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(54) **Title:** SUBSTITUTED PYRROLO(2,3-D)PYRIMIDINES FOR THE TREATMENT OF CANCER

(57) **Abstract:** Disclosed are substituted pyrrolo[2,3-d]pyrimidine compounds. The disclosed compounds are shown to be 'useful in inhibiting the growth of cancer cell lines and treating cancer and cell, proliferative disorders.



SUBSTITUTED PYRROLO[2,3-d]PYRIMIDINES FOR THE TREATMENT OF CANCER

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

[0001] The present application claims the benefit of priority under 35 U.S.C. 119(e) to U.S. Provisional Patent Application No. 61/787,893, filed on March 15, 2013, the content of which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] The field of the invention relates to substituted pyrrolo[2,3-d]pyrimidines. In particular, the field of the invention relates to substituted pyrrolo[2,3-d]pyrimidines for the treatment of cell proliferation diseases and disorders such as cancer.

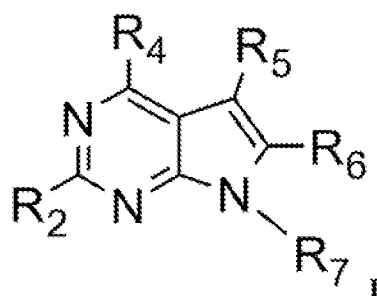
[0003] While treatment options have improved in recent years, cancer remains the second leading cause of death in the United States. Many cancers lack effective treatments and have poor long-term prognoses. In particular, multiple myeloma is the second most prevalent hematological malignancy and kills over 10,000 people annually. The median survival from this type of cancer is approximately 5-7 years. Even with the advent of several new chemotherapies, only 25-35% of patients respond to these drugs. Additional treatment options are necessary for patients who fail to respond to current therapies and for those who develop resistance to current therapies.

[0004] Here, as part of an effort to discover and evaluate new small molecules that have the potential for treating human cancer, in particular hematological malignancies, we have identified a series of novel substituted pyrrolo[2,3-d]pyrimidine compounds that display potent *in vitro* cytotoxicity against cancer cells. These compounds present unique substitution patterns that impart on them activity against a variety of human cancer cell lines. Compound analogs have been synthesized and tested to generate robust structure-activity relationships based on multiple sites of diversification. Lead compounds possess excellent profiles as potential therapeutics based on a variety of physiochemical properties. These new compounds therefore hold promise as new potential treatments for cancer and other proliferative diseases.

SUMMARY

[0005] Disclosed are substituted pyrrolo[2,3-d]pyrimidines. The disclosed compounds may be used in pharmaceutical compositions and methods for treating cell proliferative disorders such as cancer.

[0006] In some embodiments, the substituted pyrrolo[2,3-d]pyrimidines may have a Formula I:

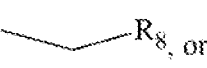


wherein:

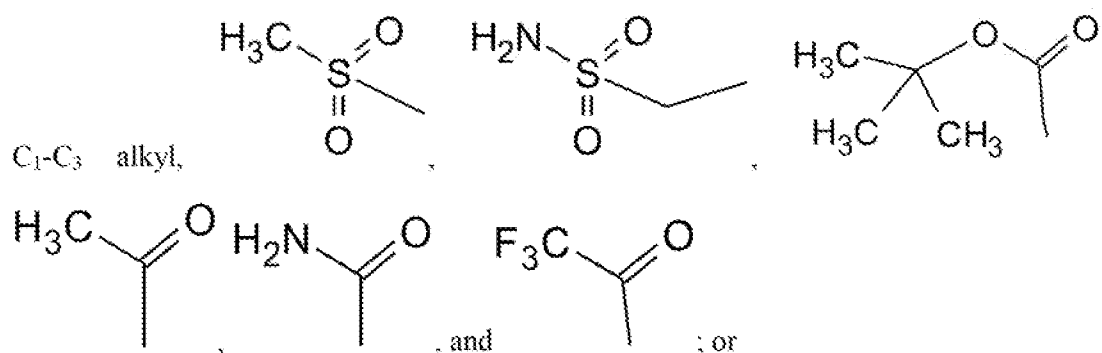
R₂ is hydrogen, halogen, or amine;

R₄ is hydrogen, C₁-C₃ alkyl optionally substituted at one or more positions with halogen, acetyl, amine, cyano, or methylsulfonyl;

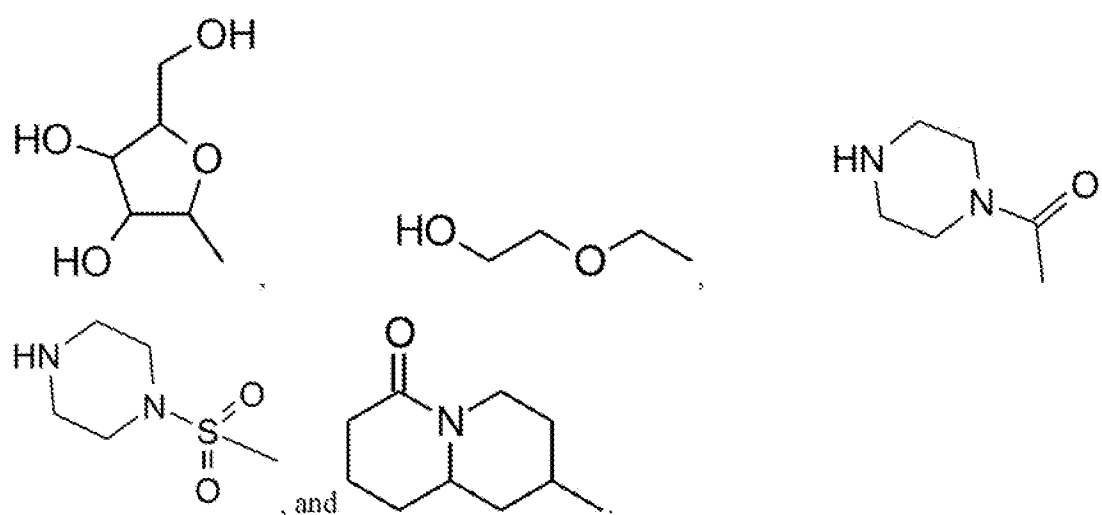
R₅ and R₆ are each independently hydrogen, C₁-C₃ alkyl optionally substituted at one or more positions with halogen; or R₅ and R₆ are linked together to form a 6-membered ring; and

R₇ is hydrogen, R₈,  R₈, or  R₈; or R₆ and R₇ are linked together to form a 6-membered ring;

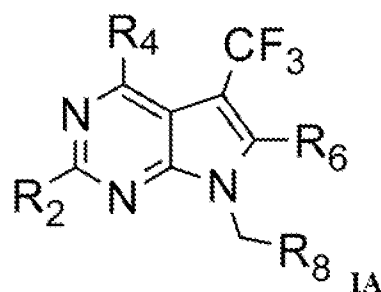
R₈ is methoxy, amine, or a 4-, 5-, or 6-membered carbocyclic or heterocyclic ring that is saturated or unsaturated, the ring optionally substituted at one or more carbon atoms with halogen, hydroxyl, methoxy, oxo, methylcarboxyl, methylamido, or methylhydroxyl; and the ring optionally substituted at a nitrogen heteroatom with a substituent selected from



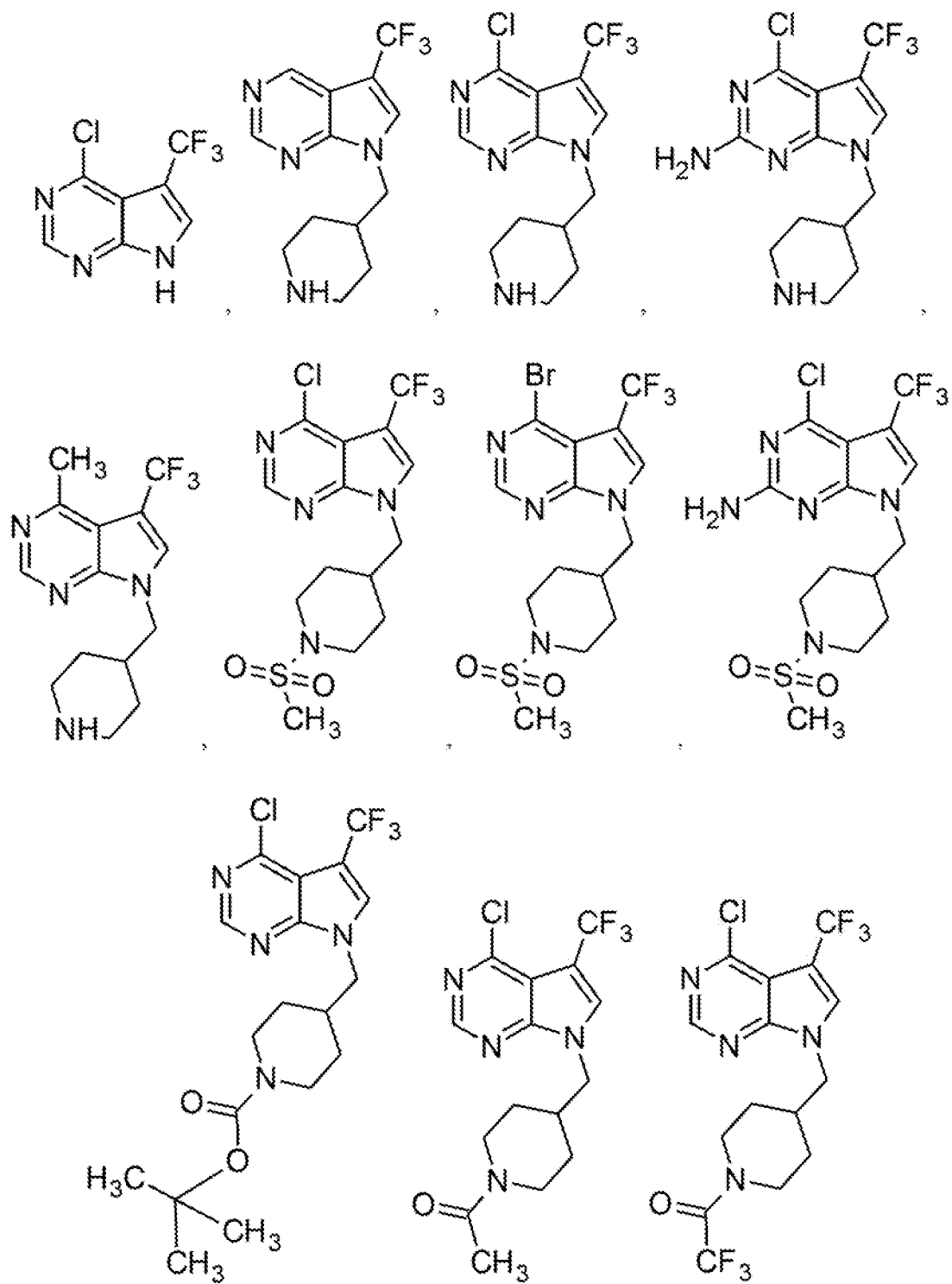
R_8 is selected from

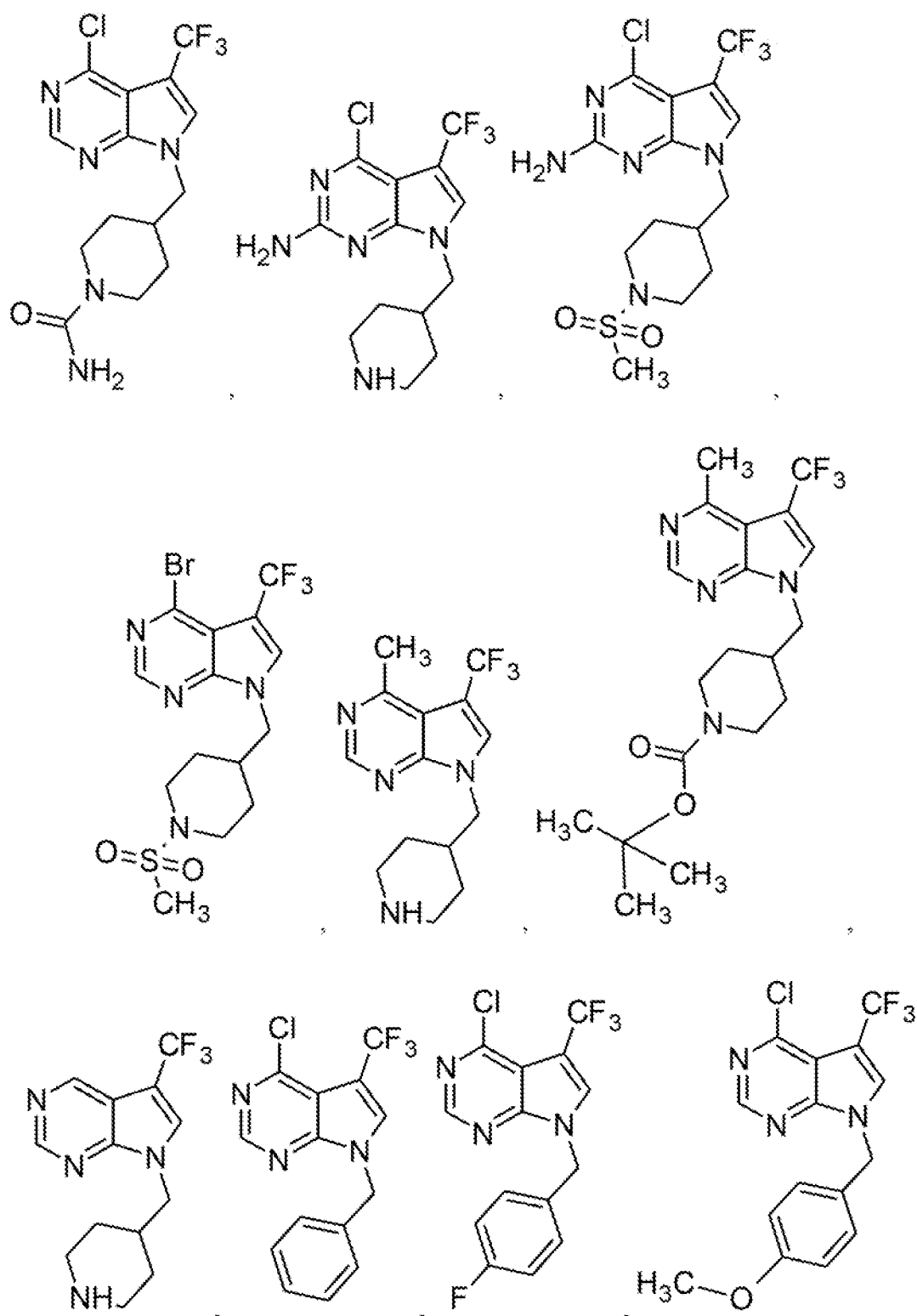


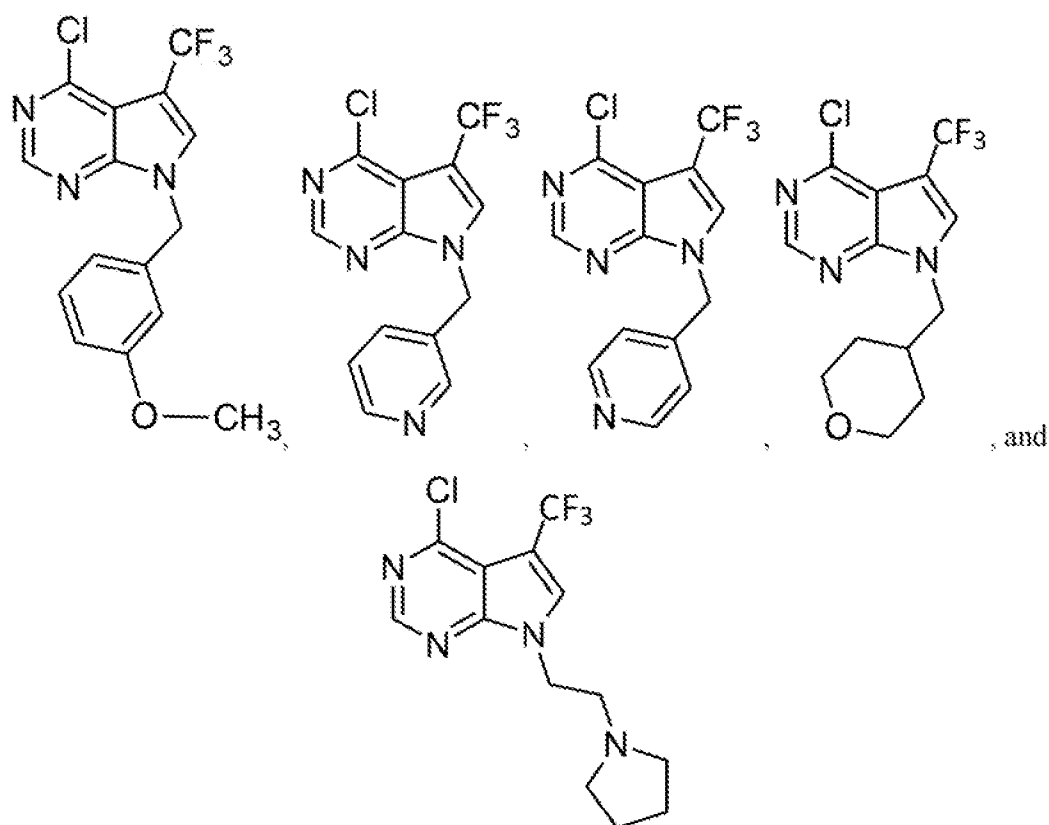
[0007] In particular, the compounds disclosed herein may have a Formula IA:



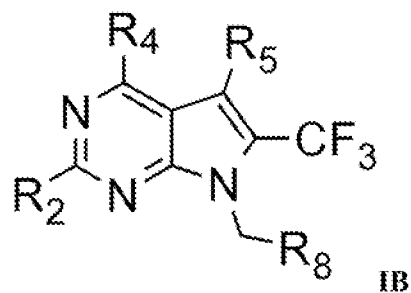
wherein: R_4 is hydrogen, halogen, or methyl; and R_2 , R_6 , and R_8 are as defined for Formula I. In some embodiments, R_8 is a ring selected from piperidine, benzene, pyridine, and oxane, which may be substituted as indicated for Formula I or unsubstituted. The compounds disclosed herein having Formula IA may include, but are not limited to:



