C. In another variation, the reaction product is further reacted with a compound of the formula

$$R_2'—X$$

to form a second reaction product of the formula

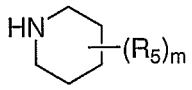


wherein

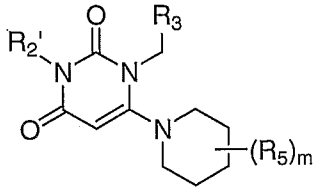
R_2' is a substituted or unsubstituted (C_{1-10})alkyl, and

X is a halide.

[0080] In still another variation, R_1 is a leaving group and the second reaction product is further reacted with a piperidine of the formula



under conditions that form a compound of the formula

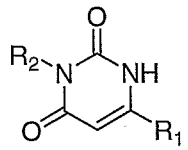


wherein

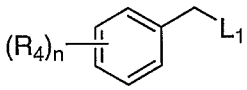
m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and

each R_5 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

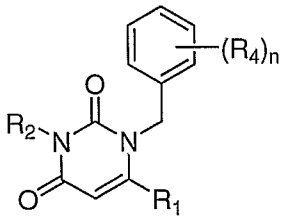
[0081] In a further embodiment, the present invention relates to a process comprising reacting a compound of the formula



with a compound of the formula



under conditions that form a reaction product of the formula



wherein

n is selected from the group consisting of 0, 1, 2, 3, 4 and 5;

R_1 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

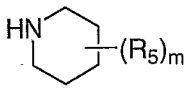
R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

each R_4 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl,

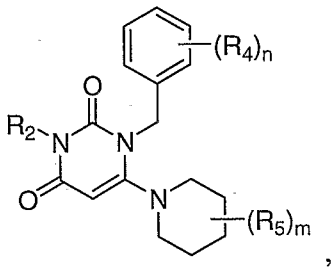
heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

L_1 is a leaving group.

[0082] In one variation, R_1 is a leaving group and the reaction product is further reacted with a piperidine of the formula



under conditions that form a second reaction product of the formula

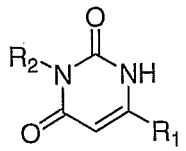


wherein

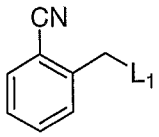
m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, and

each R_5 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

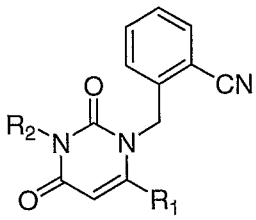
[0083] In another embodiment, the present invention relates to a process comprising reacting a compound of the formula



with a compound of the formula



under conditions that form a reaction product of the formula



,

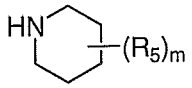
wherein

R_1 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted,

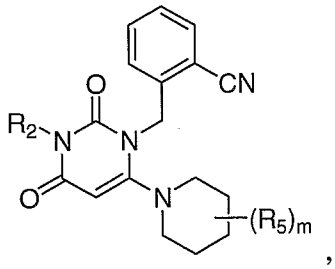
R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and

L_1 is a leaving group.

[0084] In one variation, R_1 is a leaving group and the reaction product is further reacted with a piperidine of the formula



under conditions that form a second reaction product of the formula

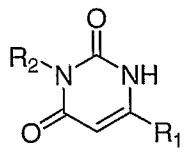


wherein

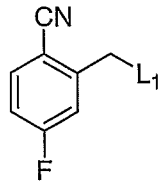
m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and

each R_5 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

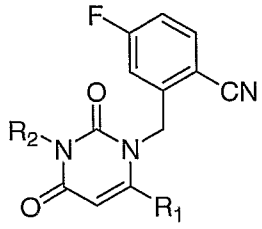
[0085] In still another embodiment, the present invention relates to a process comprising reacting a compound of the formula



with a compound of the formula



under conditions that form a reaction product of the formula



,

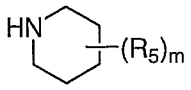
wherein

R_1 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted,

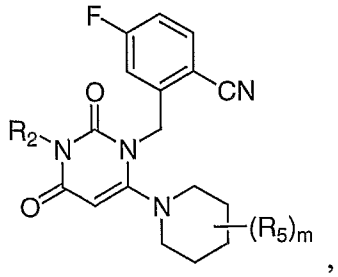
R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and

L_1 is a leaving group.

[0086] In one variation, R_1 is a leaving group and the reaction product is further reacted with a piperidine of the formula



under conditions that form a second reaction product of the formula



wherein

m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, and

each R_5 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0087] In one variation of each of the above embodiments and variations, R_1 is a leaving group. In one particular variation, R_1 is selected from the group consisting of halo (*e.g.*, chloro, bromo and iodo), and OSO_2R' where R' is alkyl, haloalkyl, or aryl optionally substituted by halo, alkyl, alkoxy or amino (*e.g.*, mesylate and tosylate). In another particular variation, R_1 is halo. In still another particular variation, R_1 is chloro.

[0088] In another variation of each of the above embodiments and variations, R_2 is hydrogen. In still another variation, R_2 is a substituted or unsubstituted C_{1-6} alkyl. In one particular variation, R_2 is methyl.

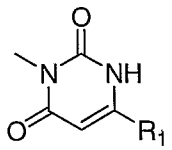
[0089] In yet another variation of each of the above embodiments and variations, R_2' is hydrogen. In a further variation, R_2' is a substituted or unsubstituted C_{1-6} alkyl. In one particular variation, R_2' is methyl.

[0090] In a further variation of each of the above embodiments and variations, R_3 is a substituted or unsubstituted aryl or heteroaryl. In another variation, R_3 is a substituted or unsubstituted phenyl. In still another variation, R_3 is a phenyl substituted with one or more substituents selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, (C_{1-10})alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted. In one particular variation, R_3 is a cyanophenyl and optionally a 2-cyanophenyl. In another particular variation, R_3 is a halocyanophenyl and optionally 2-cyano-5-fluorophenyl.

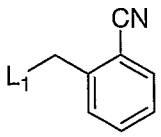
[0091] In another variation of each of the above embodiments and variations, each R_4 is independently cyano or halo.

[0092] In still another variation of each of the above embodiments and variations, at least one R_5 is amino.

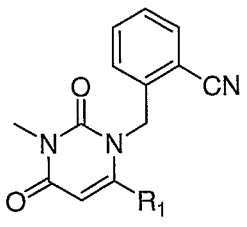
[0093] In another embodiment, the present invention relates to a process comprising reacting a compound of the formula



with a compound of the formula

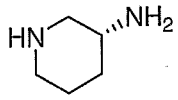


under conditions that form a reaction product of the formula

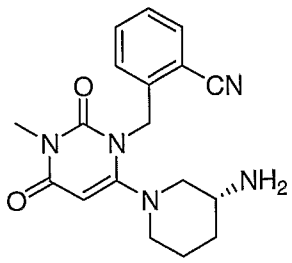


; and

reacting the reaction product with a piperidine of the formula



under conditions that form a second reaction product of the formula:



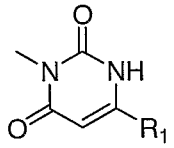
,

wherein

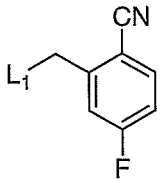
R_1 is halo, and

L_1 is a leaving group.

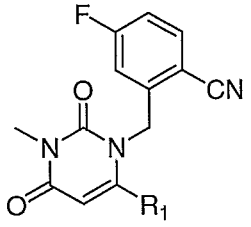
[0094] In still another embodiment, the present invention relates to a process comprising reacting a compound of the formula



with a compound of the formula

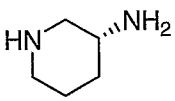


under conditions that form a reaction product of the formula

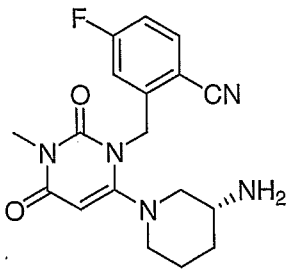


; and

reacting the reaction product with a piperidine of the formula



under conditions that form a second reaction product of the formula



wherein

R_1 is halo, and

L_1 is a leaving group.

[0095] In one variation of each of the above embodiments and variations, L_1 is halo and optionally bromo.

[0096] In one variation the pyrimidindione product is further converted to an acid addition salt. In particular variations, the acid addition salt is selected from the group consisting of acetate, citrate, hydrochloride, L-lactate, succinate, sulfate, p-toluenesulfonate, benzenesulfonate, benzoate, methanesulfonate, naphthylene-2-sulfonate, propionate, p-toluenesulfonate, hydrobromate, hydroiodate, R-mandelate, and L-tartrate.

[0097] In still another variation of each of the above embodiments and variations, the pyrimidin-dione is present as a mixture of stereoisomers. In yet another variation, the pyrimidin-dione comprises a single stereoisomer.

[0098] It is noted in regard to all of the embodiments, and any further embodiments, variations, or individual compounds described or claimed herein that all such embodiments, variations, and/or individual compounds are intended to encompass all pharmaceutical acceptable salt forms whether in the form of a single stereoisomer or mixture of stereoisomers unless it is specifically specified otherwise. Similarly, when one or more potentially chiral centers are present in any of the embodiments, variations, and/or individual compounds specified or claimed herein, both possible chiral centers are intended to be encompassed unless it is specifically specified otherwise.

Salts, Hydrates, and Prodrugs of DPP-IV Inhibitors

[0099] It should be recognized that compounds made according to the present invention for pharmaceutical applications may optionally be converted into pharmaceutically acceptable salts and prodrugs.

[0100] When compounds made according to the present invention possess a free base form, the compounds can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, e.g., hydrohalides such as hydrochloride, hydrobromide, hydroiodide; other mineral acids and their corresponding salts such as sulfate, nitrate, phosphate, etc.; and alkyl and monoarylsulfonates such as ethanesulfonate, toluenesulfonate and benzenesulfonate; and other organic acids and their corresponding salts such as acetate, tartrate, maleate, succinate, citrate, benzoate, salicylate and ascorbate. Further examples of acid addition salts include, but are not limited to: adipate, alginate, arginate, aspartate, bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptaoate, gluconate, glutamate, glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, iso-butyrate, lactate, lactobionate, malate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, pamoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate and phthalate. It should be recognized that the free base forms will typically differ from their respective salt forms somewhat in physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base forms.

[0101] When the compounds made according to the present invention possess a free acid form, a pharmaceutically acceptable base addition salt can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Examples of such bases are alkali metal hydroxides including potassium, sodium and lithium hydroxides; alkaline earth metal hydroxides such as barium and calcium hydroxides; alkali metal alkoxides, e.g. potassium ethanolate and sodium propanolate; and various organic bases such as ammonium hydroxide, piperidine, diethanolamine and N-methylglutamine. Also included are the aluminum salts of the compounds made according to the present invention. Further examples of base salts

include, but are not limited to: copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium and zinc salts. Examples of organic base salts include, but are not limited to, salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, e.g., arginine, betaine, caffeine, chloroprocaine, choline, N,N'-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, iso-propylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine and tris-(hydroxymethyl)-methylamine (tromethamine). It should be recognized that the free acid forms will typically differ from their respective salt forms somewhat in physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid forms.

[0102] Compounds that comprise basic nitrogen-containing groups may be quaternized with such agents as (C_{1-4})alkyl halides, e.g., methyl, ethyl, iso-propyl and tert-butyl chlorides, bromides and iodides; di (C_{1-4})alkyl sulfates, e.g., dimethyl, diethyl and diamyl sulfates; (C_{10-18})alkyl halides, e.g., decyl, dodecyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aryl (C_{1-4})alkyl halides, e.g., benzyl chloride and phenethyl bromide. Such salts permit the preparation of both water-soluble and oil-soluble compounds.

[0103] *N*-oxides of compounds can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0°C. Alternatively, the *N*-oxides of the compounds can be prepared from the *N*-oxide of an appropriate starting material.

[0104] Prodrug derivatives of compounds can be prepared by modifying substituents that are then converted *in vivo* to a different substituent. For example, prodrugs can be

prepared by reacting a compound with a carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, or the like) or an acylating agent. Further examples of methods of making prodrugs are described in Saulnier *et al.*(1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985.

[0105] Protected derivatives of compounds can also be made. Examples of techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

[0106] Compounds may also be conveniently prepared, or formed, as solvates (e.g. hydrates). Hydrates of compounds may be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[0107] A "pharmaceutically acceptable salt", as used herein, is intended to encompass any compound made according to the present invention that is utilized in the form of a salt thereof, especially where the salt confers on the compound improved pharmacokinetic properties as compared to the free form of compound or a different salt form of the compound. The pharmaceutically acceptable salt form may also initially confer desirable pharmacokinetic properties on the compound that it did not previously possess, and may even positively affect the pharmacodynamics of the compound with respect to its therapeutic activity in the body. An example of a pharmacokinetic property that may be favorably affected is the manner in which the compound is transported across cell membranes, which in turn may directly and positively affect the absorption, distribution, biotransformation and excretion of the compound. While the route of administration of the pharmaceutical composition is important, and various anatomical, physiological and pathological factors can critically affect bioavailability, the solubility of the compound is usually dependent upon the character of the particular salt form thereof, which it utilized. One of skill in the art will appreciate that an aqueous solution of the compound will provide the most rapid absorption of the compound into the body of a subject being treated, while lipid solutions and suspensions, as well as solid dosage forms, will result in less rapid adsorption of the compound.

Indications For Use of DPP-IV Inhibitors

[0108] DPP-IV is believed to contribute to the pathology and/or symptomology of several different diseases such that reduction of the activity of DPP-IV in a subject through inhibition may be used to therapeutically address these disease states. Examples of various diseases that may be treated using DPP-IV inhibitors are described herein. It is noted that additional diseases beyond those disclosed herein may be later identified as the biological roles that DPP-IV plays in various pathways becomes more fully understood.

[0109] One set of indications that DPP-IV inhibitors may be used to treat are those involving the prevention and treatment of diabetes and obesity, in particular type 2 diabetes mellitus, diabetic dislipidemia, conditions of impaired glucose tolerance (IGT), conditions of impaired fasting plasma glucose (IFG), metabolic acidosis, ketosis, appetite regulation and obesity.

[0110] DPP-IV inhibitors may also be used as immunosuppressants (or cytokine release suppressant drugs) for the treatment of among other things: organ transplant rejection; autoimmune diseases such as inflammatory bowel disease, multiple sclerosis and rheumatoid arthritis; and the treatment of AIDS.

[0111] DPP-IV inhibitors may also be used for treating various cancers including breast cancer, lung cancer and prostate cancer.

[0112] DPP-IV inhibitors may also be used to treat dermatological diseases such as psoriasis, rheumatoid arthritis (RA) and lichen planus.

[0113] DPP-IV inhibitors may also be used to treat infertility and amenorrhea.

[0114] DPP-IV inhibitors may also be used to modulate cleavage of various cytokines (stimulating hematopoietic cells), growth factors and neuropeptides. For example, such conditions occur frequently in patients who are immunosuppressed, for example, as a consequence of chemotherapy and/or radiation therapy for cancer.

[0115] DPP-IV inhibitors may also be used prevent or reduce cleavage of N-terminal Tyr-Ala from growth hormone-releasing factor. Accordingly, these inhibitors may be used in the treatment of short stature due to growth hormone deficiency (Dwarfism) and for promoting GH-dependent tissue growth or re-growth.

[0116] DPP-IV inhibitors may also be used to address disease states associated with cleavage of neuropeptides and thus may be useful for the regulation or normalization of neurological disorders.

[0117] For oncology indications, DPP-IV inhibitors may be used in conjunction with other agents to inhibit undesirable and uncontrolled cell proliferation. Examples of other anti-cell proliferation agents that may be used in conjunction with the DPP-IV inhibitors of the present invention include, but are not limited to, retinoid acid and derivatives thereof, 2-methoxyestradiol, ANGIOSTATIN™ protein, ENDOSTATIN™ protein, suramin, squalamine, tissue inhibitor of metalloproteinase-I, tissue inhibitor of metalloproteinase-2, plasminogen activator inhibitor-1, plasminogen activator inhibitor-2, cartilage-derived inhibitor, paclitaxel, platelet factor 4, protamine sulfate (clupeine), sulfated chitin derivatives (prepared from queen crab shells), sulfated polysaccharide peptidoglycan complex (sp-pg), staurosporine, modulators of matrix metabolism, including for example, proline analogs ((l-azetidine-2-carboxylic acid (LACA)), cishydroxyproline, d,l-3,4-dehydroproline, thiaproline, beta.-aminopropionitrile fumarate, 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone, methotrexate, mitoxantrone, heparin, interferons, 2 macroglobulin-serum, chimp-3, chymostatin, beta.-cyclodextrin tetradecasulfate, eponemycin; fumagillin, gold sodium thiomalate, d-penicillamine (CDPT), beta.-1-anticollagenase-serum, alpha.2-antiplasmin, bisantrene, lobenzarit disodium, n-2-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA", thalidomide; angostatic steroid, carboxyaminoimidazole; metalloproteinase inhibitors such as BB94. Other anti-angiogenesis agents that may be used include antibodies, preferably monoclonal antibodies against these angiogenic growth factors: bFGF, aFGF, FGF-5, VEGF isoforms, VEGF-C, HGF/SF and Ang-1/Ang-2. Ferrara N. and Alitalo, K. "Clinical application of angiogenic growth factors and their inhibitors" (1999) Nature Medicine 5:1359-1364.

