



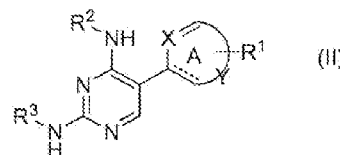
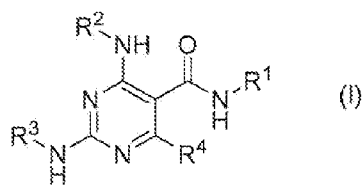
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(54) **Title:** PYRIMIDINE COMPOUNDS FOR THE TREATMENT OF CANCER



(57) **Abstract:** Compounds of Formula I or II: are described, along with pharmaceutical compositions containing the same and methods of using such compounds for the treatment of cancer.



**PYRIMIDINE COMPOUNDS  
FOR THE TREATMENT OF CANCER**

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**Related Applications**

This application is related to PCT Application Nod. PCT/US2011/036215 filed May 12, 2011 (Attorney Docket No. 5470-549WO); PCT/US2012/058298 filed Oct 01, 2012 (Attorney Docket No. 5470-610WO); and PCT/US2013/042033, filed May 21, 2013 (Attorney Docket No. 5470-627WO).

**Field of the Invention**

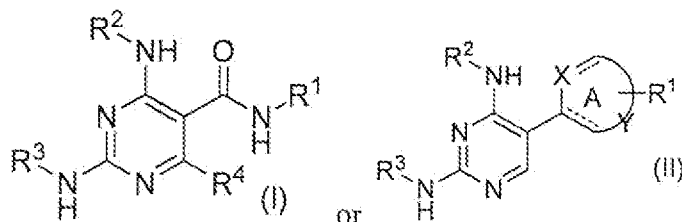
The present invention concerns compounds, compositions and methods for the treatment of cancer.

**Background of the Invention**

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in children and common varieties are cured by chemotherapy in 75%-85% of the cases. Collectively the less common T cell and rare B cell subsets represent less than 2000 cases yearly and thus can be classified as a rare disease; these subsets have a poorer prognosis. Unfortunately with either subset, resistance to and relapse from therapy is a major cause of pediatric cancer death. In addition, ALL chemotherapies can cause late complications that are increasingly recognized in pediatric survivor populations. In fact, in pediatric cancer survivors, the incidence of severe late effects (neurocognitive sequelae, auditory complications, cardiovascular dysfunction, gastrointestinal/hepatic dysfunction, growth delay, secondary malignancies, and infertility) directly related to therapy is approximately 25%. A better understanding of therapeutic resistance and its reversal could not only help those who relapse but may help lower the dose of chemotherapy needed in ALL patients thus reducing long-term toxicity for future survivors.

### Summary of the Invention

A first aspect of the invention is active compounds of **Formula I or II**:



wherein:

Ring A is a 5- or 6-membered heteroaryl group such as pyridyl, pyrimidyl, thiazol, furanyl, pyridazinyl, pyrazinyl, imidazol, etc.. The dashed line is an optional double bond. X is N or O. Y is C, S or N and can move on the ring.

R<sup>1</sup> is  $-R^5R^6$ , where R<sup>5</sup> is a covalent bond or C1 to C3 alkyl or a linker group (for example, sulfonamide, amide, etc.) and R<sup>6</sup> is cycloalkyl, heterocycloalkyl, aryl, heteroaryl alkylcycloalkyl, alkylheterocycloalkyl, alkylaryl, alkylheteroaryl, or alkyl, and wherein R<sup>6</sup> is optionally substituted one, two or three times with independently selected polar groups;

R<sup>2</sup> is  $-R^7R^8$ , where R<sup>7</sup> is a covalent bond or C1 to C3 alkyl and R<sup>8</sup> is cycloalkyl, heterocycloalkyl, aryl, heteroaryl or alkyl, and wherein R<sup>8</sup> is optionally substituted one, two or three times with independently selected polar groups;

R<sup>3</sup> is selected from the group consisting of H, alkyl, arylalkyl; cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl, and alkoxyalkyl, each of which is optionally substituted one, two or three times with independently selected polar groups;

or R<sup>2</sup> and R<sup>3</sup> together form a linking group;

R<sup>4</sup> is H, loweralkyl, halo, or loweralkoxy;

or a pharmaceutically acceptable salt thereof.

A further aspect of the invention is an active compound as described herein in a pharmaceutically acceptable carrier.

A further aspect of the invention is a method of treating cancer in a subject in need thereof, comprising administering said subject an active compound as described herein in an amount effective to treat the cancer.

A further aspect of the invention is an active compound as described herein for use in treating cancer, and/or for the preparation of a medicament for the treatment of cancer.

### Detailed Description of Preferred Embodiments

"Alkyl" as used herein alone or as part of another group, refers to a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, n-decyl, and the like. "Lower alkyl" as used herein, is a subset of alkyl, in some embodiments preferred, and refers to a straight or branched chain hydrocarbon group containing from 1 to 4 carbon atoms. Representative examples of lower alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, and the like. The term "alkyl" or "loweralkyl" is intended to include both substituted and unsubstituted alkyl or loweralkyl unless otherwise indicated and these groups may be substituted with groups selected from halo (e.g., haloalkyl), alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclo, heterocycloalkyl, hydroxyl, alkoxy (thereby creating a polyalkoxy such as polyethylene glycol), alkenyloxy, alkynyloxy, haloalkoxy, cycloalkoxy, cycloalkylalkyloxy, aryloxy, arylalkyloxy, heterocyclooxy, heterocycloalkyloxy, mercapto, alkyl-S(O)<sub>m</sub>, haloalkyl-S(O)<sub>m</sub>, alkenyl-S(O)<sub>m</sub>, alkynyl-S(O)<sub>m</sub>, cycloalkyl-S(O)<sub>m</sub>, cycloalkylalkyl-S(O)<sub>m</sub>, aryl-S(O)<sub>m</sub>, arylalkyl-S(O)<sub>m</sub>, heterocyclo-S(O)<sub>m</sub>, heterocycloalkyl-S(O)<sub>m</sub>, amino, carboxy, alkylamino, alkenylamino, alkynylamino, haloalkylamino, cycloalkylamino, cycloalkylalkylamino, arylamino, arylalkylamino, heterocycloamino, heterocycloalkylamino, disubstituted-amino, acylamino, acyloxy, ester, amide, sulfonamide, urea, alkoxyacylamino, aminoacyloxy, nitro or cyano where m= 0, 1, 2 or 3.

"Alkenyl" as used herein alone or as part of another group, refers to a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms (or in loweralkenyl 1 to 4 carbon atoms) which include 1 to 4 double bonds in the normal chain. Representative examples of alkenyl include, but are not limited to, vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2,4-heptadiene, and the like. The term "alkenyl" or "loweralkenyl" is intended to include both substituted and unsubstituted alkenyl or loweralkenyl unless otherwise indicated and these groups may be substituted with groups as described in connection with alkyl and loweralkyl above.

"Alkynyl" as used herein alone or as part of another group, refers to a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms (or in loweralkynyl 1 to 4 carbon atoms) which include 1 triple bond in the normal chain. Representative examples of

alkynyl include, but are not limited to, 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, and the like. The term "alkynyl" or "loweralkynyl" is intended to include both substituted and unsubstituted alkynyl or loweralkynyl unless otherwise indicated and these groups may be substituted with the same groups as set forth in connection with alkyl and loweralkyl above.

"Cycloalkyl" as used herein alone or as part of another group, refers to a saturated or partially unsaturated cyclic hydrocarbon group containing from 3, 4 or 5 to 6, 7 or 8 carbons (which carbons may be replaced in a heterocyclic group as discussed below). Representative examples of cycloalkyl include, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. These rings may be optionally substituted with additional substituents as described herein such as halo or loweralkyl. The term "cycloalkyl" is generic and intended to include heterocyclic groups as discussed below unless specified otherwise.

"Heterocyclic group" or "heterocyclo" as used herein alone or as part of another group, refers to an aliphatic (e.g., fully or partially saturated heterocyclo) or aromatic (e.g., heteroaryl) monocyclic- or a bicyclic-ring system. Monocyclic ring systems are exemplified by any 5 or 6 membered ring containing 1, 2, 3, or 4 heteroatoms independently selected from oxygen, nitrogen and sulfur. The 5 membered ring has from 0-2 double bonds and the 6 membered ring has from 0-3 double bonds. Representative examples of monocyclic ring systems include, but are not limited to, azetidine, azepine, aziridine, diazepine, 1,3-dioxolane, dioxane, dithiane, furan, imidazole, imidazoline, imidazolidine, isothiazole, isothiazoline, isothiazolidine, isoxazole, isoxazoline, isoxazolidine, morpholine, oxadiazole, oxadiazoline, oxadiazolidine, oxazole, oxazoline, oxazolidine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridine, pyrimidine, pyridazine, pyrrole, pyrroline, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, tetrazine, tetrazole, thiadiazole, thiadiazoline, thiadiazolidine, thiazole, thiazoline, thiazolidine, thiophene, thiomorpholine, thiomorpholine sulfone, thiopyran, triazine, triazole, trithiane, and the like. Bicyclic ring systems are exemplified by any of the above monocyclic ring systems fused to an aryl group as defined herein, a cycloalkyl group as defined herein, or another monocyclic ring system as defined herein. Representative examples of bicyclic ring systems include but are not limited to, for example, benzimidazole, benzothiazole, benzothiadiazole, benzothiophene, benzoxadiazole, benzoxazole, benzofuran, benzopyran, benzothiopyran, benzodioxine, 1,3-benzodioxole, cinnoline, indazole, indole, indoline, indolizine, naphthyridine, isobenzofuran, isobenzothiophene, isoindole, isoindoline, isoquinoline, phthalazine, purine, pyranopyridine,

quinoline, quinolizine, quinoxaline, quinazoline, tetrahydroisoquinoline, tetrahydroquinoline, thiopyranopyridine, and the like. These rings include quaternized derivatives thereof and may be optionally substituted with groups selected from halo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclo, heterocycloalkyl, hydroxyl, alkoxy, alkenyloxy, alkynyloxy, haloalkoxy, cycloalkoxy, cycloalkylalkyloxy, aryloxy, arylalkyloxy, heterocyclooxy, heterocycloalkyloxy, mercapto, alkyl-S(O)<sub>m</sub>, haloalkyl-S(O)<sub>m</sub>, alkenyl-S(O)<sub>m</sub>, alkynyl-S(O)<sub>m</sub>, cycloalkyl-S(O)<sub>m</sub>, cycloalkylalkyl-S(O)<sub>m</sub>, aryl-S(O)<sub>m</sub>, arylalkyl-S(O)<sub>m</sub>, heterocyclo-S(O)<sub>m</sub>, heterocycloalkyl-S(O)<sub>m</sub>, amino, alkylamino, alkenylamino, alkynylamino, haloalkylamino, cycloalkylamino, cycloalkylalkylamino, arylamino, arylalkylamino, heterocycloamino, heterocycloalkylamino, disubstituted-amino, acylamino, acyloxy, ester, amide, sulfonamide, urea, alkoxyacylamino, aminoacyloxy, nitro or cyano where m = 0, 1, 2 or 3.

"Aryl" as used herein alone or as part of another group, refers to a monocyclic carbocyclic ring system or a bicyclic carbocyclic fused ring system having one or more aromatic rings. Representative examples of aryl include, azulenyl, indanyl, indenyl, naphthyl, phenyl, tetrahydronaphthyl, and the like. The term "aryl" is intended to include both substituted and unsubstituted aryl unless otherwise indicated and these groups may be substituted with the same groups as set forth in connection with alkyl and loweralkyl above.

"Arylalkyl" as used herein alone or as part of another group, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, 2-naphth-2-ylethyl, and the like.

"Heteroaryl" as used herein is as described in connection with heterocyclo above.

"Alkoxy" as used herein alone or as part of another group, refers to an alkyl or loweralkyl group, as defined herein (and thus including substituted versions such as polyalkoxy), appended to the parent molecular moiety through an oxy group, -O-. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy and the like.

"Halo" as used herein refers to any suitable halogen, including -F, -Cl, -Br, and -I.

"Mercapto" as used herein refers to an -SH group.

"Azido" as used herein refers to an -N<sub>3</sub> group.

"Cyano" as used herein refers to a -CN group.

"Formyl" as used herein refers to a -C(O)H group.

"Carboxylic acid" as used herein refers to a  $-C(O)OH$  group.

"Hydroxyl" as used herein refers to an  $-OH$  group.

"Nitro" as used herein refers to an  $-NO_2$  group.

"Acyl" as used herein alone or as part of another group refers to a  $-C(O)R$  radical, where R is any suitable substituent such as aryl, alkyl, alkenyl, alkynyl, cycloalkyl or other suitable substituent as described herein.

"Alkylthio" as used herein alone or as part of another group, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a thio moiety, as defined herein. Representative examples of alkylthio include, but are not limited, methylthio, ethylthio, tert-butylthio, hexylthio, and the like.

"Amino" as used herein means the radical  $-NH_2$ .

"Alkylamino" as used herein alone or as part of another group means the radical  $-NHR$ , where R is an alkyl group.

"Arylalkylamino" as used herein alone or as part of another group means the radical  $-NHR$ , where R is an arylalkyl group.

"Disubstituted-amino" as used herein alone or as part of another group means the radical  $-NR_aR_b$ , where  $R_a$  and  $R_b$  are independently selected from the groups alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclo, heterocycloalkyl.

"Acylamino" as used herein alone or as part of another group means the radical  $-NR_aR_b$ , where  $R_a$  is an acyl group as defined herein and  $R_b$  is selected from the groups hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclo, heterocycloalkyl.

"Acyloxy" as used herein alone or as part of another group means the radical  $-OR$ , where R is an acyl group as defined herein.

"Ester" as used herein alone or as part of another group refers to a  $-C(O)OR$  radical, where R is any suitable substituent such as alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Amide" as used herein alone or as part of another group refers to a  $-C(O)NR_aR_b$  radical, where  $R_a$  and  $R_b$  are any suitable substituent such as alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Sulfoxyl" as used herein refers to a compound of the formula  $-S(O)R$ , where R is any suitable substituent such as alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Sulfonyl" as used herein refers to a compound of the formula  $-S(O)(O)R$ , where R is any suitable substituent such as amino, alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Sulfonate" as used herein refers to a compound of the formula  $-S(O)(O)OR$ , where R is any suitable substituent such as alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Sulfonic acid" as used herein refers to a compound of the formula  $-S(O)(O)OH$ .

"Sulfonamide" as used herein alone or as part of another group refers to a  $-S(O)_2NR_aR_b$  radical, where  $R_a$  and  $R_b$  are any suitable substituent such as H, alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Urea" as used herein alone or as part of another group refers to an  $-N(R_c)C(O)NR_aR_b$  radical, where  $R_a$ ,  $R_b$  and  $R_c$  are any suitable substituent such as H, alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Alkoxyacylamino" as used herein alone or as part of another group refers to an  $-N(R_a)C(O)OR_b$  radical, where  $R_a$ ,  $R_b$  are any suitable substituent such as H, alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Aminoacyloxy" as used herein alone or as part of another group refers to an  $-OC(O)NR_aR_b$  radical, where  $R_a$  and  $R_b$  are any suitable substituent such as H, alkyl, cycloalkyl, alkenyl, alkynyl or aryl.

"Polar group" as used herein refers to a group wherein the nuclei of the atoms covalently bound to each other to form the group do not share the electrons of the covalent bond(s) joining them equally; that is the electron cloud is denser about one atom than another. This results in one end of the covalent bond(s) being relatively negative and the other end relatively positive; i.e., there is a negative pole and a positive pole. Examples of polar groups include, without limitations, halo, hydroxy, alkoxy, carboxy, nitro, cyano, amino (primary, secondary and tertiary), amido, ureido, sulfonamido, sulfinyl, sulfhydryl, silyl, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, C-amido, N-amido, sulfonyl, N-*tert*-butoxycarbonyl (or "*t*-BOC") groups, phosphono, morpholino, piperazinyl, tetrazolo, and the like. See, e.g., U.S. Pat. No. 6,878,733, as well as alcohol, thiol, polyethylene glycol, polyol (including sugar, aminosugar, uronic acid), sulfonamide, carboxamide, hydrazide, N-hydroxycarboxamide, urea, metal chelates (including macrocyclic ligand or crown ether metal chelates). The polar group can be an ionic group.

"Ionic group" as used herein includes anionic and cationic groups, and includes groups (sometimes referred to as "ionogenic" groups) that are uncharged in one form but can be easily converted to ionic groups (for example, by protonation or deprotonation in aqueous solution). Examples include but are not limited to carboxylate, sulfonate, phosphate, amine, N-oxide, and ammonium (including quaternized heterocyclic amines such as imidazolium

and pyridinium) groups. See, e.g., U.S. Pat. Nos. 6,478,863; 6,800,276; and 6,896,246. Additional examples include uronic acids, carboxylic acid, sulfonic acid, amine, and moieties such as guanidinium, phosphoric acid, phosphonic acid, phosphatidyl choline, phosphonium, borate, sulfate, etc.

“Deuterium” as used herein alone or as part of another group, refers to a safe, non-radioactive relative of hydrogen. Any hydrogen in a group or substituent described above may be replaced with deuterium to provide a “deuterated” compound, in some embodiments to modify and/or improve metabolic stability, resulting in better safety, tolerability and/or efficacy.

“Linking group” or “linker group” as used herein are generally bivalent aromatic, aliphatic, or mixed aromatic and aliphatic groups. Thus linking groups include linear or branched, substituted or unsubstituted aryl, alkyl, alkylaryl, or alkylarylalkyl linking groups, where the alkyl groups are saturated or unsaturated, and where the alkyl and aryl groups optionally containing independently selected heteroatoms such as 1, 2, 3 or 4 heteroatoms selected from the group consisting of N, O, and S. In some embodiments, linking groups containing from 2 to 20 carbon atoms are preferred. Numerous examples of suitable linking groups are known, including but not limited to those described in, US Patents Nos. 8,247,572; 8,097,609; 6,624,317; 6,613,345; 6,596,935; and 6,420,377, the disclosures of which are incorporated by reference herein in their entirety.

“Treat” as used herein refers to any type of treatment that imparts a benefit to a patient afflicted with a disease, including improvement in the condition of the patient (e.g., in one or more symptoms), delay in the progression of the disease, delay in onset of the disease, etc.

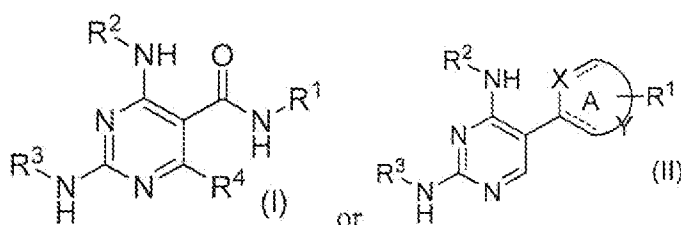
“Pharmaceutically acceptable” as used herein means that the compound or composition is suitable for administration to a subject to achieve the treatments described herein, without unduly deleterious side effects in light of the severity of the disease and necessity of the treatment.

Active compounds of the present invention may optionally be administered in conjunction with other compounds useful in the treatment of cancer. The other compounds may optionally be administered concurrently. As used herein, the word “concurrently” means sufficiently close in time to produce a combined effect (that is, concurrently may be simultaneously, or it may be two or more events occurring within a short time period before or after each other).

The present invention is primarily concerned with the treatment of human subjects, but the invention may also be carried out on animal subjects, particularly mammalian subjects such as mice, rats, dogs, cats, livestock and horses for veterinary purposes, and for drug screening and drug development purposes. Subjects may be of any age, including infant, juvenile, adolescent, adult, and geriatric subjects.

### I. Active compounds.

As noted above, the present invention provides active compounds of **Formula I or II**:



wherein:

R<sup>1</sup> is -R<sup>5</sup>R<sup>6</sup>, where R<sup>5</sup> is a covalent bond, C1 to C3 alkyl or a linker group (for example, sulfonamide, amide, etc.) and R<sup>6</sup> is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocycloalkyl, alkylaryl, alkylheteroaryl or alkyl, and wherein R<sup>6</sup> is optionally substituted one, two or three times with independently selected polar groups;

R<sup>2</sup> is -R<sup>7</sup>R<sup>8</sup>, where R<sup>7</sup> is a covalent bond or C1 to C3 alkyl and R<sup>8</sup> is cycloalkyl, heterocycloalkyl, aryl, heteroaryl or alkyl, and wherein R<sup>8</sup> is optionally substituted one, two or three times with independently selected polar groups;

R<sup>3</sup> is selected from the group consisting of H, alkyl, arylalkyl; cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl, and alkoxyalkyl, each of which is optionally substituted one, two or three times with independently selected polar groups;

or R<sup>2</sup> and R<sup>3</sup> together form a linking group;

R<sup>4</sup> is H, loweralkyl, halo, or loweralkoxy;

or a pharmaceutically acceptable salt thereof.

In some embodiments of the foregoing, R<sup>5</sup> is a covalent bond; in other embodiments, R<sup>5</sup> is C1 to C3 alkylene such as -CH<sub>2</sub>- or R<sup>5</sup> is a linker group (for example, sulfonamide, amide, etc.).

In some embodiments of the foregoing,  $R^7$  is a covalent bond; in other embodiments,  $R^7$  is C1 to C3 alkylene such as  $-\text{CH}_2-$ .

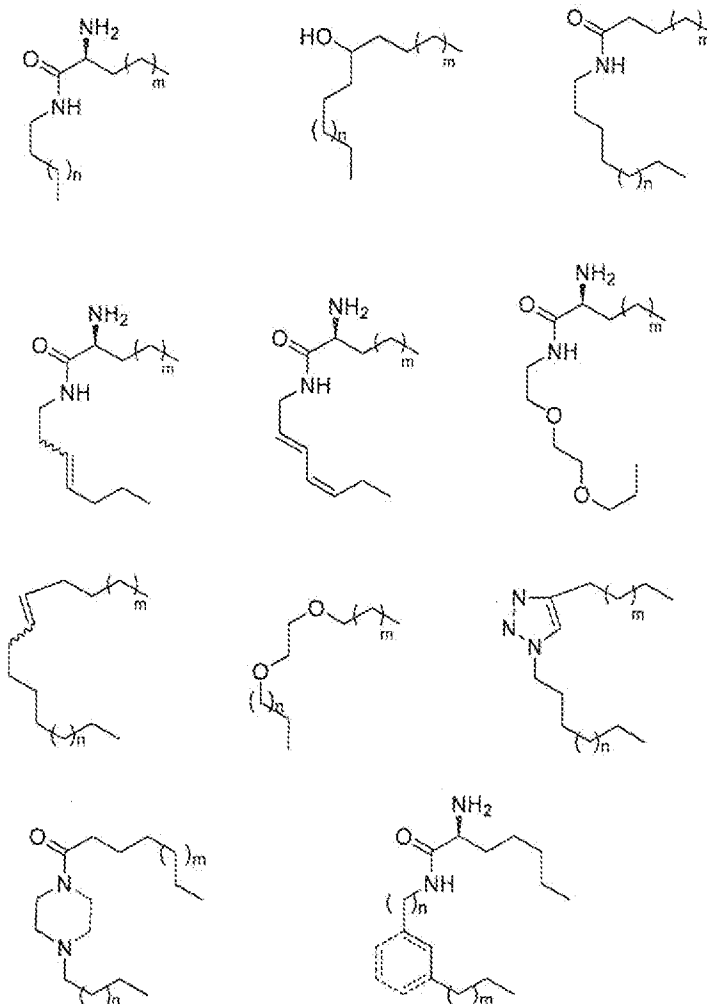
In some embodiments,  $R^6$  is phenyl, piperidyl, or C1-C8 alkyl, or C3 to C8 cycloalkyl, which phenyl, piperidyl, alkyl, or cycloalkyl alkyl is unsubstituted or substituted from 1 to 3 times with sulfono, halo, amino, nitro, alkyl, alkoxy, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

In some embodiments, wherein  $R^8$  is C1-C8 alkyl or cyclohexyl, which alkyl or cyclohexyl is unsubstituted or substituted from 1 to 3 times with hydroxyl or amino.