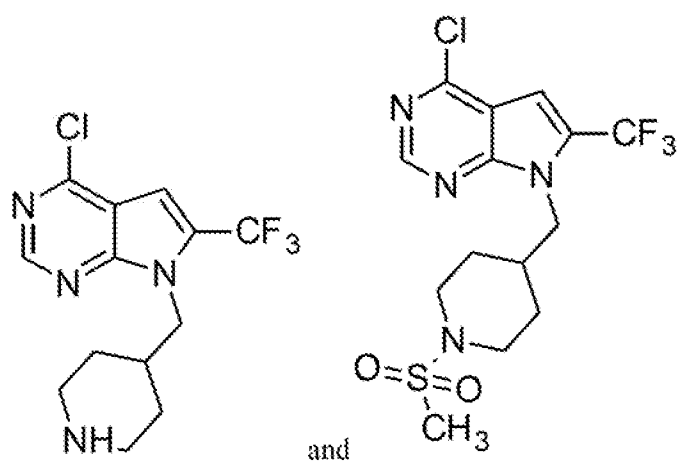




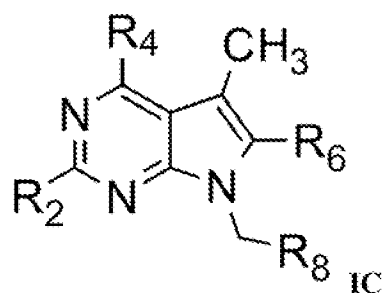
[0008] In particular, the compounds disclosed herein may have a Formula IB:



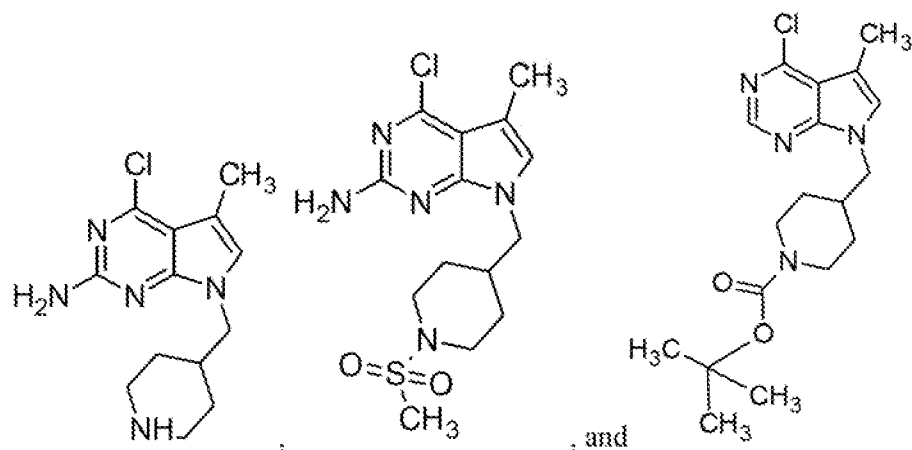
wherein: R_4 is hydrogen, halogen, or methyl; and R_2 , R_5 , and R_8 are as defined for Formula I. In some embodiments, R_8 is a ring selected from piperidine, benzene, pyridine, and oxane, which may be substituted as indicated for Formula I or unsubstituted. The compounds disclosed herein having Formula IB may include, but are not limited to:



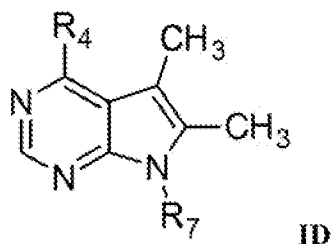
[0009] In particular, the compounds disclosed herein may have a Formula IC:



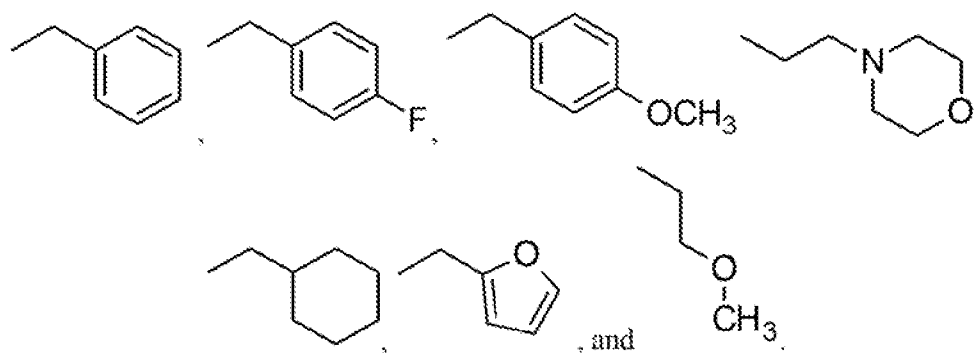
[0010] wherein: R_4 is hydrogen, halogen, or methyl; and R_2 , R_6 , and R_8 are as defined for Formula I. In some embodiments, R_8 is a ring selected from piperidine, benzene, pyridine, and oxane, which may be substituted as indicated for Formula I or unsubstituted. The compounds disclosed herein having Formula IC may include, but are not limited to



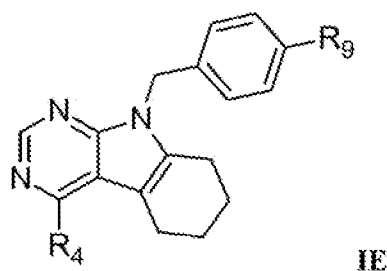
[0011] Other of the substituted pyrrolo[2,3-d]pyrimidine compounds disclosed herein may have a Formula ID:



wherein R_4 is halogen or amine; and R_7 is as defined for Formula I. In some embodiments, R_4 is chlorine and R_7 is selected from

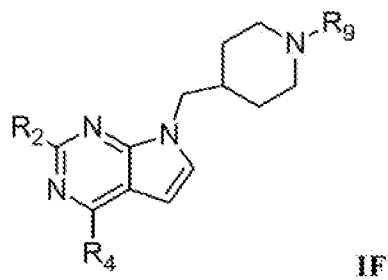


[0012] Other of the substituted pyrrolo[2,3-d]pyrimidine compounds disclosed herein may have a Formula IE:



otherwise referred to as a “tricyclic 6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]indole core,” wherein: R_4 is halogen; and R_9 is hydrogen or halogen. In some preferred embodiments, R_4 is chlorine. In other preferred embodiments, R_9 is halogen, and in particular, fluorine.

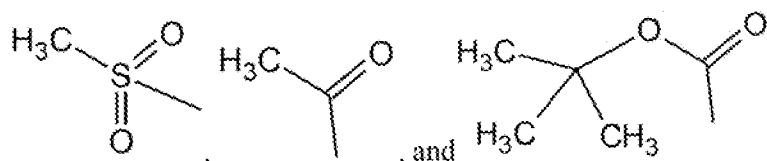
[0013] Other of the substituted pyrrolo[2,3-d]pyrimidine compound disclosed herein may have a Formula IF:



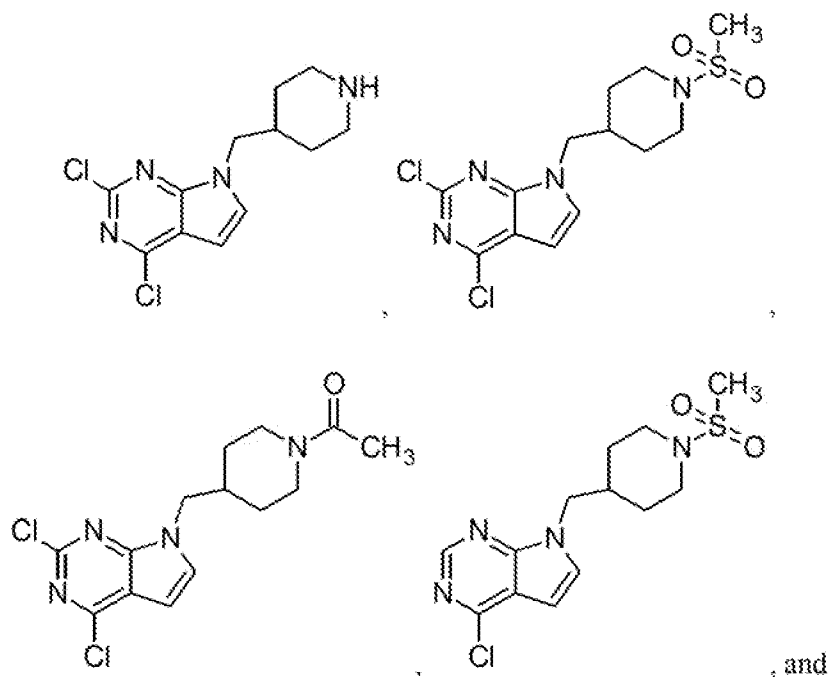
wherein: R_2 is hydrogen or halogen;

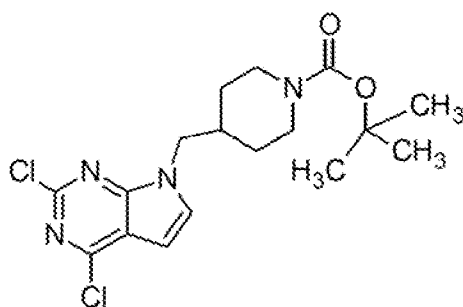
R_4 is halogen; and

R_9 is hydrogen, or is selected from



In some preferred embodiments, R_4 is chlorine. Specific compounds having Formula IF may include, but are not limited to:





[0014] Also disclosed are pharmaceutical compositions that comprise the disclosed compounds together with a carrier, diluent, or excipient. The pharmaceutical compositions may comprise an effective amount of the compounds (or salts, esters, amides, or solvates thereof) for treating and/or preventing a disease, disorder, or condition which may include cell proliferation diseases, disorders, or conditions, such as cancer.

[0015] Also disclosed are methods of treating cancer that include administering the disclosed compounds, for example, where the compounds are formulated as a pharmaceutical composition and administered to a patient having cancer or suspected of having cancer. Cancers treated by the disclosed methods may include, but are not limited to multiple myeloma, leukemia, non-small cell lung cancer, colon cancer, cancer of the central nervous system, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] FIG. 1. Treatment of MM.1S cells with substituted pyrrolo[2,3-d]pyrimidine compounds or 8-amino adenosine.

[0017] FIG. 2. Inhibition of leukemia cell lines by NUCL 381-3, NUCL 383-3, and Doxorubicin (left to right).

[0018] FIG. 3. Inhibition of non-small lung cancer cell lines by NUCL 381-3, NUCL 383-3, and Doxorubicin (left to right).

[0019] FIG. 4. Inhibition of colon cancer cell lines by NUCL 381-3, NUCL 383-3, and Doxorubicin (left to right).

[0020] FIG. 5. Inhibition of central nervous system (CAN) cancer cell lines by NUCL 381-3, NUCL 383-3, and Doxorubicin (left to right).

[0021] FIG. 6. Inhibition of melanoma cell lines by NUCL 381-3, NUCL 383-3, and Doxorubicin (left to right).

[0022] FIG. 7. Inhibition of ovarian cancer cell lines by NUCL 381-3, NUCL 383-3, and Doxorubicin (left to right).

[0023] FIG. 8. Inhibition of renal cancer cell lines by NUCL 381-3, NUCL 383-3, and Doxorubicin (left to right).

[0024] FIG. 9. Inhibition of prostate cancer cell lines by NUCL 381-3, NUCL 383-3, and Doxorubicin (left to right).

[0025] FIG. 10. Inhibition of breast cancer cell lines by NUCL 381-3, NUCL 383-3, and Doxorubicin (left to right).

[0026] FIG. 11. Inhibition of THP-1 cell lines treated with Compounds 381, 383, 409 (as test compounds) and Compound 501 (as a negative control) as compared to 8-amino adenosine (8NH₂-Ado) and 8-chloro adenosine (8Cl-Ado) (as positive controls).

[0027] FIG. 12. Inhibition of K562 cell lines treated with Compounds 381, 383, 409 (as test compounds) and Compound 501 (as a negative control) as compared to 8-amino adenosine (8NH₂-Ado) and 8-chloro adenosine (8Cl-Ado) (as positive controls). FIG. 13. Inhibition of Kasumi-1 cell lines.

[0028] FIG. 13. Inhibition of Kasumi-1 cell lines treated with Compounds 381, 383, 409 (as test compounds) and Compound 501 (as a negative control) as compared to 8-amino adenosine (8NH₂-Ado) and 8-chloro adenosine (8Cl-Ado) (as positive controls).

[0029] FIG. 14. Inhibition of U937 cell lines treated with Compounds 381, 383, 409 (as test compounds) and Compound 501 (as a negative control) as compared to 8-amino adenosine (8NH₂-Ado) and 8-chloro adenosine (8Cl-Ado) (as positive controls).

[0030] FIG. 15. Inhibition of RNA synthesis in U937 cell lines treated with Compounds 381, 383, 409 (as test compounds) and Compound 501 (as a negative control) as compared to 8-amino adenosine (8NH₂-Ado) and 8-chloro adenosine (8Cl-Ado) (as positive controls).

[0031] FIG. 16. Inhibition of RNA synthesis in U937 cell lines treated with Compounds 381, 383, 409 (as test compounds) and Compound 501 (as a negative control) as compared to 8-amino adenosine (8NH₂-Ado) and 8-chloro adenosine (8Cl-Ado) (as positive controls).

[0032] FIG. 17. Immunoblot of cell lysates from U937 cell lines treated with Compounds 381, 383, 409 (as test compounds) and Compound 501 (as a negative control) as compared to 8-amino adenosine (8NH₂-Ado) and 8-chloro adenosine (8Cl-Ado) (as positive controls).

DETAILED DESCRIPTION

[0033] The present invention is described herein using several definitions, as set forth below and throughout the application.

[0034] Unless otherwise specified or indicated by context, the terms “a”, “an”, and “the” mean “one or more.” For example, “a compound” should be interpreted to mean “one or more compounds.”

[0035] As used herein, “about,” “approximately,” “substantially,” and “significantly” will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which they are used. If there are uses of these terms which are not clear to persons of ordinary skill in the art given the context in which they are used, “about” and “approximately” will mean plus or minus $\leq 10\%$ of the particular term and “substantially” and “significantly” will mean plus or minus $>10\%$ of the particular term.

[0036] As used herein, the terms “include” and “including” have the same meaning as the terms “comprise” and “comprising” in that these latter terms are “open” transitional terms that do not limit claims only to the recited elements succeeding these

transitional terms. The term “consisting of,” while encompassed by the term “comprising,” should be interpreted as a “closed” transitional term that limits claims only to the recited elements succeeding this transitional term. The term “consisting essentially of,” while encompassed by the term “comprising,” should be interpreted as a “partially closed” transitional term which permits additional elements succeeding this transitional term, but only if those additional elements do not materially affect the basic and novel characteristics of the claim.

[0037] As used herein, a “patient” may be interchangeable with “subject” or “individual” and means an animal, which may be a human or non-human animal, in need of treatment.

[0038] A “patient in need of treatment” may include a patient having a disease, disorder, or condition that is responsive to therapy with a substituted pyrrolo[2,3-d]pyrimidine. For example, a “patient in need of treatment” may include a patient having a cell proliferative disease, disorder, or condition such as cancer (*e.g.*, cancers such as multiple myeloma, leukemia, non-small cell lung cancer, colon cancer, cancer of the central nervous system, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer).

[0039] As used herein, the phrase “effective amount” shall mean that drug dosage that provides the specific pharmacological response for which the drug is administered in a significant number of patients in need of such treatment. An effective amount of a drug that is administered to a particular patient in a particular instance will not always be effective in treating the conditions/diseases described herein, even though such dosage is deemed to be a therapeutically effective amount by those of skill in the art.

[0040] The formulae of the compounds disclosed herein should be interpreted as encompassing all possible stereoisomers, enantiomers, or epimers of the compounds unless the formulae indicates a specific stereoisomer, enantiomer, or epimer. The formulae of the compounds disclosed herein should be interpreted as encompassing salts, esters, amides, or solvates thereof of the compounds.

[0041] The disclosed compounds may be effective in inhibiting cell proliferation of cancer cells. For example, the disclosed compound may be effective in inhibiting cell proliferation of one or more types of cancer cells including: multiple myeloma cells, such as MM.1S cells; leukemia cells, such as CCRF-CEM, HL-60(TB), MOLT-4, RPMI-8226 and SR; non-small lung cancer cells, such as A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, NCI-H460 and NCI-H522; colon cancer cells, such as COLO 205, HCC-2998, HCT-116, HCT-15, HT29, KM12 and SW-620; CNS: SF-268, SF-295, SF-539, SNB-19, SNB-75 and U251; melanoma cancer cells, such as LOX IMVI, MALME-3M, M14, MDA-MB-435, SK-MEL-2, SK-MEL-28, SK-MEL-5, UACC-257 and UACC-62; ovarian cancer cells, such as IGR-OV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, NCI/ADR-RES and SK-OV-3; renal cancer cells, such as 786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10 and UO-31; prostate cancer cells, such as DU-145 and PC-3; and breast cancer cells, such as MCF7, MDA-MB-231/ATCC, MDA-MB-468, HS 578T, BT-549 and T-47D.

[0042] Cell proliferation and inhibition thereof by the presently disclosed compounds may be assessed by cell viability methods disclosed in the art including colorimetric assays that utilize dyes such as MTT, XTT, and MTS to assess cell viability. Preferably, the disclosed compounds have an IC₅₀ of less than about 10 μ M, 5 μ M, 1 μ M, or 0.5 μ M in the selected assay.

[0043] The compounds utilized in the methods disclosed herein may be formulated as pharmaceutical compositions that include: (a) a therapeutically effective amount of one or more compounds as disclosed herein; and (b) one or more pharmaceutically acceptable carriers, excipients, or diluents. The pharmaceutical composition may include the compound in a range of about 0.1 to 2000 mg (preferably about 0.5 to 500 mg, and more preferably about 1 to 100 mg). The pharmaceutical composition may be administered to provide the compound at a daily dose of about 0.1 to 100 mg/kg body weight (preferably about 0.5 to 20 mg/kg body weight, more preferably about 0.1 to 10 mg/kg body weight). In some embodiments, after the pharmaceutical composition is administered to a patient (e.g., after about 1, 2, 3, 4, 5, or 6 hours post-administration), the concentration of the compound at the site of action is about 2 to 10 μ M.

[0044] The compounds utilized in the methods disclosed herein may be formulated as a pharmaceutical composition in solid dosage form, although any pharmaceutically acceptable dosage form can be utilized. Exemplary solid dosage forms include, but are not limited to, tablets, capsules, sachets, lozenges, powders, pills, or granules, and the solid dosage form can be, for example, a fast melt dosage form, controlled release dosage form, lyophilized dosage form, delayed release dosage form, extended release dosage form, pulsatile release dosage form, mixed immediate release and controlled release dosage form, or a combination thereof.

[0045] The compounds utilized in the methods disclosed herein may be formulated as a pharmaceutical composition that includes a carrier. For example, the carrier may be selected from the group consisting of proteins, carbohydrates, sugar, talc, magnesium stearate, cellulose, calcium carbonate, and starch-gelatin paste.