Examples

[0118] As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Standard single-letter or thee-letter abbreviations are generally used to

designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams); mg (milligrams);

L (liters); mL (milliliters);

μL (microliters); psi (pounds per square inch);

M (molar); mM (millimolar);

i.v. (intravenous); Hz (Hertz);

MHz (megahertz); mol (moles);

mmol (millimoles); RT (ambient temperature);

min (minutes);h (hours);

mp (melting point); TLC (thin layer chromatography);

Tr (retention time); RP (reverse phase);

MeOH (methanol); i-PrOH (isopropanol);

TEA (triethylamine); TFA (trifluoroacetic acid);

TFAA (trifluoroacetic anhydride); THF (tetrahydrofuran);

DMSO (dimethylsulfoxide); EtOAc (ethyl acetate);

DME (1,2-dimethoxyethane); DCM (dichloromethane);

DCE (dichloroethane); DMF (N,N-dimethylformamide);

DMPU (N,N'-dimethylpropyleneurea); CDI (1,1-carbonyldiimidazole);

IBCF (isobutyl chloroformate); HOAc (acetic acid);

HOSu (N-hydroxysuccinimino); HOBT (1-hydroxybenzotriazole);

Et_2O (diethyl ether); EDCI (ethylcarbodiimino hydrochloride);

BOC (tert-butyloxycarbonyl); FMOC (9-fluorenylmethoxycarbonyl);

DCC (dicyclohexylcarbodiimino); CBZ (benzyloxycarbonyl);

Ac (acetyl); atm (atmosphere);

TMSE (2-(trimethylsilyl)ethyl); TMS (trimethylsilyl);

TIPS (triisopropylsilyl); TBS (t-butyldimethylsilyl);
DMAP (4-dimethylaminopyridine); Me (methyl);
OMe (methoxy); Et (ethyl);
Et (ethyl); tBu (tert-butyl);
HPLC (high pressure liquid chromatography);
BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride);
TBAF (tetra-n-butylammonium fluoride);

mCPBA (meta-chloroperbenzoic acid.

[0119] All references to ether or Et_2O are to diethyl ether; brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions conducted under an inert atmosphere at RT unless otherwise noted.

[0120] ^1H NMR spectra were recorded on a Bruker Avance 400. Chemical shifts are expressed in parts per million (ppm). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

[0121] Low-resolution mass spectra (MS) and compound purity data were acquired on a Waters ZQ LC/MS single quadrupole system equipped with electrospray ionization (ESI) source, UV detector (220 and 254 nm), and evaporative light scattering detector (ELSD). Thin-layer chromatography was performed on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid, Ninhydrin or p-anisaldehyde solution. Flash column chromatography was performed on silica gel (230-400 mesh, Merck).

[0122] It will be readily recognized that certain compounds made according to the present invention have atoms with linkages to other atoms that confer a particular stereochemistry to the compound (e.g., chiral centers). It is recognized that synthesis of compounds according to the present invention may result in the creation of mixtures of different stereoisomers (enantiomers, diastereomers). Unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all of the different possible stereoisomers.

[0123] Various methods for separating mixtures of different stereoisomers are known in the art. For example, a racemic mixture of a compound may be reacted with an optically active resolving agent to form a pair of diastereoisomeric compounds. The diastereomers may then be separated in order to recover the optically pure enantiomers. Dissociable complexes may also be used to resolve enantiomers (e.g., crystalline diastereoisomeric salts). Diastereomers typically have sufficiently distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) that they can be readily separated by taking advantage of these dissimilarities. For example, diastereomers can typically be separated by chromatography or by separation/resolution techniques based upon differences in solubility. A more detailed description of techniques that can be used to resolve stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

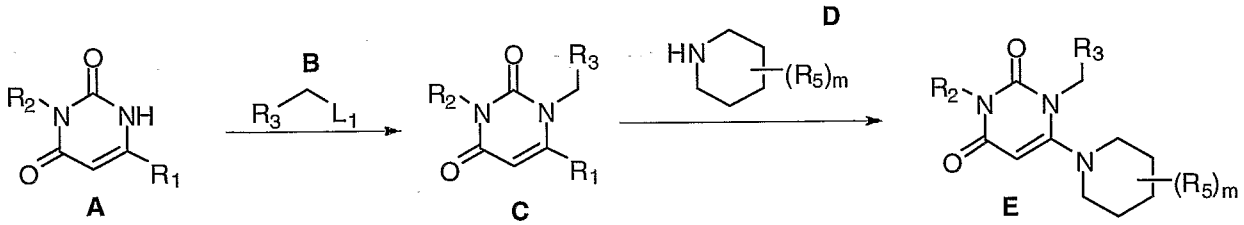
[0124] Compounds made according to the present invention can also be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of compounds, dissociable complexes are preferred (e.g., crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

Synthetic Schemes Of The Present Invention

[0125] Several illustrative reaction schemes according to the present invention are provided in the following examples. These reaction schemes may be used to make DPP-IV inhibitors, as well as intermediates in the preparation of DPP-IV inhibitors.

[0126] In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

Scheme 1:



[0127] **Compound C.** A mixture of an optionally substituted 3,6-disubstituted uracil (**A**), Compound **B** and a base (*e.g.*, K_2CO_3, $CsCO_3$ or diisopropylethylamine) in a solvent (*e.g.*, DMSO, NMP or DMF) is optionally stirred for at least about 1 hour, and optionally at least about 2 hours, at a temperature between 50 and 70°C, and optionally at a temperature between 55 and 65°C. The reaction is optionally cooled (*e.g.*, 20-30°C), diluted with water and optionally extracted with an organic solvent (*e.g.*, EtOAc or isopropanol). The organics are dried (*e.g.*, over $MgSO_4$ or Na_2SO_4) and the solvent removed. The residue is optionally purified using any of a variety of purification techniques known in the art, including column chromatography.

[0128] **Compound E.** Compound **C** , an optionally susbstituted piperidine (**D**) and a base (*e.g.*, sodium bicarbonate or K_2CO_3) are stirred (*e.g.*, in a sealed tube) with an alcohol (*e.g.*, MeOH, EtOH or isopropanol) at a temperature between 80 and 110°C, and optionally between 90 and 100°C, for at least about 1h, and optionally at least about 2h. The mixture is optionally dried by stirring the reactants with activated molecular sieves

(4A). The reaction is filtered (*e.g.*, through Celite), concentrated *in vacuo*, diluted with $CHCl_3$ or CH_2Cl_2, and then washed with water. The water phase is extracted with $CHCl_3$ or CH_2Cl_2, and the combined organic phases are washed with water, dried (*e.g.*, Na_2SO_4), and filtered. TFA is added and the solution is then concentrated *in vacuo*. The residue is dissolved in a small amount of alcohol (*e.g.*, MeOH), and Et_2O or hexanes is added to force precipitation. The mixture can then be allowed to stand at RT overnight. Solvents are then decanted, and the solid washed with Et_2O to give the TFA salt.

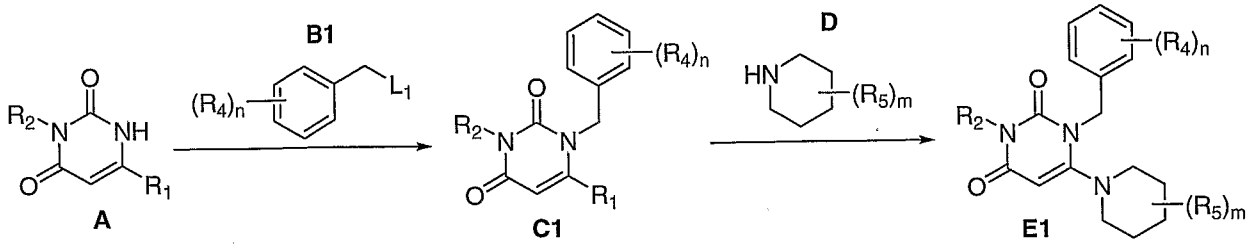
[0129] Alternatively, compound **C** can be reacted with an optionally substituted piperidine dihydrochloride (**D**) in water and an alcohol (*e.g.*, isopropanol) at a temperature between 55 and 70°C, and optionally between 60 and 65°C, until completion (*e.g.*, for at least about 12h). The mixture is optionally cooled (*e.g.*, to a temperature between 35 and 50°C). The inorganic salts are removed by filtration and the filter cake washed (*e.g.*, with a heated alcohol). The filtrate is optionally concentrated, diluted with a sovent (*e.g.*, THF), and acidified with HCl while optionally maintaining the temperature below 20°C. The resultant slurry is optionally cooled, and agitated to allow crystals to grow. The slurry is filtered and the filter cake optionally washed and dried to give the HCl salt.

[0130] The HCl salt can be converted to a benzoic acid salt as follows. The HCl salt is dissolved in water at a temperature between 35 and 50°C, and optionally between 40 and 45°C, and washed (*e.g.*, with isopropyl acetate) to remove dimer. The mixture is optionally heated, and free-based from the water layer into the organic layer (*e.g.*, by the addition of solid potassium carbonate). The layers are separated and the organic layer optionally washed to remove residual salts. The organic solution is optionally concentrated, treated with 2B alcohol, and optionally concentrated again. The solution is optionally filtered and benzoic acid is added while optionally maintaining the temperature of the solution between 60 and 75°C, and optionally between 65 and 70°C. The solution is then crystallized (*e.g.*, by cooling to a temperature between -5 and 10°C and stirring). The solution is filtered, optionally washed, optionally conditioned under nitrogen, and dried, to provide the benzoic acid salt.

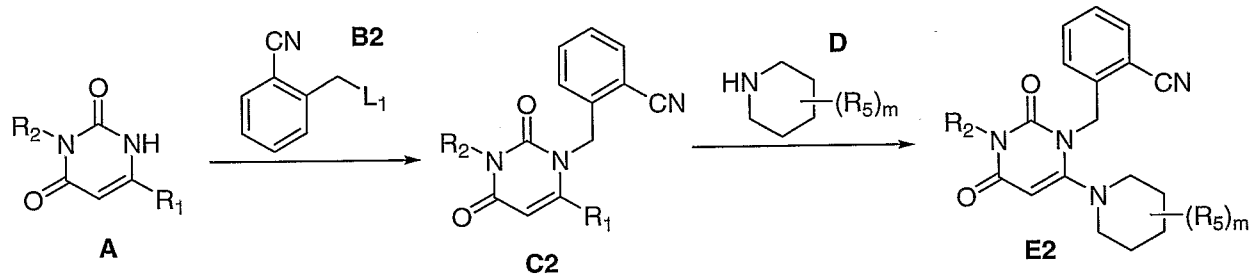
[0131] By varying the substituents on Compounds **A**, **B** and **D**, a wide variety of compounds can be synthesized using the methods of the present invention. By way of

example, and not limitation, several variations of Scheme 1 are provided below as Schemes 1a-1e.

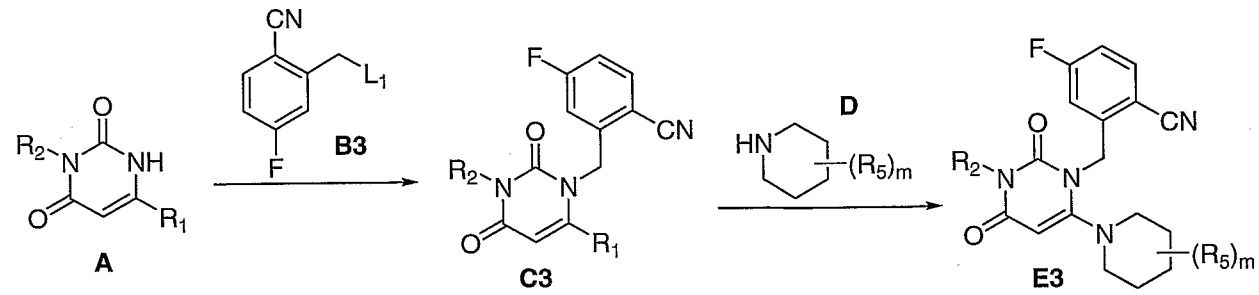
Scheme 1a:



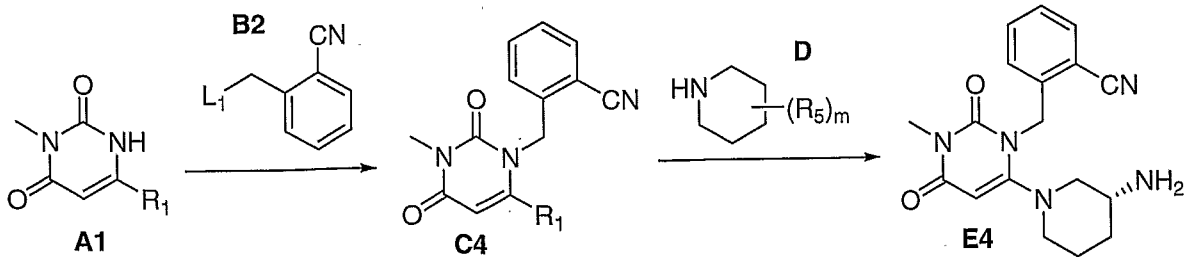
Scheme 1b:



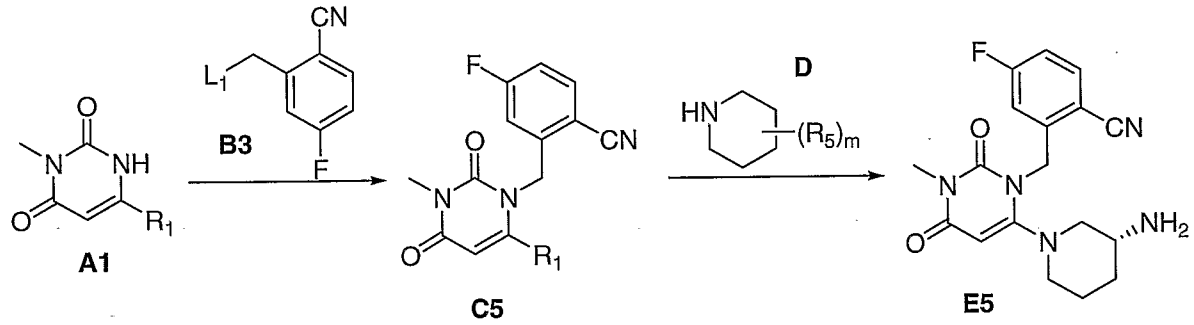
Scheme 1c:



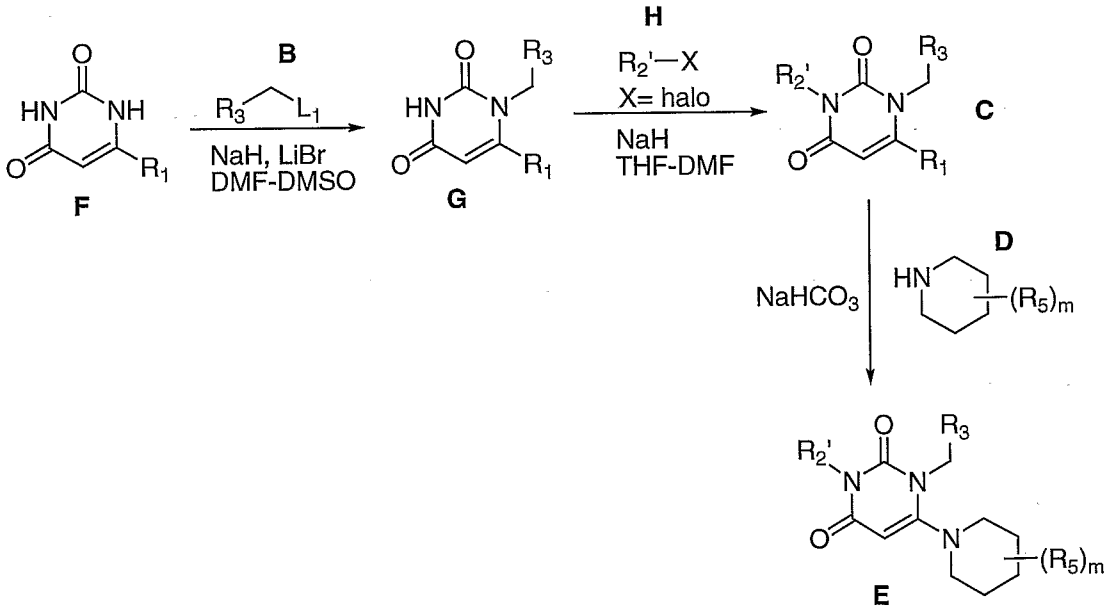
Scheme 1d:



Scheme 1e:



Scheme 2:



[0132] **Compound G.** To a solution of an optionally 6-substituted uracil (**F**) in a mixture of DMF-DMSO (6:1) under nitrogen at a temperature between –5 and 5°C, is added sodium hydride (60%) in portions. After at least about 15 minutes and optionally

at least about 30 minutes, lithium bromide is added and the mixture stirred for at least about 15 min at a temperature between –5 and 5°C. A solution of Compound **B** in DMF is added. The mixture is then stirred at this temperature for at least about 30 minutes and optionally at least about 1h, and then RT overnight. It will be understood that alkylation may be performed under standard conditions known in the art, including the use of a base such as NaH, LiH and the like in an organic solvent or mixture of solvents. The solvent may include DMSO, THF, DMF and the like, or mixtures thereof. In addition, additives may be used, including LiBr, LiI, NaI and the like.