In some embodiments,  $R^3$  is C1-C8 alkyl, C3-C8 cycloalkyl, C4-C12 cycloalkylalkyl, C3-C8 heterocycloalkyl, C4-C12 heterocycloalkylalkyl, C4-C12 arylalkyl, C4-C12 heteroarylalkyl, each of which is unsubstituted or substituted from one to three times with hydroxyl, halo, or alkoxy.

In some embodiments,  $R^4$  is H.

Specific examples of linking groups include, but are not limited to:



where each n and m is independently 0, 1, 2, 4, 5, or 6; and where each of the linking group structures illustrated above may optionally be substituted, e.g., substituted one, two, or three times with independently selected polar groups.

Particular examples of compounds of the present invention include but are not limited to those set forth in Tables 1-7 below.

The active compounds disclosed herein can, as noted above, be provided in the form of their pharmaceutically acceptable salts. Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Examples of such salts are (a) acid addition salts formed with inorganic acids, for example hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid and the like; and salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, and the like; (b) salts formed from elemental anions such as chlorine, bromine, and iodine, and (c) salts derived from bases, such as ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium, and salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine.

Active compounds as described herein can be prepared in accordance with known procedures, or variations thereof that will be apparent to those skilled in the art.

## **2. Pharmaceutical formulations.**

The active compounds described above may be formulated for administration in a pharmaceutical carrier in accordance with known techniques. See, e.g., Remington, *The Science And Practice of Pharmacy* (9<sup>th</sup> Ed. 1995). In the manufacture of a pharmaceutical formulation according to the invention, the active compound (including the physiologically acceptable salts thereof) is typically admixed with, *inter alia*, an acceptable carrier. The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from 0.01 or 0.5% to 95% or 99% by weight of the active compound. One or more active compounds may be incorporated in the

formulations of the invention, which may be prepared by any of the well known techniques of pharmacy comprising admixing the components, optionally including one or more accessory ingredients.

The formulations of the invention include those suitable for oral, rectal, topical, buccal (e.g., sub-lingual), vaginal, parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous), topical (*i.e.*, both skin and mucosal surfaces, including airway surfaces), transdermal administration, and intraventricular injection (injection into a ventricle of the brain, e.g., by an implanted catheter or osmotic reservoir, such as in the case of morbid obesity) and although the most suitable route in any given case will depend on the nature and severity of the condition being treated and on the nature of the particular active compound which is being used.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above). In general, the formulations of the invention are prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture. For example, a tablet may be prepared by compressing or molding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid binder.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising the active compound in a flavoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration comprise sterile aqueous and non-aqueous injection solutions of the active compound, which

preparations are preferably isotonic with the blood of the intended recipient. These preparations may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Aqueous and non-aqueous sterile suspensions may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or water-for-injection immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described. For example, in one aspect of the present invention, there is provided an injectable, stable, sterile composition comprising a compound of Formula (I), or a salt thereof, in a unit dosage form in a sealed container. The compound or salt is provided in the form of a lyophilizate which is capable of being reconstituted with a suitable pharmaceutically acceptable carrier to form a liquid composition suitable for injection thereof into a subject. The unit dosage form typically comprises from about 10 mg to about 10 grams of the compound or salt. When the compound or salt is substantially water-insoluble, a sufficient amount of emulsifying agent which is physiologically acceptable may be employed in sufficient quantity to emulsify the compound or salt in an aqueous carrier. One such useful emulsifying agent is phosphatidyl choline.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include petroleum jelly, lanoline, polyethylene glycols, alcohols, transdermal enhancers, and combinations of two or more thereof.

Formulations suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Formulations suitable for transdermal administration may also be delivered by iontophoresis (*see, for example, Pharmaceutical Research* 3 (6):318 (1986)) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or bis/tris buffer (pH 6) or ethanol/water and contain from 0.1 to 0.2M active ingredient.

Further, the present invention provides liposomal formulations of the compounds

disclosed herein and salts thereof. The technology for forming liposomal suspensions is well known in the art. When the compound or salt thereof is an aqueous-soluble salt, using conventional liposome technology, the same may be incorporated into lipid vesicles. In such an instance, due to the water solubility of the compound or salt, the compound or salt will be substantially entrained within the hydrophilic center or core of the liposomes. The lipid layer employed may be of any conventional composition and may either contain cholesterol or may be cholesterol-free. When the compound or salt of interest is water-insoluble, again employing conventional liposome formation technology, the salt may be substantially entrained within the hydrophobic lipid bilayer which forms the structure of the liposome. In either instance, the liposomes which are produced may be reduced in size, as through the use of standard sonication and homogenization techniques.

Of course, the liposomal formulations containing the compounds disclosed herein or salts thereof, may be lyophilized to produce a lyophilizate which may be reconstituted with a pharmaceutically acceptable carrier, such as water, to regenerate a liposomal suspension.

Other pharmaceutical compositions may be prepared from the water-insoluble compounds disclosed herein, or salts thereof, such as aqueous base emulsions. In such an instance, the composition will contain a sufficient amount of pharmaceutically acceptable emulsifying agent to emulsify the desired amount of the compound or salt thereof. Particularly useful emulsifying agents include phosphatidyl cholines, and lecithin.

In addition to compounds of formula (I) or their salts, the pharmaceutical compositions may contain other additives, such as pH-adjusting additives. In particular, useful pH-adjusting agents include acids, such as hydrochloric acid, bases or buffers, such as sodium lactate, sodium acetate, sodium phosphate, sodium citrate, sodium borate, or sodium gluconate. Further, the compositions may contain microbial preservatives. Useful microbial preservatives include methylparaben, propylparaben, and benzyl alcohol. The microbial preservative is typically employed when the formulation is placed in a vial designed for multidose use. Of course, as indicated, the pharmaceutical compositions of the present invention may be lyophilized using techniques well known in the art.

### **3. Dosage and routes of administration.**

As noted above, the present invention provides pharmaceutical formulations comprising the active compounds (including the pharmaceutically acceptable salts thereof),

in pharmaceutically acceptable carriers for oral, rectal, topical, buccal, parenteral, intramuscular, intradermal, or intravenous, and transdermal administration.

The therapeutically effective dosage of any specific compound, the use of which is in the scope of present invention, will vary somewhat from compound to compound, and patient to patient, and will depend upon the condition of the patient and the route of delivery. As a general proposition, a dosage from about 0.1 to about 50 mg/kg will have therapeutic efficacy, with all weights being calculated based upon the weight of the active compound, including the cases where a salt is employed. Toxicity concerns at the higher level may restrict intravenous dosages to a lower level such as up to about 10 mg/kg, with all weights being calculated based upon the weight of the active base, including the cases where a salt is employed. A dosage from about 10 mg/kg to about 50 mg/kg may be employed for oral administration. In some embodiments, a dosage from about 0.5 mg/kg to 5 mg/kg may be employed for intramuscular injection. In some embodiments, dosages are 1  $\mu\text{mol}/\text{kg}$  to 50  $\mu\text{mol}/\text{kg}$ , and more preferably 22  $\mu\text{mol}/\text{kg}$  and 33  $\mu\text{mol}/\text{kg}$  of the compound for intravenous or oral administration. The duration of the treatment can be once per day for a period of two to three weeks or until the condition is essentially controlled.

Active compounds may be administered as pharmaceutically acceptable prodrugs, which are those prodrugs of the active compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, commensurate with a reasonable risk/benefit ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, *Prodrugs as Novel delivery Systems*, Vol. 14 of the A.C.S. Symposium Series and in Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated by reference herein. *See also* US Patent No. 6,680,299. Examples include a prodrug that is metabolized in vivo by a subject to an active drug having an activity of active compounds as described herein, wherein the prodrug is an ester of an alcohol or carboxylic acid group, if such a group is present in the compound; an acetal or ketal of an alcohol group, if such a group is present in the compound; an N-Mannich base or an imine of an amine

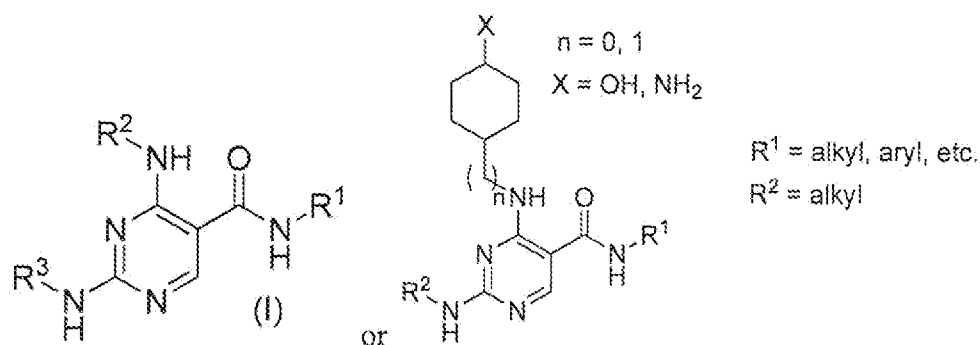
group, if such a group is present in the compound; or a Schiff base, oxime, acetal, enol ester, oxazolidine, or thiazolidine of a carbonyl group, if such a group is present in the compound, such as described in US Patent No. 6,680,324 and US Patent No. 6,680,322.

As noted above, the active compounds described herein are useful for the treatment of cancer. Example cancers that may be treated by the compounds and methods of the invention include, but are not limited to, myeloid leukemia, lymphoblastic leukemia, melanoma, breast, lung, colon, liver, gastric, kidney, ovarian, uterine, and brain cancer.

The present invention is explained in greater detail in the following non-limiting Examples.

### Examples 1-11

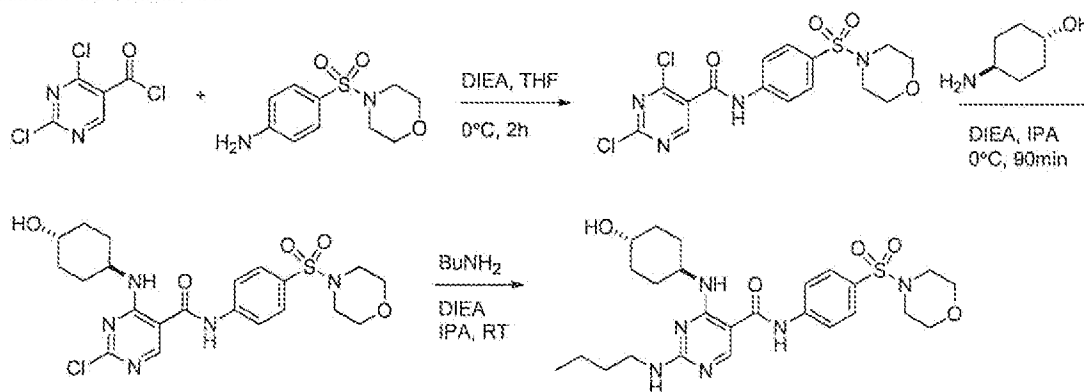
General Structure I:



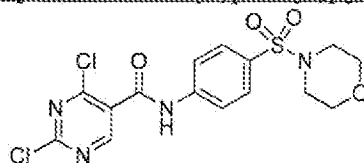
### Example 1

2-(Butylamino)-4-(((1r,4r)-4-hydroxycyclohexyl)amino)-N-(4-(morpholin-sulfonyl)phenyl)pyrimidine-5-carboxamide

General Procedure A:

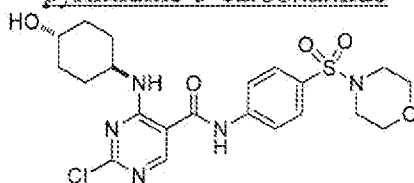


2,4-Dichloro-N-(4-(morpholin-4-yl)phenyl)pyrimidine-5-carboxamide



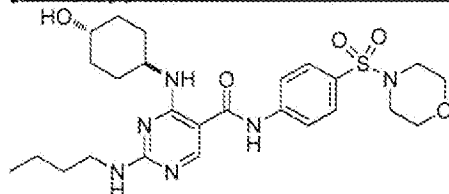
A solution of 2,4-dichloropyrimidine-5-carbonyl chloride (422mg, 2.0 mmol) in dichloromethane (10 mL) was added 4-(morpholinosulfonyl)aniline (508 mg, 2.1 mmol) and DIEA (387 mg, 3.0 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. Then, water was added. The resulting mixture was extracted with EtOAc (3x). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was purified on ISCO to give the title compound as a white solid (701.2 mg, 84%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ 11.98 – 11.90 (m, 1H), 8.29 (d, *J* = 6.4 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 3.65 – 3.56 (m, 4H), 2.87 – 2.78 (m, 4H); MS *m/z* 418.30 [M+H]<sup>+</sup>.

2-Chloro-4-(((1*r*,4*r*)-4-hydroxycyclohexyl)amino)-*N*-(4-(morpholinosulfonyl)phenyl)pyrimidine-5-carboxamide



A solution of 2,4-dichloro-*N*-(4-(morpholinosulfonyl)phenyl)pyrimidine-5-carboxamide (700mg, 1.68 mmol) in IPA (15 mL) was added *trans*-4-aminocyclohexanol (231.4 mg, 2.2 mmol) and DIEA (387 mg, 3.0 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 50 min and warmed to room temperature and stirred for another 50 min. Then the solvent was removed, the residue was dissolved in a mixture of CH<sub>2</sub>CL<sub>2</sub> and methanol (20 mL, 3:2, v/v), the suspension was filtered through a filter paper to give the title compound as a white solid (683.4 mg, 82%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ 10.71 (s, 1H), 8.69 (s, 1H), 7.96 – 7.89 (m, 2H), 7.76 – 7.70 (m, 2H), 4.57 (s, 1H), 3.93 – 3.81 (m, 1H), 3.64 – 3.57 (m, 4H), 3.49 – 3.40 (m, 1H), 2.88 – 2.78 (m, 4H), 1.95 – 1.86 (m, 2H), 1.85 – 1.76 (m, 2H), 1.38 – 1.20 (m, 4H); MS *m/z* 496.20 [M+H]<sup>+</sup>.

2-(Butylamino)-4-(((1*r*,4*r*)-4-hydroxycyclohexyl)amino)-*N*-(4-(morpholinosulfonyl)phenyl)pyrimidine-5-carboxamide



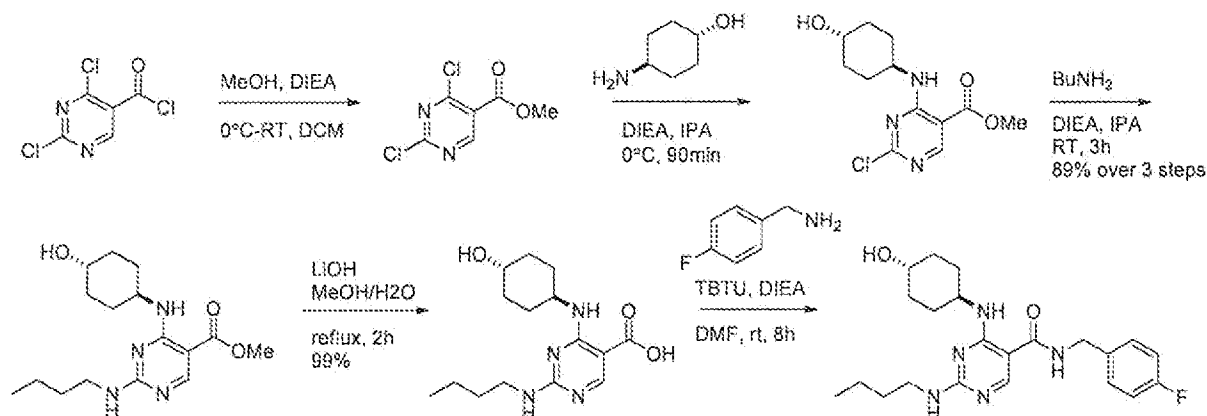
A solution of 2-chloro-4-(((1*r*,4*r*)-4-hydroxycyclohexyl)amino)-*N*-(4-(morpholinosulfonyl)phenyl)pyrimidine-5-carboxamide (86mg, 0.17 mmol) in IPA (10mL) was added butylamine (59.6 mg, 0.81 mmol) and DIEA (124.7 mg, 0.96 mmol) at room temperature. The resulting mixture was stirred for 3h at room temperature. Water was then

added. The resulting mixture was extracted with EtOAc (3X). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. The residue was purified on ISCO to give the title compound as a white solid (59.3 mg, 64%).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}+\text{CDCl}_3$ )  $\delta$  8.21 (s, 1H), 7.71 – 7.64 (m, 2H), 7.59 – 7.53 (m, 2H), 3.93 – 3.77 (m, 1H), 3.74 – 3.64 (m, 4H), 3.63 – 3.58 (m, 4H), 3.56 – 3.46 (m, 1H), 3.26 (t,  $J = 7.1$  Hz, 2H), 2.91 – 2.81 (m, 4H), 2.05 – 1.95 (m, 2H), 1.93 – 1.82 (m, 2H), 1.50 – 1.41 (m, 2H), 1.33 – 1.17 (m, 6H), 0.83 (t,  $J = 7.3$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_3\text{OD}+\text{CDCl}_3$ )  $\delta$  166.8, 156.4, 143.5, 128.8, 128.6, 120.3, 120.2, 69.2, 66.0, 45.9, 41.0, 33.4, 31.6, 30.2, 20.0, 13.7; MS  $m/z$  533.30  $[\text{M}+\text{H}]^+$ .

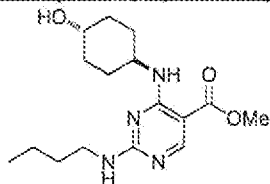
### Example 2

#### 2-(Butylamino)-N-(4-fluorobenzyl)-4-(((trans)-4-hydroxycyclohexyl)amino)pyrimidine-5-carboxamide

General Procedure B:



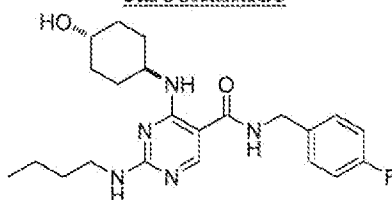
#### Methyl 2-(butylamino)-4-(((trans)-4-hydroxycyclohexyl)amino)pyrimidine-5-carboxylate



To a solution of 2,4-dichloropyrimidine-5-carbonyl chloride (500 mg, 2.38 mmol) in dichloromethane (30 mL) was added methanol (87.6 mg, 2.73 mmol) and diisopropylethylamine (369 mg, 2.86 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. Then the solvent was removed. The residue (461mg, 94%) was dissolved in IPA (20 mL) and followed by the addition of *trans*-4-aminocyclohexanol (301.6 mg, 2.62 mmol) then DIEA (461.4 mg, 3.57 mmol) dropwisely. The resulting mixture was stirred at 0 °C for 90 min. After which butylamine (208.8 mg, 2.86 mmol) was added, followed by DIEA (461.4

mg, 3.57 mmol). The resulting mixture was stirred at room temperature for 3 h. Water was then added. The resulting mixture was extracted with EtOAc (3X). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. The residue was purified on ISCO to give methyl 2-(butylamino)-4-(((*trans*-4-hydroxycyclohexyl)amino)pyrimidine-5-carboxylate (682.6 mg, 89% over 3 steps).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.21 (s, 1H), 8.77 (s, 1H), 6.29 (s, 1H), 4.81 – 4.64 (m, 1H), 4.51 (s, 3H), 4.46-4.38 (m, 1H), 4.13-4.11 (m, 2H), 2.89-2.81 (m, 2H), 2.74 (d,  $J = 9.7$  Hz, 2H), 2.35 – 2.25 (m, 2H), 2.23 – 2.00 (m, 6H), 1.67 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.9, 162.5, 161.3, 160.3, 95.5, 69.7, 51.2, 48.3, 41.1, 33.8, 31.7, 30.3, 20.1, 13.8; MS  $m/z$  323.20  $[\text{M}+\text{H}]^+$ .

2-(Butylamino)-*N*-(4-fluorobenzyl)-4-(((*trans*)-4-hydroxycyclohexyl)amino)pyrimidine-5-carboxamide

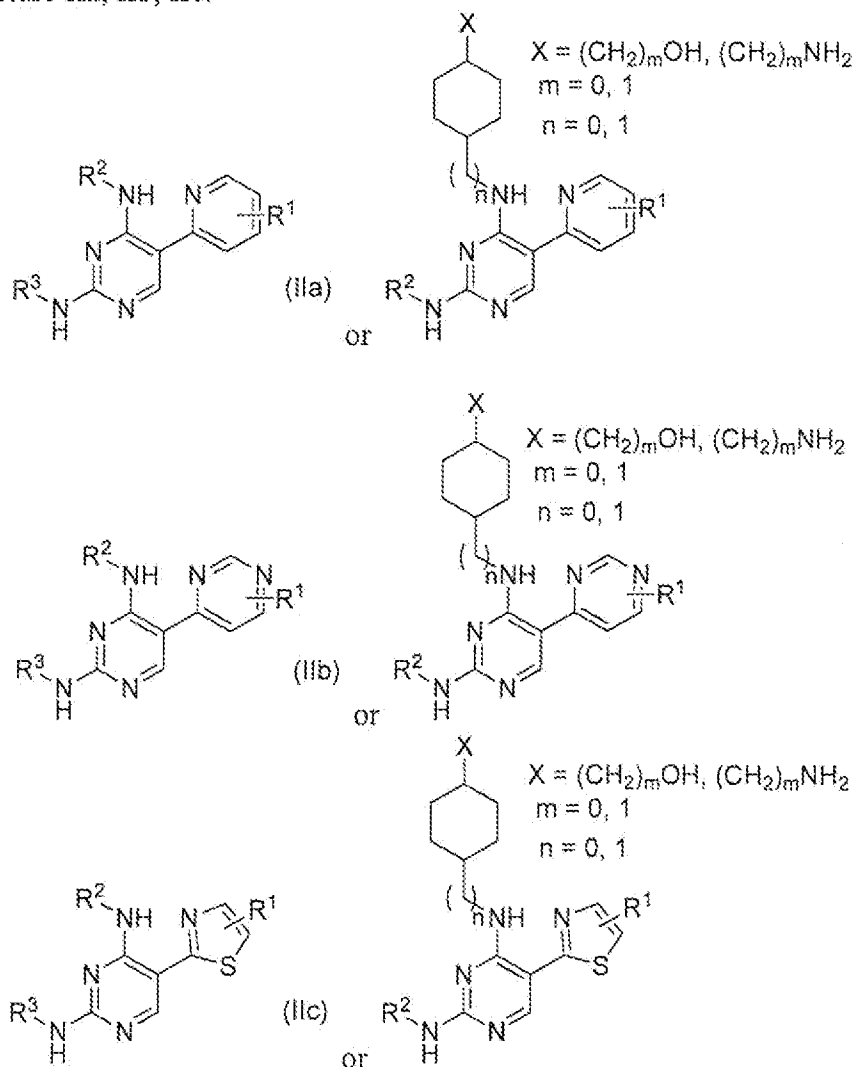


A mixture of methyl 2-(butylamino)-4-(((*trans*-4-hydroxycyclohexyl)amino)pyrimidine-5-carboxylate (682.6 mg, 2.12 mmol) and lithium hydroxide monohydrate (888.4 mg, 21.2 mmol) in a mixture of methanol and water (25 mL, 3:2, v/v) was heated at reflux for 2h. Then the reaction mixture was cooled to room temperature and acidified by a 4.0N solution of HCl (4N) to pH 3. The resulting mixture was extracted with EtOAc (4x). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to provide 2-(butylamino)-4-(((1*r*,4*r*)-4-hydroxycyclohexyl)amino)pyrimidine-5-carboxylic acid (647.1 mg, 99%), which was used in the next step without further purifications. MS  $m/z$  309.30  $[\text{M}+\text{H}]^+$ .