[0046] The compounds utilized in the methods disclosed herein may be formulated as a pharmaceutical composition that includes one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, and effervescent agents. Filling agents may include lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC™). Suitable lubricants, including agents that act on the flowability of the powder to be compressed, may include colloidal silicon dioxide, such as Aerosil®200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel. Examples of sweeteners may include any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acesulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like. Examples of preservatives may include potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quaternary compounds such as benzalkonium chloride.

[0047] Suitable diluents may include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

[0048] Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

[0049] Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

[0050] The compounds utilized in the methods disclosed herein may be formulated as a pharmaceutical composition for delivery via any suitable route. For example, the pharmaceutical composition may be administered via oral, intravenous, intramuscular, subcutaneous, topical, and pulmonary route. Examples of pharmaceutical compositions for oral administration include capsules, syrups, concentrates, powders and granules.

[0051] The compounds utilized in the methods disclosed herein may be administered in conventional dosage forms prepared by combining the active ingredient with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

[0052] Pharmaceutical compositions comprising the compounds may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or

parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

[0053] Pharmaceutical compositions adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

[0054] Pharmaceutical compositions adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis.

[0055] Pharmaceutical compositions adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, impregnated dressings, sprays, aerosols or oils and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

[0056] For applications to the eye or other external tissues, for example the mouth and skin, the pharmaceutical compositions are preferably applied as a topical ointment or cream. When formulated in an ointment, the compound may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the compound may be formulated in a cream with an oil-in-water cream base or a water-in-oil base. Pharmaceutical compositions adapted for topical administration to the eye include eye drops where the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

[0057] Pharmaceutical compositions adapted for topical administration in the mouth include lozenges, pastilles and mouth washes.

[0058] Pharmaceutical compositions adapted for rectal administration may be presented as suppositories or enemas.

[0059] Pharmaceutical compositions adapted for nasal administration where the carrier is a solid include a coarse powder having a particle size (e.g., in the range 20 to 500 microns) which is administered in the manner in which snuff is taken (*i.e.*, by rapid inhalation through the nasal passage from a container of the powder held close up to the nose). Suitable formulations where the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

[0060] Pharmaceutical compositions adapted for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurized aerosols, nebulizers or insufflators.

[0061] Pharmaceutical compositions adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations.

[0062] Pharmaceutical compositions adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

[0063] Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented

as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavoring or coloring agents.

EXAMPLES

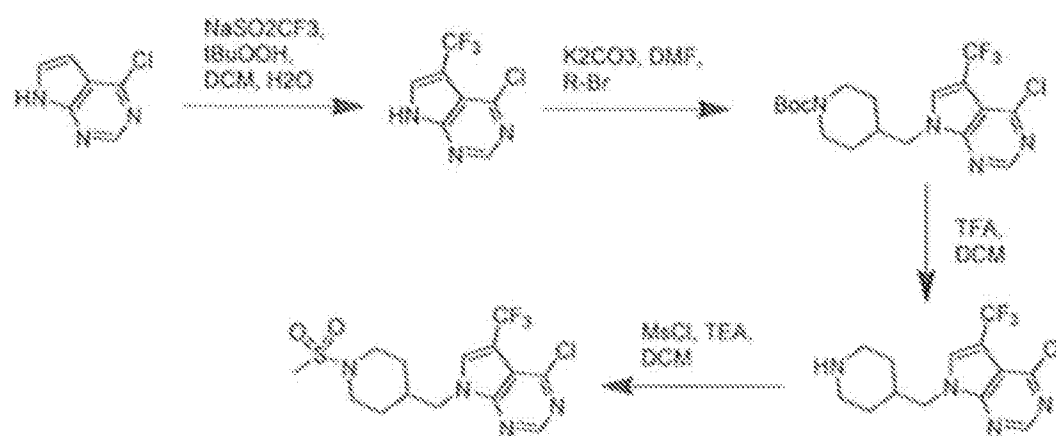
[0064] The following Examples are illustrative and are not intended to limit the scope of the claimed subject matter.

[0065] Example 1 – Synthesis of Substituted Pyrrolo[2,3-d]pyrimidine Compounds

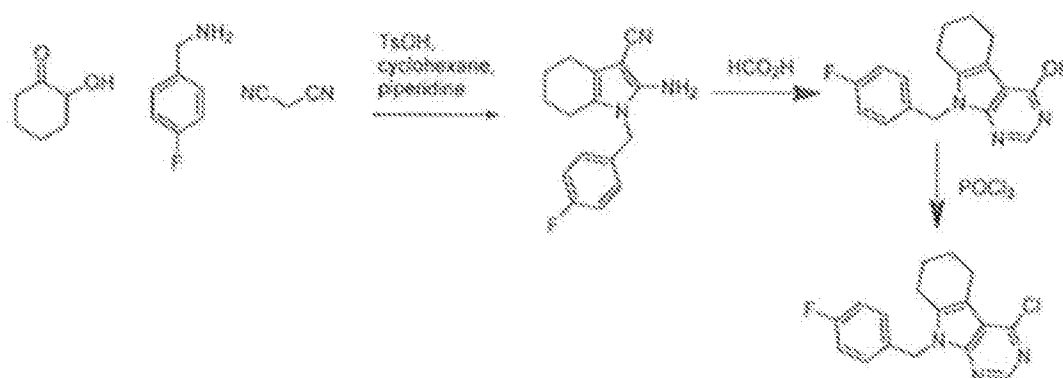
[0066] Synthesis

[0067] The substituted pyrrolo[2,3-d]pyrimidines disclosed herein may be synthesized using the following Schemes I and II:

Scheme I



Scheme II



The synthesis and use of 5,6-disubstituted pyrrolo[2,3-d]pyrimidines are disclosed in the art. (See, e.g., patent document nos.: U.S. 8,633,205; U.S. 8,580,802; U.S. 8,507,672; U.S. 8,501,752; U.S. 8,420,657; U.S. 8,258,143; U.S. 8,183,248; U.S. 8,093,229; U.S. 7,981,902; U.S. 7,951,812; U.S. 7,951,810; U.S. 7,625,894; U.S. 7,544,672; U.S. 7,531,546; U.S. 7,358,250; U.S. 7,279,474; U.S. 6,066,732; U.S. 6,051,577; U.S. 5,869,485; U.S. 5,686,457; U.S. 5,254,687; U.S. 4,229,453; U.S. 2010/0144705; U.S. 2003/0018700; DE 2818676; DE 1916050; DE 1916011; WO 2012/012712; and WO 2008/006547; the contents of which are incorporated herein by reference in their entireties).

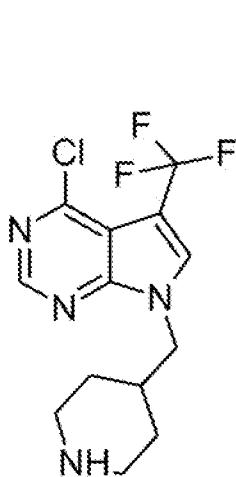
[0068] The presently disclosed substituted pyrrolo[2,3-d]pyrimidines may include a trifluoromethyl group. Trifluoromethylation of heterocycles is disclosed in Ji Y. *et al.*, "Innate C-H trifluoromethylation of heterocycles," PNAS, 2011, 108; 14411-14415, the content of which is incorporated herein by reference in its entirety.

[0069] Example 2 -- Inhibition of MM.1S Cells by Substituted Pyrrolo[2,3-d]pyrimidine Compounds

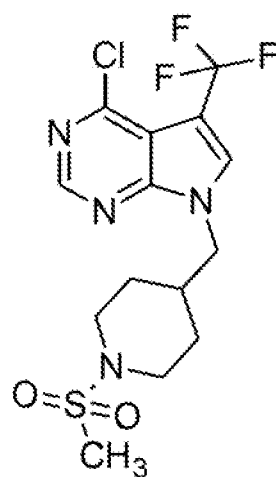
[0070] Summary. The substituted pyrrolo[2,3-d]pyrimidines disclosed herein are effective at reducing the proliferation of a number of cancer cell lines including MM.1S cancer cells, which are a multiple myeloma-derived cell line. MM.1 S is a multiple myeloma-derived cell line and therefore compounds that are cytotoxic against these cells

have potential for treating this and other cancer types. Common structural features of the substituted pyrrolo[2,3-d]pyrimidines typically include a chlorine substitution at the 4-position. The 5- and 6-positions of the fused heterocyclic ring may be substituted on one or both of the carbons. For example, the 5- and 6-positions can each independently be small alkyl groups or joined to form a tricyclic 6,7,8,9-tetrahydro-5H-pyrimido[4,5-b]indole core system. When mono-substituted, a trifluoromethyl group at the 5-position provides particularly potent compounds. The N7 can be substituted with a wide variety of groups, including functionatized benzyl groups and heterocycles. The present compounds are shown to inhibit cell proliferation of multiple myeloma MM.1 S cells using the well-validated MTS cell proliferation assay. A number of the tested compounds have an IC_{50} of 10 μ M or lower in the MM.1 S MTS assay. Several compounds have an IC_{50} of less than 1 μ M.

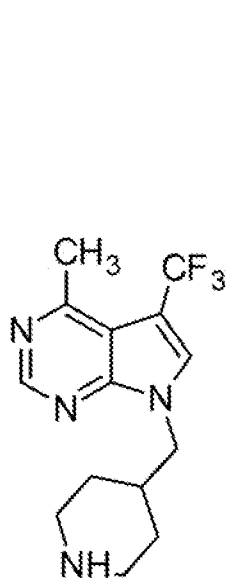
[0071] Experimental. MM.1 S cells were treated with test compounds including NUCC-000381, NUCC-00383, NUCC-000501, NUCC-000482, and 8-amino adenosine, having the following formulas, respectively:



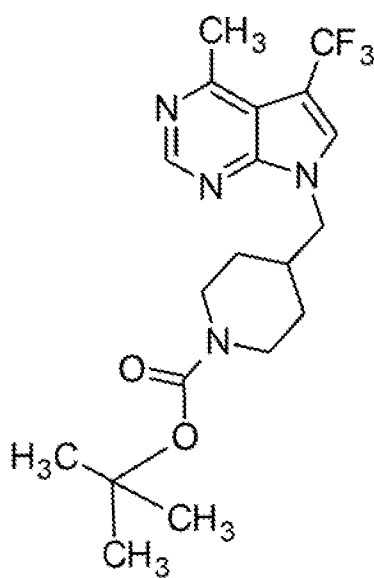
NUCC-000381,



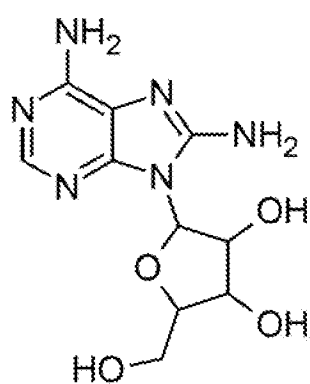
NUCC-00383,



NUCC-000501,



NUCC-000482, and



8-amino-adenosine.

As shown in FIG. 1, the compounds were administered at concentrations ranging from 0.1 μ M, 0.3 μ M, 1 μ M, 3 μ M, and 10 μ M. Cell viability was assessed by MTS assay as follows.

[0072] MTS Cell Titer 96 assay. The MTS CellTiter 96 assay is a colorimetric method to assess the number of viable cells based on the conversion of a tetrazlium compound (MTS) to a formazan product by the mitochondrial dehydrogenase enzyme of the cells. This assay is used to determine the number of viable cells remaining following a drug treatment in comparison to the number of viable cells that are only treated with the drug vehicle (control cells). The amount of formazan product in the control cells is normalized to 100% and the amount of formazan in the drug treated cells is expressed as a percentage of control. This is used to generate dose response curve and estimate the drug concentration that produced a 50% decrease in the number of viable cells.

[0073] Results. NUCC-00381 and NUCC-000383 were each as effective in decreasing cell proliferation as 8-amine-adenosine, a compound under development for therapeutic application. In contrast, NUCC-000501 and NUCC-000482 were not effective in decreasing cell proliferation. Notably, NUCC-000501 and NUCC-000482 differ structurally from NUCC-00381 and NUCC-000383 based on the presence of a 4-methyl substituent rather than a 4-chloro substituent. Additional compounds that were synthesized and tested in the multiple myeloma MM.1S/MTS cell proliferation assay are disclosed in Tables 1-13.

Table 1.

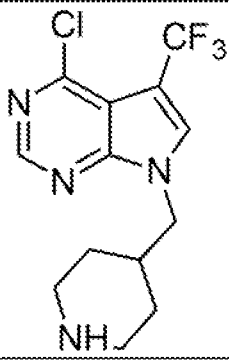
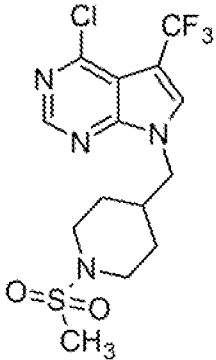
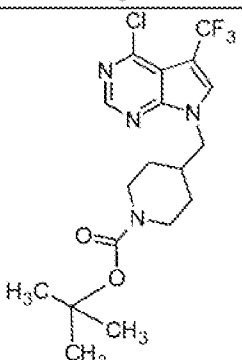
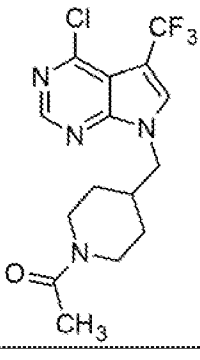
Compound ID	Structure	Estimated IC ₅₀ (μm)
NUCC-0000381		0.6
NUCC-0000383		0.9
NUCC-0000357		1.5
NUCC-0000383		1.5

Table 2.

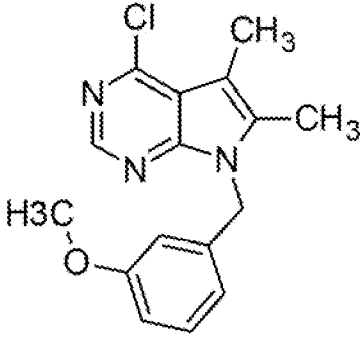
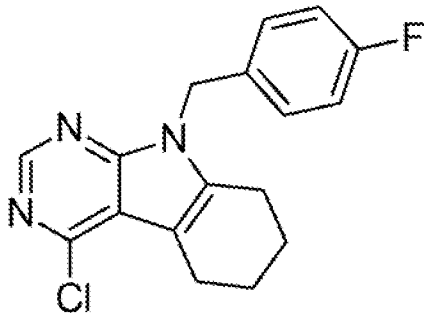
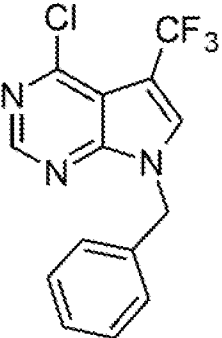
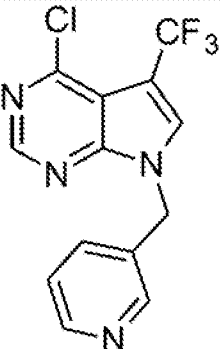
Compound ID	Structure	Estimated IC ₅₀ (μm)
NUCC-0000409		1.5
NUCC-0000412		2.5
NUCC-0000315		3
NUCC-0000326		3

Table 3.

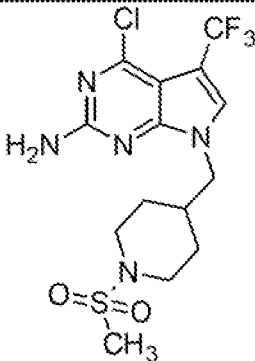
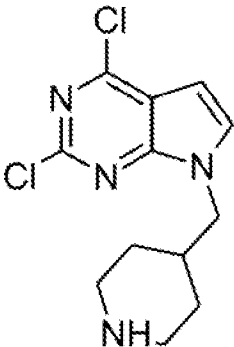
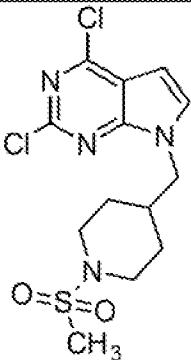
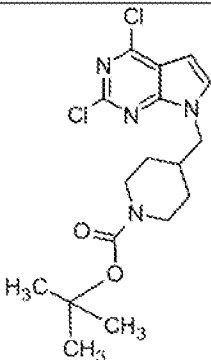
Compound ID	Structure	Estimated IC ₅₀ (μm)
NUCC-0000576		3
NUCC-0000575		3
NUCC-0000577		5
NUCC-0000571		5

Table 4.

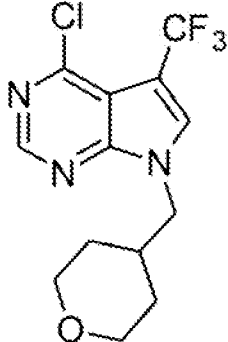
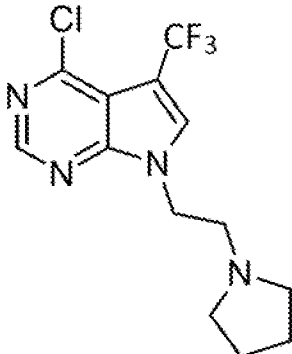
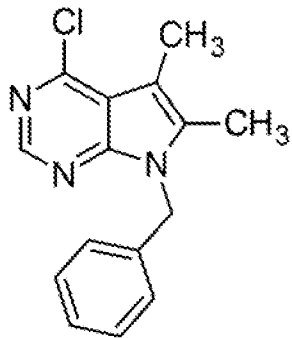
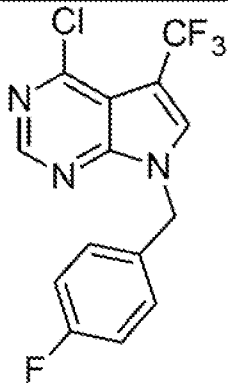
Compound ID	Structure	Estimated IC ₅₀ (μm)
NUCC-0000329		3
NUCC-0000358		3
NUCC-0000280		5
NUCC-0000325		5

Table 5.