[0133] The mixture is then evaporated and co-evaporated with water *in vacuo* to remove most of the solvent, and then poured into ice water. The precipitate is collected by filtration. The crude product is suspended in hot AcOEt-$CHCl_3$, sonicated, allowed to stand at a temperature of between –5 and 5°C for at least about 30 minutes, and optionally at least about 1h, and then filtered to give the title compound. It will also be understood by those skilled in the art that purification may be accomplished using various methods known in the art, including washing with an aqueous/organic solvent or mixture of solvents, recrystallization and/or column chromatography. Non-limiting examples of organic solvents and solvent mixtures may include ethyl acetate, isopropyl acetate, acetone, THF and the like.

[0134] **Compound C.** To a cold (between –5 and 5°C, and optionally about 0°C) solution of an optionally 1,6-disubstituted uracil (**G**) in DMF-THF under nitrogen, is added NaH (60%) in portions, followed by adding LiBr. The mixture is stirred at a temperature between –5 and 5°C and optionally about 0°C, for at least about 10 minutes and optionally at least 20 minutes. Compound **H** is added and the flask sealed. The mixture is maintained at this temperature for at least about 5 minutes and optionally at least about 10 minutes; RT for at least about 1h and optionally at least about 2h; and at a temperature between 25 and 45°C and optionally between 30 and 40°C overnight. The product can then be concentrated *in vacuo*. It will be understood that alkylation may be performed under standard conditions known in the art, including the use of a base such as NaH, LiH or the like in an organic solvent or mixture of solvents. The solvent may include DMSO, THF, DMF and the like, or mixtures thereof. In addition, additives may

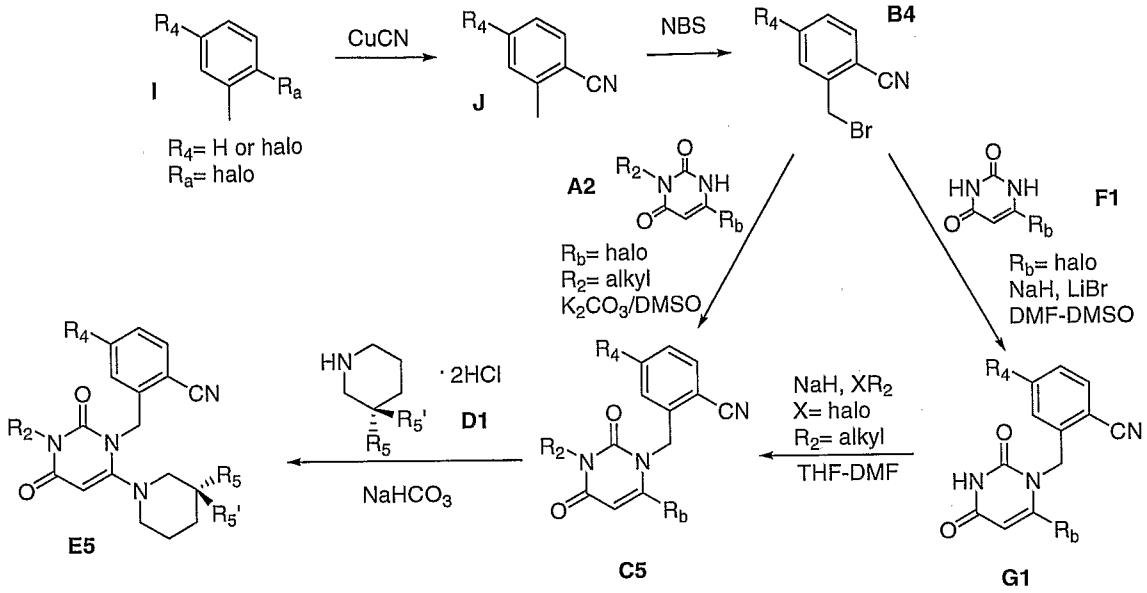
be used, including LiBr, LiI, NaI and the like. For example, the alkylation can be performed using iodomethane and K_2CO_3 in acetone.

[0135] The residue is dissolved (*e.g.*, in $CHCl_3$), washed with water and brine, dried (*e.g.*, Na_2SO_4), filtered, and then concentrated *in vacuo*. The crude product is crystallized from, for example, THF-Hexanes to give the title compound. It will also be understood by those skilled in the art that Compound **C** may be purified in a variety of organic solvents or solvent mixtures. For example, Compound **C** can be purified by adding a mixture of dichloromethane and heptane. Optionally, Compound **C** may be further purified in an organic solvent or mixture of solvents such as dichloromethane, chloroform, acetonitrile, THF, ethyl acetate, isopropyl acetate and the like. In one particular embodiment, the product is purified and washed with ethyl acetate.

[0136] **Compound E.** Compound **C**, an optionally substituted piperidine (**D**) and sodium bicarbonate or K_2CO_3 are stirred in a sealed tube with an alcohol (*e.g.*, MeOH or EtOH) at a temperature between 80 and 110°C, and optionally between 90 and 100°C, for at least about 1h, and optionally at least about 2h. The mixture is optionally dried by stirring the reactants with activated molecular sieves (4A). The reaction is filtered (*e.g.*, through Celite), concentrated *in vacuo*, diluted with $CHCl_3$ or CH_2Cl_2, and then washed with water. The water phase is extracted with $CHCl_3$ or CH_2Cl_2, and the combined organic phases are washed with water, dried (*e.g.*, Na_2SO_4), and filtered. TFA is added and the solution is then concentrated *in vacuo*. The residue is dissolved in a small amount of alcohol (*e.g.*, MeOH), and Et_2O or hexanes is added to force precipitation. The mixture can then be allowed to stand at RT overnight. Solvents are then decanted, and the solid washed with Et_2O to give the TFA salt.

[0137] It will be understood that Scheme 2 provides an alternate method to that of Scheme 1. Specifically, Scheme 2 allows for substitution at the 3-position of Compound **C** after alkylation at the 1-position. Accordingly, Scheme 2 can be performed with Scheme 1 whenever R_2 of Scheme 1 is hydrogen or a protecting group.

Scheme 3:



[0138] **Compound J.** A mixture of an optionally substituted 2-halotoluene (**A**) and CuCN in DMF is refluxed, optionally for at least 24 hours. The reaction is diluted with water and extracted with an organic solvent (*e.g.*, hexane). The organics are optionally dried (*e.g.*, over $MgSO_4$ or Na_2SO_4) and the solvent removed to give Compound **J**.

[0139] **Compound B4.** A mixture of an optionally susbstituted 2-methylbenzonitrile (**J**), N-bromosuccinimide (NBS) and azobisisobutylnitrile (AIBN) in CCl_4 is refluxed under nitrogen, optionally for at least 2 hours. The reaction is cooled to room temperature and the solid removed by filtration. The organic solution can be concentrated to Compound **B4**, which can be used in the next steps without further purification. Alternatively, the crude product can be purified using any of a variety of purification techniques known in the art, including washing with an aqueous/organic solvent or mixture of solvents, recrystallization and/or column chromatography.

[0140] Compound **B4** can also be prepared as follows. 2-Methylbenzonitrile (**J**) in DCE is treated with AIBN and heated to a temperature between 70 and 80°C. DBH in DCE is added and the mixture stirred (*e.g.*, for >30 min). The reaction is optionally monitored for completion by, for example, measuring the amount of residual benzonitrile using HPLC. Additional AIBN optionally can be added to move the reaction toward completion. A base (*e.g.*, K_2CO_3, $CsCO_3$ or diisopropylethylamine) and diethyl

phosphite are added, and the mixture is optionally stirred until completion. The mixture can be optionally washed and purified.

[0141] **Compound G1.** To a solution of a 6-halouracil (**F1**) in a mixture of DMF-DMSO (6:1) under nitrogen at a temperature between –5 and 5°C, is added sodium hydride (60%) in portions. After at least about 15 minutes and optionally at least about 30 minutes, lithium bromide is added and the mixture stirred for at least about 15 min at a temperature between –5 and 5°C. A solution of an optionally substituted 2-bromomethylbenzonitrile (**B4**) in DMF is added. The mixture is then stirred at this temperature for at least about 30 minutes and optionally at least about 1h, and then RT overnight. It will be understood that alkylation may be performed under standard conditions known in the art, including the use of a base such as NaH, LiH and the like in an organic solvent or mixture of solvents. The solvent may include DMSO, THF, DMF and the like, or mixtures thereof. In addition, additives may be used, including LiBr, LiI, NaI and the like.

[0142] The mixture is then evaporated and co-evaporated with water *in vacuo* to remove most of the solvent, and then poured into ice water. The precipitate is collected by filtration. The crude product is suspended in hot AcOEt-$CHCl_3$, sonicated, allowed to stand at a temperature of between –5 and 5°C for at least about 30 minutes, and optionally at least about 1h, and then filtered to give the title compound. It will also be understood by those skilled in the art that purification may be accomplished using various methods known in the art, including washing with an aqueous/organic solvent or mixture of solvents, recrystallization and/or column chromatography. Non-limiting examples of organic solvents and solvent mixtures may include ethyl acetate, isopropyl acetate, acetone, THF and the like.

[0143] **Compound C5.** A mixture of a crude 3-alkyl-6-halouracil (**A2**), optionally substituted 2-bromomethylbenzonitrile (**B4**) and K_2CO_3 or $CsCO_3$ in a solvent (*e.g.*, DMSO, DMF or NMP) is stirred for at least about 1 hour, and optionally at least about 2 hours, at a temperature between 50 and 70°C, and optionally at a temperature between 55 and 65°C. The reaction is diluted with water and extracted with an organic solvent (*e.g.*, EtOAc). The organics are dried (*e.g.*, over $MgSO_4$ or Na_2SO_4) and the solvent removed.

The residue is optionally purified using any of a variety of purification techniques known in the art, including column chromatography.

[0144] Compound **C5** can also be prepared as follows. To a solution of 3-alkyl-6-halouracil (**A2**) and a base (*e.g.*, K_2CO_3, $CsCO_3$ or diisopropylethylamine) is added a solution of optionally substituted 2-bromomethylbenzonitrile (**B4**). The mixture is then heated to a temperature between 55 and 65°C for 2 hours or until completion (as determined, for example, by HPLC). Heating is then stopped and the mixture is diluted with water. The resultant slurry is optionally stirred, filtered and dried.

[0145] Alternatively, the 2-(6-halo-3-alkyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile (**C5**) can be prepared as follows. To a cold (between –5 and 5°C, and optionally about 0°C) solution of benzylated 6-halouracil (**G1**) in DMF-THF under nitrogen, is added NaH (60%) in portions, followed by adding LiBr. The mixture is stirred at a temperature between –5 and 5°C and optionally about 0°C, for at least about 10 minutes and optionally at least 20 minutes. A haloalkane is added and the flask sealed. The mixture is maintained at this temperature for at least about 5 minutes and optionally at least about 10 minutes; RT for at least about 1h and optionally at least about 2h; and at a temperature between 25 and 45°C and optionally between 30 and 40°C overnight. The product can then be concentrated *in vacuo*. It will be understood that alkylation may be performed under standard conditions known in the art, including the use of a base such as NaH, LiH or the like in an organic solvent or mixture of solvents. The solvent may include DMSO, THF, DMF and the like, or mixtures thereof. In addition, additives may be used, including LiBr, LiI, NaI and the like. For example, the alkylation can be performed using iodomethane and K_2CO_3 in acetone.

[0146] The residue is dissolved (*e.g.*, in $CHCl_3$), washed with water and brine, dried (*e.g.*, Na_2SO_4), filtered, and then concentrated *in vacuo*. The crude product is crystallized from, for example, THF-Hexanes to give the title compound. It will also be understood by those skilled in the art that the benzonitrile may be purified in a variety of organic solvents or solvent mixtures. For example, the benzonitrile can be purified by adding a mixture of dichloromethane and heptane. Optionally, the benzonitrile may be further purified in an organic solvent or mixture of solvents such as dichloromethane,

chloroform, acetonitrile, THF, ethyl acetate, isopropyl acetate and the like. In one particular embodiment, the product is purified and washed with ethyl acetate.

[0147] **Compound E5.** A 2-(6-Halo-3-alkyl-2,4-dioxo-3,4-dihydro-2-H-pyrimidin-1-ylmethyl)-benzonitrile (**C5**), a 3-substituted-piperidine dihydrochloride (**D1**) and sodium bicarbonate or K_2CO_3 are stirred in a sealed tube with an alcohol (*e.g.*, MeOH or EtOH) at a temperature between 80 and 110°C, and optionally between 90 and 100°C, for at least about 1h, and optionally at least about 2h. The mixture is optionally dried by stirring the reactants with activated molecular sieves (4A). The reaction is filtered (*e.g.*, through Celite), concentrated *in vacuo*, diluted with $CHCl_3$ or CH_2Cl_2, and then washed with water. The water phase is extracted with $CHCl_3$ or CH_2Cl_2, and the combined organic phases are washed with water, dried (*e.g.*, Na_2SO_4), and filtered. TFA is added and the solution is then concentrated *in vacuo*. The residue is dissolved in a small amount of alcohol (*e.g.*, MeOH), and Et_2O or hexanes is added to force precipitation. The mixture can then be allowed to stand at RT overnight. Solvents are then decanted, and the solid washed with Et_2O to give the TFA salt.

[0148] It will be understood by those skilled in the art that condensation with the amine or amine hydrochloride may be performed in a solvent or mixture of solvents with a base, such as potassium carbonate, sodium bicarbonate and the like, or mixtures thereof. The solvent may comprise both protic and aprotic solvents, or mixtures thereof. For example, the solvent may comprise a mixture of isopropyl alcohol and water.

[0149] The benzonitrile product may be isolated as the free base. The free base form can be isolated by washing the crude product with water, drying (*e.g.*, over Na_2SO_4 or $MgSO_4$), filtering and concentrating the product. The free base product can then be dissolved in THF. Alternatively, the free base could be dissolved in other solvents, such as dioxane, acetonitrile, ethyl acetate, dichloromethane, etc., or mixtures thereof. It will also be understood that the product may be purified using any of a variety of techniques known in the art, including by column chromatography and washing with an organic solvent or mixture of solvents. Non-limiting examples of solvent or solvent mixtures that can be used include isopropyl acetate, ethyl acetate, dichloromethane, heptane, and the like.

[0150] The free base product can also be prepared as follows. A mixture of Compound **C5**, an alcohol (*e.g.*, IPA), (R)-3-amino-piperidine dihydrochloride and a base (*e.g.*, potassium carbonate) is heated at a temperature between 55 and 65°C until completion (*e.g.*, for >20 hours) as determined, for example, by HPLC. An organic solvent or mixture of solvents such as dichloromethane, chloroform, acetonitrile, THF, ethyl acetate, isopropyl acetate and the like is then added. The resultant slurry is optionally filtered, washed and concentrated.