A solution of the acid (61 mg, 0.20 mmol), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU, 81.4 mg, 0.25 mmol, 1.3 eq) and *N,N*-diisopropylethylamine (DIEA, 77.5 mg, 0.60 mmol, 3.0 eq) in anhydrous DMF (3.0 mL) and was added 4-fluorobenzylamine (37.5 mg, 0.30 mmol, 1.5eq) in DMF (1.0 mL) dropwisely at room temperature. The resulting mixture was stirred for overnight, then diluted with EtOAc (15 mL) and washed with water (3x). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue was purified on HPLC to give the title compound (61.5 mg, 74%) as a yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.57 (d,  $J = 7.4$  Hz, 1H), 8.77 (s, 1H), 8.13 (s, 1H), 7.40 – 7.31 (m, 1H), 7.29 – 7.22 (m, 3H), 7.00 (t,  $J = 8.6$  Hz, 2H), 4.44 (d,  $J = 5.2$

Hz, 2H), 4.00 (s, 1H), 3.77 – 3.62 (m, 1H), 3.40 (dd,  $J = 13.0, 6.9$  Hz, 2H), 2.15 – 2.09 (m, 2H), 2.04 (d,  $J = 7.6$  Hz, 2H), 1.66 – 1.54 (m, 2H), 1.49 – 1.33 (m, 6H), 0.94 (t,  $J = 7.3$  Hz, 3H); MS  $m/z$  416.30  $[M+H]^+$ .

General Structure IIa, IIb, IIc:

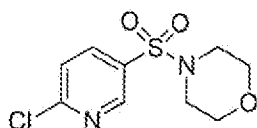
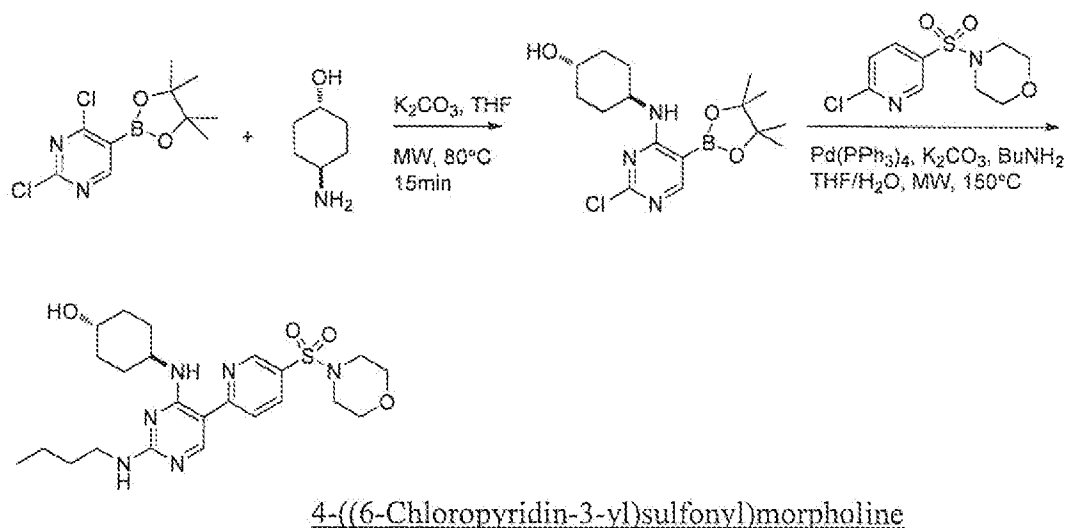


### Example 3

(1r,4r)-4-((2-(Butylamino)-5-(5-(morphinosulfonyl)pyridin-2-yl)pyrimidin-4-yl)amino)cyclohexanol

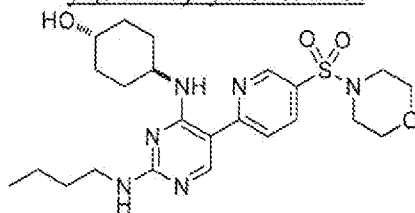
General Procedure C:

- 21 -



A solution of 2-chloropyridine-5-sulfonyl chloride (212 mg, 1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added morpholine (87.1 mg, 1.0 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min and then DIEA (194 mg, 1.5 mmol) was added dropwisely. The mixture was stirred at 0 °C for 2h. Then the mixture was diluted with EtOAc (15 mL) and washed with water (2x). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was purified on ISCO to give the title compound as a white solid (246.1 mg, 94%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.73 – 8.65 (m, 1H), 7.94 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.49 (dd, *J* = 8.3, 0.6 Hz, 1H), 3.74 – 3.63 (m, 4H), 2.99 (dd, *J* = 5.6, 3.9 Hz, 4H); <sup>13</sup>C NMR (101 MHz, cdcl<sub>3</sub>) δ 155.9, 148.7, 137.9, 131.1, 124.9, 65.9, 45.8; MS *m/z* 263.30 [M+H]<sup>+</sup>.

(1r,4r)-4-((2-(Butylamino)-5-(5-(morpholinofulfonyl)pyridin-2-yl)pyrimidin-4-yl)amino)cyclohexanol



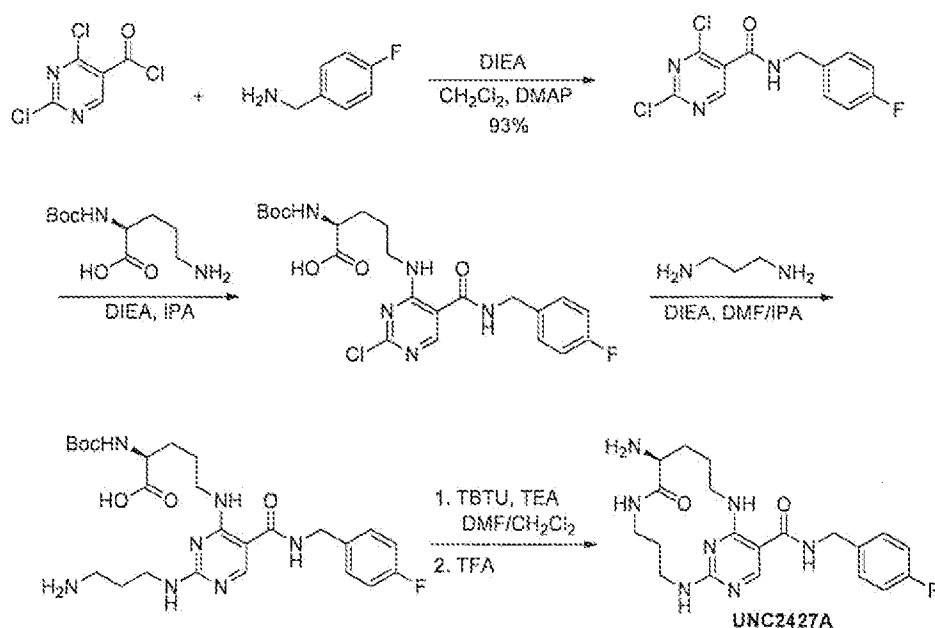
A 10 mL microwave tube was charged with 2,4-dichloropyrimidine-5-boronic acid pinacol ester (55 mg, 0.20 mmol), K<sub>2</sub>CO<sub>3</sub> (41.5 mg, 0.30 mmol) and THF (2.0 mL). The resulting mixture was then heated to 80 °C for 15 min under Microwave irradiation. Then 4-((6-chloropyridin-3-yl)sulfonyl)morpholine (52.5 mg, 0.20 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (23.1 mg, 0.02 mmol), K<sub>2</sub>CO<sub>3</sub> (41.5 mg, 0.30 mmol), butylamine (116.8 mg, 1.60 mmol) and water (0.5 mL)

were added sequentially. The resulting mixture was heated to 150 °C for 30 min under Microwave irradiation. The mixture was diluted with EtOAc (15 mL) and washed with water (2x). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The residue was purified on ISCO and HPLC to give the title compound as a white solid (27.4 mg, 28%) and (1*r*,4*r*)-4-((2-(butylamino)pyrimidin-4-yl)amino)cyclohexanol (25.7 mg, 49%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.65 (d, *J* = 7.1 Hz, 1H), 9.46 (t, *J* = 5.4 Hz, 1H), 8.87 (d, *J* = 2.2 Hz, 1H), 8.31 (s, 1H), 8.10 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 4.19 – 4.09 (m, 1H), 3.84 – 3.68 (m, 5H), 3.51 – 3.44 (m, 2H), 3.15 – 3.06 (m, 4H), 2.86 – 2.66 (m, 3H), 2.28 – 2.15 (m, 2H), 2.13 – 2.01 (m, 2H), 1.72 – 1.61 (m, 2H), 1.56 – 1.36 (m, 6H), 0.96 (t, *J* = 7.4 Hz, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 159.4, 156.9, 153.1, 146.6, 142.8, 136.8, 130.2, 118.9, 103.4, 69.2, 66.0, 49.7, 45.8, 41.3, 33.3, 31.0, 29.5, 20.1, 13.7; MS *m/z* 491.30 [M+H]<sup>+</sup>.

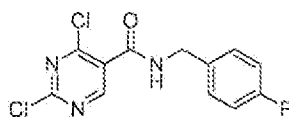
### Example 4

#### UNC2427A

General Procedure D:

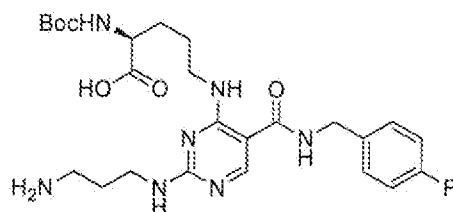


#### 2,4-Dichloro-N-(4-fluorobenzyl)pyrimidine-5-carboxamide



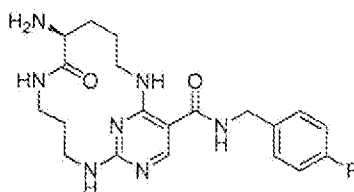
4-Fluorobenzylamine (1.78g, 14.2 mmol) in dichloromethane (5.0 mL) was added into a solution of 2,4-dichloropyrimidine-5-carbonyl chloride (3.0 g, 14.2 mmol) in dichloromethane (30 mL) at 0 °C. Then *N,N*-diisopropylethylamine (2.75g, 21.3 mmol) and 4-(dimethylamino)pyridine (17.1 mg, 0.14 mmol) were added into the mixture. The resulting mixture was allowed to warm to room temperature and stirred for 20 min. The solvent was removed and the residue was dissolved in dichloromethane and washed with water (2x). Solvent was removed and the residue was purified on ISCO to provide the title compound (3.96g, 93%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.73 (s, 1H), 7.42–7.35 (m, 2H), 7.12–7.02 (m, 2H), 4.53 (s, 2H); MS *m/z* 301.30 [M+H]<sup>+</sup>.

(S)-5-((2-((3-Aminopropyl)amino)-5-((4-fluorobenzyl)carbonyl)pyrimidin-4-yl)amino)-2-((tert-butoxycarbonyl)amino)pentanoic acid



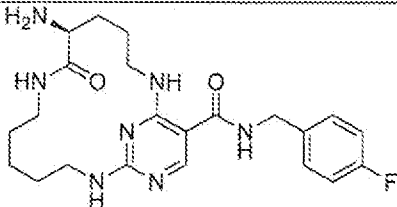
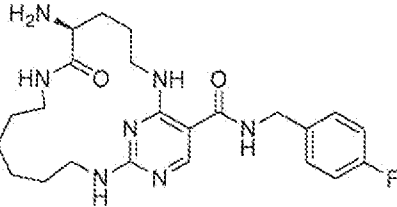
*L*-Ornithine (232 mg, 1.0 mmol), *N,N*-diisopropylethylamine (194 mg, 1.5 mmol) were added into a solution of 2,4-dichloro-*N*-(4-fluorobenzyl)pyrimidine-5-carboxamide (300 mg, 1.0 mmol) in a mixture of isopropyl alcohol and DMF (10 mL, 3:2, v/v) at room temperature. The resulting mixture was stirred for overnight. Then 1/3 of the reaction mixture was added to a solution of 1,3-diaminopropane (304 mg, 4.0 mmol) in DMF (1.0 mL) at room temperature. The reaction mixture was heated at 45 °C for 2h. The solvent was removed and the residue was purified on HPLC to give the title compound as TFA salt (92 mg, 34%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.22 (s, 1H), 7.38–7.28 (m, 2H), 7.06–6.95 (m, 2H), 4.45 (s, 2H), 4.18–4.09 (m, 1H), 3.69–3.53 (m, 4H), 3.08–2.99 (m, 2H), 2.05–1.97 (m, 2H), 1.91–1.83 (m, 1H), 1.80–1.66 (m, 3H), 1.41 (s, 9H); MS *m/z* 534.30 [M+H]<sup>+</sup>.

UNC2427A

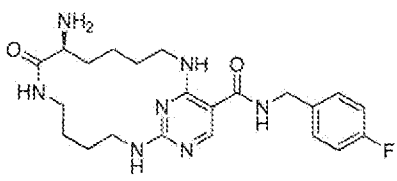
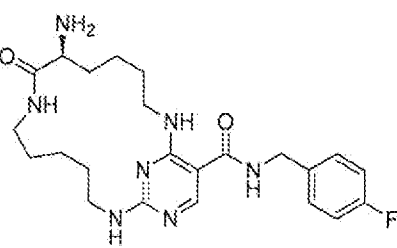
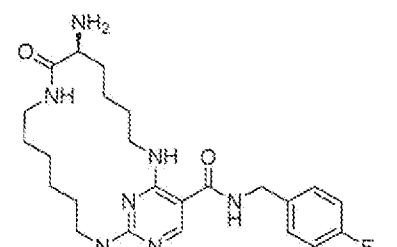
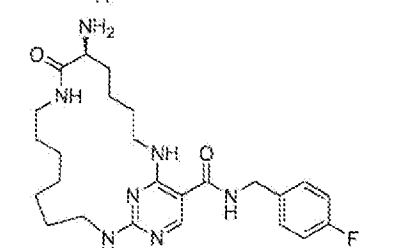
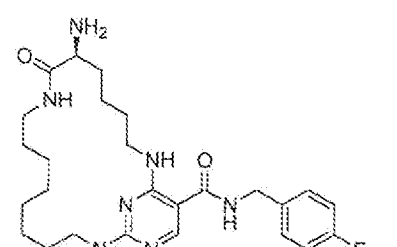
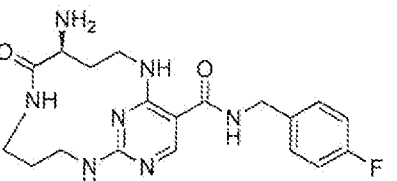


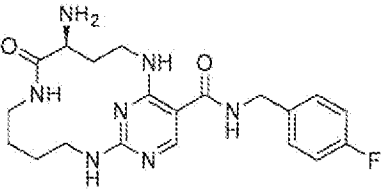
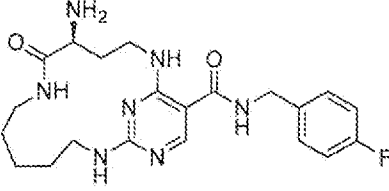
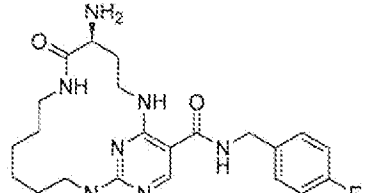
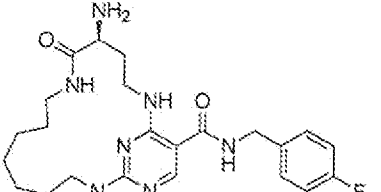
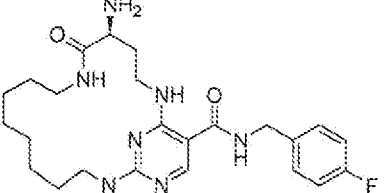
*O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU, 68.3 mg, 0.21 mmol) and triethylamine (43.5 mg, 0.43 mmol) were added to the solution of (*S*)-5-((2-((3-aminopropyl)amino)-5-((4-fluorobenzyl)carbamoyl)pyrimidin-4-yl)amino)-2-((*tert*-butoxycarbonyl)amino)pentanoic acid (70 mg, 0.085 mmol) in DMF (50 mL). The resulting mixture was diluted with dichloromethane (60 mL) and stirred at room temperature for overnight. Then the solvent was removed, the residue was dissolved in dichloromethane (5.0 mL) followed by the addition of TFA (1.0 mL). The resulting mixture was stirred at room temperature for 2.0 h. Then the solvent was removed and the residue was purified on HPLC to provide the title compound (**UNC2427A**) as TFA salt (27.4 mg, 46%);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.19 (s, 1H), 7.37–7.26 (m, 2H), 7.06–6.97 (m, 2H), 4.44 (s, 2H), 4.02–3.97 (m, 1H), 3.97–3.89 (m, 1H), 3.81–3.71 (m, 1H), 3.68–3.60 (m, 1H), 3.28–3.12 (m, 2H), 2.87–2.80 (m, 1H), 2.01–1.92 (m, 2H), 1.91–1.82 (m, 1H), 1.80–1.64 (m, 3H). MS  $m/z$  416.25  $[\text{M}+\text{H}]^+$ .

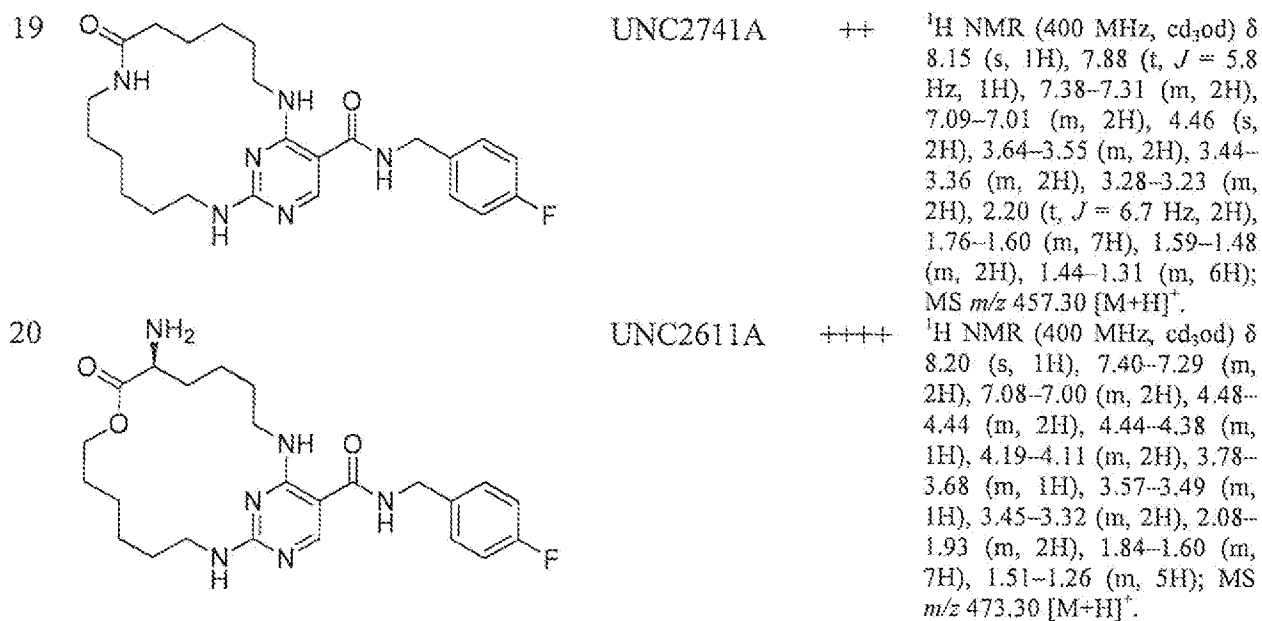
**Table 1** describes compounds prepared following procedures described in **Example 4** (General Procedure D), using appropriate reagents. (Note: Mer IC<sub>50</sub>: ++++ means < 10 nM; +++ means between 10-100nM, ++ means between 100 nM-1  $\mu\text{M}$ ; + means between 1-30  $\mu\text{M}$ ; - means inactive.)

	Structure	Compound_ID	Mer IC <sub>50</sub>	Physical Data MS $m/z$ (M+1) or/and $^1\text{H}$ NMR
1		UNC2429A	++	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ) $\delta$ 8.19 (s, 1H), 7.37–7.29 (m, 2H), 7.07–6.97 (m, 2H), 4.44 (s, 2H), 3.91–3.79 (m, 2H), 3.77–3.69 (m, 1H), 3.65–3.58 (m, 1H), 3.27–3.13 (m, 3H), 2.98–2.92 (m, 4H), 1.94–1.77 (m, 3H), 1.73–1.52 (m, 5H), 1.48–1.34 (m, 3H); MS $m/z$ 444.30 $[\text{M}+\text{H}]^+$ .
2		UNC2430A	++	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ) $\delta$ 8.20 (d, $J = 0.9$ Hz, 1H), 7.38–7.29 (m, 2H), 7.07–6.99 (m, 2H), 4.44 (s, 2H), 3.88–3.66 (m, 4H), 3.51–3.32 (m, 2H), 3.21–3.11 (m, 1H), 2.98–2.93 (m, 4H), 2.89–2.77 (m, 1H), 1.98–1.85 (m, 2H), 1.84–1.58 (m, 5H), 1.56–1.48 (m, 1H), 1.46–1.29 (m, 5H); MS $m/z$ 458.30 $[\text{M}+\text{H}]^+$ .

3		UNC2479A	++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) $\delta$ 8.21 (s, 1H), 7.36–7.30 (m, 2H), 7.07–6.99 (m, 2H), 4.45 (s, 2H), 3.94–3.85 (m, 1H), 3.80–3.74 (m, 1H), 3.74–3.65 (m, 1H), 3.55–3.45 (m, 2H), 3.38–3.30 (m, 1H), 3.23–3.11 (m, 1H), 2.96 (s, 1H), 2.89–2.80 (m, 1H), 1.97–1.81 (m, 2H), 1.77–1.55 (m, 5H), 1.54–1.43 (m, 2H), 1.43–1.21 (m, 7H); MS <i>m/z</i> 472.30 [M+H] <sup>+</sup> .
4		UNC2431A	+++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) $\delta$ 8.22 (s, 1H), 7.37–7.28 (m, 2H), 7.07–6.97 (m, 2H), 4.45 (s, 2H), 3.89–3.79 (m, 2H), 3.71–3.58 (m, 2H), 3.58–3.49 (m, 1H), 3.44–3.34 (m, 1H), 2.95 (s, 1H), 2.90–2.80 (m, 1H), 1.98–1.84 (m, 2H), 1.74–1.66 (m, 2H), 1.65–1.57 (m, 2H), 1.56–1.51 (m, 1H), 1.50–1.42 (m, 1H), 1.39–1.25 (m, 8H); MS <i>m/z</i> 486.30 [M+H] <sup>+</sup> .
5		UNC2342A	++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) $\delta$ 8.44 (d, <i>J</i> = 2.5 Hz, 1H), 7.81–7.73 (m, 2H), 7.53–7.46 (m, 2H), 4.33 (s, 2H), 4.07–3.93 (m, 4H), 3.82–3.64 (m, 4H), 3.41–3.34 (m, 2H), 3.28–3.07 (m, 4H), 2.90–2.82 (m, 1H), 2.04–1.95 (m, 2H), 1.94–1.85 (m, 1H), 1.83–1.68 (m, 3H); MS <i>m/z</i> 483.30 [M+H] <sup>+</sup> .
6		UNC2341A	++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) $\delta$ 8.45 (s, 1H), 7.81–7.75 (m, 2H), 7.53–7.48 (m, 2H), 4.34 (s, 2H), 4.08–3.98 (m, 2H), 3.92–3.85 (m, 1H), 3.80–3.66 (m, 3H), 3.61–3.52 (m, 1H), 3.47–3.32 (m, 4H), 3.27–3.11 (m, 3H), 2.99–2.96 (m, 1H), 2.95–2.88 (m, 1H), 1.96–1.86 (m, 3H), 1.86–1.75 (m, 2H), 1.72–1.61 (m, 2H), 1.48–1.33 (m, 1H); MS <i>m/z</i> 497.30 [M+H] <sup>+</sup> .
7		UNC2481A	+	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) $\delta$ 8.17 (s, 1H), 7.37–7.30 (m, 2H), 7.06–7.00 (m, 2H), 4.44 (s, 2H), 3.89–3.78 (m, 2H), 3.77–3.72 (m, 2H), 3.69–3.62 (m, 1H), 3.49–3.33 (m, 3H), 3.02–2.93 (m, 2H), 1.98–1.76 (m, 5H), 1.73–1.62 (m, 3H), 1.60–1.49 (m, 2H); MS <i>m/z</i> 430.30 [M+H] <sup>+</sup> .