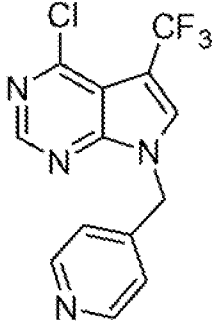
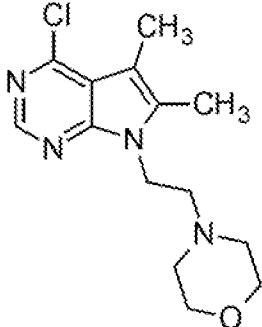
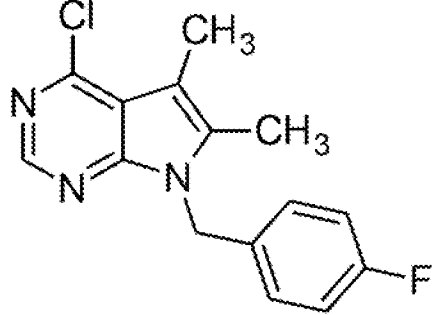
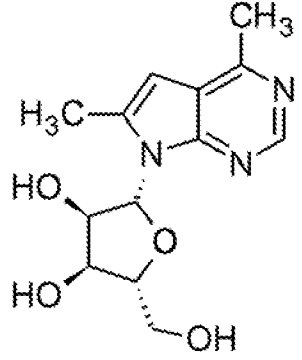
Compound ID	Structure	Estimated IC ₅₀ (μm)
NUCC-0000327		5
NUCC-0000413		5
NUCC-0000360		7
NUCC-0000477		8

Table 6.

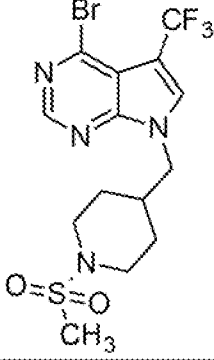
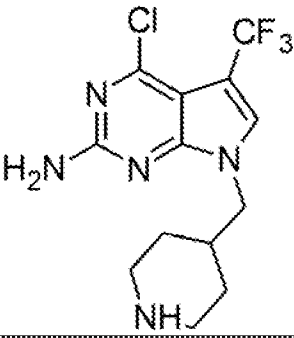
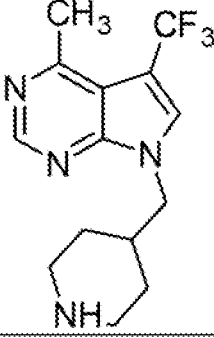
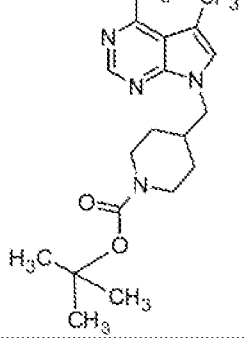
Compound ID	Structure	Estimated IC ₅₀ (μm)
NUCC-0000598		2
NUCC-0000570		3
NUCC-0000501		Inactive
NUCC-0000482		Inactive

Table 7.

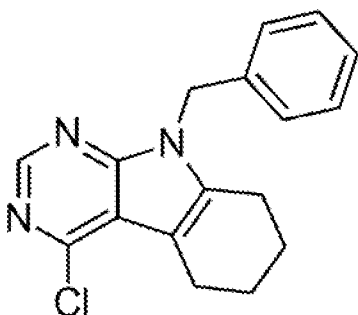
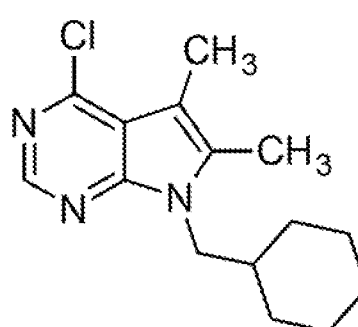
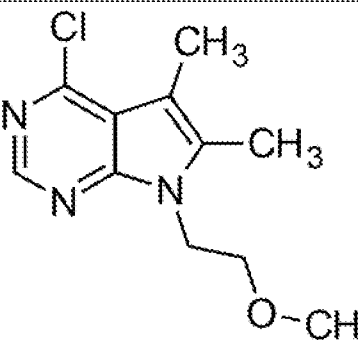
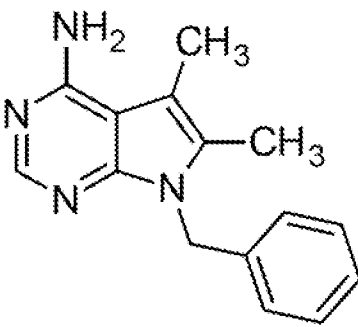
Compound ID	Structure	Estimated IC50 (μm)
NUCC-0000308		10
NUCC-0000359		10
NUCC-0000361		10
NUCC-0000362		10

Table 8.

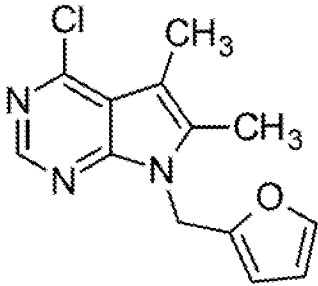
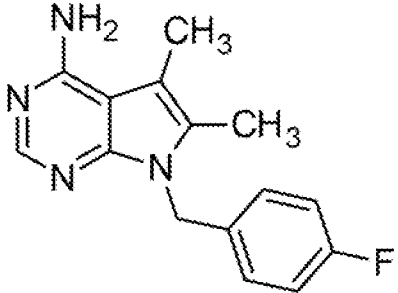
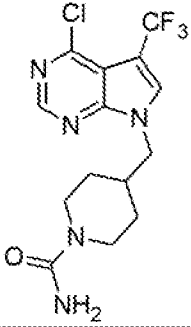
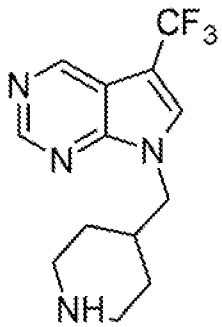
Compound ID	Structure	Estimated IC ₅₀ (μm)
NUCC-0000363		10
NUCC-0000375		10
NUCC-0000469		10
NUCC-0000470		10

Table 9.

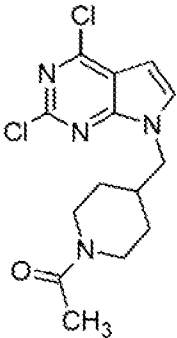
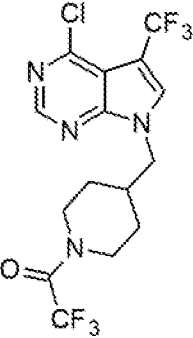
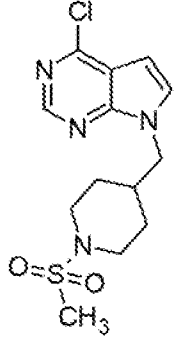
Compound ID	Structure	Estimated IC ₅₀ (μm)
NUCC-0000595		3
NUCC-0000593		5
NUCC-0000578		5

Table 10.

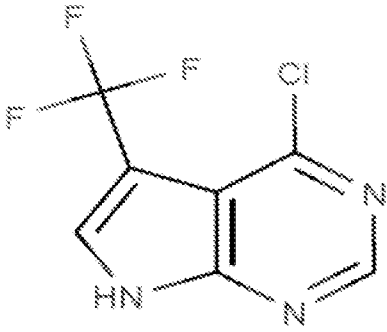
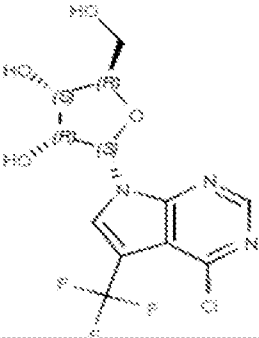
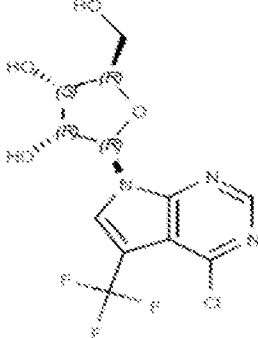
Compound ID	Structure	Estimated IC ₅₀ (μm)
NUCC-0054043		7
NUCC-0054042		0.3
NUCC-0054041		0.3

Table 11.

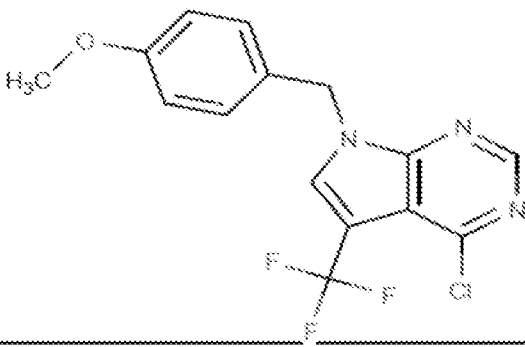
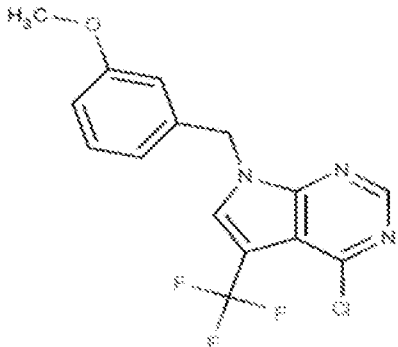
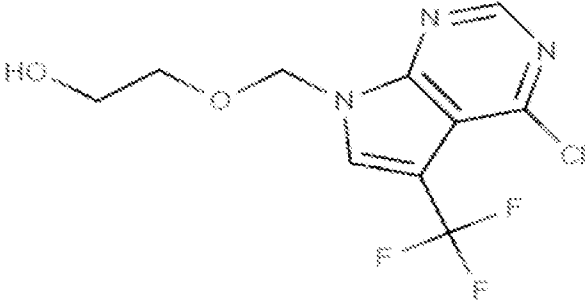
Compound ID	Structure	Estimated IC ₅₀ (μm)
NUCC-0054038		2
NUCC-0054037		2
NUCC-0050715		5

Table 12.

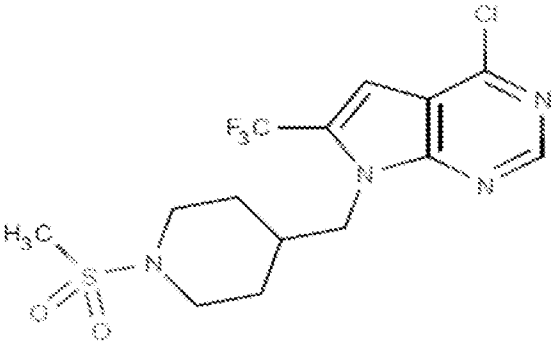
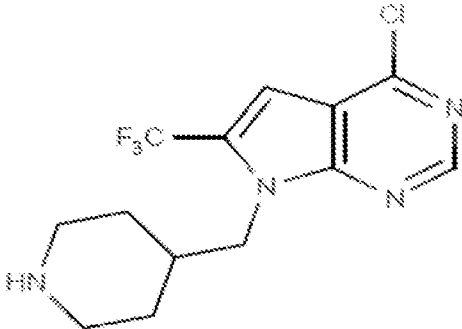
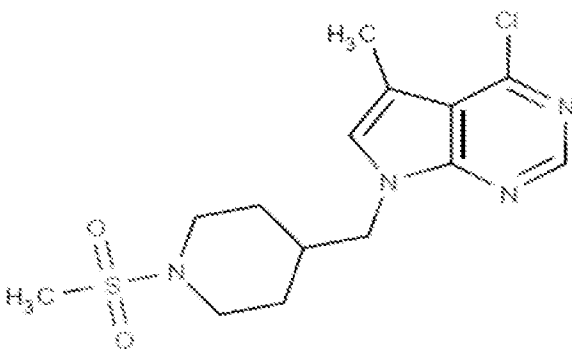
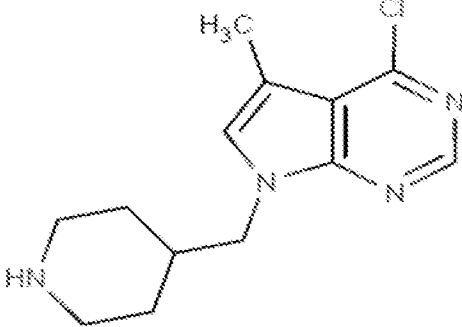
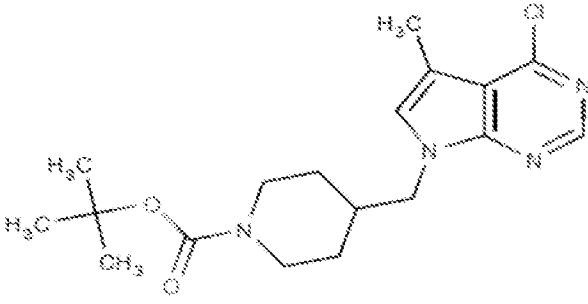
Compound ID	Structure	Estimated IC ₅₀ (μm)
NUCC-0054151		>10
NUCC-0054150		>10

Table 13.

Compound ID	Structure	Estimated IC ₅₀ (μm)
NUCC-0054040		3
NUCC-0054039		1
NUCC-0054036		2

[0074] Example 3 – Evaluation of NUCL 381-3 and NUCL 383-3 for Inhibiting Growth of NCI-60 cell lines

[0075] Summary. NUCL 381-3 and NUCL 383-3 (referred to as “NUCC-00381” and “NUCC-000383” above, respectively) were administered to a variety of cancer cell lines in order to test their ability to inhibit cell growth as compared to doxorubicin. NUCL 381-3 and NUCL 383-3 were found to reduce cell viability for a number of cell lines and in some instances, they exhibited an activity similar to or better than that of doxorubicin.

[0076] Experimental

[0077] Cell lines. Tested cell lines included, Leukemia: CCRF-CEM, HL-60(TB), MOLT-4, RPMI-8226 and SR; Non-Small Cell Lung: A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, NCI-H460 and NCI-H522; Colon: COLO 205, HCC-2998, HCT-116, HCT-15, HT29, KM12 and SW-620; CNS: SF-268, SF-295, SF-539, SNB-19, SNB-75 and U251; Melanoma: LOX IMVI, MALME-3M, M14, MDA-MB-435, SK-MEL-2, SK-MEL-28, SK-MEL-5, UACC-257 and UACC-62; Ovarian: IGR-OV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, NCI/ADR-RES and SK-OV-3; Renal: 786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10 and UO-31; Prostate: DU-145 and PC-3; and Breast: MCF7, MDA-MB-231/ATCC, MDA-MB-468, HS 578T, BT-549 and T-47D.

[0078] Media. The cells were cultured in RPMI1640 media supplemented with 10% Fetal Bovine Serum (FBS), 2mM glutamine and with 5% CO₂ and 37°C. For experiment, 5% of FBS and 50 ug/mL of gentamycin were used. Test articles were 10µM of NUCL 381-3 or 10µM NUCL 383-3. The positive control was 10µM of doxorubicin.

[0079] Study. Cells were plated in 96 well plates. The cells were plated in triplicate. Cells were plated at the densities based on NCI recommendation. Time zero cells (Tz) were fixed the following day with 50% or 80% ice cold Trichloroacetic acid (TCA) and washed 5x with water. At 48 hours post addition of treatments, all remaining plates were fixed in 80% ice cold Trichloroacetic acid (TCA) and washed 5x with water.

After drying, one hundred microliters of 0.4% Sulphorhodamine B (SRB) in 1% acetic acid was added to each plate including the Tzero plate and incubated for 10 minutes at room temperature. After 5 additional washes with 1% acetic acid, plates were allowed to dry. One hundred microliters of Trizma base was added to each well and plates were read at 515 nm.

[0080] Calculations. Percent of growth was calculated by the following formulas: $[Ti/C] \times 100$, where: Tz= absorbance readings for wells at time zero without treatment; C= absorbance readings of untreated cells (without treatment); and Ti= absorbance reading of wells with treatment. Results are presented in Table 14 and in FIGS. 2-10.

Table 14.

Cell Line Name	Type of cell	Percent viability		
		NUCL 381-3	NUCL 383-3	Doxorubicin
CCRF-CEM	Leukemia	52.77	54.00	43.56
HL-60(TB)	Leukemia	25.78	22.46	24.97
K-562	Leukemia	8.38	10.15	17.10
MOLT-4	Leukemia	75.54	17.91	30.38
RPMI-8226	Leukemia	100.00	100.00	44.22
SR	Leukemia	16.70	36.98	11.13
A549	Non-Small Cell Lung	28.25	100.00	86.80
EKVX	Non-Small Cell Lung	57.45	84.58	35.55
HOP-62	Non-Small Cell Lung	15.67	88.48	19.66
HOP-92	Non-Small Cell Lung	56.76	97.57	98.52
NCI-H226	Non-Small Cell Lung	54.88	29.52	34.20
NCI-H23	Non-Small Cell Lung	42.34	46.10	27.56
NCI-H322M	Non-Small Cell Lung	68.09	53.75	42.58
NCI-H460	Non-Small Cell Lung	26.36	69.10	35.01
NCI-H522	Non-Small Cell Lung	38.73	21.70	18.15
COLO 205	Colon	79.55	92.96	2.33
HCC-2998	Colon	93.49	73.20	20.91
HCT-116	Colon	20.12	15.03	14.91
HCT-15	Colon	40.38	38.78	31.06
HT29	Colon	33.33	30.28	34.92
KM12	Colon	30.97	99.47	71.76
SW-620	Colon	27.25	25.66	18.98
SF-268	CNS	3.37	1.77	6.91
SF-295	CNS	44.41	56.17	11.16
SF-539	CNS	7.40	4.93	6.83

SNB-19	CNS	28.89	21.40	37.30
SNB-75	CNS	83.26	23.34	36.00
U251	CNS	15.06	2.47	22.00
LOX IMVI	Melanoma	26.02	35.77	24.39
MALME-3M	Melanoma	100.69	42.69	15.75
M14	Melanoma	96.17	78.51	25.47
MDA-MB-435	Melanoma	65.54	46.59	17.45
SK-MEL-2	Melanoma	105.56	14.66	11.58
SK-MEL-28	Melanoma	93.27	4.54	29.70
SK-MEL-5	Melanoma	100.45	6.11	7.01
UACC-257	Melanoma	87.17	74.72	100.23
UACC-62	Melanoma	46.28	8.26	4.85
IGR-OV1	Ovarian	36.94	77.53	8.63
OVCAR-3	Ovarian	48.69	95.45	16.81
OVCAR-4	Ovarian	53.04	96.96	102.87
OVCAR-5	Ovarian	76.83	104.07	57.14
OVCAR-8	Ovarian	31.66	73.88	14.98
NCI/ADR-RES	Ovarian	93.28	98.95	78.81
SK-OV-3	Ovarian	56.48	74.22	47.81
786-0	Renal	94.21	69.52	17.62
A498	Renal	93.77	100.69	62.93
ACHN	Renal	23.28	77.77	40.21
CAKI-1	Renal	86.77	46.83	0.00
RXF 393	Renal	12.01	7.81	8.68
SN12C	Renal	42.15	25.78	45.36
TK-10	Renal	88.53	73.91	35.87
UO-31	Renal	19.66	3.37	28.19
PC-3	Prostate	8.43	3.55	50.00
DU-145	Prostate	29.78	11.24	72.47
MCF7	Breast	89.78	108.31	69.14
MDA-MB-231	Breast	48.51	33.90	41.84
MDA-MB-468	Breast	101.73	93.85	45.81
HS 578T	Breast	53.92	50.13	51.47
BT-549	Breast	103.01	79.20	62.51
T-47D	Breast	60.76	63.34	37.46
MM1S	Multiple Myeloma	52.32	58.17	26.41

[0081] Example 4 — Inhibition of Viability of Acute Leukemia Cell Lines by Substituted Pyrrolo[2,3-d]pyrimidine Compounds

[0082] Compounds 381, 383, 409 (as test compounds) and Compound 501 (as a negative control) were administered to a variety of acute leukemia cell lines (THP-1, K562, Kasumi-1, and U937) in order to test their ability to inhibit cell growth as compared to 8-amino adenosine (8NH₂-Ado) and 8-chloro adenosine (8Cl-Ado) (as positive controls) as in the previous Examples. The results are presented in Figures 11-14. All test compounds were found to reduce cell viability significantly, and Compound 381 and Compound 383 had inhibitory activities approaching those of 8NH₂-Ado and 8Cl-Ado.