[0151] Alternatively, the benzonitrile product can be converted to a variety of acid addition salts. For example, the benzonitrile product (*e.g.*, about 10 mg) in an alcohol (*e.g.*, MeOH, 1 mL) is treated with various acids (*e.g.*, between 0.8 and 1.5 equivalents and optionally about 1.05 equivalents). The solutions are allowed to stand open to the air, optionally for at least about 2 days and optionally for at least about 3 days. If a precipitate forms, the mixture is filtered and the salt dried. If no solid forms, the mixture is concentrated *in vacuo* and the residue isolated. Using this approach, salts including, but not limited to, those produced from the following acids can be prepared: benzoic, p-toluenesulfonic, succinic, R-(-)-Mandelic and benzenesulfonic.

[0152] The benzoic acid salt can be formed by treating the benzonitrile product with benzoic acid using conventional methods for the formation of acid addition salts.

[0153] Likewise, the HCl salt can be obtained by suspending the TFA salt in DCM or $CHCl_3$, washing with saturated Na_2CO_3 or K_2CO_3, drying the organic layer *in vacuo*, dissolving the residue in a solvent (*e.g.*, acetonitrile), adding between 1 and 2 equivalents, and optionally between 1.2 and 1.8 equivalents, of HCl in an organic solvent (*e.g.*, dioxane) at a temperature between –5 and 5°C, and removing the solvent.

[0154] The HCl salt can also be prepared as follows. To a solution of free base in CH_2Cl_2 or $CHCl_3$ is added hydrochloric acid (*e.g.*, 2 M HCl). The slurry is optionally stirred, filtered and washed (*e.g.*, with CH_2Cl_2 or $CHCl_3$, and then THF). The material is then slurried in THF, filtered and optionally dried.

[0155] Further, the toluenesulfonate salt can be prepared as follows. A stock solution of free base (*e.g.*, 200μ of a 0.03M solution) is dissolved in dichoromethane and concentrated under a slow stream of nitrogen. The resulting free base is dissolved in a solvent (*e.g.*, 150μL of acetic acid, acetone, ethanol, THF or dicholormethane) and the

solution shaken for at least 5 minutes and optionally at least 10 minutes. The shaken solution is then charged with toluenesulfonic acid (about 1.05 equivalents; 50 μL of a 0.126M solution) in dioxane. The solution is shaken optionally for at least 2 hours and optionally at least 3 hours. The solvents are then removed under a stream of nitrogen to provide the toluenesulfonate salt.

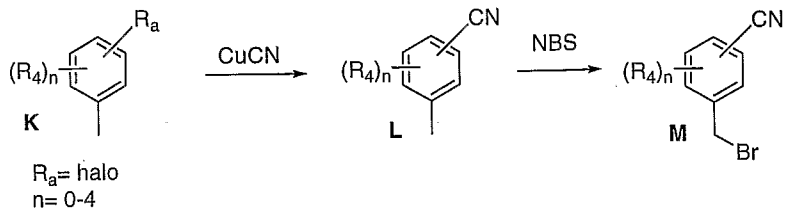
[0156] The toluenesulfonate salt can also be prepared by dissolving the free base (*e.g.*, about 2g) in about 10 volumes of acetonitrile. The solution is heated to a temperature between 65 and 85°C, and optionally between 70 and 80°C, for at least about 5 minutes and optionally at least about 10 minutes. Then, p-toluenesulfonic acid (*e.g.*, 1.05 equivalents) is added and the solution held at a temperature between 65 and 85°C, and optionally between 70 and 80°C, for at least about 5 minutes. The temperature is optionally ramped down (at about 25°C/hr) and the mixture stirred at room temperature overnight. The product can be dried in a vacuum oven at a temperature between 40 and 60°C, and optionally between 45 and 55°C, and pressure between 690 and 710 mm Hg, and optionally about 698.5 mm Hg, with a nitrogen sweep for at least about 15 hours and optionally at least about 18 hours.

[0157] In addition, the methanesulfonate salt can be prepared as follows. The benzonitrile product (*e.g.*, a 10.5g aliquot) is mixed with isopropylacetate (*e.g.*, 400 mL). The slurry is heated to a temperature between 60 and 90°C, optionally between 70 and 80°C, and optionally about 75°C, and filtered (*e.g.*, through #3 Whatman filter paper). The solution is reheated to a temperature between 60 and 90°C, optionally between 70 and 80°C, and optionally about 75°C, and methanesulfonic acid (*e.g.*, 30.84 mL of a 1M solution) is added. The suspension is cooled to room temperature, optionally at a rate of about 20°C/hr. After at least about 30 minutes and optionally at least about 1 hr at room temperature, the solid is filtered and dried to obtain the methanesulfonate salt.

[0158] The succinate salt can be prepared as follows. To a mixture of the HCl salt of Compound **E5** and CH_2Cl_2 or $CHCl_3$ is added a base (*e.g.*, a 50% NaOH solution) until the pH of the mixture is >11, and optionally >12. The mixture optionally is stirred and the organic layer separated. The aqueous layer is extracted (*e.g.*, with CH_2Cl_2 or $CHCl_3$) and the combined organic layers are washed with water. The organic layer optionally is filtered and concentrated to afford the free base. The free base is slurried (*e.g.*, in THF

and/or IPA) and heated (*e.g.*, at a temperature between 55 and 65°C) until complete dissolution of the free base is observed. A solution of succinic acid is added, optionally while maintaining the mixture temperature at >50°C. The material is optionally stirred, filtered, washed and dried.

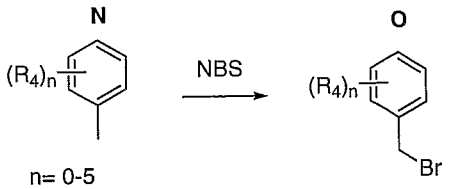
Scheme 4:



[0159] **Compound L.** A mixture of an optionally substituted halotoluene (**K**) and CuCN in DMF is refluxed, optionally for at least 24 hours. The reaction is diluted with water and extracted with an organic solvent (*e.g.*, hexane, ethylacetate, etc.). The organics are optionally dried (*e.g.*, over $MgSO_4$ or Na_2SO_4) and the solvent removed to give Compound **L**.

[0160] **Compound M.** A mixture of an optionally substituted methylbenzonitrile (**L**), N-bromosuccinimide (NBS) and azobisisobutylnitrile (AIBN) in CCl_4 is refluxed under nitrogen, optionally for at least 2 hours. The reaction is cooled to room temperature and the solid removed by filtration. The organic solution can be concentrated to give Compound **M**, which can be used in the next steps without further purification. Alternatively, the crude product can be purified using any of a variety of purification techniques known in the art, including washing with an aqueous/organic solvent or mixture of solvents, recrystallization and/or column chromatography.

Scheme 5:



[0161] **Compound O.** A mixture of an optionally substituted methylbenzene (**N**), N-bromosuccinimide (NBS) and azobisisobutylnitrile (AIBN) in CCl_4 is refluxed under

nitrogen, optionally for at least 2 hours. The reaction is cooled to room temperature and the solid removed by filtration. The organic solution can be concentrated to give compound **O**, which can be used in the next steps without further purification. Alternatively, the crude product can be purified using any of a variety of purification techniques known in the art, including washing with an aqueous/organic solvent or mixture of solvents, recrystallization and/or column chromatography.

[0162] In each of the above steps, the isolation and/or purification steps of the intermediate compounds may be avoided if the intermediates from the reaction mixture are obtained as relatively pure compounds and the by-products or impurities of the reaction mixture do not interfere with the subsequent reaction steps. Where feasible, one or more isolation steps may be eliminated to provide shorter processing times, and the elimination of further processing may also afford higher overall reaction yields.

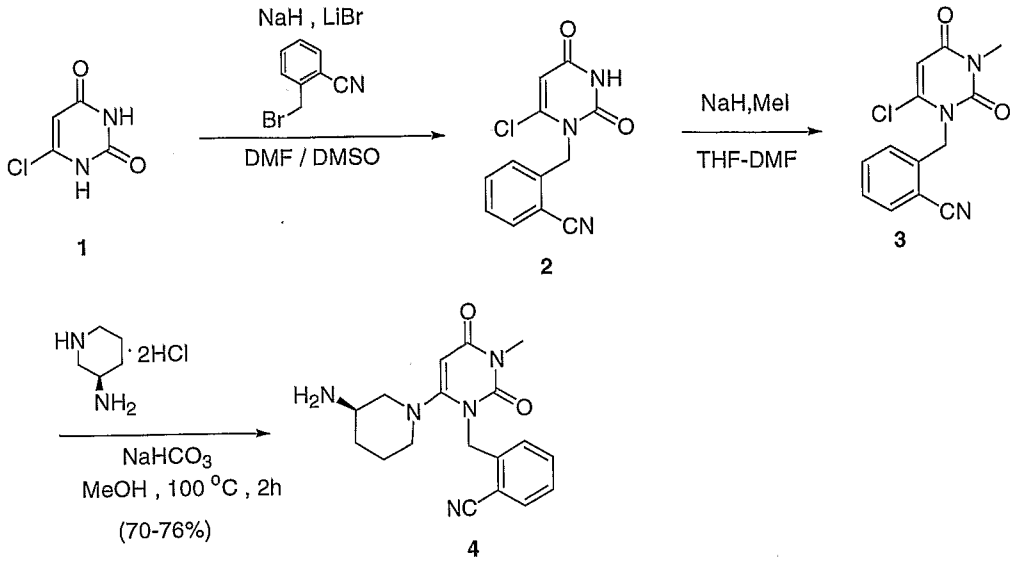
[0163] By varying the substituent groups in the above schemes, a wide variety of different DPP-IV inhibitors may be synthesized. In the above reaction scheme, the various substituents may be selected from among the various substituents otherwise taught herein.

[0164] Descriptions of the syntheses of particular compounds based on the above reaction schemes are set forth herein.

Examples Of DPP-IV Inhibitors

[0165] The present invention is further exemplified, but not limited by, the following examples that describe the synthesis of particular compounds.

Experimental Methods



[0166] 2-(6-Chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile (2). To a solution of 6-chlorouracil (20 g, 122 mmol) in a mixture of DMF-DMSO (6:1, 600 mL) under nitrogen at 0°C, was added sodium hydride (60%, 5.5 g, 137 mmol) in portions. After 0.5h, lithium bromide (8 g, 96 mmol) was added into the mixture and stirred for 15 min at 0°C. A solution of α-Bromo-*o*-tolunitrile (25.1 g, 128 mmol) in DMF (30 mL) was added dropwise, and stirred at this temperature for 1 h, and then RT overnight. The mixture was evaporated and co-evaporated with water *in vacuo* to remove most of the DMF, and then poured into ice water (1L). The precipitate was collected by filtration. The crude product was suspended in hot AcOEt-$CHCl_3$ and sonicated for 5 min, allowed to stand at 0°C for 1h, and then filtered to give a white solid of the title compound (19 g) in 54% yield. ^{1}H-NMR (400 MHz, DMSO): δ 11.82 (s, 1H), 7.87 (d, 1H, J = 7.6 Hz), 7.71 (t, 1H, J = 7.6 Hz), 7.51 (t, 1H, J = 7.6 Hz), 7.37 (d, 1H, J = 8 Hz), 6.06 (s, 1H), 5.31 (s, 2H). MS (ES) [m+H] calc'd for $C_{12}H_9ClN_3O_2$, 262.0; found 262.0.

[0167] 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-benzonitrile (3). To a cold (0°C) solution of benzylated 6-chlorouracil **2** (10 g, 38 mmol) in DMF-THF (1:1, 300 mL) under nitrogen, was added NaH (60%, 1.6 g, 39.9 mmol) in portions, followed by adding LiBr (2g). The mixture was stirred at RT for 20 min. After adding iodomethane (5.4 mL, 76 mmol), the flask was sealed and stirred at this temperature for 10 min, RT for 2h, and 35°C overnight, and then concentrated *in*

vacuo. The residue was dissolved in $CHCl_3$ and washed with water and brine, dried (Na_2SO_4), and filtered then concentrated *in vacuo*. The crude product was crystallized from THF-Hexanes to give 7.6 g (72%) of the title compound **3**. ^1H NMR (400 MHz, DMSO): δ 7.87 (d, 1H, J = 7.6 Hz), 7.70 (t, 1H, J = 7.6 Hz), 7.51 (t, 1H, J = 7.6 Hz), 7.40 (d, 1H, J = 8 Hz), 6.21 (s, 1H), 5.38 (s, 2H), 3.28 (s, 3H). MS (ES) [m+H] calc'd for $C_{13}H_{11}ClN_3O_2$, 276.1; found 276.1.

[0168] 2-{6-[3(R)-Amino-piperidin-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (4). 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2-H-pyrimidin-1-ylmethyl)-benzonitrile (330 mg, 1.08 mmol), (*R*)-3-amino-piperidine dihydrochloride (246 mg, 1.4 mmol) and sodium bicarbonate (500 mg, 5.4 mmol) were stirred with 200 mg activated molecular sieves (4A) in dry MeOH (5 mL) at 100°C for 2 h. The reaction was filtered through Celite, concentrated *in vacuo*, and then diluted with $CHCl_3$, and washed with water. The water phase was extracted with $CHCl_3$ and the combined organic phases were washed with water, dried (Na_2SO_4), and filtered. TFA (1mL) was added into the solution which was then concentrated *in vacuo*. The residue was dissolved in a small amount of MeOH, and Et_2O was added to force precipitation. The mixture was allowed to stand at RT overnight. Solvents were decanted, and the solid was washed with Et_2O two times to give 270 mg TFA salt of product **4** as an off-white powder. The TFA salt of **4** has ^1H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.82 (d, 1H, J = 7.6 Hz), 7.65 (t, 1H, J = 7.6 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.23 (d, 1H, J = 8.0 Hz), 5.42 (s, 1H), 5.50-5.00 (ABq, 2H, J = 41.6, 15.2 Hz), 3.30 (m, 2H), 3.16 (s, 3H), 2.91 (m, 1H), 2.76 (m, 2H), 1.93 (m, 1H), 1.79 (m, 1H), 1.51 (m, 2H). MS (ES) [m+H] calc'd for $C_{18}H_{22}N_5O_2$, 340.2; found, 340.2.

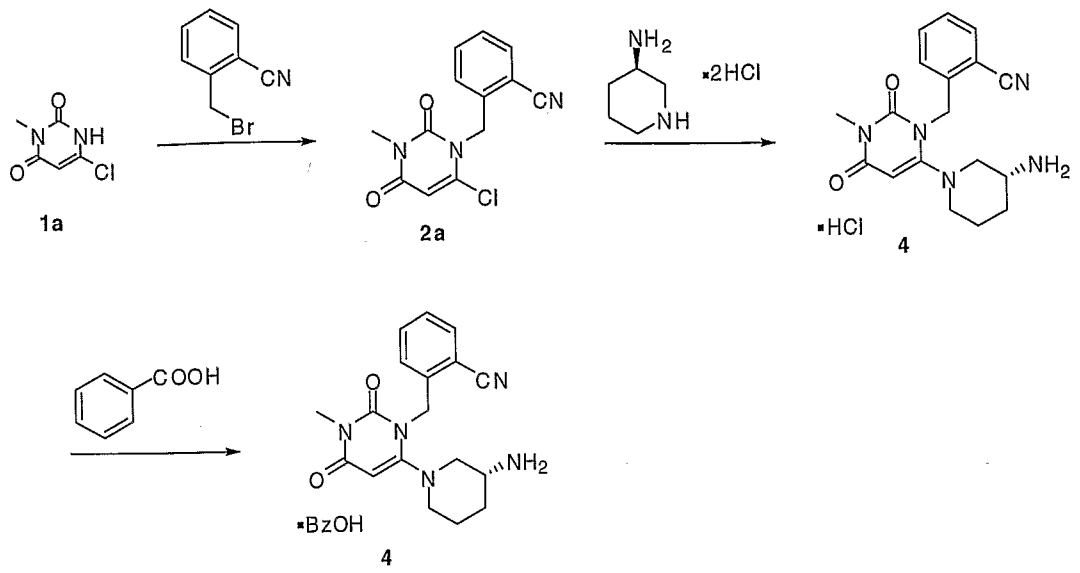
[0169] The benzoic acid salt was formed by treating the benzonitrile product with benzoic acid to form 2-[6-(3-amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile benzoate (**4**). Preparation and isolation of the benzoate salt was performed by conventional methods for the formation of acid addition salts. ^1H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.82 (d, 1H, J = 7.6 Hz), 7.65 (t, 1H, J = 7.6 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.23 (d, 1H, J = 8.0 Hz), 5.42 (s, 1H), 5.50-5.00 (ABq, 2H, J = 41.6, 15.2 Hz), 3.30 (m, 2H), 3.16 (s, 3H), 2.91 (m, 1H), 2.76 (m, 2H),

1.93 (m, 1H), 1.79 (m, 1H), 1.51 (m, 2H). MS (ES) [m+H] calc'd for $C_{18}H_{22}N_5O_2$, 340.2; found, 340.2.