8		UNC2483A	+++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.17 (s, 1H), 7.37–7.30 (m, 2H), 7.08–6.99 (m, 2H), 4.45 (s, 2H), 3.91–3.80 (m, 2H), 3.79–3.71 (m, 1H), 3.59–3.51 (m, 1H), 3.48–3.39 (m, 2H), 3.22–3.13 (m, 1H), 2.89–2.80 (m, 1H), 1.94–1.76 (m, 3H), 1.75–1.27 (m, 10H); MS <i>m/z</i> 445.30 [M+H] <sup>+</sup> .
9		UNC2484A	+++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.17 (s, 1H), 7.36–7.30 (m, 2H), 7.08–6.99 (m, 2H), 4.45 (s, 2H), 3.81–3.74 (m, 1H), 3.73–3.66 (m, 1H), 3.65–3.59 (m, 2H), 3.53–3.45 (m, 2H), 2.99–2.94 (m, 1H), 2.87–2.82 (m, 1H), 1.90–1.81 (m, 2H), 1.75–1.54 (m, 6H), 1.50–1.31 (m, 5H); MS <i>m/z</i> 458.25 [M+H] <sup>+</sup> .
10		UNC2541A	++++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.18 (s, 1H), 7.36–7.29 (m, 2H), 7.07–6.98 (m, 2H), 4.44 (s, 2H), 3.84 (t, J = 5.6 Hz, 1H), 3.73–3.63 (m, 2H), 3.52–3.40 (m, 2H), 3.01–2.89 (m, 2H), 1.97–1.84 (m, 2H), 1.75–1.42 (m, 9H), 1.41–1.29 (m, 5H); MS <i>m/z</i> 472.30 [M+H] <sup>+</sup> .
11		UNC2486A	++++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.19 (s, 1H), 7.37–7.30 (m, 2H), 7.07–6.99 (m, 2H), 4.45 (s, 2H), 3.82–3.75 (m, 1H), 3.75–3.63 (m, 2H), 3.61–3.54 (m, 1H), 3.48–3.41 (m, 1H), 3.37–3.30 (m, 1H), 2.89–2.80 (m, 1H), 1.93–1.82 (m, 2H), 1.76–1.60 (m, 4H), 1.57–1.27 (m, 11H); MS <i>m/z</i> 486.30 [M+H] <sup>+</sup> .
12		UNC2487A	++++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.06 (s, 1H), 7.26–7.21 (m, 2H), 6.98–6.90 (m, 2H), 5.28 (s, 2H), 4.39 (s, 2H), 3.39–3.34 (m, 2H), 3.31–3.23 (m, 3H), 3.20–3.11 (m, 1H), 1.68–1.56 (m, 4H), 1.56–1.50 (m, 2H), 1.48–1.38 (m, 2H), 1.34–1.19 (m, 10H); MS <i>m/z</i> 500.35 [M+H] <sup>+</sup> .
13		UNC2573A	+	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.22 (s, 1H), 7.37–7.29 (m, 2H), 7.06–6.98 (m, 2H), 4.45 (s, 2H), 3.95–3.89 (m, 1H), 3.85–3.75 (m, 1H), 3.70–3.59 (m, 2H), 3.53–3.40 (m, 2H), 2.87–2.77 (m, 1H), 2.36–2.23 (m, 1H), 2.18–2.08 (m, 1H),

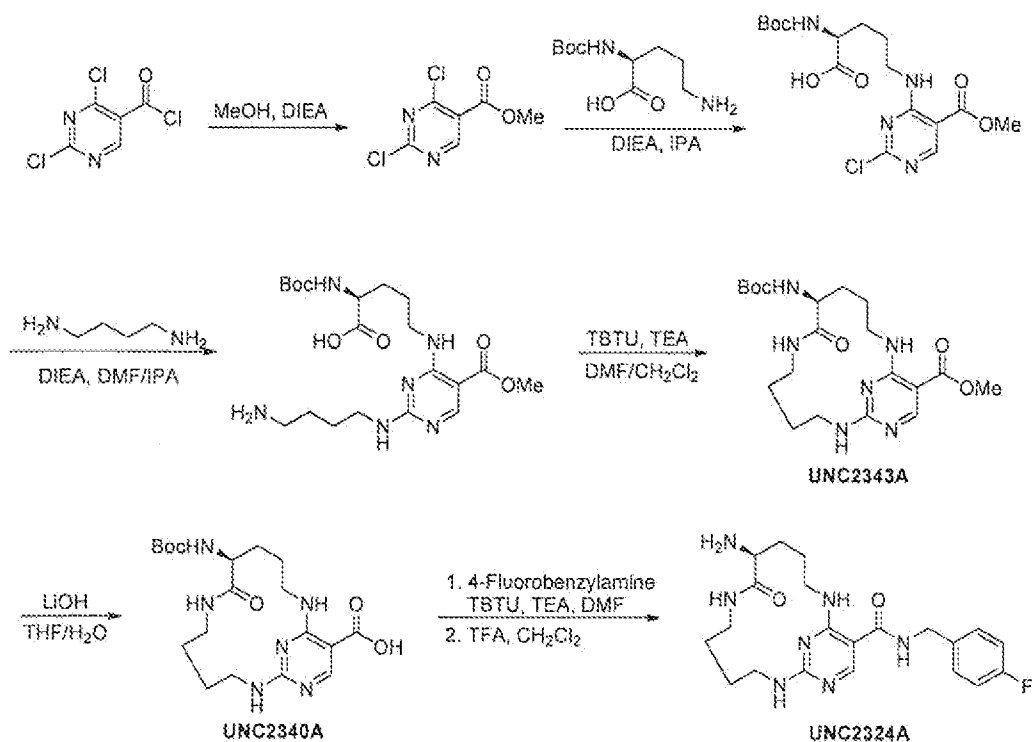
14		UNC2574A	++	2.06–1.95 (m, 1H), 1.72–1.59 (m, 1H); MS $m/z$ 402.20 $[M+H]^+$ . $^1H$ NMR (400 MHz, $CD_3OD$ ) $\delta$ 8.21 (s, 1H), 7.38–7.27 (m, 2H), 7.07–6.97 (m, 2H), 4.45 (s, 2H), 4.01–3.95 (m, 1H), 3.94–3.85 (m, 1H), 3.78–3.69 (m, 1H), 3.67–3.57 (m, 1H), 3.46–3.37 (m, 1H), 3.24–3.15 (m, 1H), 3.05–2.91 (m, 5H), 2.20–2.10 (m, 2H), 2.03–1.91 (m, 1H), 1.79–1.69 (m, 2H), 1.63–1.47 (m, 2H); MS $m/z$ 416.25 $[M+H]^+$ .
15		UNC2575A	++	$^1H$ NMR (400 MHz, $CD_3OD$ ) $\delta$ 8.23 (s, 1H), 7.37–7.29 (m, 2H), 7.07–6.98 (m, 2H), 4.45 (s, 2H), 3.92–3.74 (m, 3H), 3.63–3.52 (m, 2H), 3.26–3.21 (m, 1H), 2.96 (s, 1H), 2.89–2.82 (m, 1H), 2.21–2.13 (m, 2H), 1.74–1.59 (m, 3H), 1.58–1.43 (m, 3H); MS $m/z$ 430.25 $[M+H]^+$ .
16		UNC2576A	++	$^1H$ NMR (400 MHz, $CD_3OD$ ) $\delta$ 8.24 (s, 1H), 7.38–7.29 (m, 2H), 7.07–6.98 (m, 2H), 4.45 (s, 2H), 3.92–3.73 (m, 2H), 3.69–3.59 (m, 2H), 3.52 (ddd, $J = 20.6, 13.5, 6.4$ Hz, 2H), 3.24–3.10 (m, 2H), 2.98–2.93 (m, 4H), 2.25–2.14 (m, 2H), 1.68–1.59 (m, 3H), 1.55–1.48 (m, 2H), 1.45–1.34 (m, 4H); MS $m/z$ 444.30 $[M+H]^+$ .
17		UNC2577A	++	$^1H$ NMR (400 MHz, $CD_3OD$ ) $\delta$ 8.24 (s, 1H), 7.40–7.28 (m, 2H), 7.08–6.97 (m, 2H), 4.45 (s, 2H), 3.88–3.80 (m, 1H), 3.78–3.69 (m, 1H), 3.68–3.53 (m, 3H), 2.93–2.83 (m, 1H), 2.39–2.28 (m, 1H), 2.16–2.04 (m, 1H), 1.71–1.26 (m, 11H); MS $m/z$ 458.30 $[M+H]^+$ .
18		UNC2578A	++	$^1H$ NMR (400 MHz, $CD_3OD$ ) $\delta$ 8.25 (s, 1H), 7.38–7.29 (m, 2H), 7.07–6.99 (m, 2H), 4.46 (s, 2H), 3.87–3.66 (m, 4H), 3.51–3.43 (m, 1H), 2.91–2.84 (m, 1H), 2.45–2.33 (m, 1H), 2.11–2.03 (m, 1H), 1.67–1.53 (m, 3H), 1.51–1.13 (m, 10H); MS $m/z$ 472.30 $[M+H]^+$ .



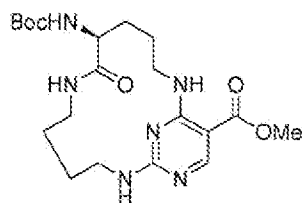
## Example 5

## UNC2324A

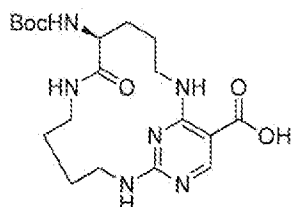
General Procedure E:

UNC2343A

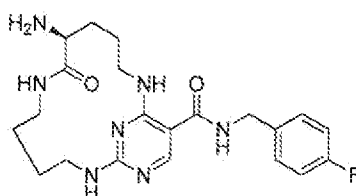
- 29 -



To a solution of 2,4-dichloropyrimidine-5-carbonyl chloride (500 mg, 2.38 mmol) in dichloromethane (30 mL) was added methanol (87.6 mg, 2.73 mmol) and diisopropylethylamine (369 mg, 2.86 mmol) at 0 °C. The resulting mixture was stirred for at 0 °C 1 h. Then the solvent was removed. The residue (412mg, 2.0 mmol) was dissolved in IPA (20 mL) followed by the addition of *L*-Ornithine (465 mg, 2.0 mmol) and *N,N*-diisopropylethylamine (388 mg, 3.0 mmol). The resulting mixture was stirred at 0 °C for 90 min, then dichloromethane (5.0 mL) was added. The resulting mixture was stirred at 0 °C for 1.0 h and at room temperature overnight. Solvent was removed and the residue (MS  $m/z$  403.30  $[M+H]^+$ ) was dissolved in DMF (5.0 mL) and was added dropwise into a solution of 1,4-diaminobutane (1.68g, 19.1 mmol) in DMF (1.0 mL) at room temperature. The resulting mixture was heated to 45 °C for 1h. The solvent was removed and the residue was dissolved in ethyl acetate (35 mL) and washed with water (3x). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. The residue was purified on HPLC to provide (*S*)-5-((2-((4-aminobutyl)amino)-5-(methoxycarbonyl)pyrimidin-4-yl)amino)-2-((*tert*-butoxycarbonyl)amino)pentanoic acid as a semisolid (MS  $m/z$  455.30  $[M+H]^+$ ). The semisolid (595 mg, 1.31 mmol) was dissolved in DMF (150 mL), then TBTU (546.4 mg, 1.70 mmol) and DIEA (508 mg, 3.93 mmol) were added sequentially. The resulting mixture was stirred at room temperature overnight. The solvent was removed. The residue was dissolved in ethyl acetate and washed with water (3x). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated. The residue was purified on HPLC to provide the title compound (**UNC2343A**).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.42 (s, 1H), 4.08–3.99 (m, 1H), 3.90–3.84 (m, 3H), 3.59–3.47 (m, 2H), 3.46–3.31 (m, 2H), 3.28–3.21 (m, 1H), 3.09–2.95 (m, 1H), 1.90–1.52 (m, 8H), 1.51–1.32 (m, 9H); MS  $m/z$  437.30  $[M+H]^+$ .

**UNC2340A**

Lithium hydroxide (200 mg, 8.3 mmol) was added to a solution of **UNC2343A** (724 mg, 1.66 mmol) in a mixture of THF and H<sub>2</sub>O (20 mL, 3:2, v/v). The resulting mixture was heated at 75 °C overnight. Then the reaction mixture was acidified to pH 4, then extracted with a mixture of CH<sub>2</sub>Cl<sub>2</sub> and IPA (3:1, v/v) to give the title compound (**UNC2340A**) (406 mg, 58%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.36 (s, 1H), 8.11 (s, 1H), 4.12–4.02 (m, 1H), 3.61–3.47 (m, 2H), 3.34 (s, 1H), 3.28–3.17 (m, 1H), 3.06–2.93 (m, 1H), 2.90–2.84 (m, 1H), 1.89–1.52 (m, 7H), 1.42 (s, 9H); MS *m/z* 423.25 [M+H]<sup>+</sup>.

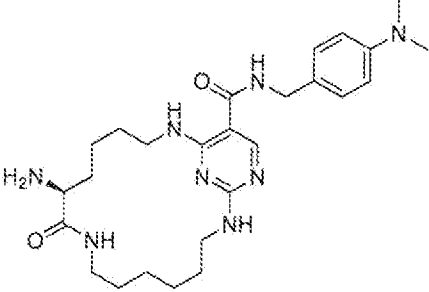
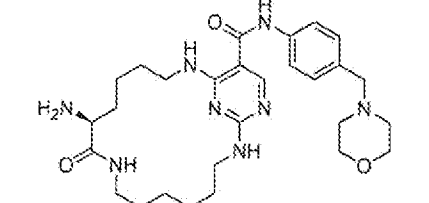
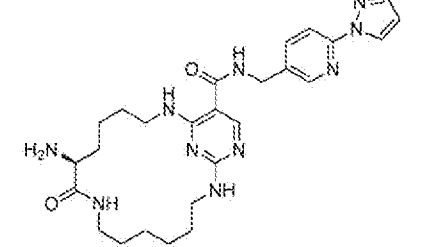
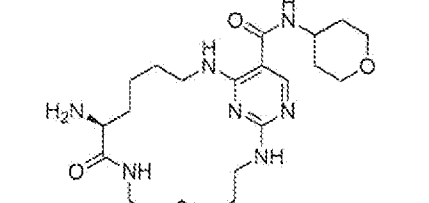
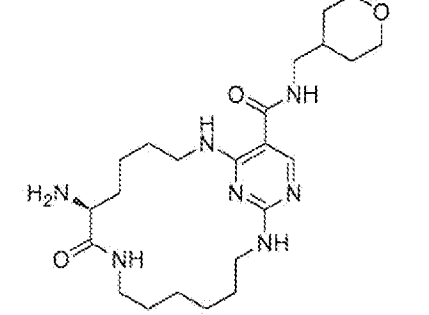
**UNC2324A**

4-Fluorobenzylamine (65.1 mg, 0.5 mmol), TBTU (128.2 mg, 0.4 mmol) and triethylamine (68 mg, 0.67 mmol) were added to a solution of **UNC2340A** (40 mg, 0.095 mmol) in anhydrous DMF (20 mL) at room temperature. The resulting mixture was stirred for 2h, then solvent was removed, the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and washed with water (2x). TFA (1.0 mL) was then added and stirred at room temperature for 2.0 h, condensed and purified on HPLC to provide the title compound (**UNC2324A**) (26 mg, 52%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.19 (s, 1H), 7.37–7.26 (m, 2H), 7.07–6.96 (m, 2H), 4.44 (s, 2H), 3.88–3.82 (m, 1H), 3.77–3.68 (m, 1H), 3.58–3.47 (m, 2H), 3.43–3.35 (m, 1H), 3.26–3.13 (m, 2H), 2.98–2.93 (m, 2H), 2.92–2.84 (m, 1H), 1.92–1.81 (m, 3H), 1.81–1.53 (m, 5H), 1.44–1.29 (m, 1H); MS *m/z* 430.20 [M+H]<sup>+</sup>.

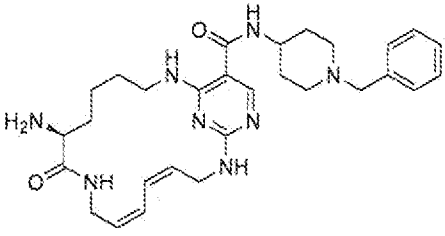
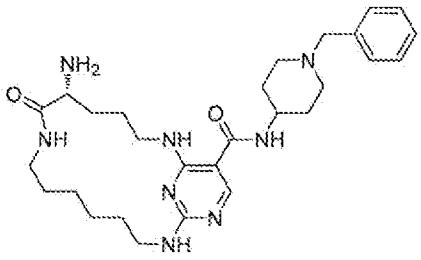
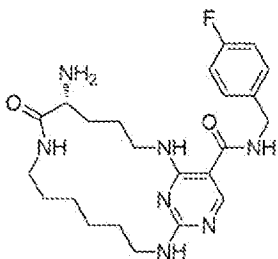
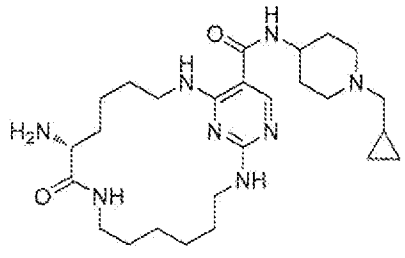
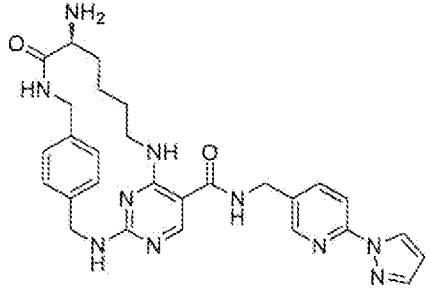
**Table 1** describes compounds prepared following procedures described in **Example 5** (General Procedure E), using appropriate reagents.

	Structure	Compound_ID	Mer IC <sub>50</sub>	Physical Data MS <i>m/z</i> (M+1) or/and <sup>1</sup> H NMR
1		UNC2589A	++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.21 (s, 1H), 7.39–7.35 (m, 4H), 4.50–4.47 (m, 2H), 3.97–3.91 (m, 3H), 3.87–3.83 (m, 1H), 3.40–3.33 (m, 5H), 3.09–3.01 (m, 4H), 2.87 (s, 4H), 1.93–1.82 (m, 4H), 1.79–1.70 (m, 2H), 1.69–1.57 (m, 3H), 1.44–1.30 (m, 2H); MS <i>m/z</i>

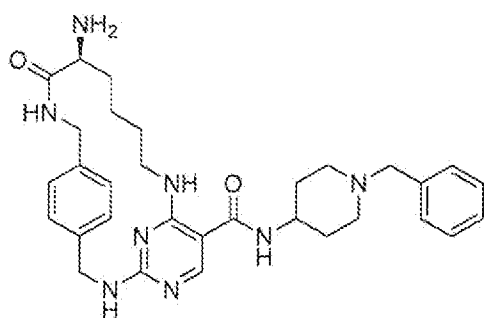
2		UNC2615A	++++	<p>524.40 [M+H]<sup>+</sup>.  <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  <math>\delta</math> 8.92 (s, 1H), 8.79 (d, <i>J</i> = 5.5 Hz, 1H), 8.67 (d, <i>J</i> = 8.0 Hz, 1H), 8.43 (s, 1H), 8.08 (dd, <i>J</i> = 7.8, 5.9 Hz, 1H), 4.71 (s, 2H), 3.92 (t, <i>J</i> = 5.3 Hz, 1H), 3.76–3.60 (m, 2H), 3.58–3.36 (m, 2H), 3.38–3.22 (m, 1H), 3.03–2.89 (m, 1H), 2.05–1.84 (m, 2H), 1.82–1.52 (m, 6H), 1.52–1.28 (m, 6H); MS (ESI): 455.4 [M + H]<sup>+</sup>.</p>
3		UNC2616A	++++	<p><sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  <math>\delta</math> 8.81 (d, <i>J</i> = 6.0 Hz, 2H), 8.49 (s, 1H), 8.10 (d, <i>J</i> = 6.1 Hz, 2H), 4.80 (s, 2H), 3.92 (t, <i>J</i> = 5.3 Hz, 1H), 3.82–3.60 (m, 2H), 3.59–3.38 (m, 2H), 3.37–3.31 (m, 1H), 3.05–2.91 (m, 1H), 2.04–1.83 (m, 2H), 1.82–1.54 (m, 6H), 1.54–1.23 (m, 6H); MS (ESI): 455.3 [M + H]<sup>+</sup>.</p>
4		UNC2625A	++++	<p><sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  <math>\delta</math> 8.36 (s, 1H), 4.20–4.03 (m, 1H), 3.91 (t, <i>J</i> = 5.3 Hz, 1H), 3.82–3.61 (m, 2H), 3.60–3.39 (m, 4H), 3.37–3.21 (m, 1H), 3.20–3.04 (m, 2H), 3.04–2.88 (m, 1H), 2.24–2.07 (m, 2H), 2.04–1.81 (m, 4H), 1.81–1.23 (m, 12H); MS (ESI): 447.4 [M + H]<sup>+</sup>.</p>
5		UNC2702A	+++	<p><sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  <math>\delta</math> 8.78 (d, <i>J</i> = 5.4 Hz, 1H), 8.59 (t, <i>J</i> = 7.6 Hz, 1H), 8.50 (s, 1H), 8.11 (d, <i>J</i> = 8.0 Hz, 1H), 7.99 (t, <i>J</i> = 8.0 Hz, 1H), 4.86 (s, 2H), 3.90 (t, <i>J</i> = 5.3 Hz, 1H), 3.77–3.61 (m, 2H), 3.60–3.38 (m, 2H), 3.35–3.25 (m, 1H), 2.95 (dt, <i>J</i> = 13.2, 4.5 Hz, 1H), 2.02–1.83 (m, 2H), 1.82–1.28 (m, 12H); MS (ESI): 455.4 [M + H]<sup>+</sup>.</p>
6		UNC2626A	+++	<p><sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  <math>\delta</math> 8.16 (s, 1H), 7.16 (d, <i>J</i> = 8.3 Hz, 1H), 6.53 (d, <i>J</i> = 2.3 Hz, 1H), 6.46 (dd, <i>J</i> = 8.3, 2.4 Hz, 1H), 4.40 (s, 2H), 3.90 (t, <i>J</i> = 5.5 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.73–3.63 (m, 2H), 3.55–3.39 (m, 2H), 2.97 (s, 1H), 2.03–1.83 (m, 2H), 1.77–1.31 (m, 13H); MS (ESI): 514.3 [M + H]<sup>+</sup>.</p>

7		UNC2701A	++++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.31 (s, 1H), 7.60 (dd, <i>J</i> = 23.0, 8.5 Hz, 4H), 4.54 (s, 2H), 3.90 (t, <i>J</i> = 5.4 Hz, 1H), 3.78–3.61 (m, 2H), 3.61–3.37 (m, 2H), 3.35–3.31 (m, 1H), 3.27 (s, 6H), 2.99–2.87 (m, 1H), 2.03–1.85 (m, 2H), 1.81–1.55 (m, 6H), 1.55–1.25 (m, 6H); MS (ESI): 497.4 [M + H] <sup>+</sup> .
8		UNC2703A	++++	<sup>1</sup> H NMR (400 MHz, D <sub>2</sub> O) δ 8.28 (s, 1H), 7.59 (dd, <i>J</i> = 21.0, 8.7 Hz, 4H), 4.41 (s, 2H), 4.23–4.08 (m, 2H), 4.03 (t, <i>J</i> = 5.7 Hz, 1H), 3.87–3.44 (m, 8H), 3.38–3.23 (m, 3H), 3.09–3.01 (m, 1H), 2.03–1.90 (m, 2H), 1.83–1.55 (m, 6H), 1.53–1.27 (m, 6H); MS (ESI): 539.4 [M + H] <sup>+</sup> .
9		UNC2709A	++++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.57 (d, <i>J</i> = 2.5 Hz, 1H), 8.43 (d, <i>J</i> = 1.4 Hz, 1H), 8.23 (s, 1H), 7.99–7.85 (m, 2H), 7.75 (d, <i>J</i> = 1.2 Hz, 1H), 6.53 (dd, <i>J</i> = 2.5, 1.8 Hz, 1H), 4.54 (s, 2H), 3.86 (t, <i>J</i> = 5.5 Hz, 1H), 3.78–3.63 (m, 2H), 3.60–3.39 (m, 2H), 3.30–3.24 (m, 1H), 2.98–2.89 (m, 1H), 1.99–1.82 (m, 2H), 1.82–1.20 (m, 12H); MS (ESI): 521.4 [M + H] <sup>+</sup> .
10		UNC2704A	++++	<sup>1</sup> H NMR (400 MHz, D <sub>2</sub> O) δ 8.06 (s, 1H), 4.13–3.95 (m, 4H), 3.89–3.74 (m, 2H), 3.72–3.56 (m, 4H), 3.55–3.39 (m, 2H), 3.36–3.23 (m, 1H), 3.05 (dt, <i>J</i> = 13.4, 4.7 Hz, 1H), 1.96 (dd, <i>J</i> = 13.5, 11.0 Hz, 4H), 1.72–1.60 (m, 6H), 1.53–1.24 (m, 6H); MS (ESI): 448.3 [M + H] <sup>+</sup> .
11		UNC2705A	++++	<sup>1</sup> H NMR (400 MHz, D <sub>2</sub> O) δ 8.03 (s, 1H), 4.15–3.93 (m, 3H), 3.91–3.82 (m, 1H), 3.81–3.41 (m, 8H), 3.39–3.16 (m, 3H), 3.05 (dt, <i>J</i> = 13.5, 4.8 Hz, 1H), 2.03–1.80 (m, 3H), 1.79–1.49 (m, 7H), 1.49–1.30 (m, 6H); MS (ESI): 462.4 [M + H] <sup>+</sup> .