[0083] Compounds 381, 383, 409 (as test compounds) and Compound 501 (as a negative control) were administered to U937 cells in order to test their ability to inhibit DNA synthesis and RNA synthesis as compared to 8-amino adenosine (8NH₂-Ado) and 8-chloro adenosine (8Cl-Ado) (as positive controls). In the test, the incorporated amount of tritiated labeled thymidine (for DNA synthesis) or tritiated labeled uridine (for RNA synthesis) by the U937 cells was measured over time. As illustrated in Figure 15 and Figure 16, the amount of incorporated label decreases over time indicating inhibition of both DNA and RNA synthesis.

[0084] The impact of the compounds on proteins associated with cell death was assessed via performing an immunoblot. (See Figure 17). PARP cleavage indicated activation of the caspase cascade and cell death by induction of apoptosis. Similarly detection of cleaved caspase 3 indicated activation of caspase activity and cell death by apoptosis. GAPDH was included as a loading control to indicate approximately equal loading of protein. Induction of apoptosis was observed for 8-Cl-Ado and 8-NH₂-Ado (positive controls) and well as for Compounds 381 and 383.

[0085] In the foregoing description, it will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. The terms and expressions which have been employed are used as terms of description and not of

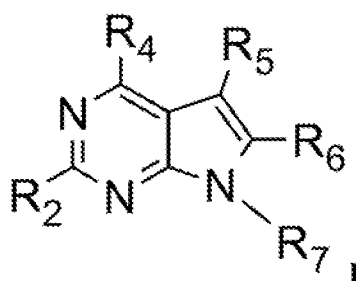
limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention. Thus, it should be understood that although the present invention has been illustrated by specific embodiments and optional features, modification and/or variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

[0086] Citations to a number of patent and non-patent references are made herein. The cited references are incorporated by reference herein in their entireties. In the event that there is an inconsistency between a definition of a term in the specification as compared to a definition of the term in a cited reference, the term should be interpreted based on the definition in the specification.

CLAIMS

We claim:

1. A compound having a Formula I:



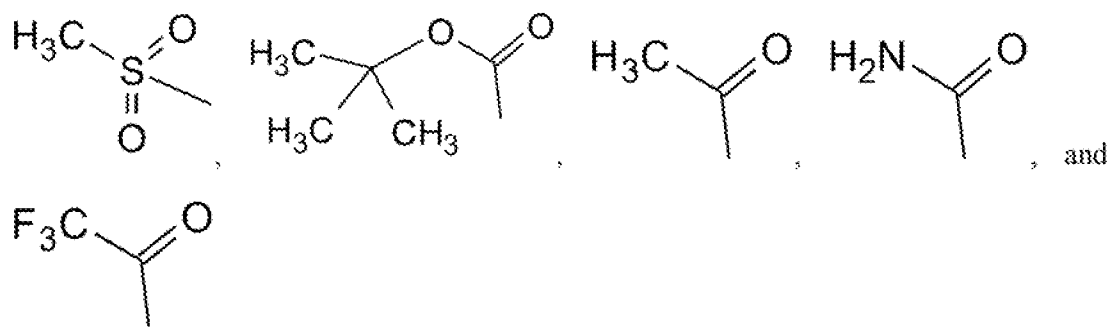
wherein:

R₂ is hydrogen, halogen, or amine;

R₄ is hydrogen, C₁-C₃ alkyl, halogen, or -NH₂;

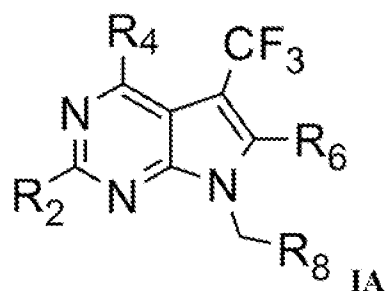
R₅ and R₆ are each independently hydrogen, C₁-C₃ alkyl optionally substituted at one or more positions with halogen, or R₅ and R₆ are linked together to form a 6-membered ring; and

R₇ is hydrogen, R₈, or R₈, wherein R₈ is methoxy or a 5- or 6-membered carbocyclic or heterocyclic ring that is saturated or unsaturated, the ring optionally substituted at one or more carbon atoms with halogen or methoxy, and the ring optionally substituted at a nitrogen heteroatom with a substituent selected from



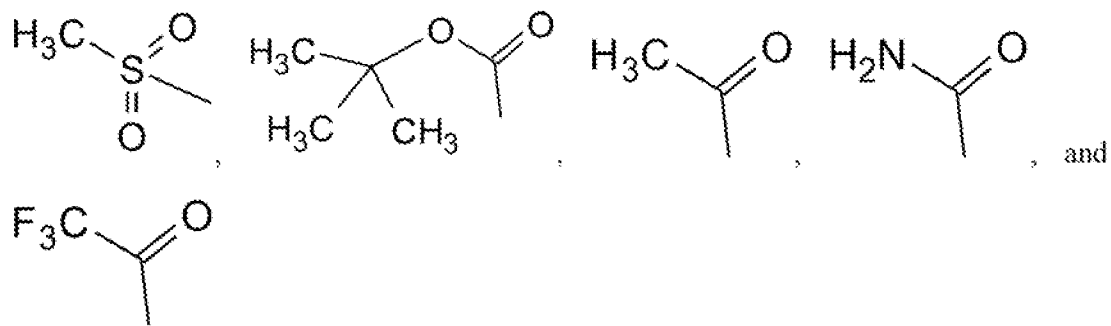
2. The compound of claim 1, wherein R₅ is -CF₃.
3. The compound of claim 1, wherein R₄ is halogen.

4. The compound of claim 3, wherein R_4 is chlorine.
5. The compound of claim 1 having a Formula IA:

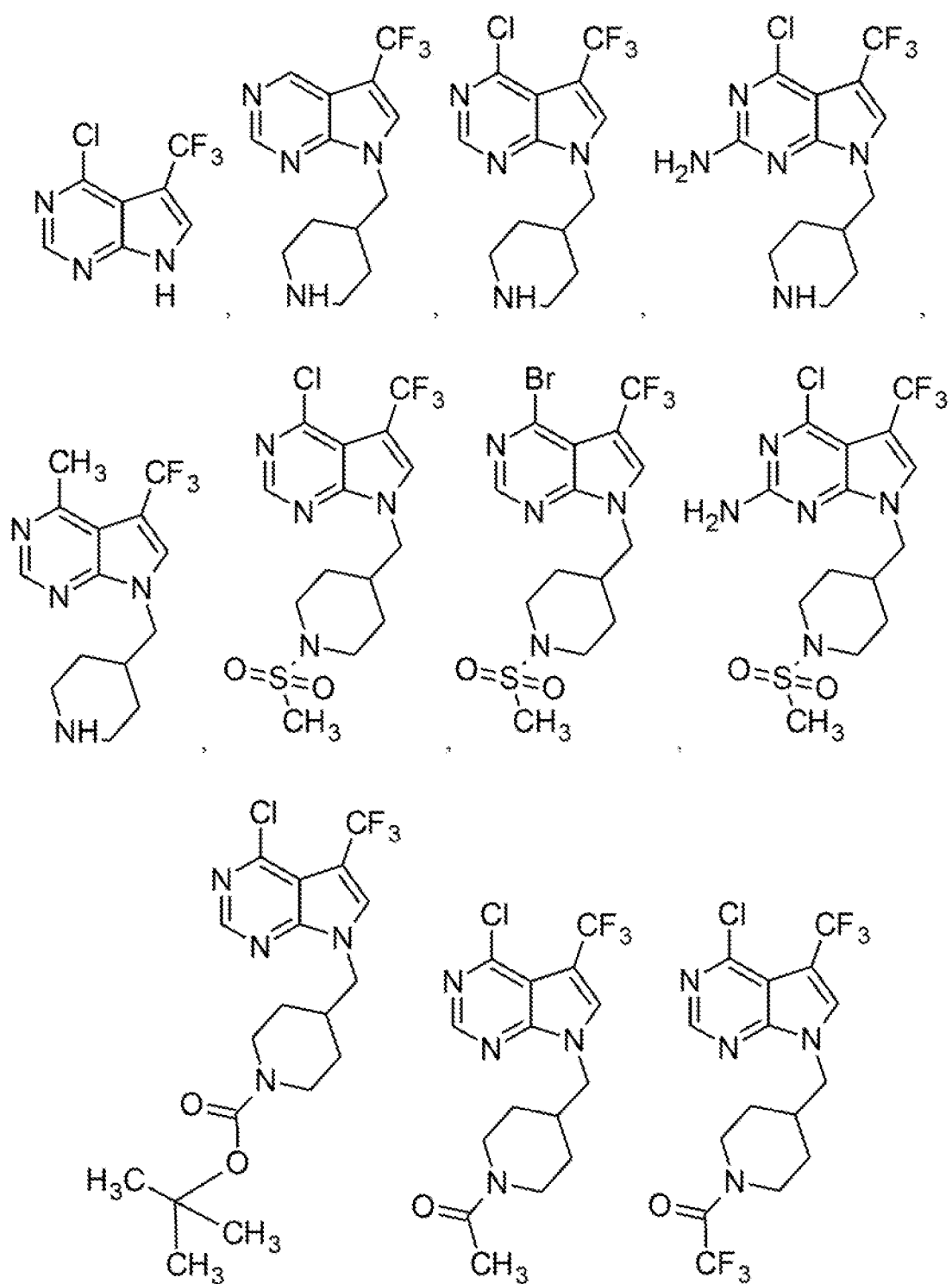


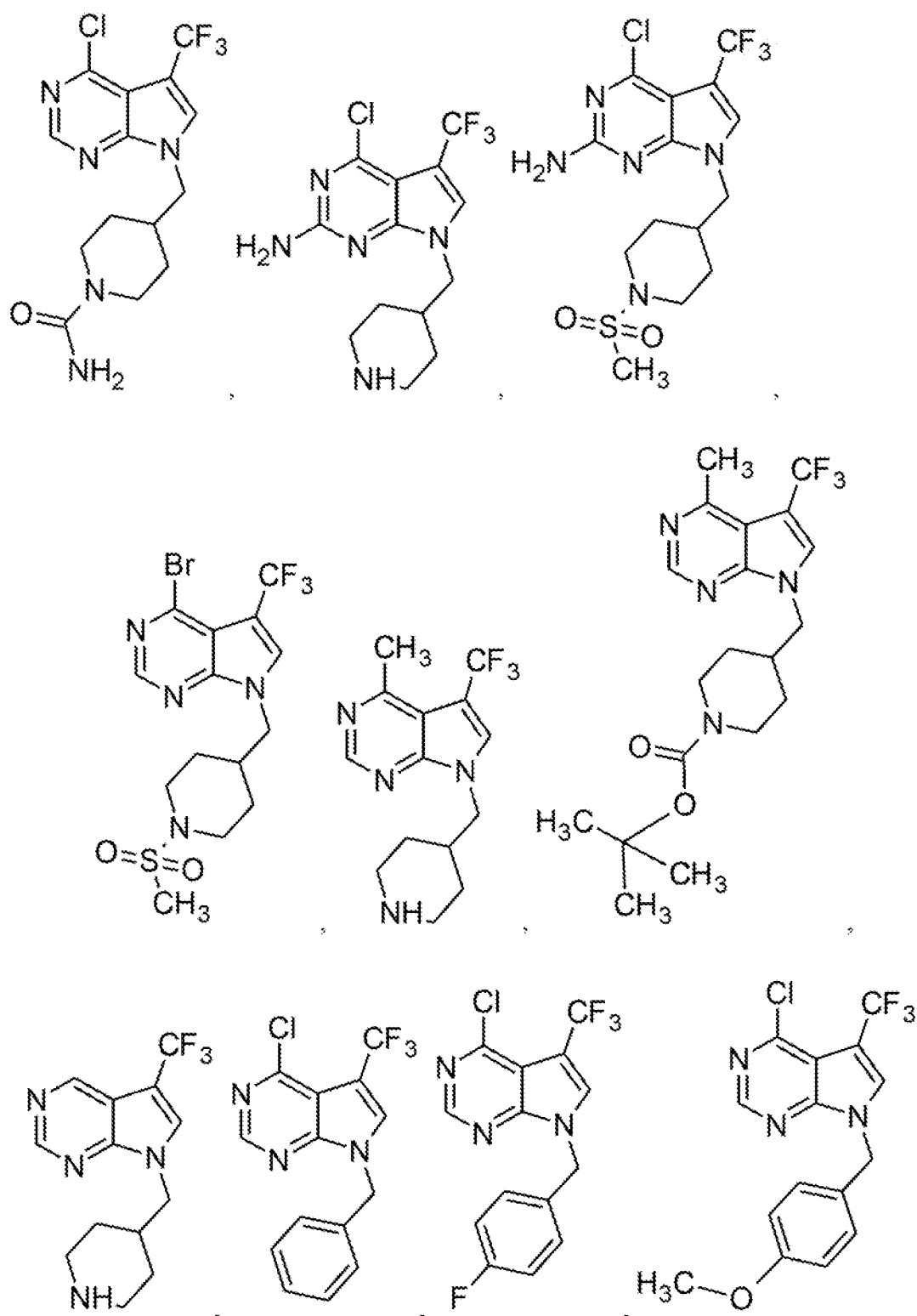
wherein: R_4 is hydrogen, halogen, or methyl; and R_2 , R_6 , and R_8 are as defined for Formula I.

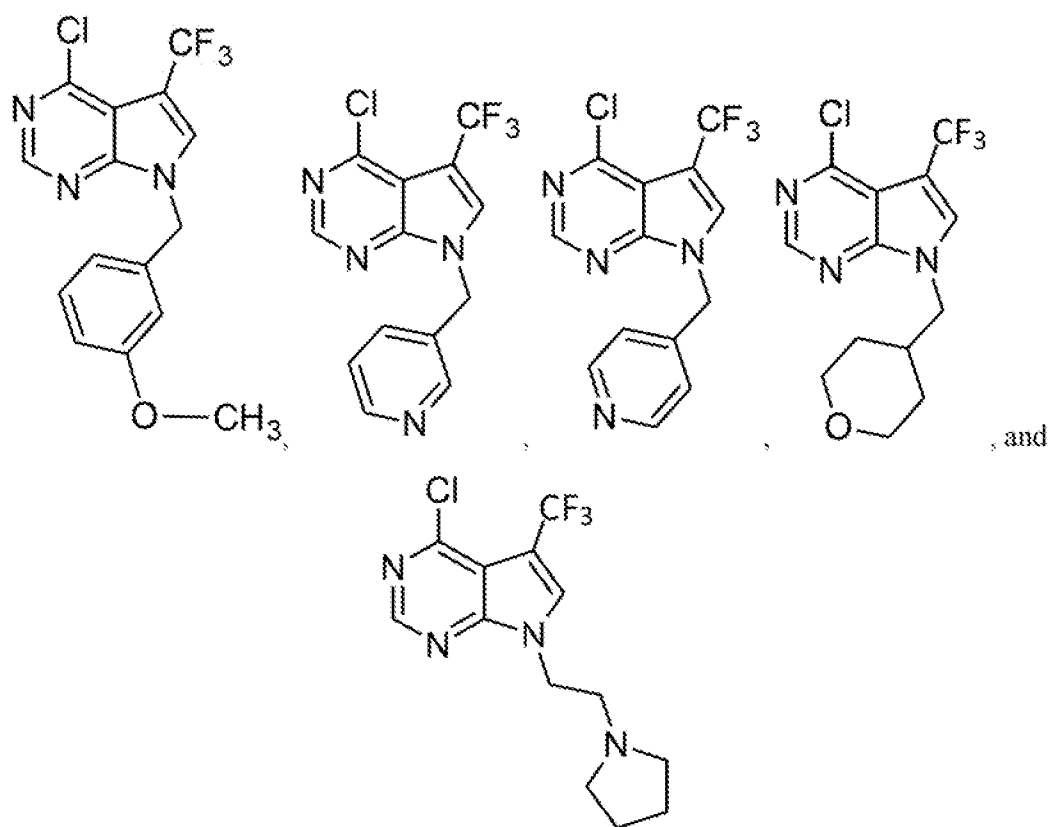
6. The compound of claim 5, wherein R_8 is a ring selected from piperidine, benzene, pyridine, and oxane, which may be substituted at one or more carbon atoms with halogen or methoxy, and which may be substituted at a nitrogen heteroatom with a substituent selected from



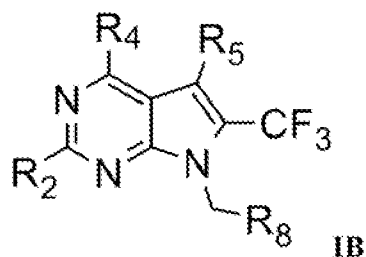
7. The compound of claim 5, having a formula selected from:





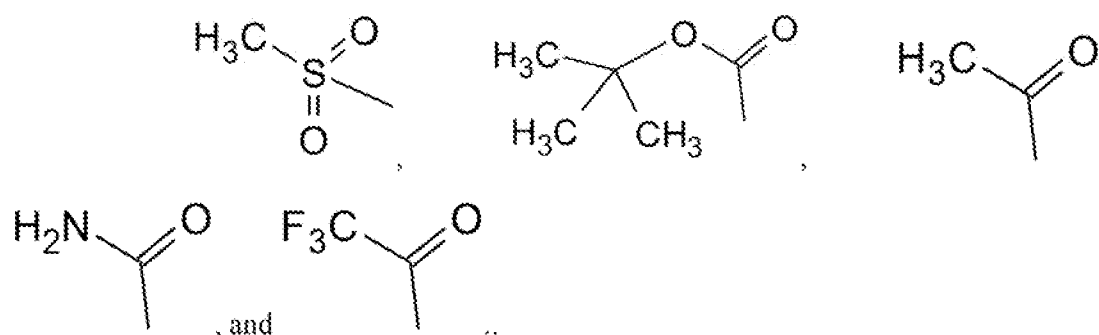


8. The compound of claim 1 having a Formula IB:

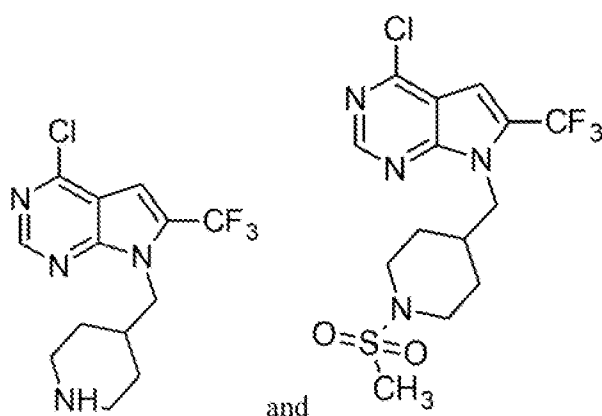


wherein: R₄ is hydrogen, halogen, or methyl; and R₂, R₅, and R₈ are as defined for Formula I.