[0170] Following the same procedure described above, the HCl addition salt was prepared as follows. A free base form of **4** was isolated after the crude product was washed with water, dried over Na_2SO_4, filtered and concentrated. The free base product was then dissolved in THF. The solution was then stirred and 1.2 equivalents of 4M HCl in dioxane was added dropwise. After 10 min stirring, the suspended mixture was allowed to stand at RT for 1h, and then filtered to give the solid HCl salt form of **4.** ^{1}H-NMR (400 MHz, DMSO-D6): δ 7.82 (d, 1H, J = 7.6 Hz), 7.65 (t, 1H, J = 7.6 Hz), 7.46 (t, 1H, J = 7.6 Hz), 7.23 (d, 1H, J = 8.0 Hz), 5.42 (s, 1H), 5.20, 5.08 (ABq, 2H, J = 41.6, 15.2 Hz), 3.30 (m, 2H), 3.16 (s, 3H), 2.91 (m, 1H), 2.76 (m, 2H), 2.50 (bs, 2 H), 1.93 (m, 1H), 1.79 (m, 1H), 1.51 (m, 2H). MS (ES) [m+H] calc'd for $C_{18}H_{22}N_5O_2$, 340.2; found, 340.2.

[0171] Further, the toluenesulfonate salt was prepared as follows. A 200μL aliquot of a 0.03M stock solution of free base was dissolved in dichoromethane and concentrated under a slow stream of nitrogen. The resulting free base was dissolved in 150 μL of solvent (*e.g.*, acetic acid, acetone, ethanol, THF or dicholormethane) and the solution shaken for 10 minutes. The shaken solution was then charged with 50 μL of a 0.126M solution of touenesulfonic acid (1.05 equivalents) in dioxane. The solution was shaken for 3 hours, followed by removal of the solvents under a stream of nitrogen to provide the toluenesulfonate salt.

[0172] The toluenesulfonate salt was also prepared by dissolving 2g of the free base in 10 volumes of acetonitrile and heating the solution to 75°C for 10 minutes. Then p-toluenesulfonic acid (1.05 equivalents) was added and the solution held at 75°C for 5 minutes. The temperature was ramped down (at about 25°C/hr) and stirred at room temperature overnight. The product (2.64 g) was dried in a vacuum oven at 50°C and 698.5 mm Hg with a nitrogen sweep for 18 hours.



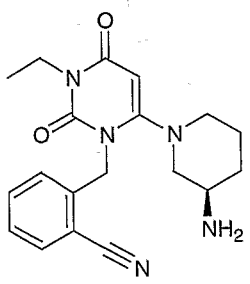
[0173] 2-((6-chloro-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)benzonitrile (2a). To a solution of 6-chloro-3-methyluracil (1 equiv., 1 wt.), N-methylpyrrolidone (NMP; 4 vol.) and diisopropylethylamine (Hünig's base, 1.5 equiv., 1.21 wt.), was added a solution of α-bromotoluoylnitrile (1.1 equiv., 1.35 wt.) and toluene (4 vol.). The mixture was heated at 60-70°C and agitated for 2-3 hrs, or until completion. The solution was then cooled to 20-30°C, quenched with deionized water (5 vol.) at less than 35°C, agitated for 30 min, cooled to 0-5°C, and then agitated for at least one hour. The resultant slurry was filtered, reslurried in isopropanol, displacement washed with isopropanol, and dried under vacuum at 55-60°C.

[0174] (R)-2-((6-(3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)benzonitrile (4). Compound 2a was reacted with 1.1 equivalents of (R)-3-aminopiperidine dihydrochloride in isopropanol and water at 60-65°C until completion (*e.g.*, 16 hrs). Potassium carbonate (4.4 equiv.) was added (over 1 – 1.5 hours) while maintaining the temperature between 60 and 65°C. After cooling to 40-45°C, the inorganic salts were removed by filtration and the filter cake was washed with heated (*e.g.*, 40-45°C) isopropanol. The filtrate was concentrated to approximately 5 volumes, diluted with THF at 0-5°C, and acidified with 6M hydrochloric acid while maintaining the temperature below 15°C. The resultant slurry was cooled to 0-5°C, agitated to allow crystals to grow (*e.g.*, 12 hrs or more), and then filtered. The filter cake

was displacement washed twice with isopropanol (2.5 vol. per wash) and dried to provide the HCl salt of compound 4 as a white crystalline solid.

[0175] The HCl salt of compound 4 was dissolved in water at 40-45°C and washed with isopropyl acetate to remove the dimer. The resulting mixture was heated to 50°C and free-based from the water layer into the organic layer by the addition of solid potassium carbonate, while maintaining the batch temperature at 50-55°C. The layers were separated and the aqueous layer was extracted once more at 50°C with isopropyl acetate. The organic layers were then combined and washed with 23% sodium chloride in water to remove residual potassium salts. The organic solution was concentrated under reduced pressure to approximately 4 volumes. 2B alcohol (4 vol.) was added and the solution was concentrated under reduced pressure until 4 volumes remained. Another 4 volumes of 2B alcohol was added and the solution was again concentrated under reduced pressure until 4 volumes remained. The resulting solution was clarified through a Niagara filter, followed by a 1.2 micron in-line filter, to remove precipitated sodium chloride and particulates. A hot (65-70°C) solution of benzoic acid in 2B ethanol was added while maintaining the solution at 65-70°C. The solution was then crystallized by cooling to 0-5°C and stirring for 12 hrs. The solution was filtered, followed by slurry and displacement washes with 2B alcohol. The wet cake was then conditioned under nitrogen for 2 hours. The cake was dried for 8 hrs at 40-50°C, to provide the benzoic acid salt of compound 4 as a white crystalline solid.

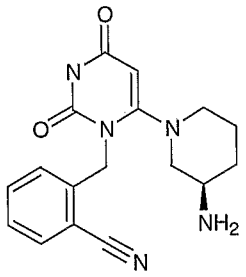
Compound 5



[0176] **2-{6-[3(R)-Amino-piperidin-1-yl]-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile TFA salt (5).** The title compound, 5, was prepared from compound 2 using the procedures described in the preparation of compounds 3 and 4, except that ethyl bromide was used in place of iodomethane. ^{1}H-NMR (400 MHz,

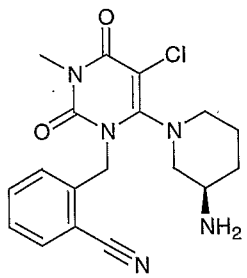
$CDCl_3$-CD_3OD 10:1): δ 7.66 (d, *J*=7.8 Hz, 1 H), 7.59 (td, *J*=7.8, 1.4 Hz, 1 H), 7.40 (t, *J*=7.6 Hz, 1 H), 7.26 (d, *J*=7.6 Hz, 1 H), 5.41 (s, 1 H), 5.13 - 5.23 (ABq, 2H, J = 41.6, 15.2 Hz), 3.91 (q, *J*=7.1 Hz, 2 H), 3.37 (m, 2 H), 2.87 - 2.98 (m, 2 H), 2.70 (m, 1 H), 2.12 (m, 1 H), 1.88 (m, 1 H), 1.67 (m, 2 H), 1.15 (t, *J*=6.9 Hz, 3 H). MS (ES) [m+H] calc'd for $C_{19}H_{24}N_5O_2$, 354.2; found, 354.2.

Compound 6



[0177] 2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (6). The title compound 6 was prepared from compound 2 by the procedure used in the preparation of compound 4. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.65 (d, *J*=7.5 Hz, 1 H), 7.58 (t, *J*=7.8 Hz, 1 H), 7.39 (t, *J*=7.5 Hz, 1 H), 7.27 (d, *J*=7.8 Hz, 1 H), 5.32 (s, 1 H), 5.13 - 5.13 (ABq, 2H, J = 30.0, 15.0 Hz), 3.39 (m, 2 H), 2.95 (m, 2 H), 2.69 (m, 1 H), 2.12 (m, 1 H), 1.85 (m, 1 H), 1.64 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{20}N_5O_2$, 326.2; found, 326.2.

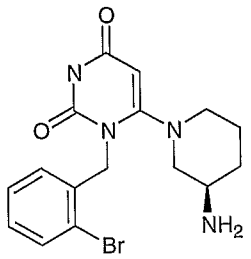
Compound 7



[0178] 2-{6-[3(R)-Amino-piperidin-1-yl]-5-chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (7). Compound 4 (40 mg, 0.1 mmol) in $CHCl_3$ (2 mL) was treated with $SOCl_2$ (200μL) at 100°C for 30 min, concentrated, and then purified by LC-MS to give the title compound **7**. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.73 (d, *J*=7.6 Hz, 1 H), 7.64 (t, *J*=7.6 Hz, 1 H), 7.45 (t, *J*=7.6 Hz, 1 H), 7.14 (d, *J*=8.1 Hz, 1 H), 5.32 - 5.42 (m, 2 H), 3.43 (s, 3 H), 3.33 - 3.40 (m, 2 H), 3.17 (m,

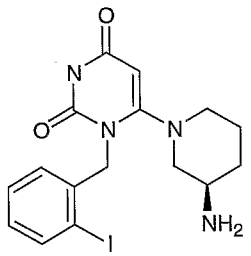
2 H), 2.87 (s, 1 H), 2.08 (m, 1 H), 1.70 (m, 1 H), 1.32 - 1.43 (m, 2 H). MS (ES) [m+H] calc'd for $C_{18}H_{21}ClN_5O_2$, 374.1; found, 374.1.

Compound 8



[0179] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-1H-pyrimidine-2,4-dione (8). The title compound was prepared in two steps. The first step was accomplished using the procedure for the preparation of compound 2, except that 2-bromobenzylbromide was used in the place of α-Bromo-*o*-tolunitrile. The crude product was then converted to the title compound by the method used in the preparation of compound 4. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.52 (d, *J*=8.1Hz, 1 H), 7.24 (t, *J*=7.8 Hz, 1 H), 7.10 (t, *J*=7.8 Hz, 1 H), 6.89 (d, *J*=7.579 Hz, 1 H), 5.27 (s, 1 H), 4.92 - 5.04 (ABq, *J* = 34.1, 15.0 Hz, 2H), 3.27 (bd, *J*=10.4Hz, 1 H), 3.09 - 3.18 (m, 1 H), 2.89 (m, 1 H), 2.70 (t, *J*=10.9Hz, 1 H), 2.48 (t, *J*=12.0 Hz, 1 H), 2.03 (m, 1 H), 1.60 - 1.71 (m, 1 H), 1.42 - 1.53 (m, 2 H). MS (ES) [m+H] calc'd for $C_{16}H_{20}BrN_4O_2$, 379.1; found, 379.1.

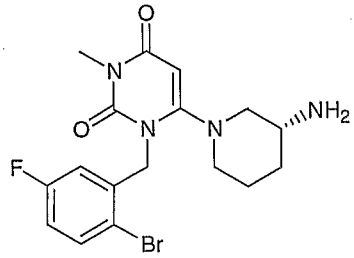
Compound 9



[0180] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-iodo-benzyl)-1H-pyrimidine-2,4-dione (9). The title compound was prepared by the procedure described in the preparation of compound 8, except that 2-iodobenzyl chloride was used as the benzylating reagent. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.76 (d, *J*=7.6Hz, 1 H), 7.21 (t, *J*=7.3 Hz, 1 H), 6.89 (t, *J*=7.2 Hz, 1 H), 6.79 (d, *J*=7.3 Hz, 1 H), 5.26 (s, 1H), 4.79 – 4.92 (ABq, *J* = 34.1, 6.7.0 Hz, 2H), 3.27 (m, 1 H), 3.13 (s, 1 H), 2.85 (d, *J*=11.6 Hz, 1 H), 2.70 (m, 1 H), 2.41

(m, 1 H), 2.02 (m, 1 H), 1.60 (m, 1 H), 1.45 (m, 2 H). MS (ES) [m+H] calc'd for $C_{16}H_{20}IN_4O_2$, 427.1; found, 427.1.

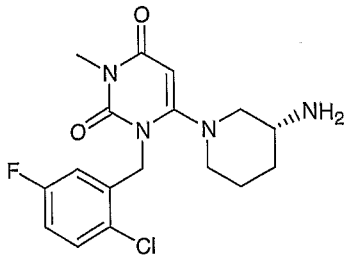
Compound 10



[0181] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (10). To a solution of 6-chlorouracil (220 mg, 1.5 mmol) in a mixture of dry DMF-DMSO (6:1, 5 mL) under nitrogen at 0°C, was added sodium hydride (60%, 61 mg, 1.8 mmol) in portions. After 0.5h, lithium bromide (83 mg, 1 mmol) was added and the mixture was stirred for 15 min at 0°C. A solution of 2-bromo-5-fluoro-benzyl bromide (497 mg, 1.8 mmol) in DMF (30 mL) was added dropwise, and stirred at this temperature for 1 h, and then RT overnight. The mixture was evaporated and co-evaporated with water *in vacuo* to remove most of the DMF, and then poured into ice-water. The precipitate was collected by filtration, and then suspended in cold MeOH and filtered. The solution was concentrated to give the crude monobenzylated product.

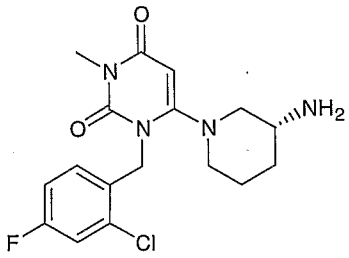
[0182] The crude product was treated with NaH and MeI using the procedure described in the preparation of compound 3, followed by the procedure used in the preparation of compound 4 to give the title compound. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.46 (dd, *J*=8.7, 5.2 Hz, 1 H), 6.82 (td, *J*=8.3, 2.9Hz, 1 H), 6.59 (dd, *J*=9.1, 3.0 Hz, 1 H), 5.28 (s, 1H), 4.99 - 5.06 (ABq, *J* = 41.7, 16.7 Hz, 2H), 3.28 (m, 1H), 3.23 (s, 3 H), 3.13 - 3.21 (m, 1 H), 2.86 (bd, *J*=12.6 Hz, 1 H), 2.71 (t, *J*=10.5 Hz, 1 H), 2.47 (t, *J*=11.0 Hz, 1 H), 2.00 - 2.08 (m, 1 H), 1.65 - 1.74 (m, 1 H), 1.42 - 1.53 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{21}BrFN_4O_2$, 411.1; found, 411.1.

Compound 11



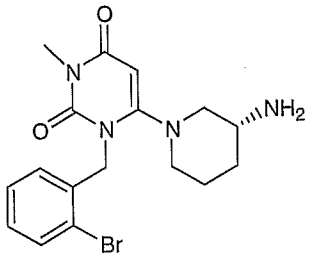
[0183] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-5-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (11). The title compound was prepared from compound 1 using the same procedures as the preparation of compound 10, except that 2-chloro-5-fluoro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.34 - 7.40 (dd, *J*=8.5, 5.1 Hz, 1 H), 6.97 (td, *J*=8.3, 2.9 Hz, 1 H), 6.72 (dd, *J*=9.0, 2.9 Hz, 1 H), 5.41 (s, 1 H), 5.11 - 5.19 (ABq, *J* = 41.7, 16.7 Hz, 2H), 3.37 (s, 1 H), 3.32 (s, 3H), 3.23 - 3.30 (m, 1 H), 2.96 (d, *J*=12.1 Hz, 1 H), 2.81 (t, *J*=10.2 Hz, 1 H), 2.59 (t, *J*=11.1 Hz, 1 H), 2.13 (d, *J*=10.4 Hz, 1 H), 1.76 - 1.86 (m, 1 H), 1.52 - 1.63 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{21}ClFN_4O_2$, 367.1; found 367.1.