12		UNC2706B	++++	$^1\text{H NMR}$ (400 MHz, $\text{D}_2\text{O}$ ) $\delta$ 8.23 (s, 1H), 7.46 (d, $J = 8.8$ Hz, 2H), 7.17 (d, $J = 8.7$ Hz, 2H), 4.03 (t, $J = 5.4$ Hz, 1H), 3.88 (d, $J = 12.5$ Hz, 2H), 3.78–3.43 (m, 6H), 3.25 (dd, $J = 42.0, 11.7$ Hz, 5H), 3.12–2.93 (m, 4H), 2.06–1.85 (m, 2H), 1.85–1.56 (m, 6H), 1.56–1.23 (m, 6H); MS (ESI): 538.4 $[\text{M} + \text{H}]^+$ .
13		UNC2834A	++++	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ) $\delta$ 8.42–8.23 (m, 1H), 7.60 (s, 2H), 7.50 (s, 3H), 4.49–4.30 (m, 2H), 4.19–4.02 (m, 1H), 3.93 (s, 1H), 3.78–3.62 (m, 2H), 3.65–3.40 (m, 4H), 3.31–3.10 (m, 3H), 2.96 (d, $J = 13.3$ Hz, 1H), 2.26–1.83 (m, 6H), 1.82–1.56 (m, 6H), 1.57–1.26 (m, 6H); MS (ESI): 537.4 $[\text{M} + \text{H}]^+$ .
14		UNC2835A	++	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ) $\delta$ 8.00 (s, 1H), 3.95–3.87 (m, 1H), 3.86–3.76 (m, 2H), 3.76–3.61 (m, 2H), 3.59–3.39 (m, 2H), 3.31–3.24 (m, 3H), 3.15 (s, 3H), 3.01–2.90 (m, 1H), 2.75 (s, 3H), 2.04–1.85 (m, 2H), 1.86–1.55 (m, 6H), 1.53–1.28 (m, 6H); MS (ESI): 435.4 $[\text{M} + \text{H}]^+$ .
15		UNC2836A	++++	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ) $\delta$ 8.31 (s, 1H), 7.62 (dd, $J = 35.5, 8.1$ Hz, 4H), 4.54 (s, 2H), 4.19–4.01 (m, 4H), 3.91 (s, 1H), 3.79–3.60 (m, 6H), 3.59–3.41 (m, 2H), 3.30–3.25 (m, 1H), 3.02–2.87 (m, 1H), 2.04–1.84 (m, 2H), 1.84–1.55 (m, 6H), 1.51–1.28 (m, 6H); MS (ESI): 539.4 $[\text{M} + \text{H}]^+$ .
16		UNC2837A	+++	$^1\text{H NMR}$ (400 MHz, $\text{CD}_3\text{OD}$ ) $\delta$ 8.53 (s, 1H), 8.41 (s, 1H), 8.24 (s, 1H), 7.89 (s, 2H), 7.72 (s, 1H), 6.50 (s, 1H), 4.52 (s, 2H), 4.08 (t, $J = 4.7$ Hz, 1H), 3.73–3.53 (m, 3H), 3.48–3.32 (m, 2H), 3.09–2.98 (m, 1H), 1.87–1.20 (m, 14H); MS (ESI): 544.3 $[\text{M} + \text{Na}]^+$ .

17		UNC2910A	+++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.35 (s, 1H), 7.65–7.55 (m, 2H), 7.52–7.43 (m, 3H), 6.33–6.12 (m, 2H), 5.86–5.68 (m, 2H), 4.34 (s, 2H), 4.26–3.88 (m, 5H), 3.76–3.42 (m, 5H), 3.16 (t, <i>J</i> = 12.4 Hz, 2H), 2.24–2.14 (m, 2H), 2.05–1.89 (m, 3H), 1.66–1.33 (m, 4H), 1.24–1.13 (m, 1H); MS (ESI): 533.4 [M + H] <sup>+</sup> .
18		UNC2967A	++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.48–8.37 (m, 1H), 8.21 (s, 1H), 7.54–7.40 (m, 4H), 4.43–4.21 (m, 2H), 4.05 (t, <i>J</i> = 11.7 Hz, 1H), 3.96 (s, 1H), 3.89–3.62 (m, 4H), 3.53 (d, <i>J</i> = 12.7 Hz, 2H), 3.43–3.34 (m, 2H), 3.12 (t, <i>J</i> = 12.4 Hz, 2H), 2.89–2.78 (m, 1H), 2.29–1.93 (m, 3H), 1.93–1.44 (m, 8H), 1.44–1.27 (m, 4H); MS (ESI): 523.4 [M + H] <sup>+</sup> .
19		UNC2968A	++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.27 (s, 1H), 7.37 (dd, <i>J</i> = 8.5, 5.4 Hz, 2H), 7.05 (t, <i>J</i> = 8.7 Hz, 2H), 4.47 (s, 2H), 3.96–3.68 (m, 4H), 3.49–3.34 (m, 2H), 2.92–2.81 (m, 1H), 2.05–1.62 (m, 6H), 1.62–1.29 (m, 6H); MS (ESI): 458.3 [M + H] <sup>+</sup> .
20		UNC3038A	++++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.33 (s, 1H), 4.11 (s, 1H), 3.90 (t, <i>J</i> = 5.4 Hz, 1H), 3.79–3.65 (m, 3H), 3.62–3.38 (m, 3H), 3.29–3.23 (m, 1H), 3.22–2.84 (m, 5H), 2.33–1.83 (m, 6H), 1.78–1.57 (m, 6H), 1.53–1.30 (m, 6H), 1.20–1.10 (m, 1H), 0.86–0.69 (m, 2H), 0.54–0.37 (m, 2H); MS (ESI): 501.4 [M + H] <sup>+</sup> .
21		UNC2914A	+++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.62 (d, <i>J</i> = 2.7 Hz, 1H), 8.48 (d, <i>J</i> = 2.0 Hz, 1H), 8.37 (s, 1H), 8.15 (dd, <i>J</i> = 8.6, 2.2 Hz, 1H), 8.03 (d, <i>J</i> = 8.6 Hz, 1H), 7.85 (d, <i>J</i> = 1.5 Hz, 1H), 7.35 (d, <i>J</i> = 8.1 Hz, 2H), 7.27 (d, <i>J</i> = 8.1 Hz, 2H), 6.62 (dd, <i>J</i> = 2.6, 1.8 Hz, 1H), 4.74 (d, <i>J</i> = 13.7 Hz, 1H), 4.60–4.48 (m, 4H), 3.95–3.83 (m, 2H), 3.76–3.55 (m, 1H), 3.43–3.32 (m, 1H), 3.28–3.15 (m, 1H), 1.86–1.72 (m, 2H), 1.31–1.10 (m, 2H), 1.03–0.88 (m, 1H), 0.56–0.43 (m, 1H). MS <i>m/z</i> 541.3

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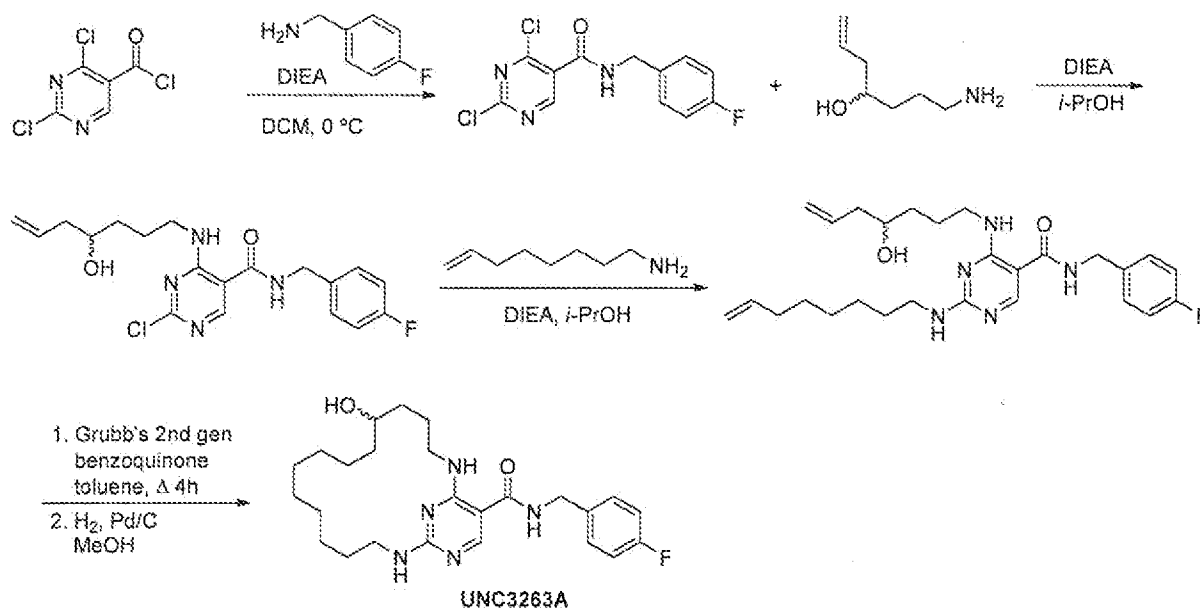
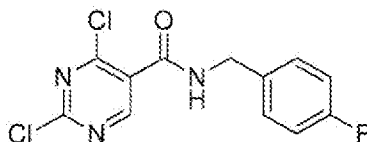
UNC2916A +++

[M+H]<sup>+</sup>  
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  
 δ 8.35 (s, 1H), 7.62–7.53 (m, 2H), 7.53–7.46 (m, 3H), 7.40–7.33 (m, 2H), 7.31–7.23 (m, 2H), 4.81–4.71 (m, 1H), 4.61–4.49 (m, 2H), 4.46 (s, 1H), 4.33 (s, 2H), 4.12–3.99 (m, 1H), 3.94–3.82 (m, 2H), 3.77–3.67 (m, 1H), 3.62–3.47 (m, 2H), 3.45–3.33 (m, 2H), 3.26–3.08 (m, 4H), 2.23–2.11 (m, 2H), 2.01–1.87 (m, 2H), 1.77 (dd, *J* = 13.4, 7.9 Hz, 2H), 1.28–1.10 (m, 3H), 1.03–0.87 (m, 1H), 0.57–0.42 (m, 1H).  
 MS *m/z* 557.35 [M+H]<sup>+</sup>.

## Example 6

## UNC3263A

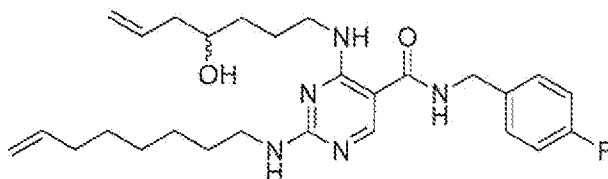
General Procedure F:

2,4-Dichloro-N-[(4-fluorophenyl)methyl]pyrimidine-5-carboxamide

A solution of 2,4-dichloropyrimidine-5-carbonyl chloride (3.35 g, 15.8 mmol) in dichloromethane (53 mL) was added (4-fluorophenyl)methanamine (1.32 g, 10.56 mmol) and

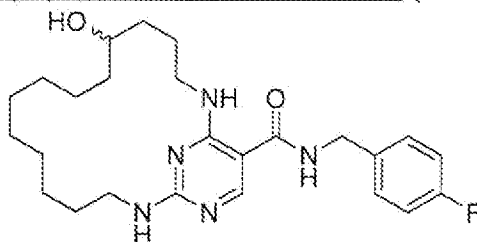
DIEA (3.7 mL, 21 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, the solvent was removed, and the residue was purified by ISCO silica gel column to provide the title compound (1.97 g, 62%) as a yellow solid.

N-[(4-Fluorophenyl)methyl]-4-[(4-hydroxyhept-6-en-1-yl)amino]-2-[(oct-7-en-1-yl)amino]pyrimidine-5-carboxamide



A solution of 2,4-dichloro-*N*-[(4-fluorophenyl)methyl]pyrimidine-5-carboxamide (97 mg, 0.325 mmol) in *i*-PrOH (5 mL) was added 7-aminohept-1-en-4-ol (42 mg, 0.325 mmol) and DIEA (85  $\mu$ L, 0.488 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. To the reaction was added oct-7-en-1-amine (207 mg, 0.975 mmol) and DIEA (85  $\mu$ L, 0.488 mmol). The reaction was heated at 70 °C for 6 h and the volatiles were removed under a reduced pressure. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL) and washed with H<sub>2</sub>O (2.0 mL). The H<sub>2</sub>O layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  20 mL); the organic layers were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent was removed under a reduced pressure. The residue was purified by ISCO silica gel column to provide the title compound (39 mg, 25%) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.70 (s, 1H), 8.09 (s, 1H), 7.29 (dd, *J* = 8.7, 5.3 Hz, 2H), 7.07–6.98 (m, 2H), 6.08 (s, 1H), 5.90–5.71 (m, 2H), 5.18–5.04 (m, 1H), 5.03–4.89 (m, 2H), 4.51 (d, *J* = 5.7 Hz, 2H), 3.70 (s, 1H), 3.49 (s, 2H), 3.38 (dt, *J* = 9.7, 4.8 Hz, 2H), 2.35–2.12 (m, 2H), 1.80–1.68 (m, 2H), 1.59 (s, 9H), 1.44–1.31 (m, 5H).

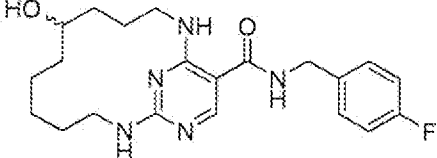
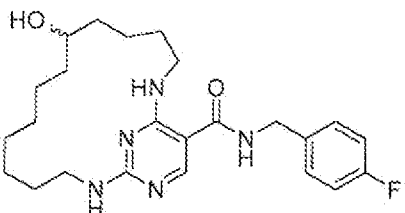
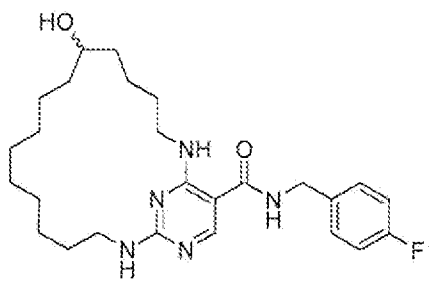
N-[(4-Fluorophenyl)methyl]-6-hydroxy-2,16,18,21-tetraazabicyclo[15.3.1]henicosa-1(20),17(21),18-triene-20-carboxamide (UNC3263A)



A solution of *N*-[(4-fluorophenyl)methyl]-4-[(4-hydroxyhept-6-en-1-yl)amino]-2-[(oct-7-en-1-yl)amino]pyrimidine-5-carboxamide (34 mg, 0.07 mmol) in toluene (35 mL) was added benzoquinone (1.5 mg, 0.014 mmol) and Grubb's 2<sup>nd</sup> generation catalyst (6.0 mg, 0.007 mmol). The mixture was refluxed under Ar overnight. After which more catalyst was

added (6.0 mg), and heated at reflux for 8 h. The volatiles were removed and the residue was purified by ISCO silica gel column to provide the RCM product as a crude brown solid. The residue was dissolved in MeOH (1.0 mL) and Pd/C (10 mg) was added. The mixture was stirred at room temperature under a hydrogen atmosphere for 24 h. The mixture was filtered through Celite and washed with MeOH then purified by HPLC to afford the title compound as a white solid (5.3 mg, 16%).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.21 (s, 1H), 7.37 (dd,  $J = 8.8, 5.4$  Hz, 2H), 7.05 (t,  $J = 8.8$  Hz, 2H), 4.47 (s, 2H), 3.73–3.60 (m, 2H), 3.58–3.41 (m, 3H), 1.84–1.72 (m, 2H), 1.72–1.62 (m, 2H), 1.61–1.45 (m, 5H), 1.43–1.26 (m, 11H). MS  $m/z$  458.3  $[\text{M}+\text{H}]^+$ .

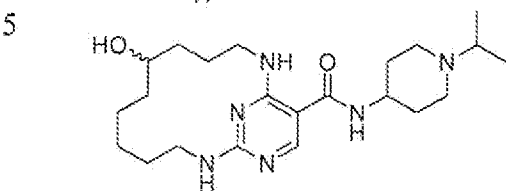
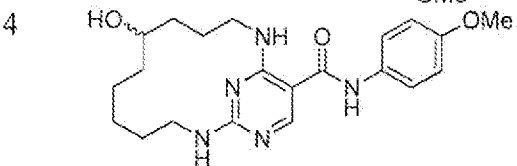
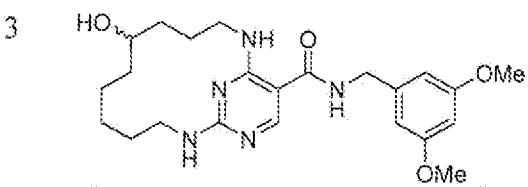
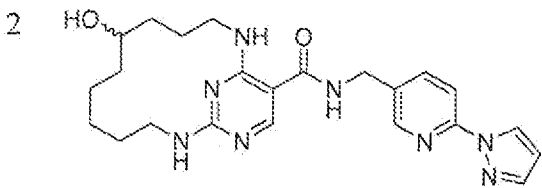
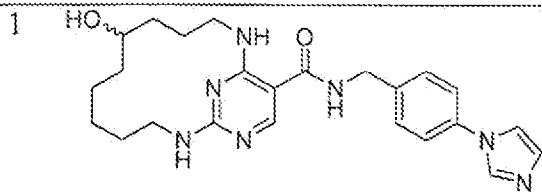
**Table 1** describes compounds prepared following procedures described in Example 6 (General Procedure F), using appropriate reagents.

	Structure	Compound_ID	Mer IC <sub>50</sub>	Physical Data MS $m/z$ (M+1) or/and $^1\text{H}$ NMR
1		UNC3388A	+++	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ) $\delta$ 8.19 (s, 1H), 7.40–7.32 (m, 2H), 7.09–7.02 (m, 2H), 4.47 (s, 2H), 3.85–3.70 (m, 3H), 3.67–3.55 (m, 1H), 1.90–1.42 (m, 14H). MS $m/z$ 402.3 $[\text{M}+\text{H}]^+$ .
2		UNC3429A	+++	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ) $\delta$ 8.19 (s, 1H), 7.37 (dd, $J = 8.7, 5.4$ Hz, 2H), 7.06 (t, $J = 8.8$ Hz, 2H), 4.47 (s, 2H), 3.81–3.70 (m, 1H), 3.66–3.55 (m, 2H), 3.54–3.46 (m, 1H), 3.45–3.35 (m, 1H), 1.85–1.72 (m, 1H), 1.72–1.59 (m, 3H), 1.58–1.30 (m, 14H). MS $m/z$ 444.3 $[\text{M}+\text{H}]^+$ .
3		UNC3431A	++	$^1\text{H}$ NMR (400 MHz, $\text{CD}_3\text{OD}$ ) $\delta$ 8.20 (s, 1H), 7.37 (dd, $J = 8.7, 5.4$ Hz, 2H), 7.05 (t, $J = 8.8$ Hz, 2H), 4.47 (s, 2H), 3.59 (dd, $J = 13.8, 6.7$ Hz, 3H), 3.53–3.40 (m, 2H), 1.77–1.60 (m, 5H), 1.60–1.27 (m, 18H). MS $m/z$ 472.3 $[\text{M}+\text{H}]^+$ .

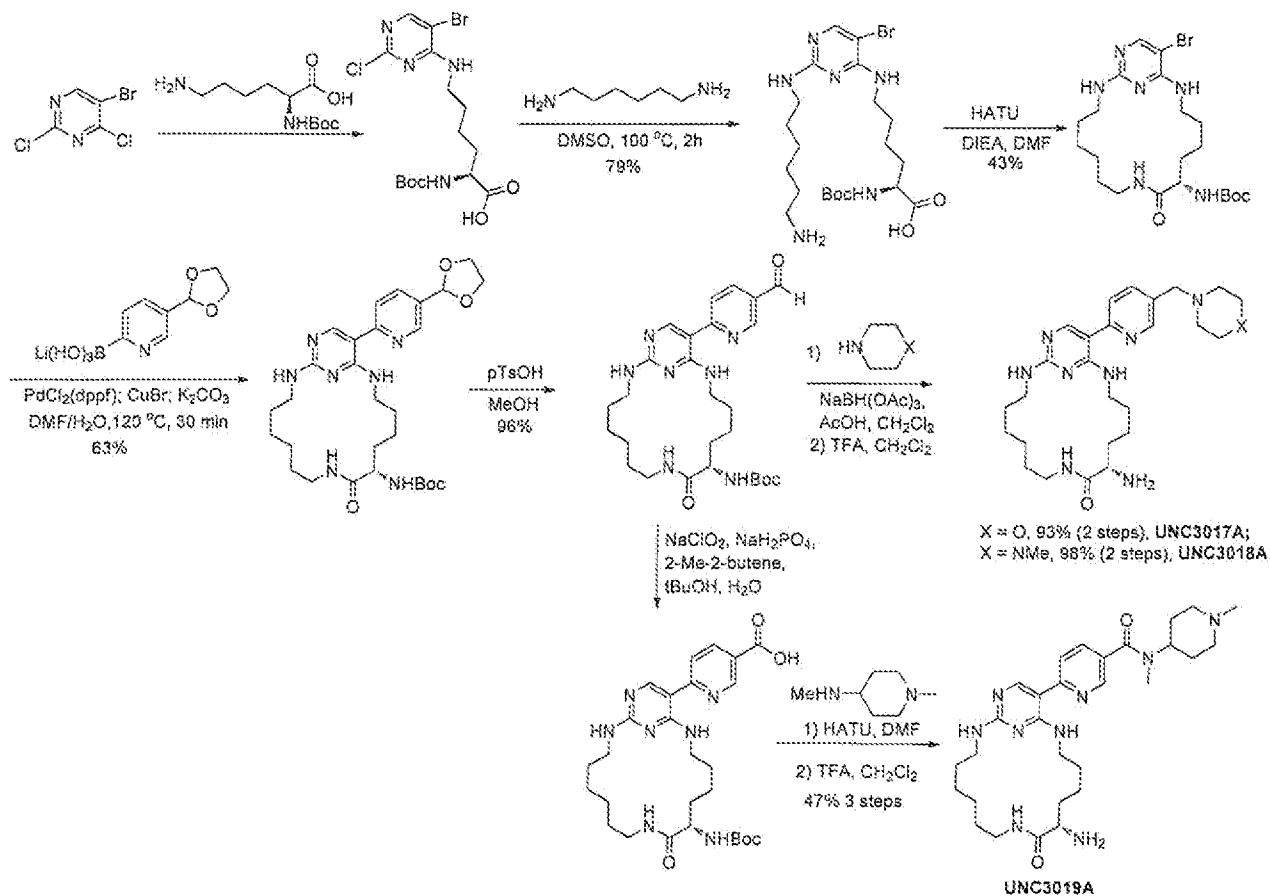
**Table 2** describes compounds can be prepared following procedures described in Example 6 (General Procedure F), using appropriate reagents.