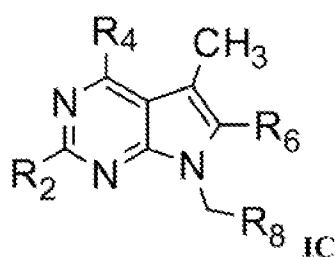
9. The compound of claim 8, wherein R₈ is a ring selected from piperidine, benzene, pyridine, and oxane, which may be substituted or unsubstituted, which may be substituted at one or more carbon atoms with halogen or methoxy, and which may be substituted at a nitrogen heteroatom with a substituent selected from



10. The compound of claim 8, having a formula selected from:

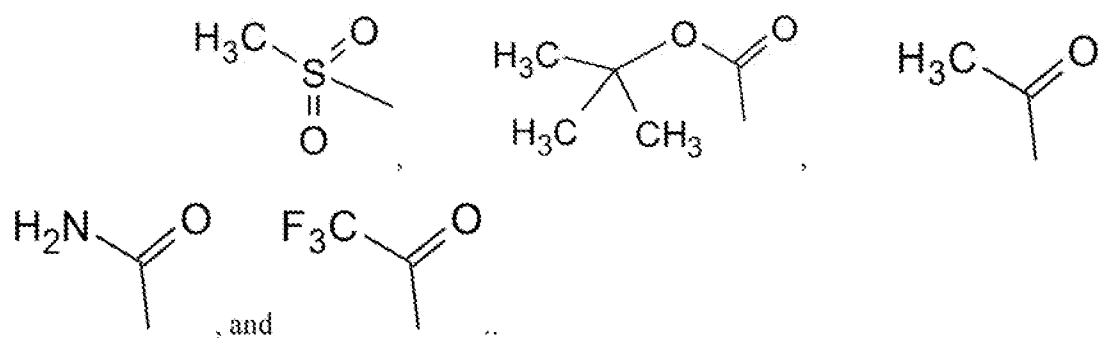


11. The compound of claim 1 having a Formula IC:

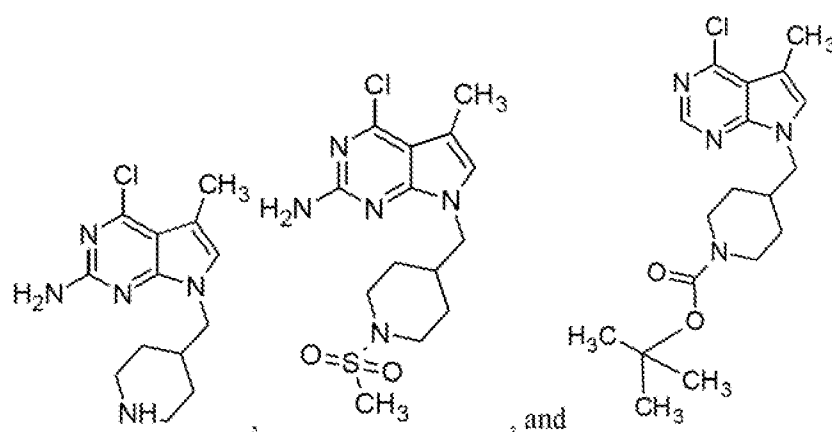


wherein: R_4 is hydrogen, halogen, or methyl; and R_2 , R_6 , and R_8 are as defined for Formula I.

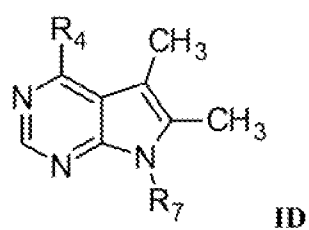
12. The compound of claim 11, wherein R_8 is a ring selected from piperidine, benzene, pyridine, and oxane, which may be substituted or unsubstituted, which may be substituted at one or more carbon atoms with halogen or methoxy, and which may be substituted at a nitrogen heteroatom with a substituent selected from



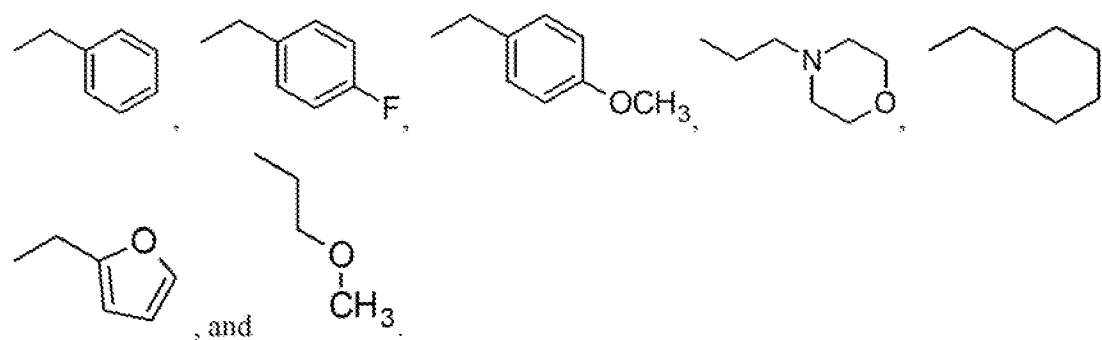
13. The compound of claim 11, having a formula selected from:



14. The compound of claim 1 having a Formula ID:

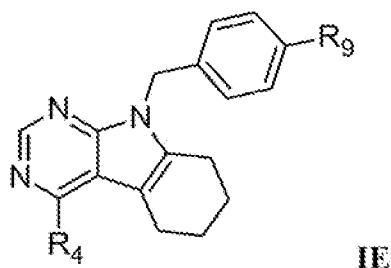


wherein R_4 is halogen or amine; and R_7 is selected from



15. The compound of claim 14, wherein R_4 is chlorine.

16. The compound of claim 1 having a Formula IE:



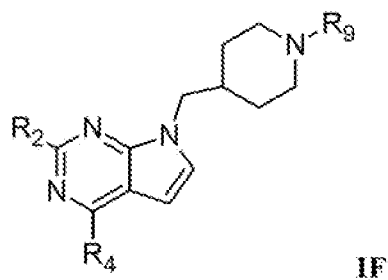
wherein: R_4 is halogen; and R_9 is hydrogen or halogen.

17. The compound of claim 16, wherein R_4 is chlorine.

18. The compound of claim 17, wherein R_9 is halogen.

19. The compound of claim 18, wherein R_9 is fluorine.

20. The compound of claim 1 having a Formula IF:

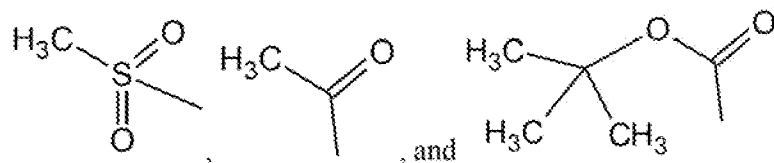


wherein:

R_2 is hydrogen or halogen;

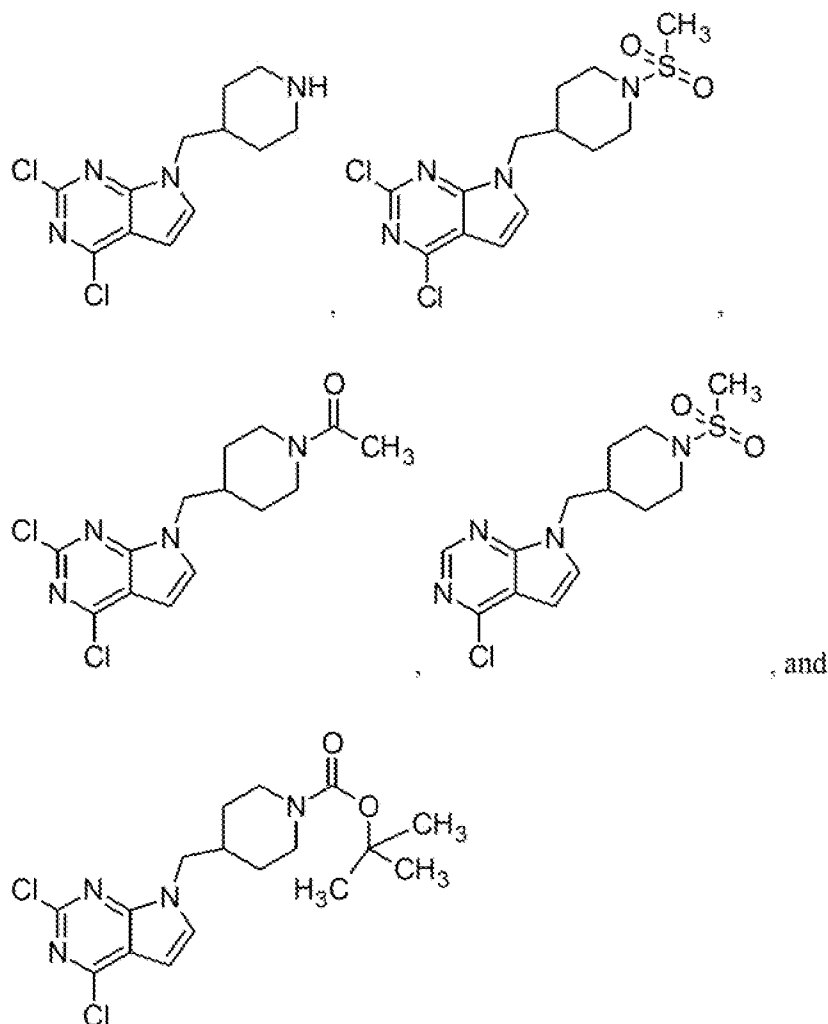
R_4 is halogen; and

R_9 is hydrogen, or is selected from



21. The compound of claim 20, wherein R_4 is chlorine.

22. The compound of claim 20, having a formula selected from:



23. A pharmaceutical composition comprising the compound of claim 1 together with a carrier, excipient, or diluent.

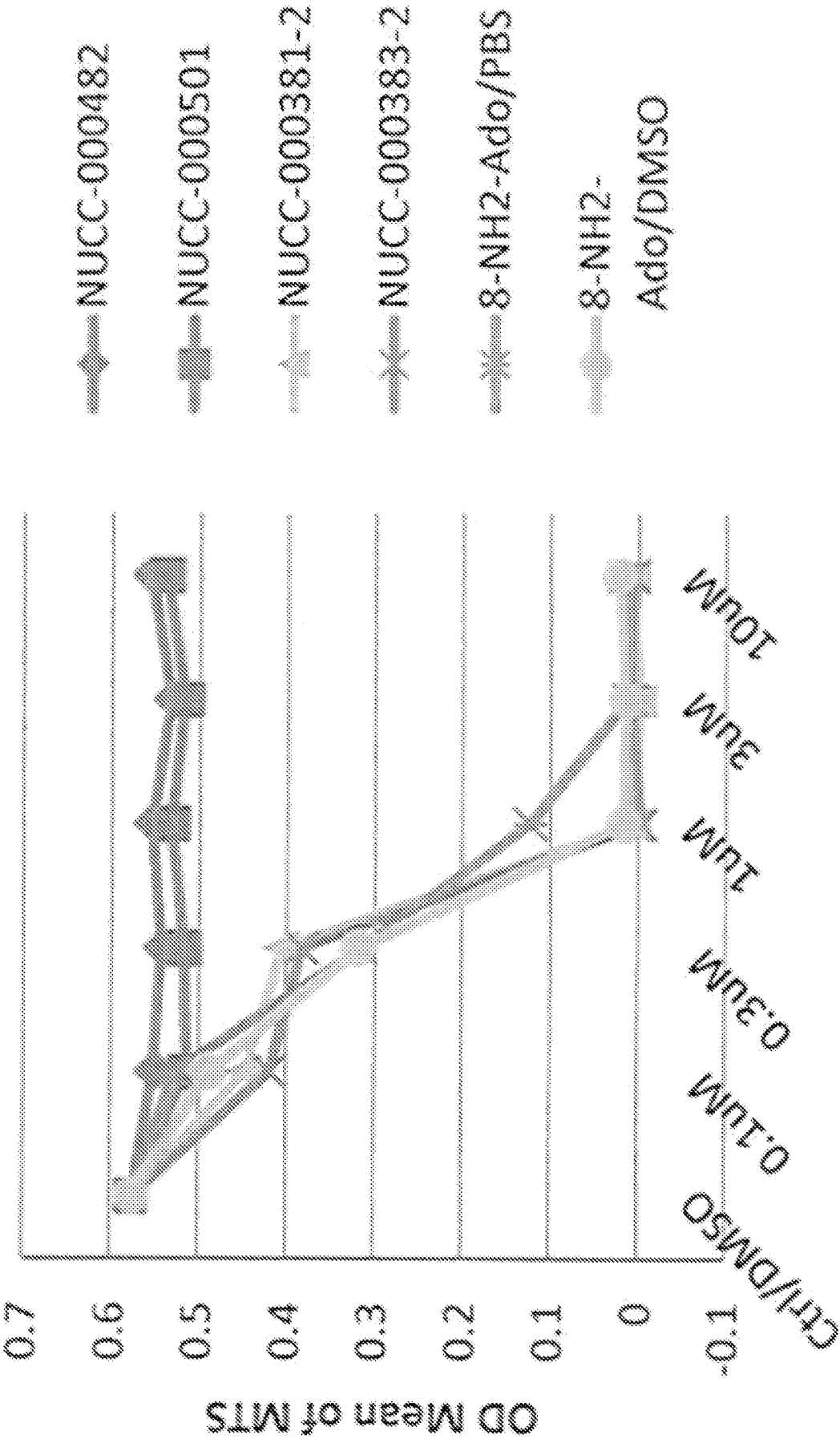
24. The composition of claim 23 comprising an effective amount of the compound for inhibiting the growth of cancer cells.

25. A method of treating cancer comprising administering the composition of claim 24 to a patient having cancer.

26. The method of claim 25, wherein the cancer is selected from a group consisting of multiple myeloma, leukemia, non-small cell lung cancer, colon cancer,

cancer of the central nervous system, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer.