Compound 12



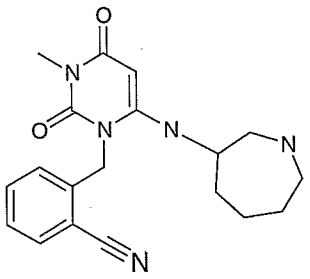
[0184] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-4-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (12). The title compound was prepared from compound 1 using the same procedures as described the preparation of compound 10, except that 2-chloro-4-fluoro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.15 (dd, *J*=8.211, 2.400 Hz, 1 H), 6.95 - 7.06 (m, 2 H), 5.40 (s, 1 H), 5.09 - 5.18 (ABq, *J* = 37.7, 15.9 Hz, 2H), 3.33 - 3.39 (m, 1 H), 3.30 (s, 3 H), 3.23 - 3.29 (m, 1 H), 2.98 (bd, *J*=12.9 Hz, 1 H), 2.79 (t, *J*=10.4 Hz, 1 H), 2.55 - 2.66 (t, *J*=11.2 Hz, 1 H), 2.13 (m, 1 H), 1.78 - 1.88 (m, 1 H), 1.55 - 1.65 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{21}ClFN_4O_2$, 367.1; found 367.1.

Compound 13

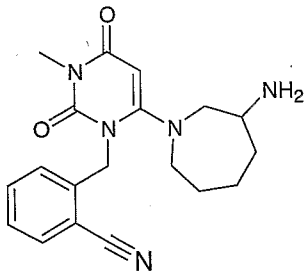


[0185] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-bromo-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (13). The title compound was prepared from compound 1 using the procedures described in the synthesis of compound 10, except that 2-bromo benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ 7.45 (d, *J*=7.8 Hz, 1 H), 7.16 (t, *J*=7.5 Hz, 1 H), 7.03 (t, *J*=7.2 Hz, 1 H), 6.80 (d, *J*=7.3 Hz, 1 H), 5.28 (s, 1 H), 4.93 - 5.05 (ABq, 2H, J = 36.4, 16.4 Hz), 3.22 (m, 1H), 3.19 (m, 3 H), 3.09 (m, 1 H), 2.84 (d, *J*=12.6 Hz, 1 H), 2.63 (t, *J*=10.5 Hz, 1 H), 2.42 (t, *J*=10.9 Hz, 1 H), 1.97 (d, *J*=11.1 Hz, 1 H), 1.58 - 1.69 (m, 1 H), 1.38 - 1.48 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{22}BrN_4O_2$, 393.1; found, 393.1.

Compound 14



Compound 15



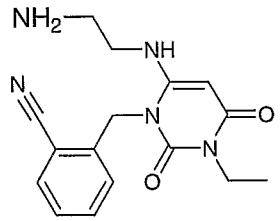
[0186] 2-{6-[Azepan-3(±)-ylamino]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (14) and 2-{6-[3(±)-Amino-azepan-1-yl]-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (15). Title compounds 14 and 15 were prepared from compound 3 (70 mg, 0.27 mmol) and azepan-3-ylamine (70 mg, 0.61 mg) using the procedure for the preparation of compound 4. Both compounds were purified by LC-MS.

[0187] Compound 14: ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.77 (d, *J*=7.8 Hz, 1 H), 7.66 (t, *J*=7.6 Hz, 1 H), 7.47 (t, *J*=8.0 Hz, 1 H), 7.36 (d, *J*=8.1 Hz, 1 H), 5.54 (s, 1 H), 5.49 (s, 1 H), 5.27 - 5.36 (ABq, *J* = 26.0, 16.4 Hz, 2H), 3.50 (m, 2 H), 3.37 (s, 2

H), 3.26 (s, 3 H), 3.12 (m, 1H), 3.04 (m, 1H), 2.07 (m, 1H), 1.86 (m, 1H), 1.60 - 1.71 (m, 3H). MS (ES) [m+H] calc'd for $C_{19}H_{24}N_5O_2$, 354.2; found, 354.2.

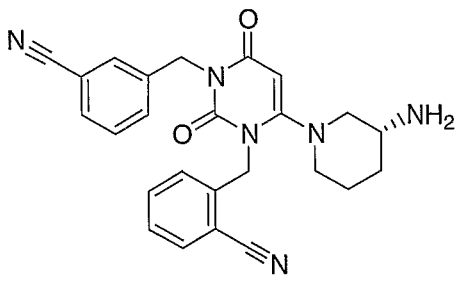
[0188] **Compound 15**: ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.77 (d, *J*=8.1 Hz, 1 H), 7.63 (t, *J*=7.6 Hz, 1 H), 7.46 (t, *J*=8.0 Hz, 1 H), 7.19 (d, *J*=7.6 Hz, 1 H), 5.48 (s, 1H), 5.44 - 5.52 (ABq, *J* = 61.9, 18.4 Hz, 2H), 3.80 (s, 1 H), 3.58-3.50 (m, 1 H), 3.39-3.39 (m, 1 H), 3.26 (s, 3 H), 3.13 (m, 1 H), 2.89 (t, *J* =12.4 Hz, 1 H), 2.04 (m, 1 H), 1.93 (m, 1 H), 1.86 (m, 2 H), 1.59 - 1.70 (m, 2 H). MS (ES) [m+H] calc'd for $C_{19}H_{24}N_5O_2$, 354.2; found, 354.2.

Compound 16



[0189] **2-[6-(2-Amino-ethylamino)-3-ethyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (16).** Compound 2 (150 mg, 0.57 mmol) in THF–DMSO (6:1, 4mL) was treated with 60% NaH (26 mg, 0.65 mmol), followed by adding ethyl bromide (300uL). In a sealed tube, ~20% crude product in dry MeOH (3 mL) was treated with $NaHCO_3$ and ethane-1,2-diamine (200μL) at 120°C for 2h, and purified by LC-MS to give the title compound 16. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.70 (d, *J*=7.8 Hz, 1 H), 7.58 (t, *J*=7.7 Hz, 1 H), 7.40 (t, *J*=7.4 Hz, 1 H), 7.12 (d, *J*=8.1 Hz, 1 H), 5.37 (s, 2 H), 3.95 (q, *J*=6.8 Hz, 2 H), 3.45 (t, *J*=5.9 Hz, 2 H), 3.11 (t, *J*=6.1 Hz, 2 H), 1.19 (t, *J*=6.8 Hz, 3 H). MS (ES) [m+H] calc'd for $C_{16}H_{20}N_5O_2$, 314.2; found 314.2.

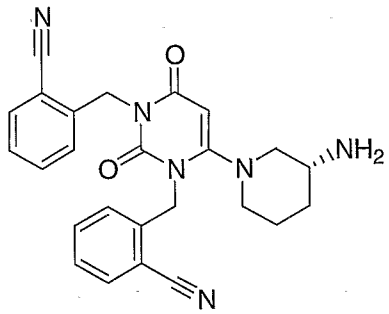
Compound 17



[0190] **2-{6-[3(R)-Amino-piperidin-1-yl]-3-(3-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (17).** Compound 2 (65 mg, 0.25

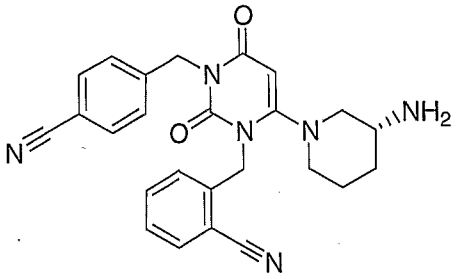
mmol) in DME-DMF (2:1, 2.5 mL) was treated with 60% NaH (15 mg, 0.38 mmol) at 0°C for 20 min, and then LiBr (25 mg) was added. 10 min later, *m*-cyano-benzyl bromide (55mg, 0.28 mg) was added, and the mixture was stirred at RT for 5h, and concentrated. The crude residue was dissolved in MeOH (3 mL). (*R*)-3-Amino-piperidine dihydrochloride (52 mg, 0.3 mmol) and sodium bicarbonate (100 mg) were added. The mixture was heated in a sealed tube at 120°C for 2h, and then filtered and concentrated. LC-MS purification gave the title compound 17 in 84% yield. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.67 (d, *J*=7.8 Hz, 1 H), 7.52 - 7.62 (m, 4 H), 7.35 - 7.46 (m, 2 H), 7.27 (d, *J*=7.8 Hz, 1 H), 5.43 (s, 1 H), 5.15 - 5.31 (ABq, *J*=40.9, 13.7 Hz, 2 H), 5.04 (s, 2 H), 3.40 (s, 1 H), 3.40 (m 1 H), 3.03 (m,1 H), 2.91 (m, 1 H), 2.76 (s, 1 H), 2.13 (s, 1 H), 1.92 (m, 1 H), 1.63 - 1.74 (m, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{25}N_6O_2$, 441.2; found 441.2.

Compound 18



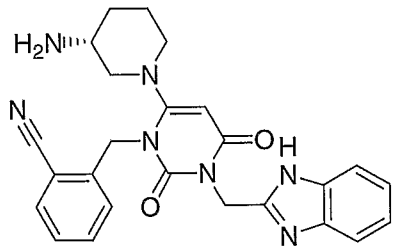
[0191] 2-{6-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (18). Title compound 18 was prepared by the methods used in the preparation of compound 17, except that α-bromo-*o*-tolunitrile was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.64 (d, *J*=6.8Hz, 1H), 7.60 (d, *J*=7.8Hz, 1H), 7.55 (t, *J*=7.8Hz, 2 H), 7.44 (t, *J*=7.6Hz, 1 H), 7.38 (t, *J*=7.5 Hz, 1 H), 7.31 (t, *J*=7.6Hz, 1H), 7.27 (d, *J*=7.8 Hz, 1H), 7.12 (d, *J*=7.8 Hz, 1 H), 5.45 (s, 1 H), 5.15 - 5.32 (m, 4 H), 3.36 - 3.47 (m, 2 H), 2.98 (m, 2 H), 2.10 (m, 1 H), 1.91 (m, 1 H), 1.68 (m, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{25}N_6O_2$, 441.2; found 441.2.

Compound 19



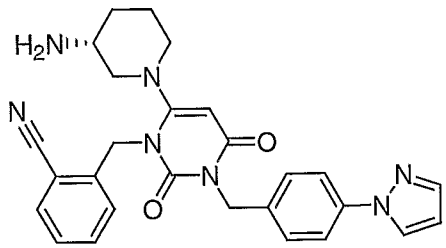
[0192] 2-{6-[3(R)-Amino-piperidin-1-yl]-3-(4-cyano-benzyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (19). Title compound 19 was prepared by the methods used in the preparation of compound 17, except that *p*-cyano-benzyl bromide was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.70 (d, *J*=7.8 Hz, 1 H), 7.56 - 7.63 (m, 3 H), 7.46 (m, 3 H), 7.29 (d, *J*=7.8 Hz, 1 H), 5.47 (s, 1 H), 5.16 - 5.36 (ABq, *J*= 51.1, 14.7 Hz, 2 H), 5.11 (s, 2 H), 3.36 - 3.47 (m, 2 H), 2.90-3.07 (m, 2 H), 2.79 (s, 1 H), 2.15 (s, 1 H), 1.95 (s, 1 H), 1.73 (s, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{25}N_6O_2$, 441.2; found 441.2.

Compound 20



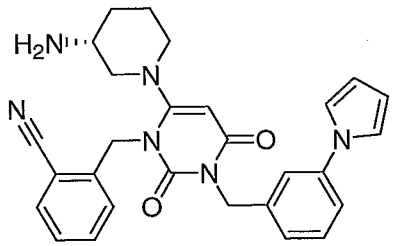
[0193] 2-[6-(3-Amino-piperidin-1-yl)-3-(1H-benzoimidazol-2-ylmethyl)-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile (20). Title compound 20 was prepared by the methods used in the preparation of compound 17, except that 2-chloromethyl benzimidazole was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.67(d, *J*=3.0Hz, 1H), 7.65-7.56(m, 2 H), 7.47 (d, *J*=3.3 Hz, 2 H), 7.46 (d, *J*=3.3 Hz, 1 H), 7.37-7.40 (m, 2 H), 5.52 (s, 3 H), 5.23 (s, 2 H), 3.51 (d, *J*=9.6 Hz, 1 H), 3.36 (m, 1 H), 2.87 - 2.92 (m, 2 H), 2.64 - 2.72 (m, 1 H), 2.09 (m, 1 H), 1.76 (m, 1 H), 1.52-1.64 (m, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{26}N_7O_2$, 456.2; found 456.2.

Compound 21



[0194] 2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(4-pyrazol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (21). Title compound 21 was prepared by the methods used in the preparation of compound 17, except that 1-(4-bromomethyl-phenyl)-1H-pyrazole was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.90 (d, *J*=2.5 Hz, 1 H), 7.71 (d, *J*=1.8 Hz, 1 H), 7.65 (d, *J*=7.6 Hz, 1 H), 7.51 - 7.58 (m, 3 H), 7.43-7.37(m, 3 H), 7.22 (d, *J*=7.8 Hz, 1 H), 6.47 (t, *J*=2.1 Hz, 1 H), 5.43 (s, 1H), 5.14 - 5.30 (ABq, *J*=41.2, 16.4 Hz, 2 H), 5.05 (s, 2 H), 3.32-3.40 (m, 2H), 2.96 (m,1 H), 2.89 (m, 1 H), 2.70 (m, 1 H), 2.10 (m, 1 H), 1.88 (m, 1 H), 1.66 (s, 2 H). MS (ES) [m+H] calc'd for $C_{27}H_{28}N_7O_2$, 482.2; found 482.2.

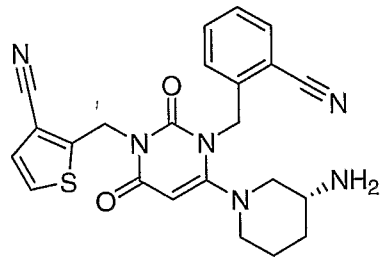
Compound 22



[0195] 2-{6-[3(R)-Amino-piperidin-1-yl]-2,4-dioxo-3-(3-pyrrol-1-yl-benzyl)-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (22). Title compound 22 was prepared by the methods used in the preparation of compound 17, except that 1-(3-bromomethyl-phenyl)-1H-pyrrole was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.59 (d, *J*=7.3 Hz, 1 H), 7.48 (t, *J*=7.7 Hz, 1 H), 7.24 - 7.36 (m, 4 H), 7.21 (t, *J*=7.6 Hz, 2 H), 7.02 (t, *J* = 2.1 Hz, 2 H), 6.32 (t, *J* = 2.0 Hz, 2 H), 5.42 (s, 1H), 5.11 - 5.20 (ABq, *J*= 44.7, 15.9 Hz, 2 H), 5.06 (s, 2 H), 3.36 (m, 2 H),

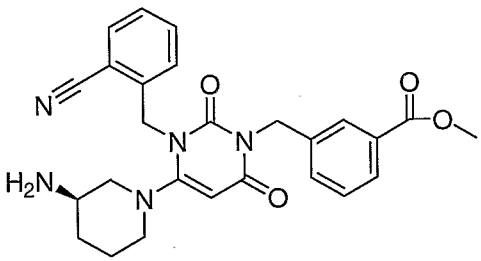
2.98 (m, 1 H), 2.89 (m, 1 H), 2.70 (m, 1 H), 2.10 (m, 1 H), 1.88 (m, 1 H), 1.73-1.58 (m, 2 H). MS (ES) [m+H] calc'd for $C_{28}H_{29}N_6O_2$, 481.2; found 481.2.

Compound 23



[0196] 6-[3 (R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl]-thiophene-3-carbonitrile (23). Title compound 23 was prepared by the methods used in the preparation of compound 17, except that 2-bromomethyl-thiophene-3-carbonitrile was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.65 (d, *J*=7.6 Hz, 1 H), 7.57 (t, *J*=7.8 Hz, 1 H), 7.40 (t, *J*=7.7 Hz, 1 H), 7.29 (d, *J*=7.8 Hz, 1 H), 7.25 (dd, *J*=5.3, 1.3 Hz, 1 H), 7.11 (dd, *J*=5.3, 1.0 Hz, 1 H), 5.45 (s, 1 H), 5.35 (s, 2 H), 5.15 - 5.33 (ABq, *J*=45.0, 15.5 Hz, 2 H), 3.38 (bd, *J*=10.1 Hz, 2 H), 2.98 (m, 2 H), 2.72 (s, 1 H), 2.12 (d, *J*=7.3 Hz, 1 H), 1.83 - 1.93 (m, 1 H), 1.61 - 1.72 (m, 2 H). MS (ES) [m+H] calc'd for $C_{23}H_{23}N_6O_4$, 447.1; found 447.1.