	Structure	Compound_ID	Mer IC <sub>50</sub>	Physical Data MS $m/z$ (M+1) or/and $^1\text{H}$
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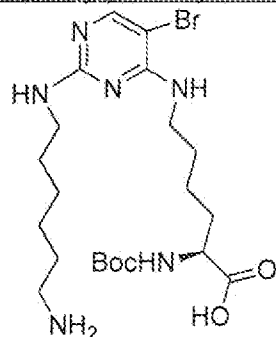
NMR

**Example 7****UNC3017A, UNC3018A & UNC3019A**

General Procedure G:

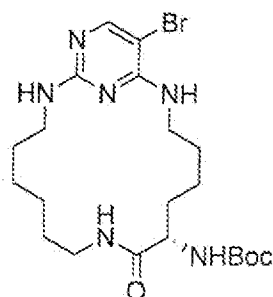


(S)-6-((2-((6-Aminohexyl)amino)-5-bromopyrimidin-4-yl)amino)-2-((tert-butoxycarbonyl)amino)hexanoic acid

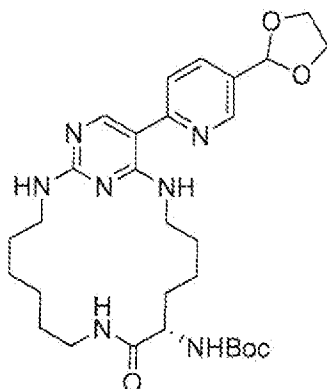


A solution of (S)-6-amino-2-((tert-butoxycarbonyl)amino)hexanoic acid (0.042 g, 0.10 mmol) in DMSO was added hexane-1,6-diamine (0.046 g, 0.40 mmol). The resulting mixture was heated at 100 °C for 2 h. After cooled to room temperature, the solvent was removed under reduced pressure. The resulting residue was purified by reverse phase ISCO column to provide title compound (0.041 g, 79%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.91 (s, 1H), 4.13–4.02 (m, 1H), 3.57 (t, *J* = 12, 2H), 3.51–3.38 (bs, 2H), 2.94 (t, *J* = 12, 2H), 1.92–1.80 (m, 1H), 1.75–1.62 (m, 7H), 1.57–1.36 (m, 15H); MS *m/z* 517.3 [M+H]<sup>+</sup>.

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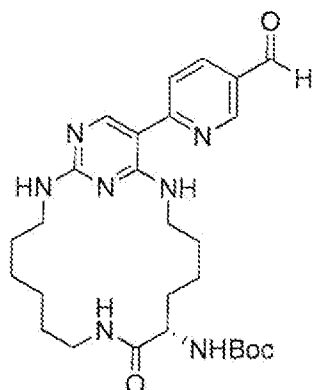


A solution of (S)-6-((2-((6-aminohexyl)amino)-5-bromopyrimidin-4-yl)amino)-2-((tert-butoxycarbonyl)amino)hexanoic acid (2.11 g, 4.08 mmol) and DIEA (1.78 mL, 10.19 mmol) in 20 mL DMF and a solution of HATU (2.01 g, 5.28 mmol) in 20 mL DMF were added to 200 mL of DMF in 16 h. After addition, the resulting mixture was stirred for 1 h. The solvent was removed under reduced pressure. The residue was purified by ISCO silica gel column to provide the desired bromide (0.87 g, 43%) contaminated with small amount of impurities. MS  $m/z$  499.3  $[M+H]^+$ .

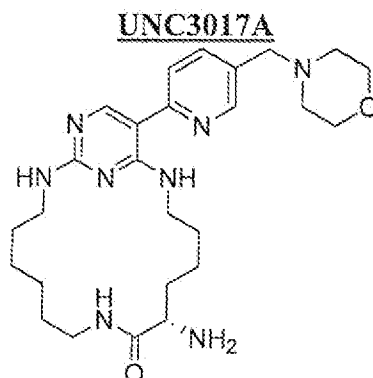


A solution of the bromide (0.66 g, 1.32 mmol) in DMF (6.6 mL) was added PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub> (0.11 g, 0.13 mmol), CuBr (0.036 g, 0.26 mmol), K<sub>2</sub>CO<sub>3</sub> (0.56 g, 9.96 mmol), (5-(1,3-dioxolan-2-yl)pyridin-2-yl)boronic acid lithium hydroxide (0.86 g, 9.96 mmol) and H<sub>2</sub>O (1.7 mL) at room temperature. The resulting mixture was heated at 120 °C for 30 min under. After cooled to room temperature, the mixture was filtered over Celite. The solvents were removed under reduced pressure. The crude residue was purified by ISCO silica gel column to provide the desired acetal (0.76 g, 63%) contaminated with small amount of impurities. MS  $m/z$  570.4  $[M+H]^+$ .

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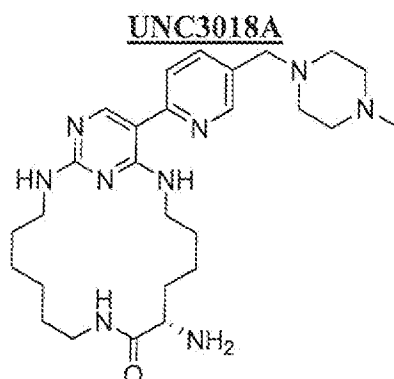


A solution of the the acetal (0.47 g, 0.83 mmol) in acetone (10 mL) was added *p*-TsOH·H<sub>2</sub>O (0.24 g, 1.25 mmol) and H<sub>2</sub>O (2.0 mL). After stirring at room temperature for 16 h, the reaction mixture was quenched with a sat. aq solution of NaHCO<sub>3</sub> and extracted with EtOAc (3X). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The resulting residue was purified by ISCO silica gel column to provide the desired aldehyde (0.42 g, 96%) contaminated with small amount of impurities. MS *m/z* 526.4 [M+H]<sup>+</sup>.

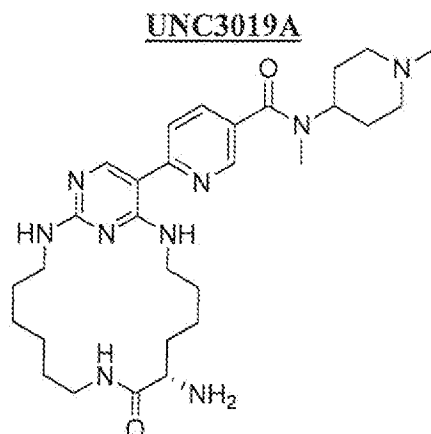


A solution of the aldehyde (0.53 g, 0.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was added morpholine (0.013 mL, 0.15 mmol) and acetic acid (0.04 mL). The resulting solution was stirred at room temperature for 2 h, then NaB(OAc)<sub>3</sub>H (0.043 g, 0.15 mmol) was added. After stirred at room temperature for 16 h, the reaction was quenched with a sat. aq. solution of NaHCO<sub>3</sub> and extracted with EtOAc (3X). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was dissolved in a mixture of CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) and TFA (1.0 mL). After stirred at room temperature for 2.0 h, the reaction was concentrated and the residue was purified by prep-HPLC to provide the desired product **UNC3017A** (0.046 g, 93%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.88 (s, 1H), 8.41 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 4.52 (s, 2H), 4.06 (d, *J* = 10.7 Hz, 2H), 3.96–3.79 (m, 4H), 3.77–3.67 (m, 1H), 3.57 (td, *J* = 12.2, 5.2 Hz, 2H), 3.45 (d, *J* = 12.4 Hz, 2H), 3.39–3.23 (m, 3H),

3.02–2.93 (m, 1H), 1.96 (dd,  $J = 10.2, 4.6$  Hz, 2H), 1.86–1.51 (m, 7H), 1.42 (d,  $J = 4.7$  Hz, 5H); MS  $m/z$  497.4  $[M+H]^+$ .



A solution of the above aldehyde (0.53 g, 0.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL) was added N-methylpiperazine (0.017 mL, 0.15 mmol) and acetic acid (0.04 mL). The resulting solution was stirred at room temperature for 2 h, then  $\text{NaB}(\text{OAc})_3\text{H}$  (0.043 g, 0.15 mmol) was added. After stirred at room temperature for 16 h, the reaction was quenched with a sat. aq. solution of  $\text{NaHCO}_3$  and extracted with EtOAc (3X). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue was dissolved in a mixture of  $\text{CH}_2\text{Cl}_2$  (2.0 mL) and TFA (1.0 mL). After stirred at room temperature for 2.0 h, the reaction was concentrated and the residue was purified by prep-HPLC to give the desired product UNC3018A (0.049 g, 98%).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.91 (d,  $J = 1.7$  Hz, 1H), 8.40 (s, 1H), 8.27 (dd,  $J = 8.5, 2.0$  Hz, 1H), 8.01 (d,  $J = 8.5$  Hz, 1H), 4.61 (s, 2H), 3.91 (t,  $J = 5.4$  Hz, 1H), 3.88–3.61 (m, 10H), 3.61–3.51 (m, 2H), 3.39–3.34 (m, 1H), 3.02 (s, 3H), 3.00–2.92 (m, 1H), 2.03–1.89 (m, 2H), 1.87–1.50 (m, 7H), 1.48–1.35 (m, 5H); MS  $m/z$  510.4  $[M+H]^+$ .



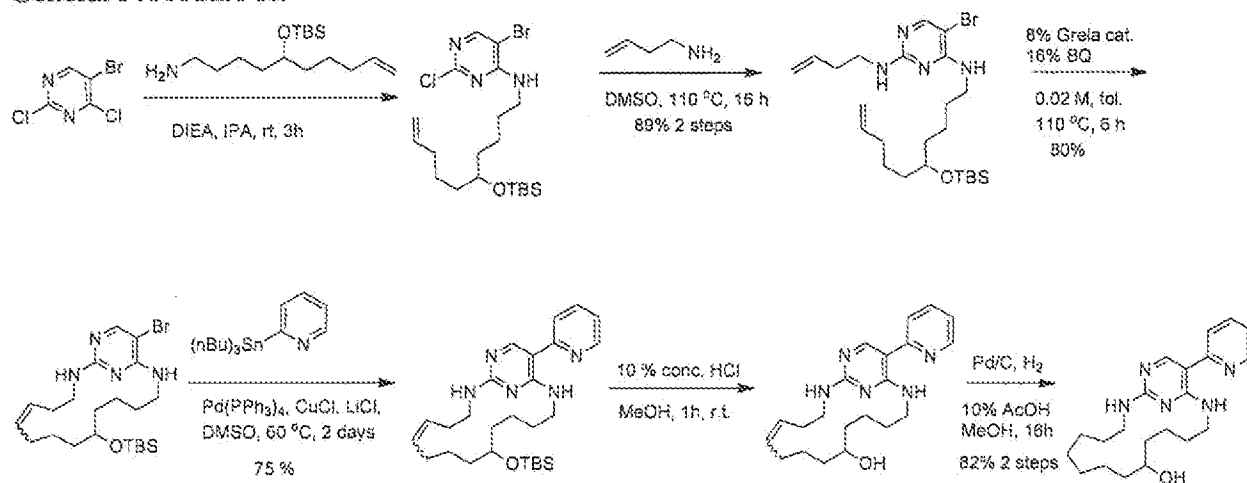
A mixture of aldehyde (0.053 g, 0.1 mmol) in 10 mL *t*BuOH was added  $\text{NaClO}_2$  (0.034 g, 80%, 0.3 mmol),  $\text{NaH}_2\text{PO}_4$  (0.041 g, 0.3 mmol), 2-Me-2-Butene (0.11 mL, 1 mmol) and 2 mL  $\text{H}_2\text{O}$ . After stirring 16 h at room temperature, the reaction was quenched with sat.

aq.  $\text{Na}_2\text{S}_2\text{O}_3$ , acidified with diluted aq. HCl to pH 4 and extracted with EtOAc (3X). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue was dissolved in 3 mL DMF. To this solution was added HATU (0.042 g, 0.11 mmol), followed by *N*,1-dimethylpiperidin-4-amine (0.014 g, 0.11 mmol). After stirring for 16 at room temperature, the reaction mixture was condensed under vacuum and purified by Prep-HPLC. The Boc protected intermediate was dissolved in 2 mL  $\text{CH}_2\text{Cl}_2$  and 1 mL TFA and stirred for 2 h. After evaporating the solvents, the residue was purified by Prep-HPLC to provide the desired product **UNC3019A** (0.026 g, 47%).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.70 (s, 1H), 8.41 (s, 1H), 8.02–7.93 (m, 2H), 3.92–3.50 (m, 8H), 3.39–3.33 (m, 1H), 3.23 (bs, 1H), 3.10–2.75 (m, 8H), 2.24 (dd,  $J = 24.3, 11.4$  Hz, 2H), 2.15–2.02 (m, 2H), 2.02–1.88 (m, 2H), 1.87–1.48 (m, 8H), 1.45–1.37 (m, 4H); MS  $m/z$  552.4  $[\text{M}+\text{H}]^+$ .

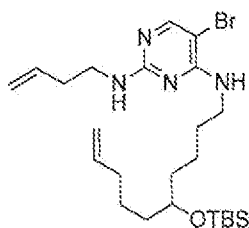
### Example 8

#### UNC3588A

General Procedure H:

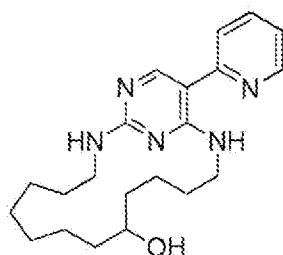


5-Bromo-*N*2-(but-3-en-1-yl)-*N*4-(5-((*tert*-butyldimethylsilyl)oxy)dec-9-en-1-yl)pyrimidine-2,4-diamine



A solution of 5-bromo-2,4-dichloropyrimidine (0.29 g, 1.28 mmol) in isopropanol (3.0 mL) was added 5-((tert-butyldimethylsilyl)oxy)dec-9-en-1-amine (0.38 g, 1.34 mmol) and DIEA (0.27 mL, 1.54 mmol) at 0 °C. The reaction solution was stirred at room temperature for 3 h. The solvent was removed under a reduced pressure to provide a yellow residue, which was dissolved in DMSO (5.0 mL). But-3-en-1-amine (0.47 mL, 5.12 mmol) was added. The resulting mixture was heated at 110 °C for 16 h, then diluted with Et<sub>2</sub>O and quenched with brine. The aqueous layer was extracted with Et<sub>2</sub>O (3X). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified by ISCO silica gel column to provide desired product (0.58 g, 89%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.85 (s, 1H), 5.91–5.72 (m, 2H), 5.18–4.91 (m, 5H), 4.85 (t, *J* = 4.9 Hz, 1H), 3.65 (p, *J* = 5.4 Hz, 1H), 3.47–3.37 (m, 4H), 2.34 (qt, *J* = 6.8, 1.3 Hz, 2H), 2.03 (q, *J* = 6.5 Hz, 2H), 1.64–1.53 (m, 2H), 1.51–1.33 (m, 8H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); MS *m/z* 511.3 [M+H]<sup>+</sup>.

**UNC3588A**



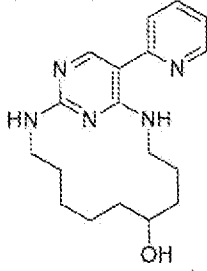
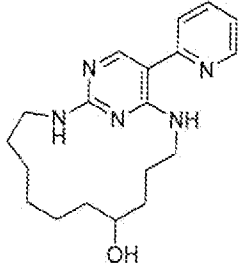
A solution of 5-bromo-*N*<sup>2</sup>-(but-3-en-1-yl)-*N*<sup>4</sup>-(5-((tert-butyldimethylsilyl)oxy)dec-9-en-1-yl)pyrimidine-2,4-diamine (0.26 g, 0.50 mmol) and benzoquinone (0.009 g, 0.08 mmol) in toluene (20 mL) was added Grell's catalyst (0.027 g, 0.04 mmol) in toluene (5.0 mL) over 1.0 h at 110 °C. The resulting dark brown solution was heated at 110 °C for another hour. After cooled to 60 °C, 2-mercaptocotinic acid (0.39 g, 2.5 mmol) was added and stirred at 60 °C for 2 h. After cooled to room temperature, the reaction mixture was filtered over Celite and washed with CH<sub>2</sub>Cl<sub>2</sub>. The filtrate was concentrated and the residue was purified by ISCO silica gel column to provide the macrocyclic intermediate as a mixture of *E* and *Z* olefin isomers (0.19 g, 80%). MS *m/z* 483.3 [M+H]<sup>+</sup>.

A schlenk flask containing LiCl (0.028 g, 0.66 mmol) and stir bar was flame dried. After cooled to room temperature, CuCl (0.054 g, 0.55 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.013 g, 0.011 mmol) was added. The reaction mixture was vacuumed and refilled with argon (4X). The intermediate from previous step (0.054 g, 0.11 mmol) in DMSO (4.0 mL), and Bu<sub>3</sub>SnPy (0.049 g, 0.13 mmol) were added under argon. The resulting reaction mixture was freeze-thawed under argon (4X). The mixture was heated at 60 °C for 2 d, then diluted with EtOAc,

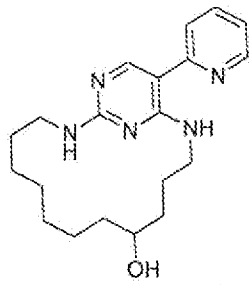
quenched with brine and a saturated aq. solution of  $\text{NaHCO}_3$ . The organic layer was washed with a sat. aq solution of  $\text{NaHCO}_3$  (3X). The combined aqueous layers were extracted with EtOAc (3X). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue was purified by ISCO silica gel column to provide Stille coupling products (0.040 g, 75%), MS  $m/z$  482.4  $[\text{M}+\text{H}]^+$ .

A solution of the Stille coupling product (0.040 g, 0.083 mmol) in MeOH (5.0 mL) was added a conc. HCl solution (0.50 mL). The resulting mixture was stirred for 1 h and concentrated under reduced pressure. After zoetrope with MeOH (3X), the residue was dissolved in MeOH (5.0 mL) and AcOH (0.50 mL) and was added Pd/C (0.009 g, 10 wt%). The reaction mixture was stirred at room temperature under hydrogen for 1 d, then filtered over Celite and washed with MeOH. The filtrate was concentrated and the residue was purified by reverse-phase HPLC to provide the desired product **UNC3588A** (0.025 g, 82% over 2 steps).  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  8.62 (ddd,  $J = 5.0, 1.6, 0.9$  Hz, 1H), 8.28 (s, 1H), 7.96–7.82 (m, 2H), 7.39 (ddd,  $J = 7.3, 5.0, 1.1$  Hz, 1H), 3.91–3.79 (m, 1H), 3.71–3.53 (m, 3H), 3.49–3.38 (m, 1H), 1.92–1.78 (m, 1H), 1.76–1.65 (m, 3H), 1.62–1.34 (m, 14H). MS  $m/z$  370.3  $[\text{M}+\text{H}]^+$ .

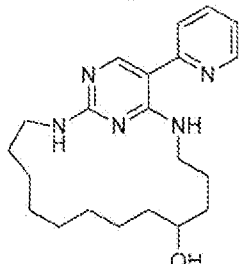
**Table 8** describes compounds can be prepared following procedures described in **Example 8** (General Procedure H), using appropriate reagents.

Structure	Compound_ID	Mer IC <sub>50</sub>	Physical Data MS $m/z$ (M+1) or/and $^1\text{H}$ NMR
1 			
2 			

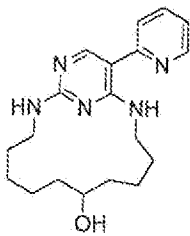
3



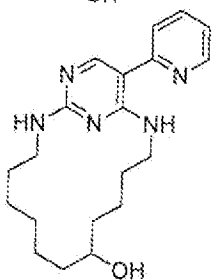
4



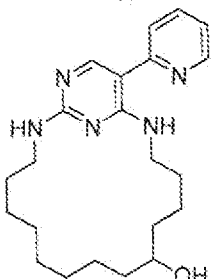
5



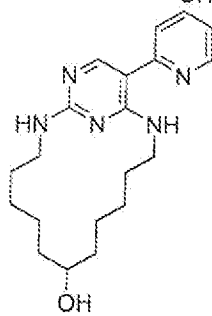
6



7



8



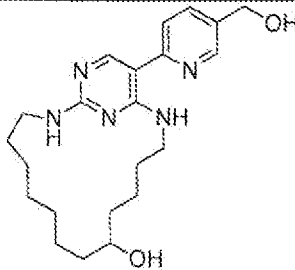
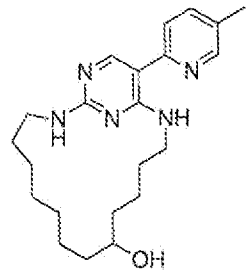


A solution of the bromide intermediate (0.17 g, 0.34 mmol) in DMF (2.0 mL) was added Pd(dppf)Cl<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (0.028 g, 0.034 mmol), CuBr (0.098 g, 0.68 mmol), K<sub>2</sub>CO<sub>3</sub> (0.14 g, 1.02 mmol), (5-(1,3-dioxolan-2-yl)pyridin-2-yl)boronic acid lithium hydroxide (0.22 g, 1.02 mmol) and water (0.50 mL). The resulting mixture was heated at 120 °C for 30 min open to air. The mixture was filtered over Celite at room temperature. The solvents were removed under a reduced pressure and the residue was purified by ISCO silica gel column to provide the desired coupling product (0.053 g, 28%) contaminated with small amount impurities; MS *m/z* [M+H]<sup>+</sup>.

A solution of the coupling product (0.053 g, 0.10 mmol) in acetone (10 mL) was added *p*-TsOH·H<sub>2</sub>O (0.029 g, 0.15 mmol) and H<sub>2</sub>O (0.80 mL). The reaction mixture was stirred at room temperature for 16 h, then quenched with a sat. aq solution of NaHCO<sub>3</sub> and extracted with EtOAc (3X). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The resulting residue was purified by ISCO silica gel column to provide the desired aldehyde intermediate (0.031 g, 78%) contaminated with small amount impurities; MS *m/z* 554.4 [M+H]<sup>+</sup>.

A solution of the aldehyde (0.031 g, 0.078 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was added morpholine (0.01 mL, 0.12 mmol) and 0.08 mL acetic acid. The resulting solution was stirred at room temperature for 2 h, then NaB(OAc)<sub>3</sub>H (0.033 g, 0.16 mmol) was added. The reaction mixture was stirred at room temperature for 16 h, quenched by a sat. aq. solution of NaHCO<sub>3</sub> and extracted with EtOAc (3X). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was dissolved in MeOH (5.0 mL) and was added Pd/C (0.015 g, 5 wt% Pd/C). The reaction mixture was stirred under hydrogen atmosphere at room temperature for 16 h, then filtrated over Celite and washed with MeOH. The filtrate was concentrated and the residue was purified with reverse-phase HPLC to provide the desired product **UNC3295A** (0.0096 g, 26%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.73 (d, *J* = 1.8 Hz, 1H), 8.40 (s, 1H), 8.06 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 4.40 (s, 2H), 3.98–3.80 (m, 5H), 3.70–3.51 (m, 3H), 3.49–3.38 (m, 1H), 3.29 (bs, 4H), 1.90–1.79 (m, 1H), 1.77–1.65 (m, 3H), 1.62–1.36 (m, 14H); MS *m/z* 469.4 [M+H]<sup>+</sup>.