FIG. 1



Leukemia cell lines

Leukemia cell lines

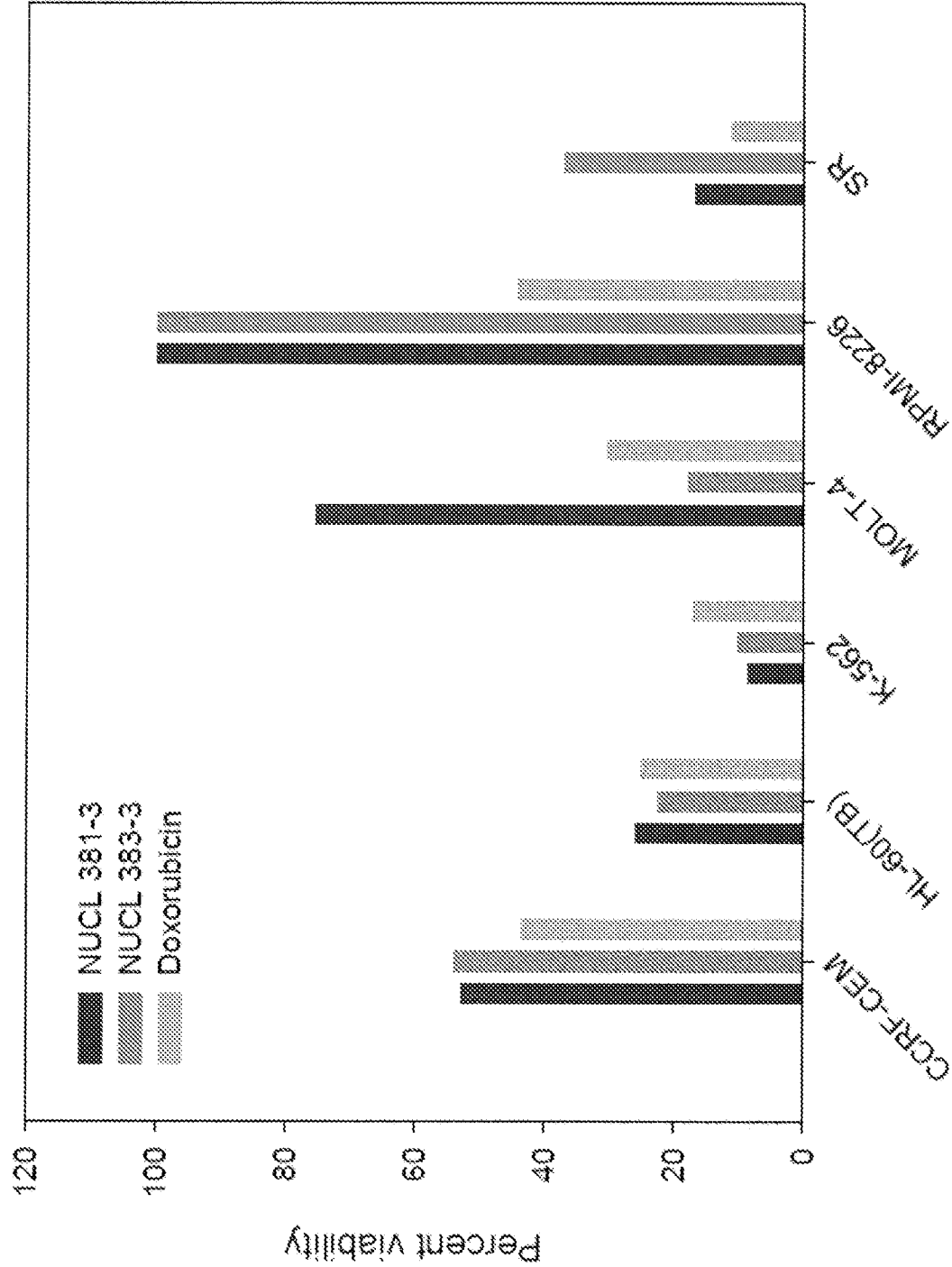


FIG. 2

Non-small lung cancer

Non-small lung cancer

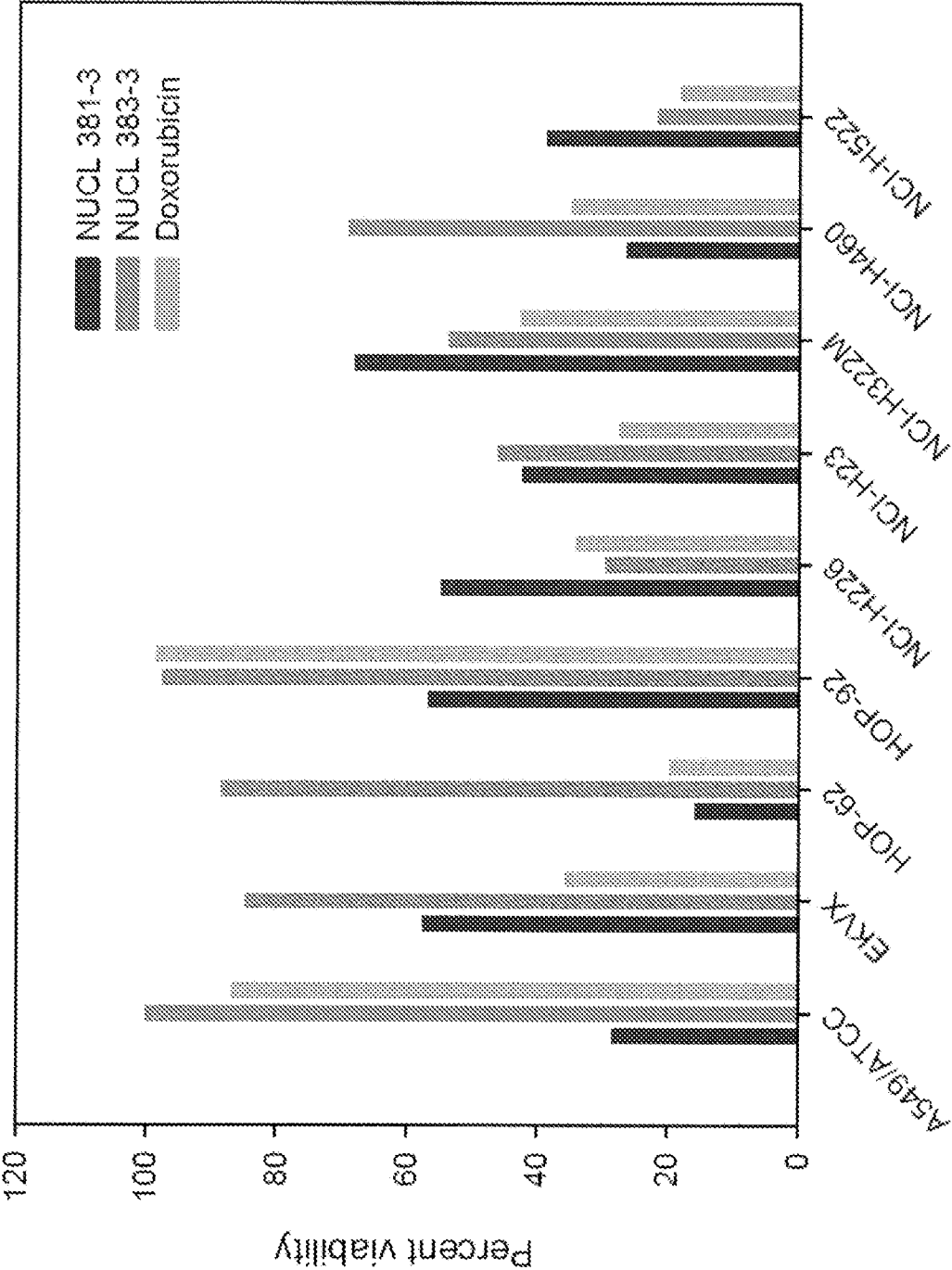


FIG. 3

Colon cell lines

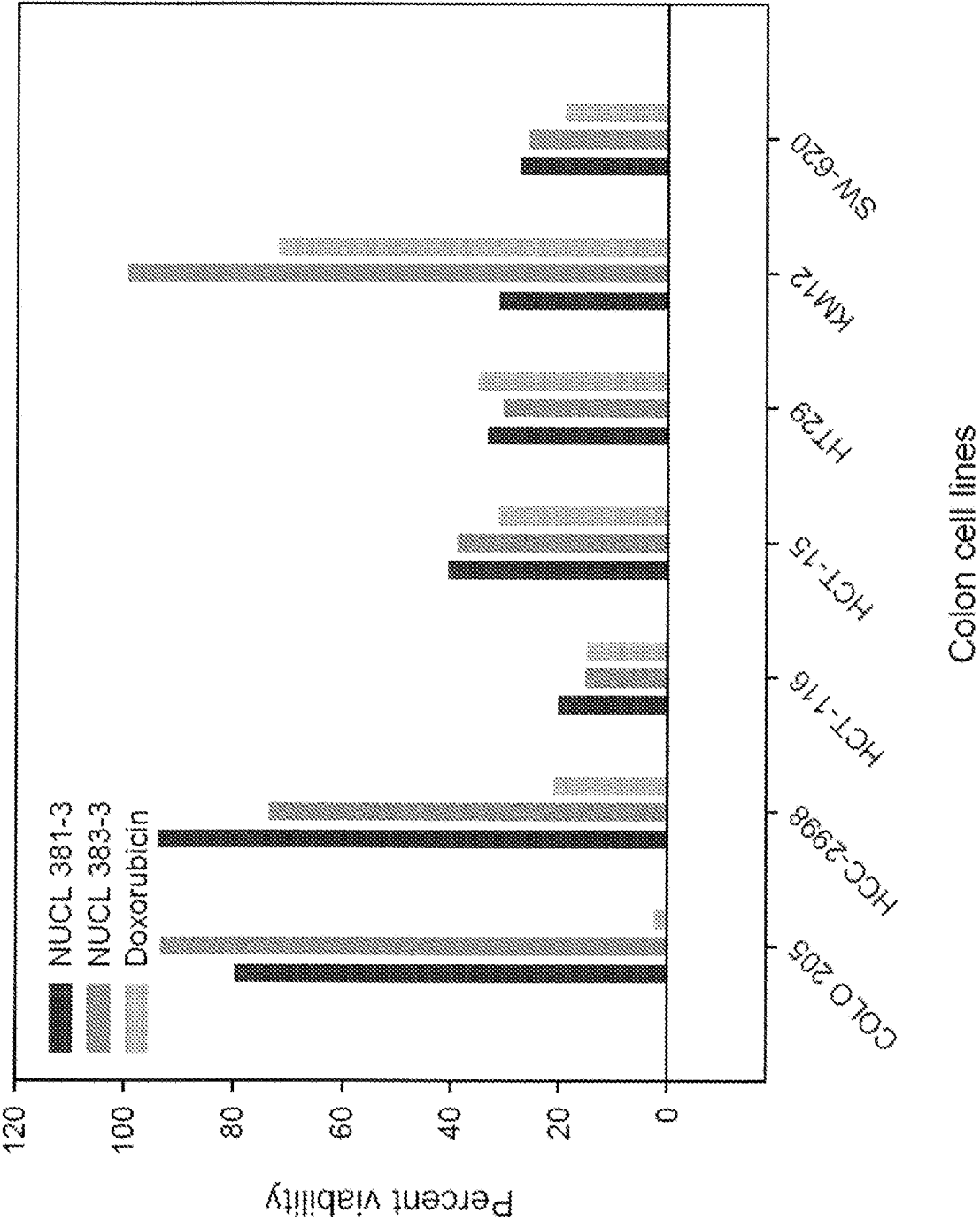


FIG. 4

CNS

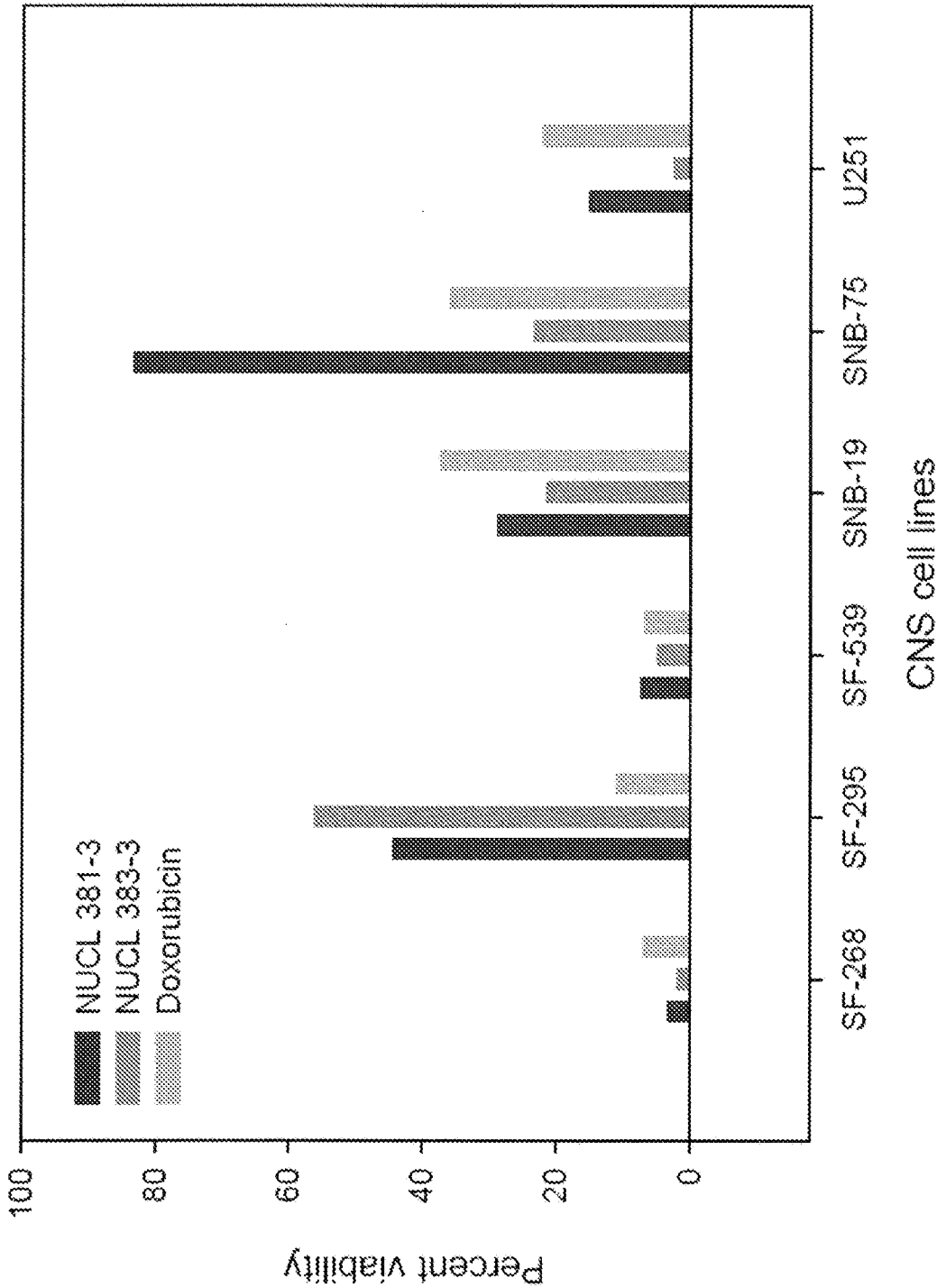


FIG. 5

Melanoma cell lines

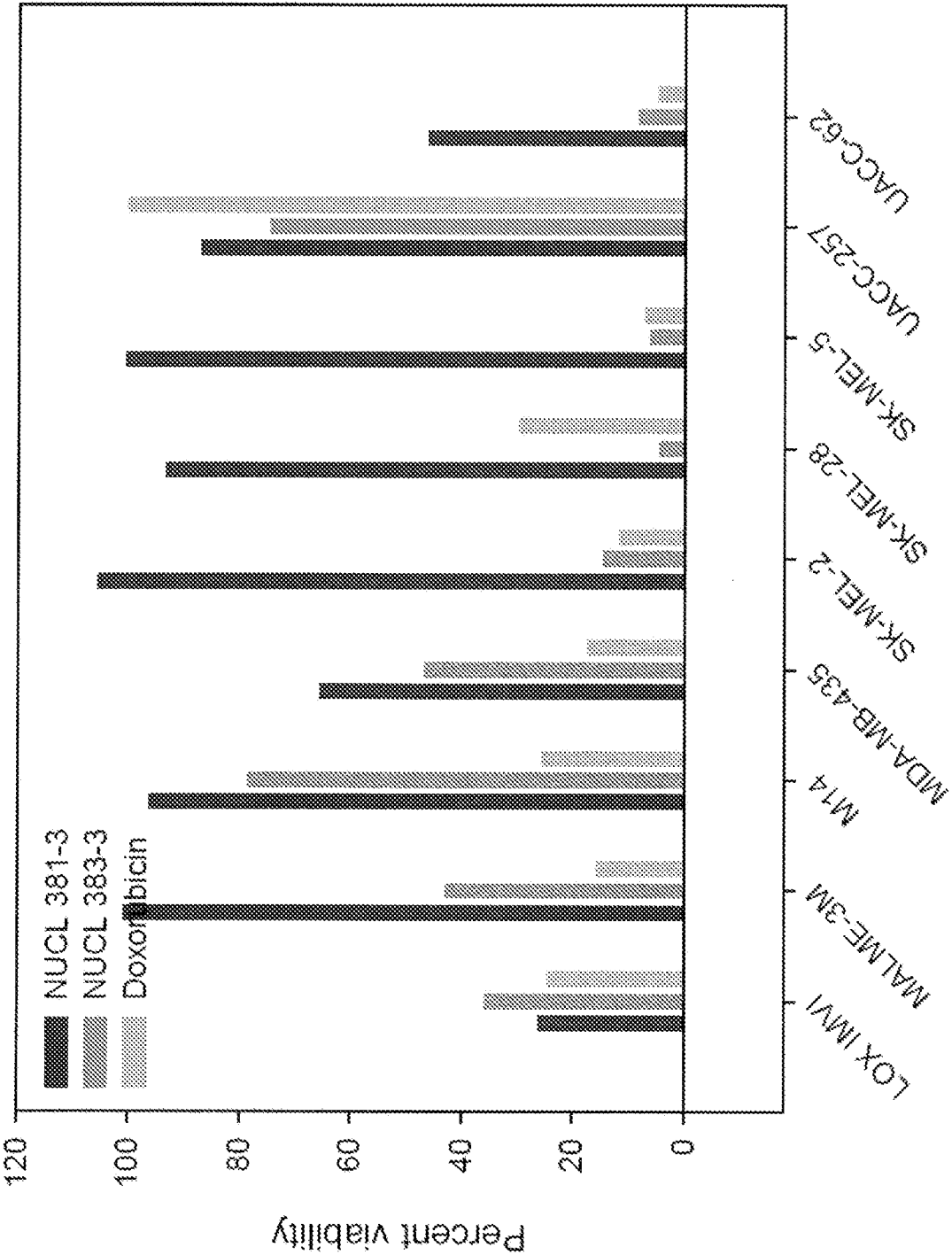


FIG. 6

Ovarian

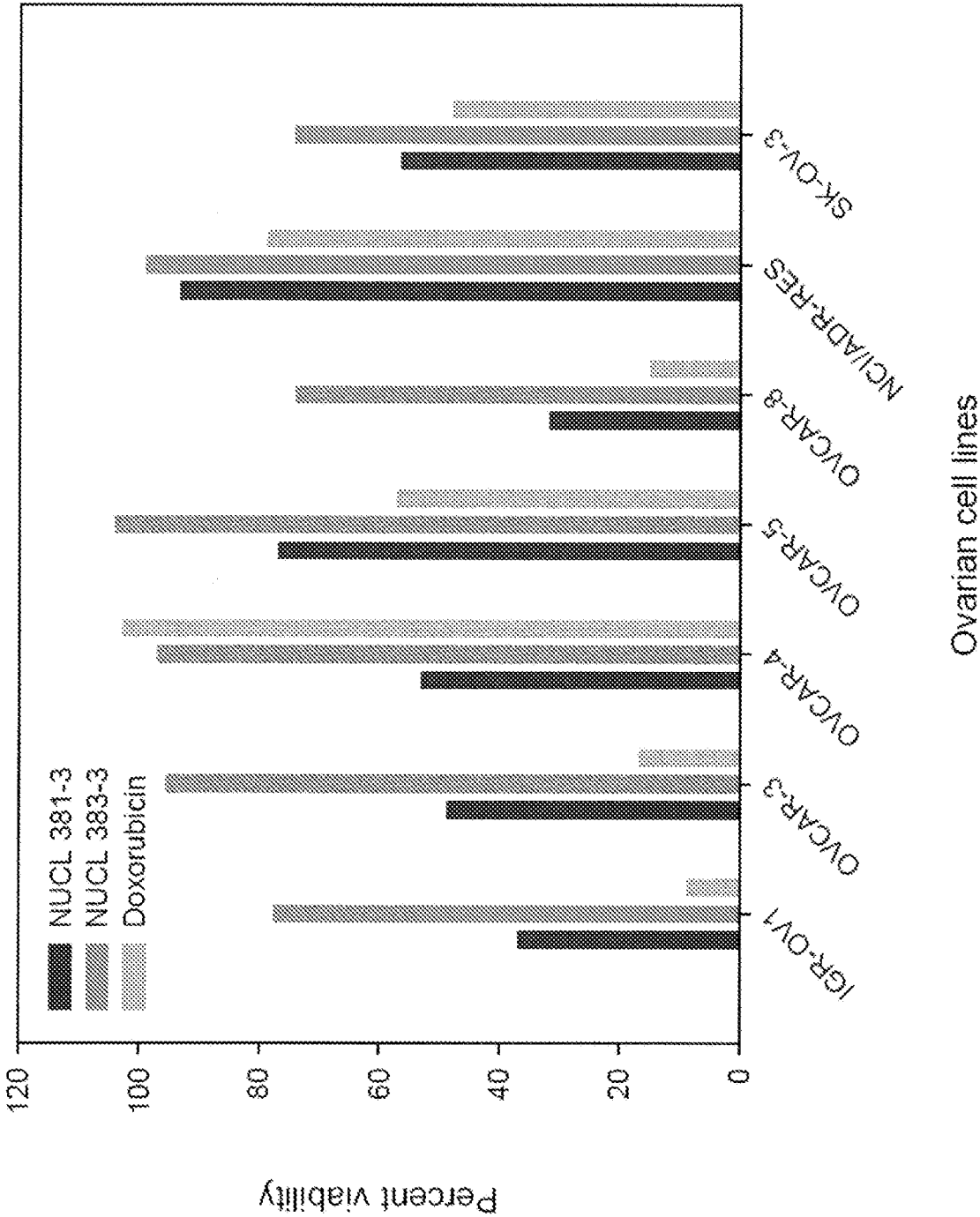