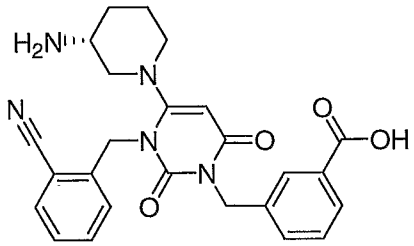
Compound 24



[0197] 3-{4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid methyl ester (24). Title compound 24 was prepared by the methods used in the preparation of compound 17, except that 3-bromomethyl-benzoic acid methyl ester was used in the place of *m*-cyano-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.99 (s, 1 H), 7.91 (d, *J*=7.8 Hz, 1 H), 7.65 (d, *J*=7.6 Hz, 1 H), 7.56 (d, *J*=7.9 Hz, 1 H), 7.52 (d, *J*=7.6 Hz, 1 H), 7.39 (t,

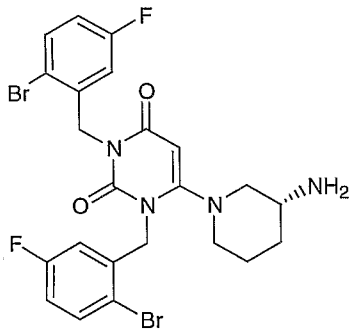
J=7.6 Hz, 1 H), 7.34 (t, *J*=7.6 Hz, 1 H), 7.23 (d, *J*=8.1 Hz, 1 H), 5.44 (s, 1 H), 5.12 - 5.31 (ABq, *J*=43.7, 15.9 Hz, 2 H), 5.08 (s, 2 H), 3.90 (s, 3 H), 3.31 - 3.39 (m, 2 H), 2.98 (d, *J*=11.9 Hz, 1 H), 2.87 (m, 1 H), 2.71 (m, 1 H), 2.11 (m, 1 H), 1.89 (m, 1 H), 1.73-1.59 (m, 2 H). MS (ES) [m+H] calc'd for $C_{26}H_{28}N_5O_4$, 474.2; found 474.2.

Compound 25



[0198] 3-{4-[3(R)-Amino-piperidin-1-yl]-3-(2-cyano-benzyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ylmethyl}-benzoic acid (25). A crude mixture of compound 24 (~50 mg) was treated with LiOH in THF-water (10:1) to give the title compound 25. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.90 (s, 1 H), 7.86 (d, *J*=7.6 Hz, 1 H), 7.60 (d, *J*=7.6 Hz, 1 H), 7.50 (t, *J*=8.2 Hz, 1 H), 7.45 (d, *J*=7.3 Hz, 1 H), 7.26 - 7.36 (m, 2H), 7.17 (d, *J*=8.1Hz, 1 H), 5.39 (s, 1 H), 5.10- 5.25 (ABq, *J*=36.9, 15.5 Hz, 2 H), 5.03 (s, 2 H), 3.31 (m,2H), 2.95 (m, 1 H), 2.81 (m, 1 H), 2.64 (m, 1 H), 2.07 (m, 1 H), 1.82 (m, 1 H), 1.51-1.68 (m, 2 H). MS (ES) [m+H] calc'd for $C_{25}H_{26}N_5O_4$, 460.2; found 460.2.

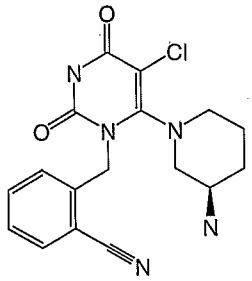
Compound 26



[0199] 6-[3 (R)-Amino-piperidin-1-yl]-1,3-bis-(2-bromo-5-fluoro-benzyl)-1H-pyrimidine-2,4-dione (26). The title compound was prepared from **1** by di-benzylation, using the procedure for the preparation of **2**, except that 2-bromo-5-fluoro-benzyl bromide was used in the place of *α*-bromo-*o*-tolunitrile, followed by treatment with 3-(R)-amino-piperidine under the conditions described in the preparation of compound 4. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ 7.42 (dd, *J*=8.6, 5.3 Hz, 2 H), 7.11 - 7.08

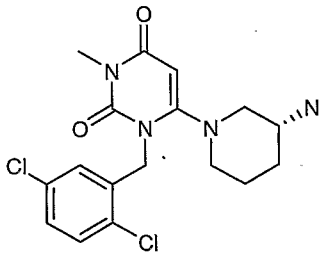
(dd, *J*=9.1, 2.2 Hz, 1 H), 7.06 (dd, *J*=9.3, 2.8 Hz, 1 H), 6.78 - 6.84 (m, 2 H), 5.71 (s, 1H), 5.29 (s, 4 H), 4.22 (d, *J*=11.1 Hz, 1 H), 3.82 (d, *J*=13.4 Hz, 1 H), 3.07 - 3.24 (m, 3 H), 2.06 (m, 1 H), 1.75 - 1.83 (m, 1 H), 1.63 - 1.72 (m, 1 H), 1.50 - 1.59 (m, 1 H). MS (ES) [m+H] calc'd for $C_{23}H_{23}Br_2F_2N_3O_2$, 583.01; found 583.01.

Compound 27



[0200] 2-{6-[3(R)-Amino-piperidin-1-yl]-5-chloro-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl}-benzonitrile (27). Compound 4 (100 mg) in THF (2 mL) was treated with 4M HCl in dioxane (1mL) at RT for 1 h, concentrated, and then purified by LC-MS to give the title compound. ^{1}H-NMR (400 MHz, DMSO-D6): δ ppm 12.0 (s, 1 H), 7.88 (d, *J*=7.6 Hz, 1 H), 7.68 (t, *J*=7.7 Hz, 1 H), 7.49 (t, *J*=7.7 Hz, 1 H), 7.36 (d, *J*=7.8 Hz, 1 H), 5.09 - 5.21 (m, 2 H), 3.17 (m, 2 H), 2.96 (t, *J*=11.1 Hz, 1 H), 2.86 (d, *J*=10.6 Hz, 1 H), 2.65 (m, 1 H), 1.90 (d, *J*=11.6 Hz, 1 H), 1.57 (d, *J*=13.1 Hz, 1 H), 1.19 - 1.31 (m, 1 H), 1.03 - 1.15 (m, 1 H). MS (ES) [m+H] calc'd for $C_{17}H_{19}ClN_5O_2$, 360.1; found, 360.1.

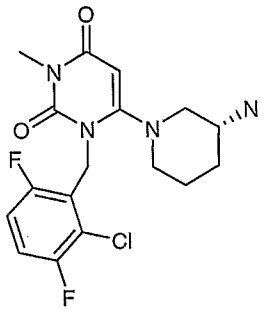
Compound 28



[0201] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2,5-*di*-chloro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (28). The title compound was prepared from compound 1 using the same procedures as in the preparation of compound 10, except that 2,5-di-chloro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. ^{1}H-NMR (400 MHz, $CDCl_3$-CD_3OD 10:1): δ ppm 7.50 (d, *J*=8.6 Hz, 1 H), 7.39 (dd, *J*=8.3, 2.526 Hz, 1 H), 7.22 (d, *J*=2.5 Hz, 1 H), 5.41 (s, 1 H), 5.01 – 4.93 (ABq, *J* = 41.9, 16.2 Hz,

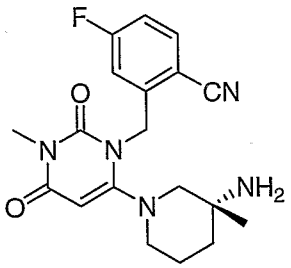
2H), 3.25 (m, 2 H), 3.10 (s, 3H), 2.85 (m, 1 H), 2.76 (m, 1 H), 2.67 (m, 1 H), 1.91 (m, 1 H), 1.75 (m, 1 H), 1.45 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{21}Cl_2N_4O_2$, 383.1; found 383.1.

Compound 29



[0202] 6-[3 (R)-Amino-piperidin-1-yl]-1-(2-chloro-3,6-*di*-fluoro-benzyl)-3-methyl-1H-pyrimidine-2,4-dione (29). The title compound was prepared from compound 1 using the same procedures as in the preparation of compound 10, except that 2-chloro-3,6-*di*-fluoro-benzyl bromide was used in the place of 2-bromo-5-fluoro-benzyl bromide. ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD 10:1) δ ppm 6.98 - 7.06 (m, 2 H), 6.90 (m, 2 H), 5.31 (s, 1 H), 5.01 – 5.20 (ABq, J = 24.2, 14.4 Hz, 2H), 3.28 - 3.37 (m, 2 H) 3.13 (s,3H), 3.01 - 2.94 (m, 1 H), 2.6-2.9 (m, 2 H), 2.10 (m, 1 H), 1.92 (m, 2 H), 1.73 (s, 1 H), 1.6-1.75 (m, 2 H). MS (ES) [m+H] calc'd for $C_{17}H_{20}ClF_2N_4O_2$, 385.1; found 385.1.

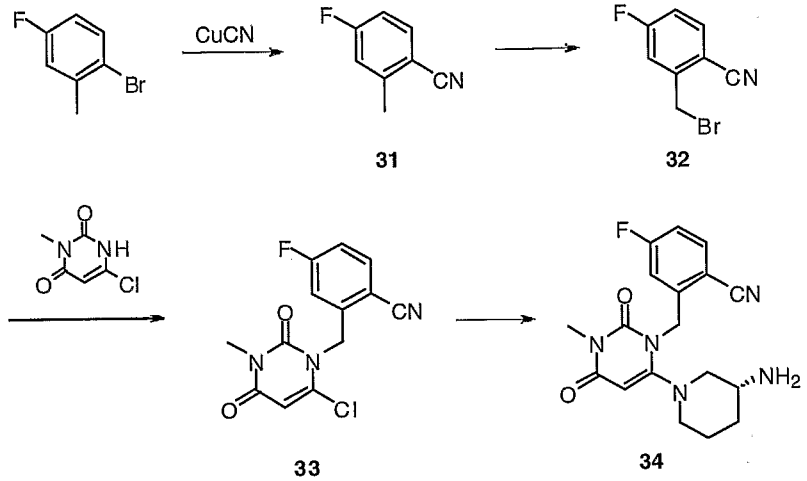
Compound 30



[0203] (R)-2-((6-(3-amino-3-methylpiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl)-4-fluorobenzonitrile (30). 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-4-fluoro-benzonitrile (300 mg, 1.0 mmol), (R)-3-amino-3-methyl-piperidine dihydrochloride (266 mg, 1.4 mmol) and sodium bicarbonate (500 mg, 5.4 mmol) were stirred in a sealed tube in EtOH (3 mL) at 100°C for 2 hrs. The final compound was obtained as TFA salt after HPLC purification. ^{1}H-NMR (400 MHz, CD3OD): δ. 7.78-7.83 (m, 1H), 7.14-7.26 (m, 2H), 5.47 (s, 1H),

5.12-5.36 (ABq, 2H, J = 105.2, 15.6 Hz), 3.21 (s, 1H), 2.72-3.15 (m, 4H), 1.75-1.95 (m, 4H), 1.39 (s, 3H). MS (ES) [m+H] calc'd for C19H22FN5O2, 372.41; found, 372.41.

Compound 34



[0204] **4-Fluoro-2-methylbenzonitrile (31).** A mixture of 2-bromo-5-fluorotoluene (3.5 g, 18.5 mmol) and CuCN (2 g, 22 mmol) in DMF (100 mL) was refluxed for 24 hours. The reaction was diluted with water and extracted with hexane. The organics were dried over $MgSO_4$ and the solvent removed to give product **31** (yield 60%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, J=5.6, 8.8 Hz, 1H), 6.93-7.06 (m, 2H), 2.55 (s, 3H).

[0205] **2-Bromomethyl-4-fluorobenzonitrile (32).** A mixture of 4-fluoro-2-methylbenzonitrile (2 g, 14.8 mmol), NBS (2.64 g, 15 mmol) and AIBN (100 mg) in CCl_4 was refluxed under nitrogen for 2 hours. The reaction was cooled to room temperature. The solid was removed by filtration. The organic solution was concentrated to give crude product as an oil, which was used in the next step without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, J= 5.2, 8.4 Hz, 1H), 7.28 (dd, J= 2.4, 8.8 Hz, 1H), 7.12 (m, 1H), 4.6 (s, 2H).

[0206] Alternatively, **32** was made as follows. 4-Fluoro-2-methylbenzonitrile (1 kg) in DCE (2 L) was treated with AIBN (122 g) and heated to 75°C. A suspension of DBH (353 g) in DCE (500 mL) was added at 75°C portionwise over 20 minutes. This operation was repeated 5 more times over 2.5 hours. The mixture was then stirred for one additional hour and optionally monitored for completion by, for example, measuring the amount of residual benzonitrile using HPLC. Additional AIBN (*e.g.*, 12.5 g) was

optionally added to move the reaction toward completion. Heating was stopped and the mixture was allowed to cool overnight. *N,N*-diisopropylethylamine (1.3 L) was added (at <10°C over 1.5 hours) and then diethyl phosphite (1.9 L) was added (at <20°C over 30 min). The mixture was then stirred for 30 minutes or until completion. The mixture was then washed with 1% sodium metabisulfite solution (5 L) and purified with water (5 L). The organic phase was concentrated under vacuum to afford **32** as a dark brown oil (3328 g), which was used without further purification (purity was 97% (AUC)).

[0207] 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-4-fluoro-benzonitrile (33). A mixture of crude 3-methyl-6-chlorouracil (0.6 g, 3.8 mmol), 2-bromomethyl-4-fluorobenzonitrile (0.86 g, 4 mmol) and K_2CO_3 (0.5 g, 4 mmol) in DMSO (10 mL) was stirred at 60°C for 2 hours. The reaction was diluted with water and extracted with EtOAc. The organics were dried over $MgSO_4$ and the solvent removed. The residue was purified by column chromatography. 0.66 g of the product was obtained (yield: 60%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, J=7.2, 8.4Hz, 1H), 7.26 (d, J-4.0Hz, 1H), 7.11-7.17 (m, 1H), 6.94 (dd, J=2.0, 9.0 Hz, 1H), 6.034 (s, 2H), 3.39 (s, 3H). MS (ES) [m+H] calc'd for $C_{13}H_9ClFN_3O_2$, 293.68; found 293.68.

[0208] Alternatively, **33** was made as follows. To a solution of 6-chloro-3-methyluracil (750 g) and *N,N*-diisopropylethylamine (998 mL) in NMP (3 L) was added (at <30°C over 25 min) a solution of **32** (2963 g crude material containing 1300 g of **32** in 3 L of toluene). The mixture was then heated at 60°C for 2 hours or until completion (as determined, for example, by HPLC). Heating was then stopped and the mixture was allowed to cool overnight. Purified water (3.8 L) was added, and the resultant slurry was stirred at ambient temperature for 1 hour and at <5°C for one hour. The mixture was then filtered under vacuum and the wet cake was washed with IPA (2 X 2.25 L). The material was then dried in a vacuum oven at 40±5°C for 16 or more hours to afford **33** as a tan solid (>85% yield; purity was >99% (AUC)).

[0209] 2-[6-(3-Amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-4-fluoro-benzonitrile (34). 2-(6-Chloro-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl)-4-fluoro-benzonitrile (300 mg, 1.0 mmol), (*R*)-3-amino-piperidine dihydrochloride (266 mg, 1.5 mmol) and sodium bicarbonate (500 mg, 5.4 mmol) were stirred in a sealed tube in EtOH (3 mL) at 100°C for 2 hrs. The final

compound was obtained as TFA salt after HPLC purification. ^{1}H-NMR (400 MHz, CD_3OD): δ. 7.77-7.84 (m, 1H), 7.16-7.27 (m, 2H), 5.46 (s, 1H), 5.17-5.34 (ABq, 2H, J = 35.2, 15.6 Hz), 3.33-3.47 (m, 2H), 3.22 (s, 3H), 2.98-3.08 (m, 1H), 2.67-2.92 (m, 2H), 2.07-2.17 (m, 1H), 1.82-1.92 (m, 1H), 1.51-1.79 (m, 2H). MS (ES) [m+H] calc'd for $C_{18}H_{20}FN_5O_2$, 357.38; found, 357.38.

[0210] Alternatively, the free base of **34** was prepared as follows. A mixture of **33** (1212 g), IPA (10.8 L), (R)-3-amino-piperidine dihydrochloride (785 g), purified water (78 mL) and potassium carbonate (2.5 kg, powder, 325 mesh) was heated at 60°C until completion (*e.g.*, for >20 hours) as determined, for example, by HPLC. Acetonitrile (3.6 L) was then added at 60°C and the mixture was allowed to cool to <25°C. The resultant slurry was filtered under vacuum and the filter cake was washed with acetonitrile (2 X 3.6 L). The filtrate was concentrated at 45°C under vacuum (for >3 hours) to afford 2.6 kg of the free base of **34**.