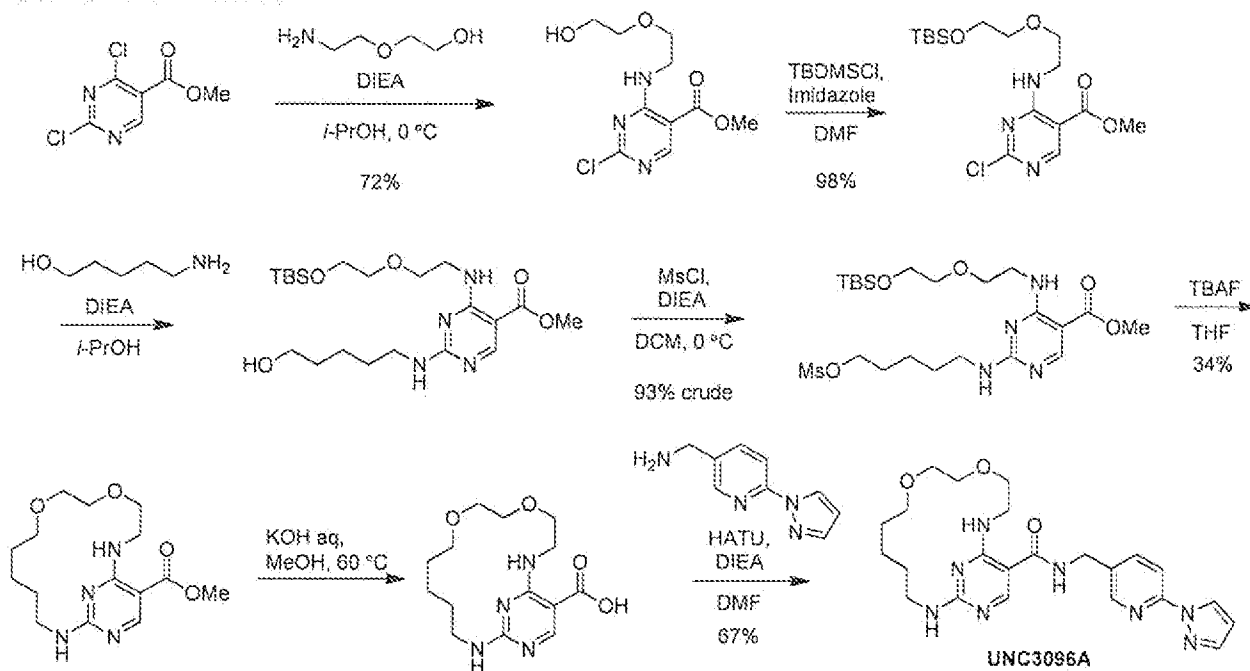
Table 6 describes compounds prepared following procedures described in Example 9 (General Procedure I), using appropriate reagents.

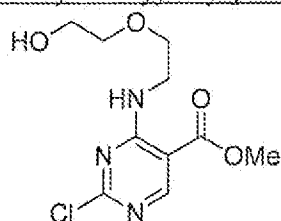
Structure	Compound_ID	Mer IC <sub>50</sub>	Physical Data
	UNC3296A	+++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.49 (d, <i>J</i> = 1.3 Hz, 1H), 8.28 (s, 1H), 7.80–7.71 (m, 2H), 4.63 (s, 2H), 3.83–3.72 (m, 1H), 3.66–3.56 (m, 1H), 3.56–3.41 (m, 2H), 3.39–3.33 (m, 1H), 1.87–1.74 (m, 1H), 1.71–1.58 (m, 4H), 1.56–1.36 (m, 13H); MS <i>m/z</i> 400.3 [M+H] <sup>+</sup> .
	UNC3334A	++	<sup>1</sup> H NMR (400 MHz, CD <sub>3</sub> OD) δ 8.46 (s, 1H), 8.22 (s, 1H), 7.74 (d, <i>J</i> = 1.6 Hz, 2H), 3.90–3.79 (m, 1H), 3.68–3.51 (m, 3H), 3.47–3.37 (m, 1H), 2.39 (s, 3H), 1.90–1.78 (m, 1H), 1.76–1.65 (m, 3H), 1.63–1.37 (m, 14H); MS <i>m/z</i> 384.3 [M+H] <sup>+</sup> .

### Example 10

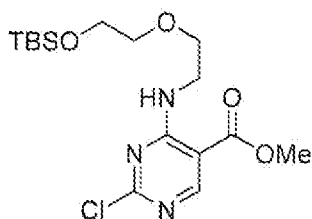
#### UNC3096A

General Procedure J:

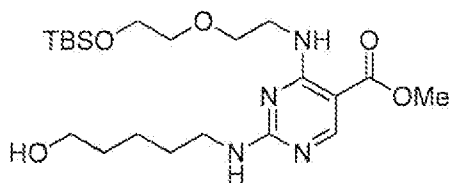


Methyl 2-chloro-4-([2-(2-hydroxyethoxy)ethyl]amino)pyrimidine-5-carboxylate

A solution of methyl 2,4-dichloropyrimidine-5-carboxylate (252 mg, 1.22 mmol) in *i*-PrOH (6 mL) was added 2-(2-aminoethoxy)ethanol (122  $\mu$ L, 1.22 mmol) and DIEA (319  $\mu$ L, 1.83 mmol) at 0 °C. After 1.5 h the volatiles were removed under a reduced pressure and the residue was purified by ISCO silica gel column to provide the title compound (243 mg, 72 %) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.67 (s, 1H), 3.90 (s, 3H), 3.82–3.74 (m, 4H), 3.70 (t,  $J = 5.2$  Hz, 2H), 3.67–3.61 (m, 2H), 2.17 (t,  $J = 6.3$  Hz, 1H).

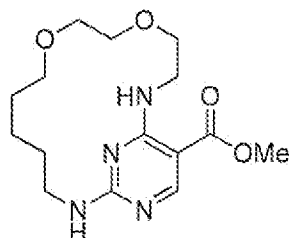
Methyl 2-chloro-4-(8,8,9,9-tetramethyl-4,7-dioxa-1-aza-8-siladecan-1-yl)pyrimidine-5-carboxylate

A solution of methyl 2-chloro-4-([2-(2-hydroxyethoxy)ethyl]amino)pyrimidine-5-carboxylate (99 mg, 0.36 mmol) in DMF (720  $\mu$ L) was added imidazole (49 mg, 0.72 mmol) followed by TBDMSCl (60 mg, 0.396 mmol). The reaction mixture was stirred at room temperature for 1 h, diluted with  $\text{H}_2\text{O}$  (2 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  2 mL). The combined organic layers were washed with brine (2  $\times$  2 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue was purified by ISCO silica gel column to provide the title compound (137 mg, 98 %) as a colorless oil.

Methyl 2-[(5-hydroxypentyl)amino]-4-(8,8,9,9-tetramethyl-4,7-dioxa-1-aza-8-siladecan-1-yl)pyrimidine-5-carboxylate

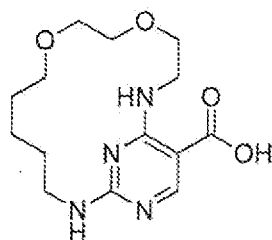
A solution of methyl 2-chloro-4-(8,8,9,9-tetramethyl-4,7-dioxo-1-aza-8-siladecan-1-yl)pyrimidine-5-carboxylate (133 mg, 0.341 mmol) in *i*-PrOH (3.4 mL) was added 5-aminopentanol (185  $\mu$ L, 1.7 mmol) and DIEA (89  $\mu$ L, 0.511 mmol). The reaction mixture was stirred at room temperature overnight. The solvents were removed under a reduced pressure and the residue was purified by ISCO silica gel column to provide the title compound (156 mg, >99%) as a colorless oil.

Methyl 5,8-dioxo-2,14,16,19-tetraazabicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-18-carboxylate



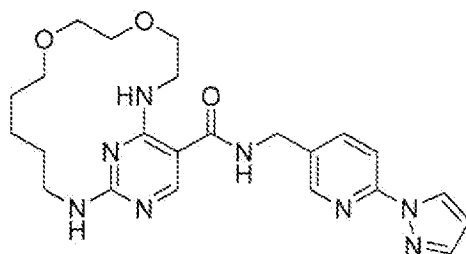
A solution of methyl 2-[(5-hydroxypentyl)amino]-4-(8,8,9,9-tetramethyl-4,7-dioxo-1-aza-8-siladecan-1-yl)pyrimidine-5-carboxylate (150 mg, 0.328 mmol) in  $\text{CH}_2\text{Cl}_2$  (3.3 mL) was added DIEA (143  $\mu$ L, 0.82 mmol) then methanesulfonylchloride (28  $\mu$ L, 0.361) at 0  $^\circ\text{C}$ . The reaction mixture was stirred for 30 min and diluted with  $\text{H}_2\text{O}$  (12 mL). The organic layer was washed with brine (10 mL) and dried to provide the crude mesylate that was used for the next step without further purification. The mesylate was dissolved in THF (7.3 mL) and TBAF (1M in THF, 585  $\mu$ L, 0.585 mmol) was added. The reaction mixture was stirred at room temperature overnight. The solvents were removed under a reduced pressure and the residue was purified by ISCO silica gel column to provide the title compound (32 mg, 34%) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.57 (s, 1H), 3.86–3.79 (m, 7H), 3.79–3.73 (m, 2H), 3.72–3.66 (m, 5H), 3.64–3.59 (m, 2H), 2.32 (dd,  $J = 9.3, 3.6$  Hz, 1H), 1.72–1.64 (m, 2H), 1.59 (dd,  $J = 10.8, 5.7$  Hz, 4H).

5,8-Dioxo-2,14,16,19-tetraazabicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-18-carboxylic acid



A solution of methyl 5,8-dioxo-2,14,16,19-tetraazabicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-18-carboxylate (32 mg, 0.099 mmol) in MeOH (1.4 mL) was added a 4.0 M KOH solution (250  $\mu$ L). The reaction mixture was heated at 60  $^{\circ}$ C overnight. The reaction was cooled and the MeOH was removed under a reduced pressure. The mixture was acidified with a 4.0 N HCl solution to pH  $\sim$  2. The aqueous layer was extracted with 3:1 CH<sub>2</sub>Cl<sub>2</sub>/*i*-PrOH (3  $\times$  5 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford the title compound (35 mg, >99%) as a white solid.

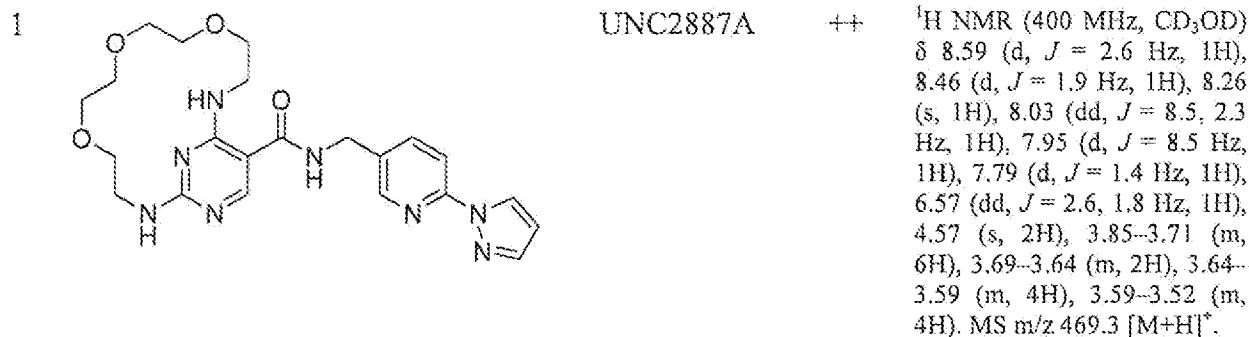
*N*-{[6-(1H-Pyrazol-1-yl)pyridin-3-yl]methyl}-5,8-dioxo-2,14,16,19-tetraazabicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-18-carboxamide (UNC3096A)



A solution of 5,8-dioxo-2,14,16,19-tetraazabicyclo[13.3.1]nonadeca-1(18),15(19),16-triene-18-carboxylic acid (30 mg, 0.099 mmol) in DMF (1.0 mL) was added [6-(1H-pyrazol-1-yl)pyridin-3-yl]methanamine (17 mg, 0.099 mmol) and DIEA (34  $\mu$ L, 0.197 mmol) followed by HATU (41 mg, 0.108 mmol). The reaction mixture was stirred at room temperature overnight, quenched with a 1.0 M NaOH solution (2.0 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  2 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified by HPLC to afford the title compound (37 mg, 67%) as a light yellow solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  8.62 (dd, *J* = 2.7, 0.4 Hz, 1H), 8.50 (d, *J* = 1.9 Hz, 1H), 8.32 (s, 1H), 8.15 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 1.3 Hz, 1H), 6.61 (dd, *J* = 2.7, 1.7 Hz, 1H), 4.59 (s, 2H), 3.85–3.63 (m, 10H), 3.63–3.55 (m, 2H), 1.81–1.65 (m, 6H). MS *m/z* 467.3 [M+H]<sup>+</sup>.

**Table 1** describes compounds prepared following procedures described in **Example 10** (General Procedure J), using appropriate reagents.

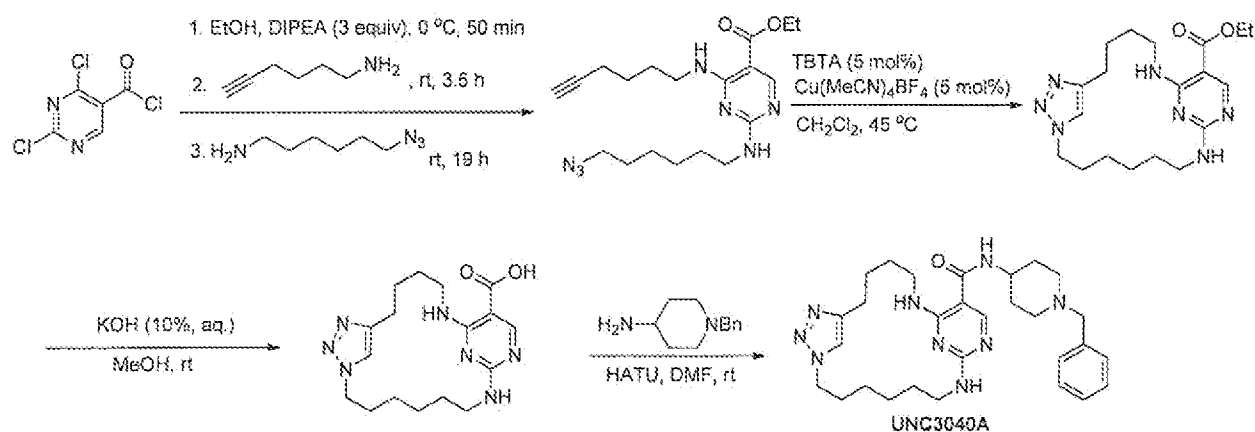
Structure	Compound_ID	Mer IC <sub>50</sub>	Physical Data MS <i>m/z</i> (M+1) or/and <sup>1</sup> H NMR
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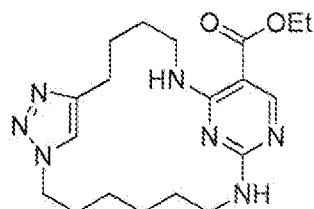
### Example 11

#### UNC3040A

#### General Procedure K:



Ethyl 2,8,9,10,17,19,22-heptaazatricyclo[16.3.1.1<sup>7,10</sup>]tricoso-1(21),7(23),8,18(22),19-pentaene-21-carboxylate

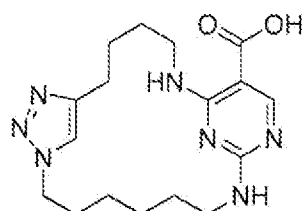


A solution of 2,4-dichloropyrimidine-5-carbonyl chloride (1.00 g, 4.76 mmol) in ethanol (6.0 mL) was added DIPEA (2.5 mL, 14.4 mmol) slowly at 0 °C under nitrogen. After 30 min, hex-5-yn-1-amine (0.476 g, 4.91 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 3.5 h, then was added dropwise to a solution of 6-azidohexan-1-amine (0.801 g, 5.64 mmol) in ethanol (4.0 mL) at 50 °C. After the reaction was complete (monitored by LCMS), the mixture was diluted with water (10 mL) and

concentrated under a reduced pressure and filtered. The yellow solid was washed with water and dried under vacuum to be used in the next step without further purification (0.723 g, 39% over 3 steps).

A solution of the yellow solid (0.130 g, 0.336 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was added TBTA (1.6 mL, 5 mg/mL in CH<sub>2</sub>Cl<sub>2</sub>, 8.0 mg, 0.016 mmol) and Cu(MeCN)<sub>4</sub>BF<sub>4</sub> (5.2 mg, 0.016 mmol). The reaction mixture was stirred under nitrogen at 45 °C for 24 h, then cooled to room temperature and concentrate. The residue was purified by silica gel column to provide the title compound (0.104 g, 80%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.34 (s, 2H), 7.58 (s, 1H), 4.36 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.34 (s, 2H), 3.19 (s, 2H), 2.82–2.66 (m, 2H), 1.84 (s, 2H), 1.67 (s, 2H), 1.62–1.44 (m, 4H), 1.40–1.02 (m, 7H).

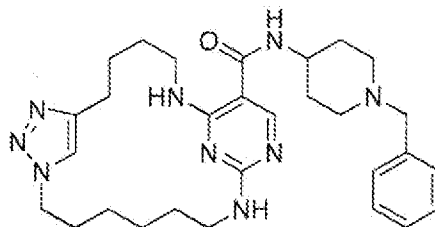
2,8,9,10,17,19,22-Heptaazatricyclo[16.3.1.1<sup>7,10</sup>]tricoso-1(21),7(23),8,18(22),19-pentaene-21-carboxylic acid



A solution of ethyl 2,8,9,10,17,19,22-heptaazatricyclo[16.3.1.1<sup>7,10</sup>]tricoso-1(21),7(23),8,18(22),19-pentaene-21-carboxylate (31 mg, 0.081 mmol) in MeOH (2.0 mL) was added an aq. KOH solution (10%, 0.50 mL). The reaction was stirred at 60 °C for 12 h. Then the reaction mixture was cooled to room temperature and adjusted to pH=3 by the addition of a HCl solution. The resulting solution was extracted by a mixture of *i*-PrOH/CH<sub>2</sub>Cl<sub>2</sub> (1:3, 10 mL × 3). The combined organic layers were washed with water and brine and concentrated under vacuum to afford the desired product (0.029 g, quant.) as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.41–8.22 (m, 1H), 5.65 (s, 2H), 4.63–4.46 (m, 1H), 3.55–3.43 (m, 1H), 3.39–3.33 (m, 1H), 3.02 (t, *J* = 6.9 Hz, 3H), 2.97–2.83 (m, 1H), 2.58–2.29 (m, 3H), 2.03–1.89 (m, 1H), 1.85–1.71 (m, 1H), 1.71–1.50 (m, 2H), 1.49–0.97 (m, 3H).

*N*-(1-benzylpiperidin-4-yl)-2,8,9,10,17,19,22-heptaazatricyclo[16.3.1.1<sup>7,10</sup>]tricoso-1(21),7(23),8,18(22),19-pentaene-21-carboxamid (UNC3040A)

- 55 -

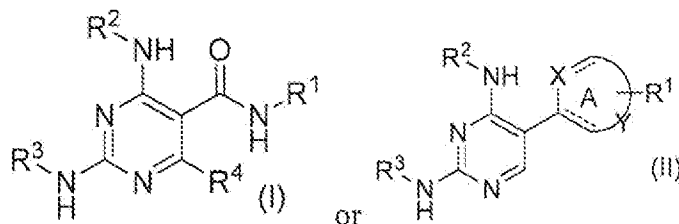


A solution of 2,8,9,10,17,19,22-Heptaazatricyclo[16.3.1.1<sup>7,10</sup>]tricosane-1(21),7(23),8,18(22),19-pentaene-21-carboxylic acid (30 mg, 0.084 mmol) in DMF (2.0 mL) was added 1-benzylpiperidin-4-amine (19.8 mg, 0.10 mmol) followed by HATU (38 mg, 0.10 mmol). The reaction mixture was stirred at room temperature overnight, quenched with a 1.0 M NaOH solution (2.0 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 2 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified by HPLC to afford the title compound **UNC3040A** (6.0 mg, 13%) as a light yellow solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 8.24 (s, 1H), 8.08–7.93 (m, 2H), 7.64–7.46 (m, 4H), 4.54–4.46 (m, 2H), 4.33 (s, 1H), 3.59–3.40 (m, 4H), 3.22–3.05 (m, 2H), 3.02–2.93 (m, 3H), 2.91–2.77 (m, 3H), 2.37–2.26 (m, 1H), 2.25–2.13 (m, 2H), 1.98–1.86 (m, 3H), 1.79–1.70 (m, 2H), 1.66–1.50 (m, 4H), 1.30–1.10 (m, 4H); MS (ESI): 554.5 [M + Na]<sup>+</sup>.

The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

That which is claimed is:

1. A compound of **Formula I** or **Formula II**:



wherein:

ring A is a 5- or 6-membered heteroaryl group, the dashed line is an optional double bond, X is N or O, and Y is C, S or N in any location in the ring;

$R^1$  is  $-R^5R^6$ , where  $R^5$  is a covalent bond, C1 to C3 alkyl or a linker group and  $R^6$  is cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkylcycloalkyl, alkylheterocycloalkyl, alkylaryl, alkylheteroaryl or alkyl, and wherein  $R^6$  is optionally substituted one, two or three times with independently selected polar groups;

$R^2$  and  $R^3$  together form a linking group;

$R^4$  is H, loweralkyl, halo, or loweralkoxy;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein  $R^5$  is a covalent bond.

3. The compound of claim 1, wherein  $R^5$  is C1 to C3 alkylene.

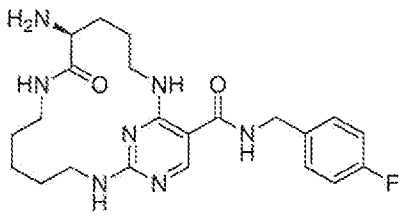
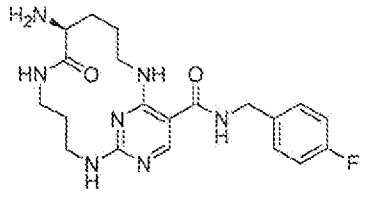
4. The compound of claim 1, wherein  $R^5$  is  $-\text{CH}_2-$ .

5. The compound of claim 1 to 4, wherein  $R^6$  is phenyl, piperidyl, C1-C8 alkyl, or C3-C8 cycloalkyl, which phenyl, piperidyl, alkyl or cycloalkyl is unsubstituted or substituted from 1 to 3 times with sulfono, halo, amino, nitro, alkyl, alkoxyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

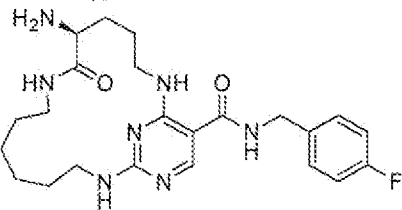
6. The compound of claim 1 to 5, wherein  $R^4$  is H.

7. The compound of claim 1, wherein said compound has a structure selected from the group consisting of:

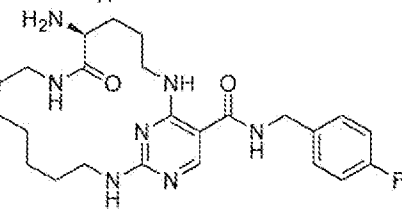
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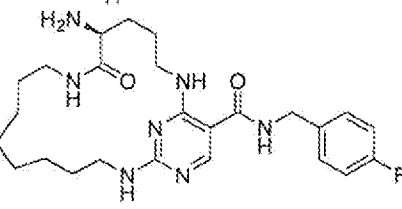
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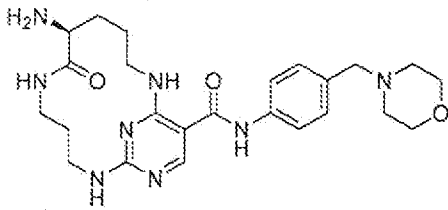
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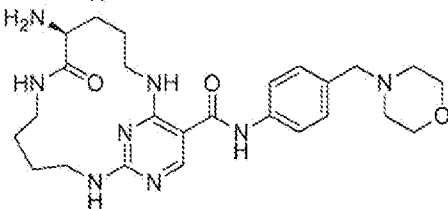
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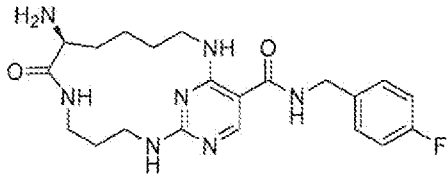
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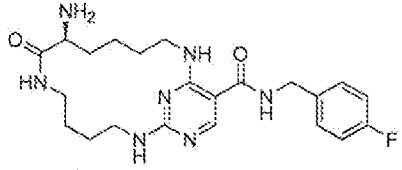
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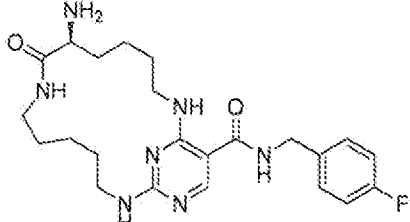
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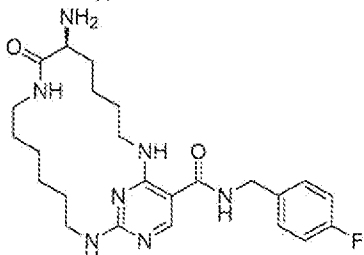
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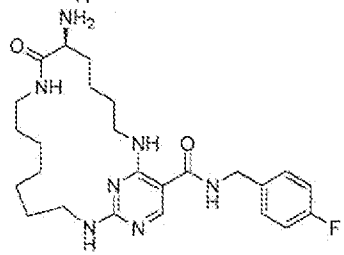
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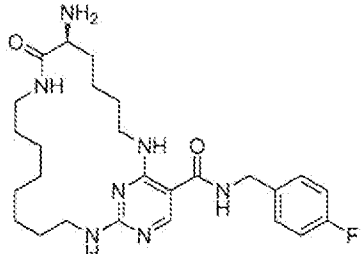
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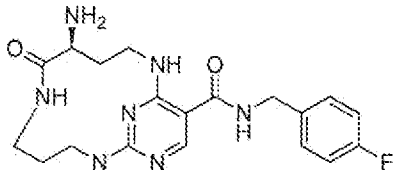
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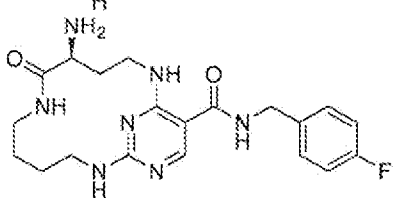
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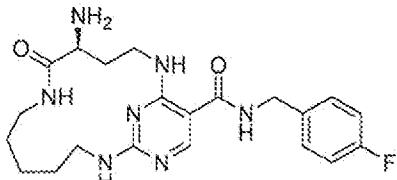
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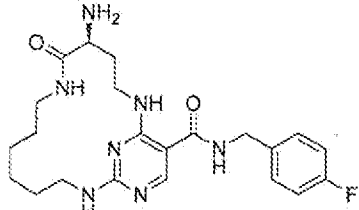
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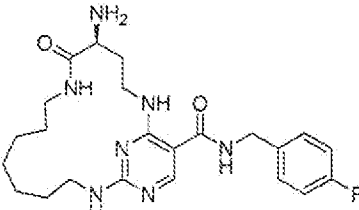
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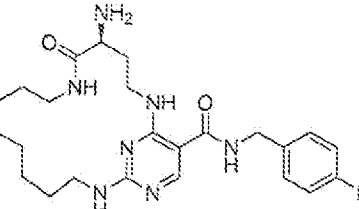
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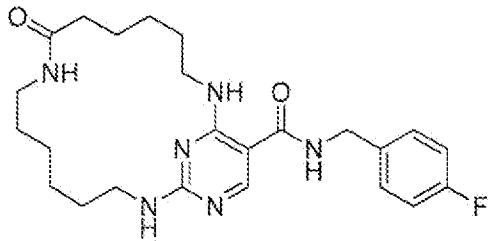
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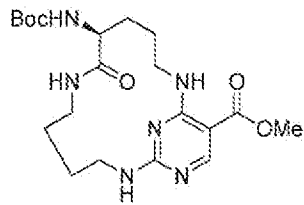


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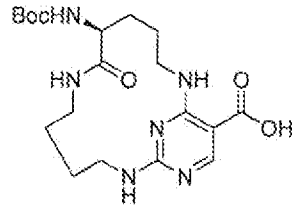


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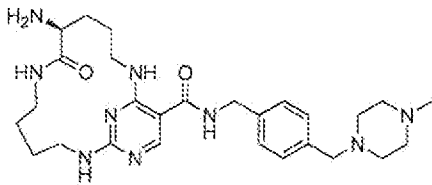
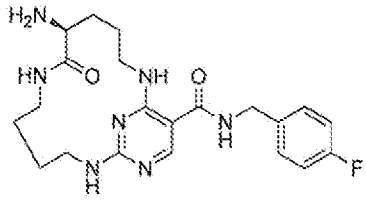
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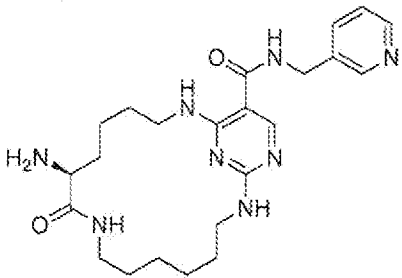
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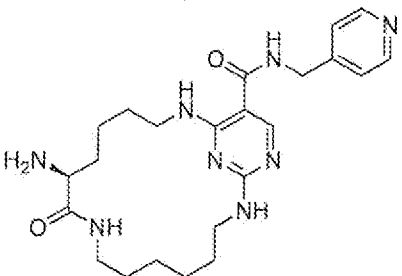
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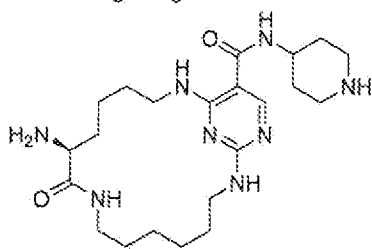
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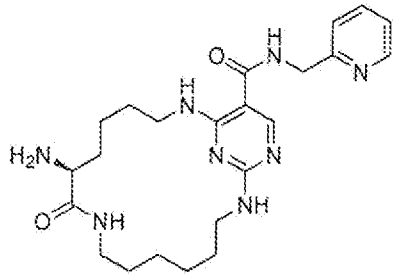
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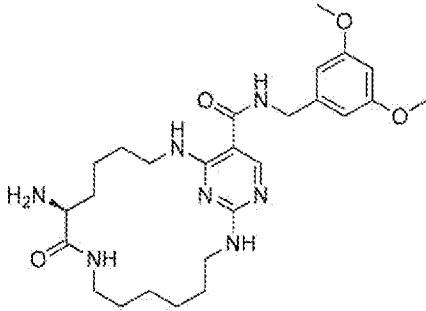
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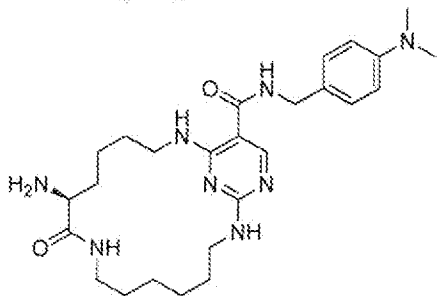
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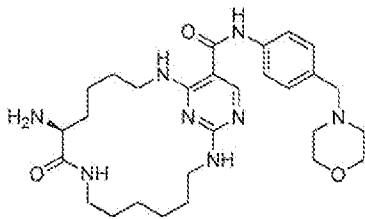
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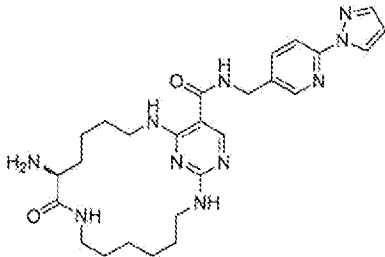
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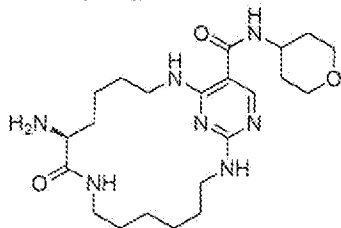
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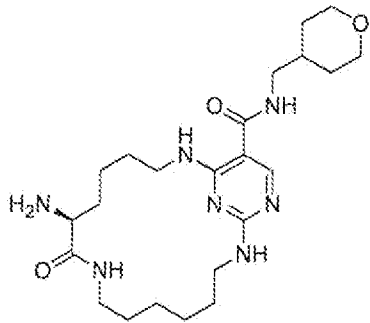
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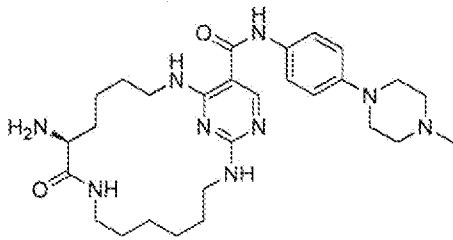
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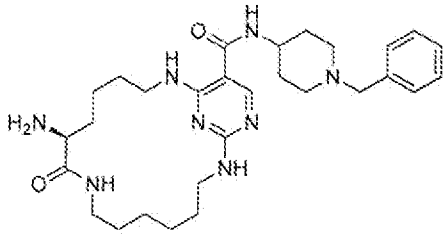
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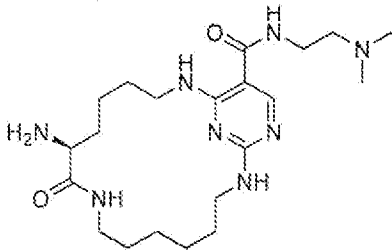
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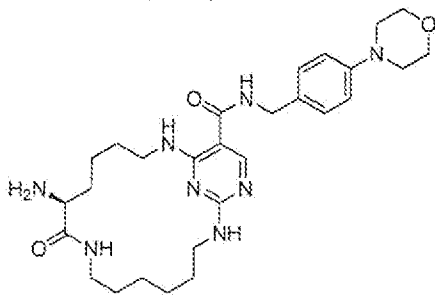
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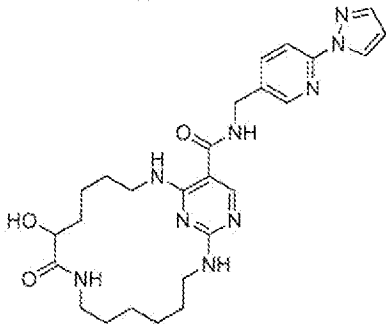
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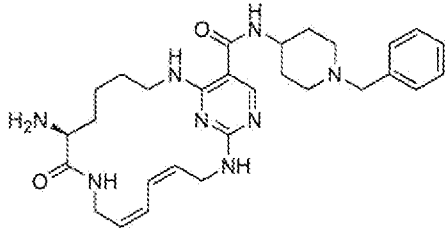
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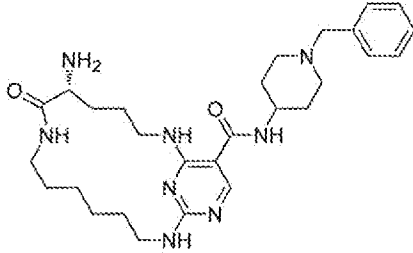
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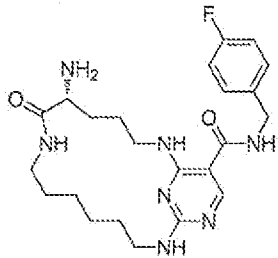
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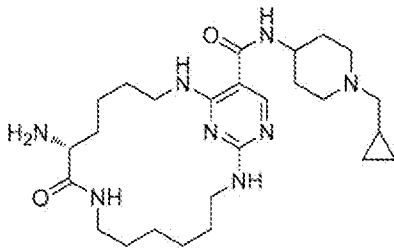
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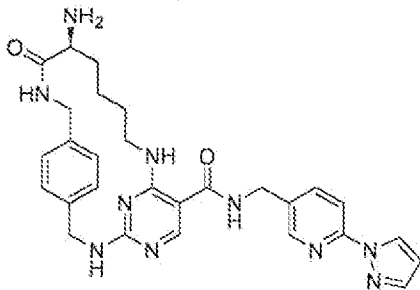
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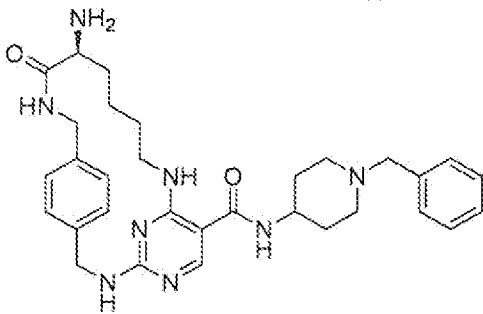
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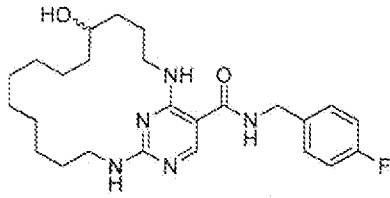
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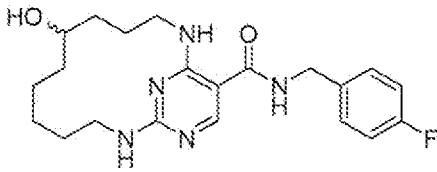
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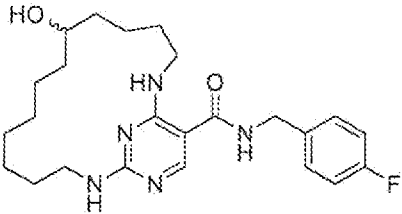
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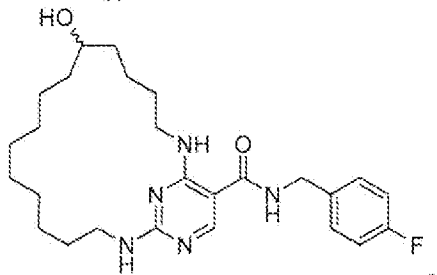
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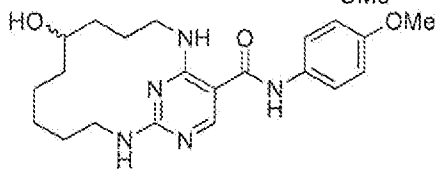
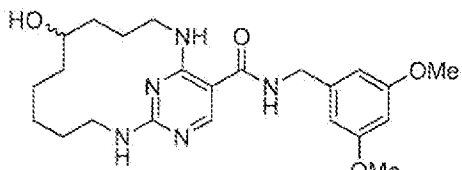
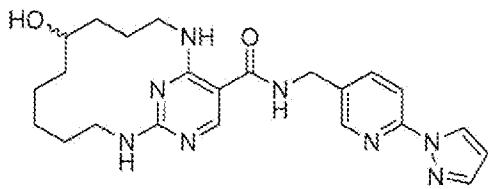
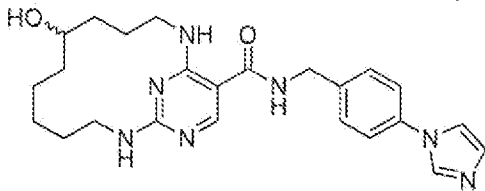
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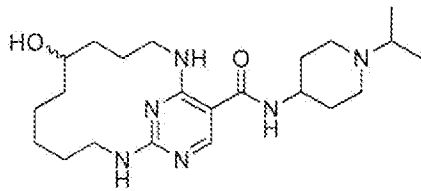


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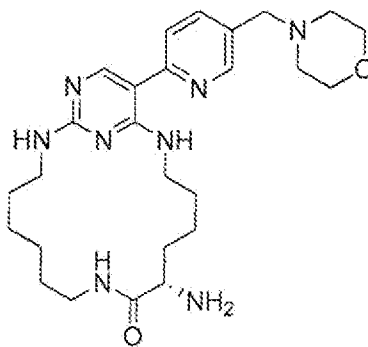


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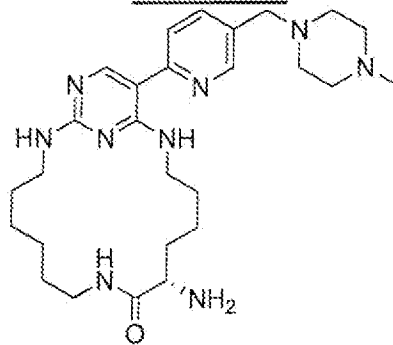




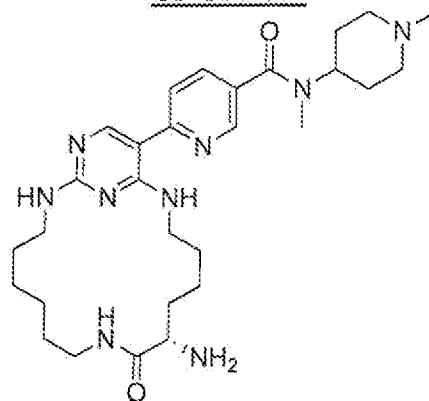
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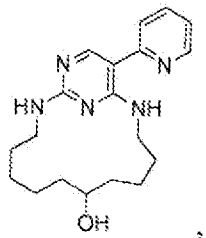
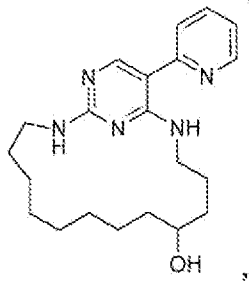
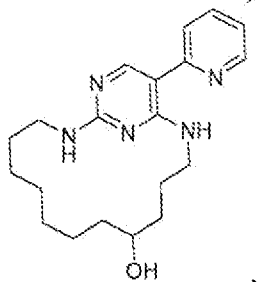
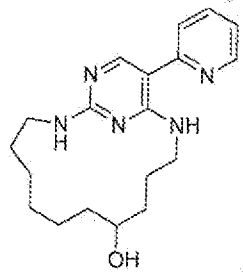
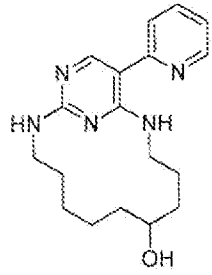
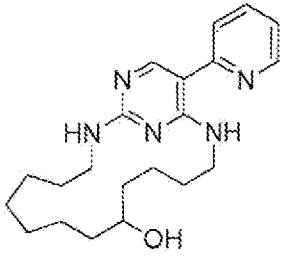
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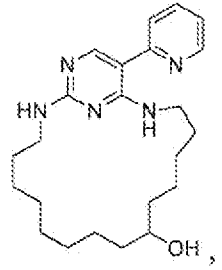
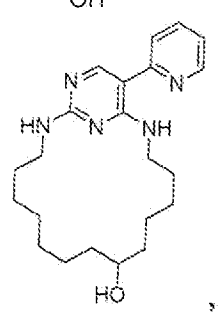
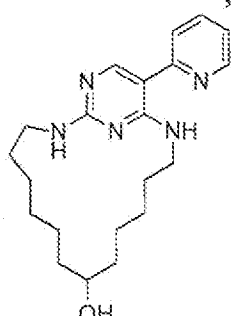
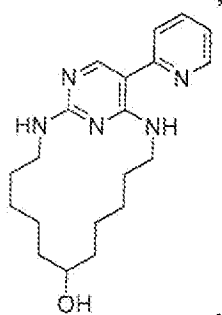
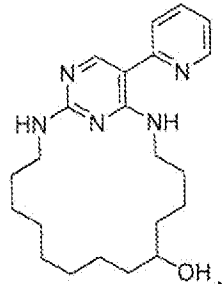
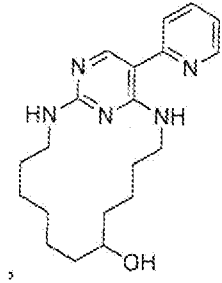


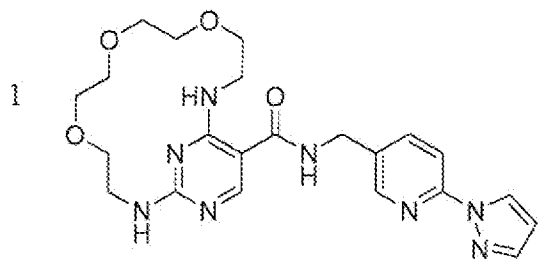
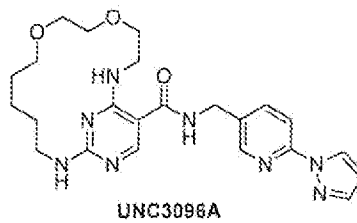
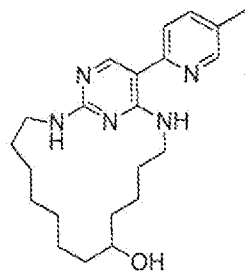
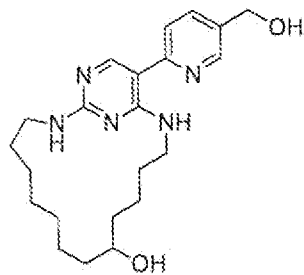
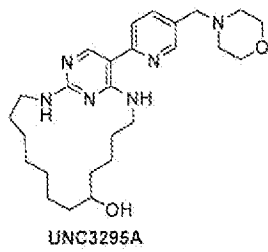
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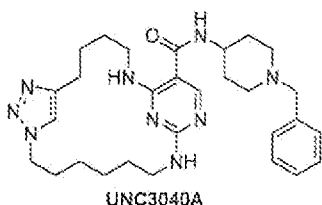
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- 69 -



and pharmaceutically acceptable salts thereof.

8. A composition comprising a compound of claim 1 to 7 in a pharmaceutically acceptable carrier.

9. A method of treating cancer in a subject in need thereof, comprising administering said subject a compound of claim 1 to 7 in an amount effective to treat said cancer.

10. The method of claim 9, wherein said cancer is selected from the group consisting of myeloid leukemia, lymphoblastic leukemia, melanoma, breast, lung, colon, liver, gastric, kidney, ovarian, uterine, and brain cancer.

11. A compound of claim 1 to 7 for use in the treatment of cancer or for the preparation of a medicament for treating cancer.

12. The use of claim 11, wherein said cancer is selected from the group consisting of myeloid leukemia, lymphoblastic leukemia, melanoma, breast, lung, colon, liver, gastric, kidney, ovarian, uterine, and brain cancer.

## INTERNATIONAL SEARCH REPORT

International application No.  
**PCT/US2013/071409****A. CLASSIFICATION OF SUBJECT MATTER****C07D 413/12(2006.01)i, A61K 31/5377(2006.01)i, A61P 35/00(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D 413/12; A61K 31/33; C07D 471/00; C07D 239/42; C07D 471/04; A61P 35/00; C07D 239/48; A61K 31/5377

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal), PubMed, NCBI, Esp@snet, PAJ, USPTO, Google

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011-090760 A1 (AVILA THERAPEUTICS, INC., et al.) 28 July 2011 See the whole document .	1-4,7
A	WO 2007-041379 A1 (BRISTOL-MYERS SQUIBB COMPANY, et al.) 12 April 2007 See the whole document .	1-4,7
A	WO 2000-039101 A1 (ASTRAZENECA UK LIMITED, et al.) 06 July 2000 See the whole document .	1-4,7
A	WO 2005-037801 A1 (SANKYO COMPANY, LIMITED, et al.) 28 April 2005 See the whole document .	1-4,7

 Further documents are listed in the continuation of Box C. See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

27 March 2014 (27.03.2014)

Date of mailing of the international search report

**31 March 2014 (31.03.2014)**

Name and mailing address of the ISA/KR

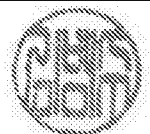
International Application Division  
Korean Intellectual Property Office  
189 Cheongsu-ro, Seo-gu, Daejeon Metropolitan City, 302-701,  
Republic of Korea

Facsimile No. +82-42-472-7140

Authorized officer

KIM, Bum Soo

Telephone No. +82-42-481-5412



**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 9-10  
because they relate to subject matter not required to be searched by this Authority, namely:  
Claims 9-10 pertain to methods for treatment of the human body by surgery or therapy, as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
2.  Claims Nos.: 10,12  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
Claims 10, 12 are unclear, since claims 10, 12 refer to the multiple dependent claim which are not searchable due to not being drafted in accordance with the third sentence of Rule 6.4(a). As a result, these claims are too unclear to make meaningful search possible.
3.  Claims Nos.: 5-6, 8-9, 11  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

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International application No.

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