[0211] The HCl salt of **34** was prepared from the TFA salt as follows. The TFA salt (**34**) was suspended in DCM, and then washed with saturated Na_2CO_3. The organic layer was dried and removed in vacuo. The residue was dissolved in acetonitrile and HCl in dioxane (1.5 eq.) was added at 0°C. The HCl salt was obtained after removing the solvent. ^{1}H-NMR (400 MHz, CD_3OD): δ. 7.77-7.84 (m, 1H), 7.12-7.26 (m, 2H), 5.47 (s, 1H), 5.21-5.32 (ABq, 2H, J = 32.0, 16.0 Hz), 3.35-3.5 (m, 2H), 3.22 (s, 3H), 3.01-3.1 (m, 1H), 2.69-2.93 (m, 2H), 2.07-2.17 (m, 1H), 1.83-1.93 (m, 1H), 1.55-1.80 (m, 2H). MS (ES) [m+H] calc'd for $C_{18}H_{20}FN_5O_2$, 357.38; found, 357.38.

[0212] Alternatively, the HCl salt was prepared from the free base as follows. To a solution of free base in CH_2Cl_2 (12 L) was added (at <35°C over 18 minutes) 2 M hydrochloric acid (3.1 L). The slurry was stirred for 1 hour and then filtered. The wet cake was washed with CH_2Cl_2 (3.6 L) and then THF (4.8 L). The wet cake was then slurried in THF (4.8 L) for one hour and then filtered. The filter cake was again washed with THF (4.8 L). The material was then dried in a vacuum oven at 50°C (with a nitrogen bleed) until a constant weight (*e.g.*, >26 hours) to afford **34** as the HCl salt as a white solid (1423 g, >85% yield).

[0213] The succinate salt of **34** was prepared from the HCl salt as follows. To a mixture of the HCl salt of **34** (1414 g), CH_2Cl_2 (7 L) and purifed water (14 L) was added

50% NaOH solution (212 mL) until the pH of the mixture was >12. The biphasic mixture was stirred for 30 min and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (5.7 L) and the combined organic layers were washed with purified water (6 L). The organic layer was then passed through an in-line filter and concentrated under vacuum at 30°C over three hours to afford the free base as an off-white solid. The free base was slurried in prefiltered THF (15 L) and prefiltered IPA (5.5 L). The mixture was then heated at 60°C until complete dissolution of the free base was observed. A prefiltered solution of succinic acid (446 g) in THF (7 L) was added (over 23 min) while maintaining the mixture temperature at >57°C. After stirring at 60°C for 15 min, the heat was turned off, the material was allowed to cool, and the slurry was stirred for 12 hours at 25±5°C. The material was filtered under vacuum and the wet cake was washed with prefiltered IPA (2 X 4.2 L). The material was then dried in a vacuum oven at 70±5°C (with a nitrogen bleed) for >80 hours to afford the succinate salt of **34** as a white solid (1546 g, >90% yield).

[0214] The product was also converted to a variety of corresponding acid addition salts. Specifically, the benzonitrile product (approximately 10 mg) in a solution of MeOH (1 mL) was treated with various acids (1.05 equivalents). The solutions were allowed to stand for three days open to the air. If a precipitate formed, the mixture was filtered and the salt dried. If no solid formed, the mixture was concentrated in vacuo and the residue isolated. In this way, salts of **34** were prepared from the following acids: benzoic, p-toluenesulfonic, succinic, R-(-)-Mandelic and benzenesulfonic. The succinate was found to be crystalline as determined by x-ray powder diffraction analysis.

[0215] In addition, the methanesulfonate salt was prepared as follows. A 10.5 g aliquot of the benzonitrile product was mixed with 400 mL of isopropylacetate. The slurry was heated to 75°C and filtered through #3 Whatman filter paper. The solution was heated back to 75°C and a 1M solution of methanesulfonic acid (30.84 mL) was added slowly over 10 minutes while stirring. The suspension was cooled to room temperature at a rate of about 20°C/hr. After 1 hr at room temperature, the solid was filtered and dried in an oven overnight to obtain the methanesulfonate salt.

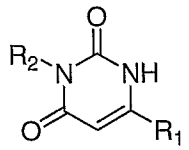
[0216] It will be apparent to those skilled in the art that various modifications and variations can be made to the methods of the present invention without departing from

the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

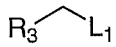
What is claimed is:

1. A process comprising:

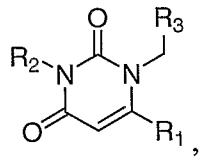
reacting a compound comprising the formula



with a compound comprising the formula



under conditions that form a reaction product comprising the formula



wherein

R_1 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted,

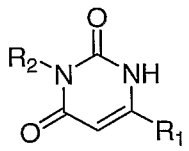
R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted,

R_3 is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and

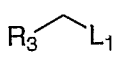
L_1 is a leaving group.

2. A process comprising:

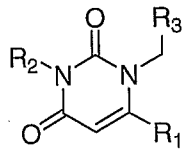
reacting a compound comprising the formula



with a compound comprising the formula



in dimethylsulfoxide in the presence of K_2CO_3 under conditions that form a reaction product comprising the formula



wherein

R_1 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted,

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted,

R_3 is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy,

heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and

L_1 is a leaving group.

3. The process of claim 2, wherein reacting is performed at a temperature between 45°C and 75°C.

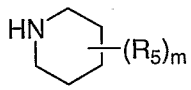
4. The process of claim 2, wherein reacting is performed for at least 1 hr.

5. The process of any one of claims 1 and 2, further comprising extracting the reaction product using ethyl acetate.

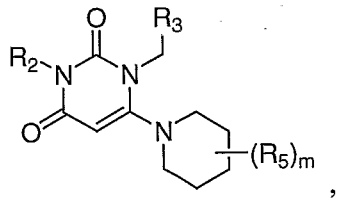
6. The process of any one of claims 1 and 2, further comprising purifying the reaction product.

7. The process of claim 6, wherein purifying the reaction product is performed by column chromatography.

8. The process of any one of claims 1-7, wherein R_1 is a leaving group and further comprising reacting the reaction product with a piperidine comprising the formula



under conditions that form a second reaction product comprising the formula



,

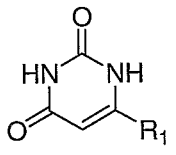
wherein

m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, and

each R_5 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

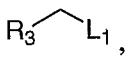
9. A process comprising:

forming a mixture of sodium hydride and lithium bromide with a compound comprising the formula



, and

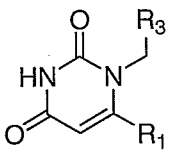
adding to the mixture a compound comprising the formula



,

wherein

the process is performed under conditions that form a reaction product comprising the formula



,

R_1 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted,

R_3 is selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, alkenyl, alkynyl, carbonyl group, cyano, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and

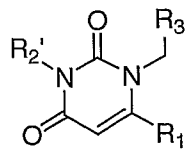
L_1 is a leaving group.

10. The process of claim 9, wherein at least a portion of the process is conducted at a temperature between -5°C and 5°C.

11. The process of claim 9, further comprising reacting the reaction product with a compound comprising the formula

$$R_2'—X$$

to form a second reaction product of the formula

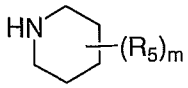


wherein

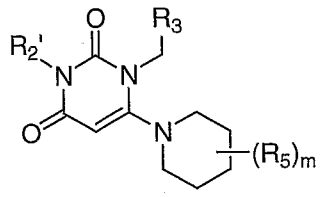
R_2' is a substituted or unsubstituted (C_{1-10})alkyl, and

X is a halide.

12. The process of claim 11, wherein R_1 is a leaving group and further comprising reacting the second reaction product with a piperidine comprising the formula



under conditions that form a compound comprising the formula



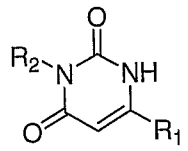
wherein

m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and

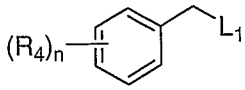
each R_5 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

13. A process comprising:

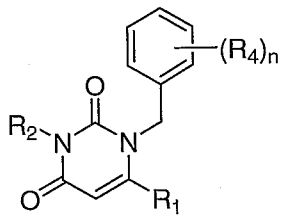
reacting a compound comprising the formula



with a compound comprising the formula



under conditions that form a reaction product comprising the formula



,

wherein

n is selected from the group consisting of 0, 1, 2, 3, 4 and 5;

R_1 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

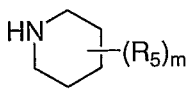
hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted;

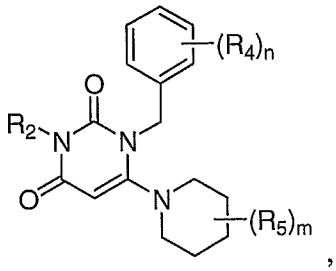
each R_4 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

L_1 is a leaving group.

14. The process of claim 13, wherein R_1 is a leaving group and further comprising reacting the reaction product with a piperidine comprising the formula



under conditions that form a second reaction product comprising the formula



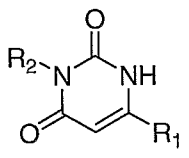
wherein

m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, and

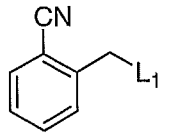
each R_5 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

15. A process comprising:

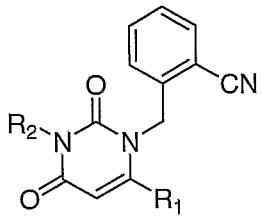
reacting a compound comprising the formula



with a compound comprising the formula



under conditions that form a reaction product comprising the formula



wherein

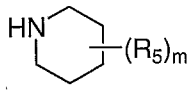
R_1 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted,

R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy,

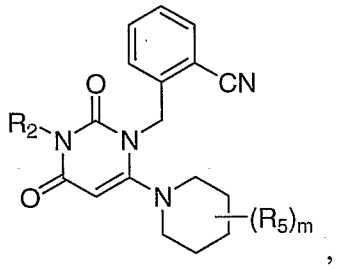
heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and

L_1 is a leaving group.

16. The process claim 15, wherein R_1 is a leaving group and further comprising reacting the reaction product with a piperidine comprising the formula



under conditions that form a second reaction product comprising the formula



wherein

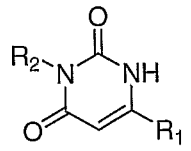
m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10; and

each R_5 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

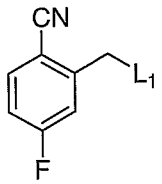
hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

17. A process comprising:

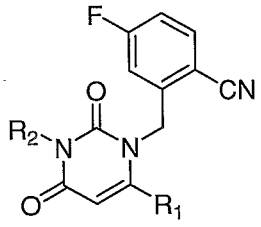
reacting a compound comprising the formula



with a compound comprising the formula



under conditions that form a reaction product comprising the formula



,

wherein

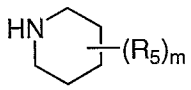
R_1 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl,

(C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted,

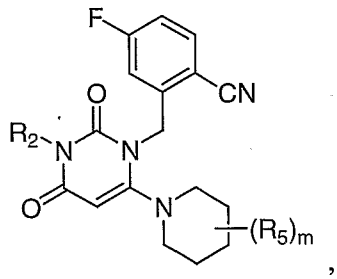
R_2 is hydrogen or selected from the group consisting of (C_{1-10})alkyl, (C_{3-12})cycloalkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl, hetero(C_{4-12})bicycloaryl, hetero(C_{4-12})bicycloaryl(C_{1-5})alkyl, carbonyl (C_{1-3})alkyl, thiocarbonyl (C_{1-3})alkyl, sulfonyl (C_{1-3})alkyl, sulfinyl (C_{1-3})alkyl, imino (C_{1-3})alkyl, amino, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted, and

L_1 is a leaving group.

18. The process of claim 17, wherein R_1 is a leaving group and further comprising reacting the reaction product with a piperidine comprising the formula



under conditions that form a second reaction product comprising the formula



,

wherein

m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, and

each R_5 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, hydroxy, alkoxy, aryloxy, heteroaryloxy, carbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, carbonyl(C_{1-3})alkyl, thiocarbonyl(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, sulfinyl(C_{1-3})alkyl, amino (C_{1-10})alkyl, imino(C_{1-3})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-5})alkyl, aryl(C_{1-10})alkyl, heteroaryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, aryl, heteroaryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

19. The process of any one of claims 1-18, wherein R_1 is halo.

20. The process of claim 19, wherein R_1 is chloro.

21. The process of any one of claims 1-8 and 13-20, wherein R_2 is hydrogen.

22. The process of any one of claims 1-8 and 13-20, wherein R_2 is a substituted or unsubstituted C_{1-6} alkyl.

23. The process of claim 22, wherein R_2 is methyl.

24. The process of any one of claims 11, 12, 19 and 20, wherein R_2' is hydrogen.

25. The process of any one of claims 11, 12, 19 and 20, wherein R_2' is a substituted or unsubstituted C_{1-6} alkyl.

26. The process of claim 25, wherein R_2' is methyl.

27. The process of any one of claims 1-12 and 19-26, wherein R_3 is a substituted or unsubstituted aryl or heteroaryl.

28. The process of claim 27, wherein R_3 is a substituted or unsubstituted phenyl.

29. The process of claim 28, wherein R_3 is a phenyl substituted with one or more substituents selected from the group consisting of halo, perhalo(C_{1-10})alkyl, CF_3, $(C_{1-}$

$_{10}$)alkyl, alkenyl, alkynyl, aryl, heteroaryl, aminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, cycloalkyl, heterocycloalkyl, amino, thio, cyano, nitro, hydroxy, alkoxy, carbonyl group, imino group, sulfonyl group and sulfinyl group, each substituted or unsubstituted.

30. The process of claim 29, wherein R_3 is a cyanophenyl.

31. The process of claim 30, wherein R_3 is 2-cyanophenyl.

32. The process of claim 29, wherein R_3 is a halocyanophenyl.

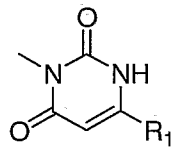
33. The process of claim 32, wherein R_3 is 2-cyano-5-fluorophenyl.

34. The process of any one of claims 13, 14 and 19-30, wherein each R_4 is independently selected from the group consisting of cyano and halo.

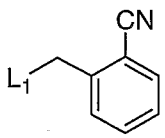
35. The process of any one of claims 8, 12, 14, 16 and 18-31, wherein at least one R_5 is amino.

36. A process comprising:

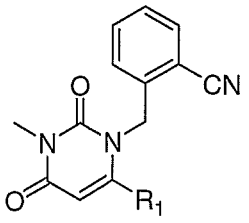
reacting a compound comprising the formula



with a compound comprising the formula

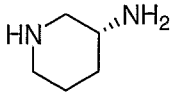


under conditions that form a reaction product comprising the formula

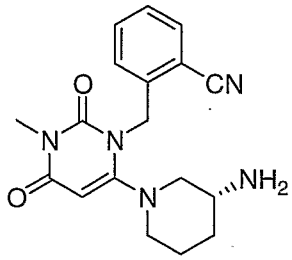


; and

reacting the reaction product with a piperidine comprising the formula



under conditions that form a second reaction product comprising the formula:



,

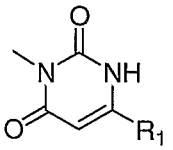
wherein

R_1 is halo, and

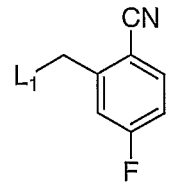
L_1 is a leaving group.

37. A process comprising:

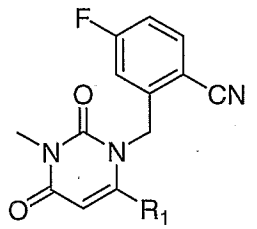
reacting a compound comprising the formula



with a compound comprising the formula

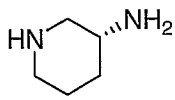


under conditions that form a reaction product comprising the formula

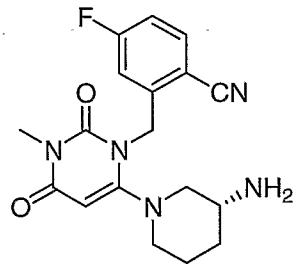


; and

reacting the reaction product with a piperidine comprising the formula



under conditions that form a second reaction product comprising the formula



,

wherein

R_1 is halo, and

L_1 is a leaving group.

38. The process of any one of claims 1-37, wherein L_1 is halo.

39. The process of claim 38, wherein L_1 is bromo.