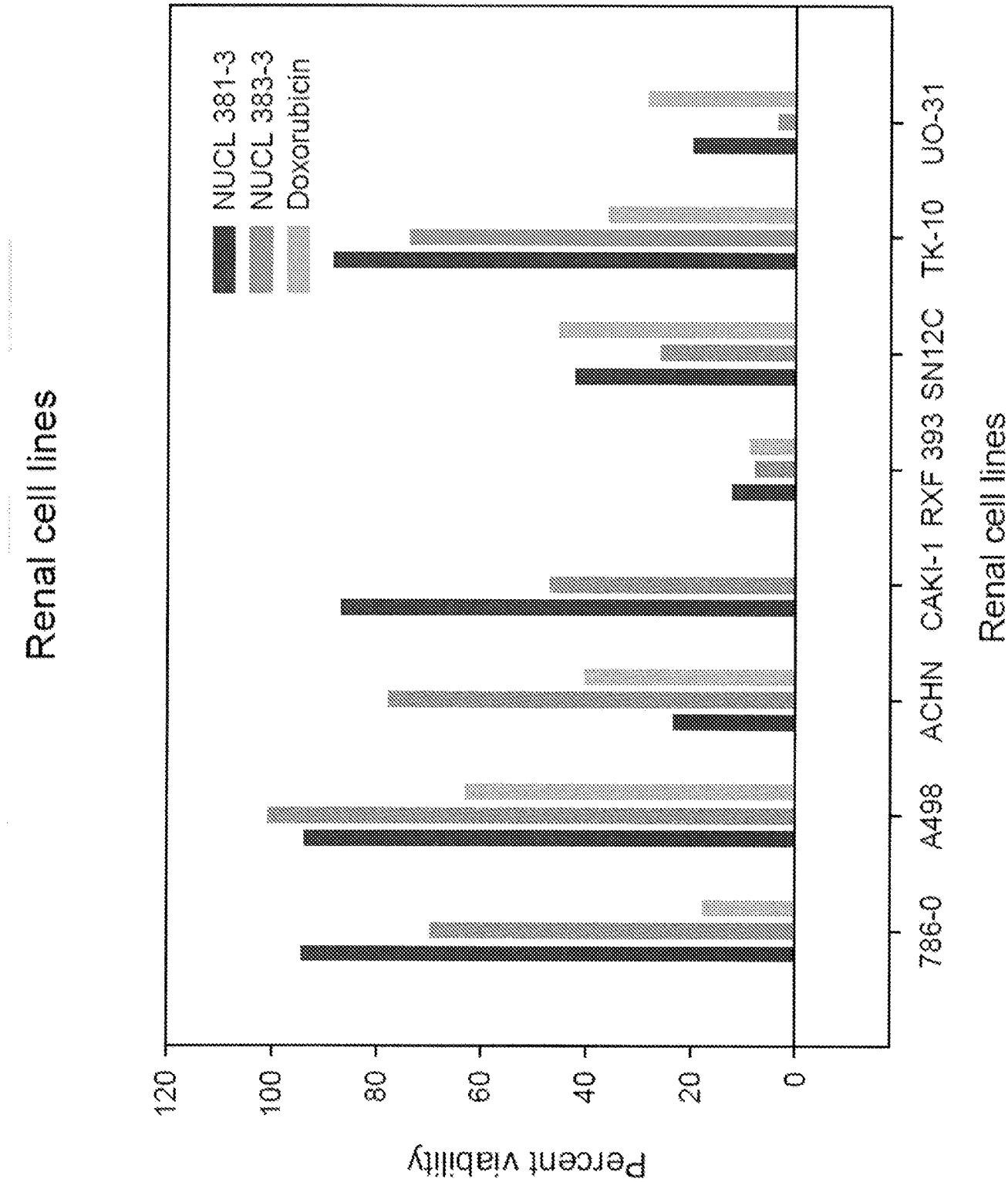


FIG. 7

FIG. 8



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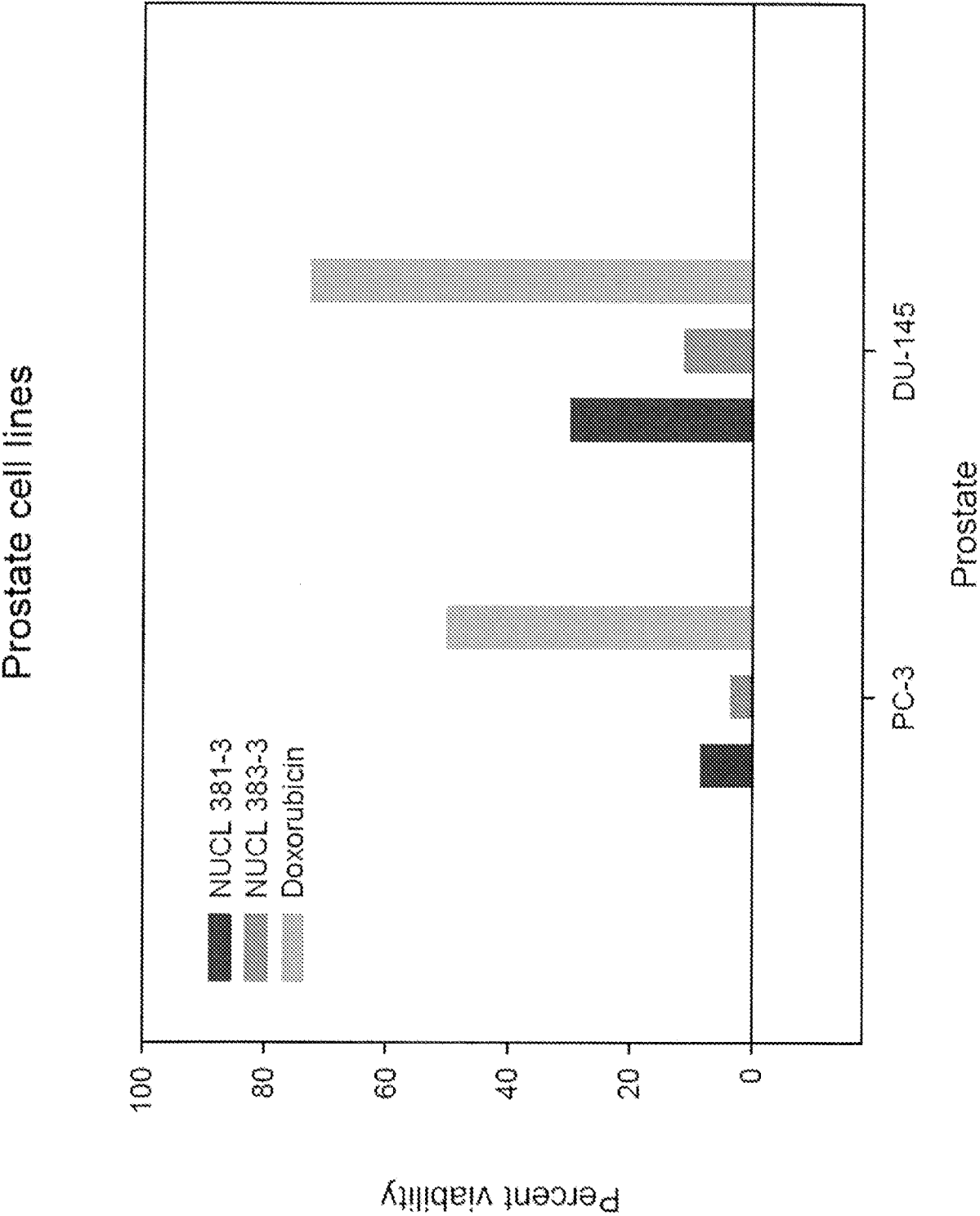


FIG. 9

Breast cancer cell lines

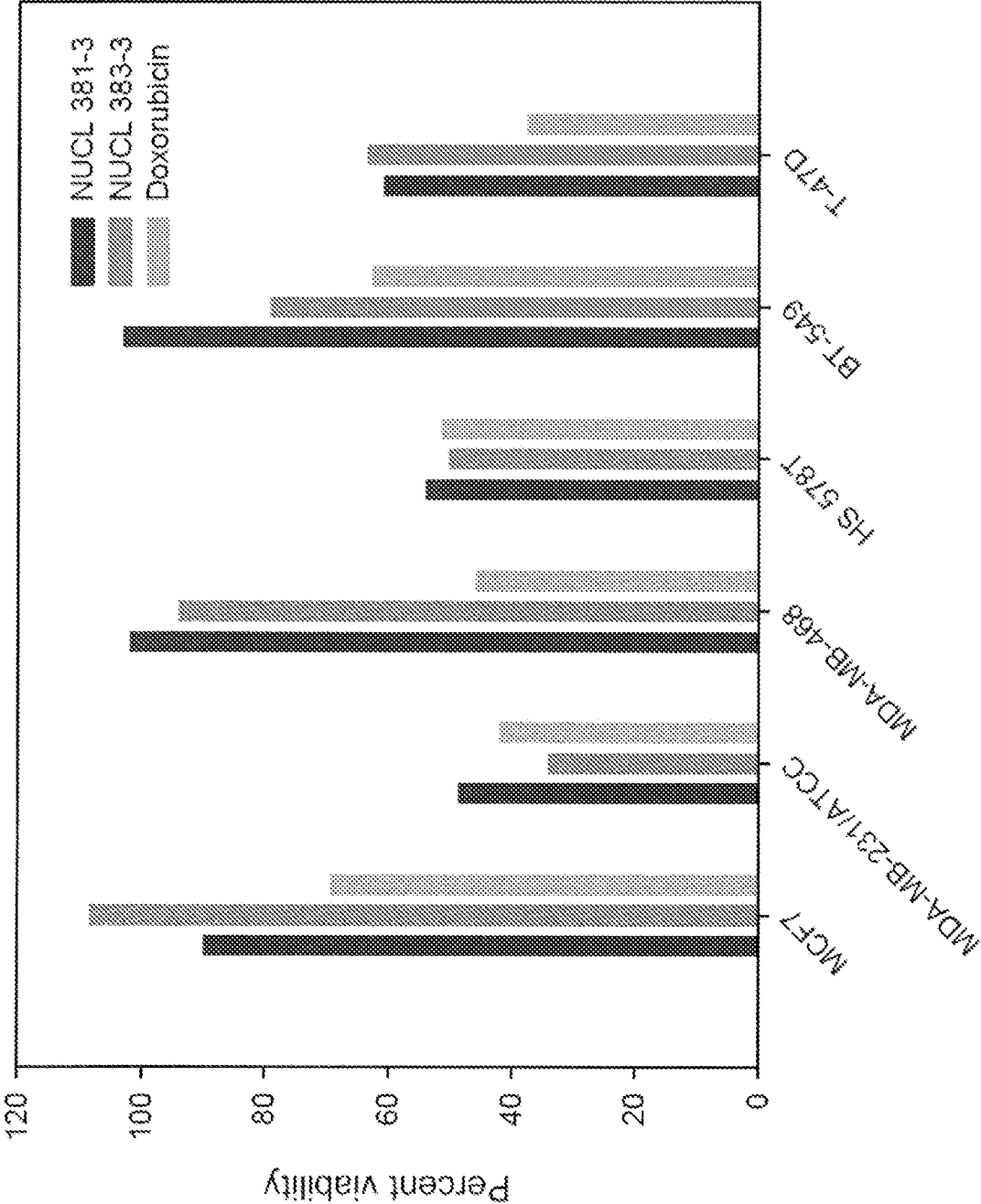
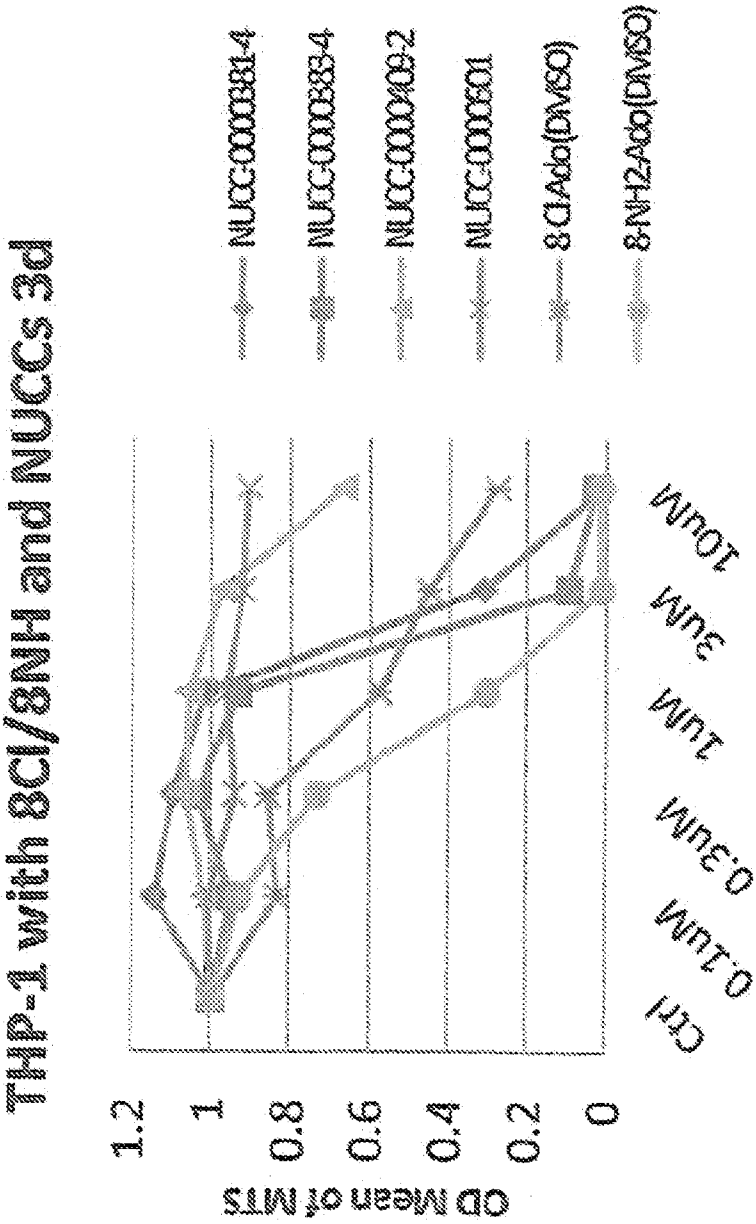


FIG. 10

FIG. 11



K562 with 8Cl/8NH and NUCCs 3d

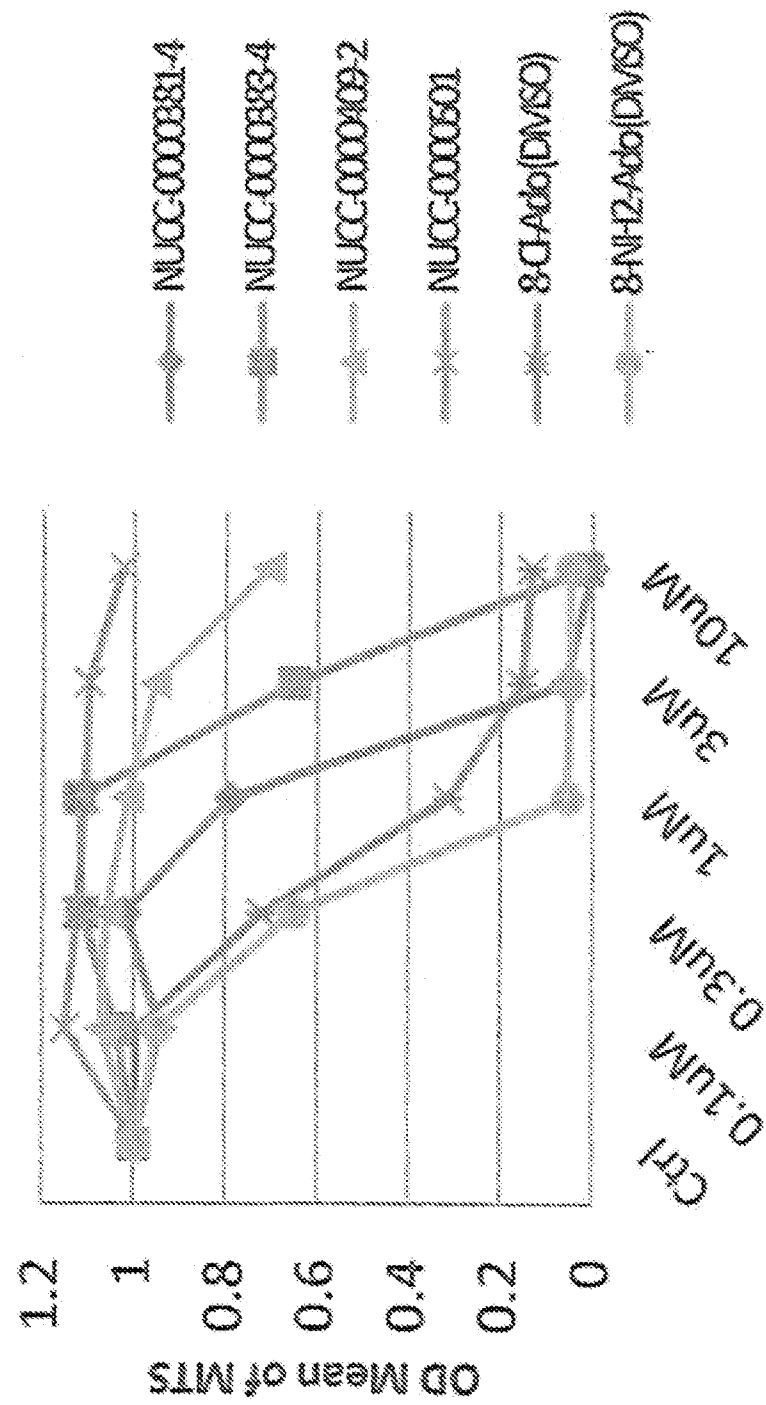


FIG. 12

Kasumi-1 with 8Cl/8NH and NUCCs 3d

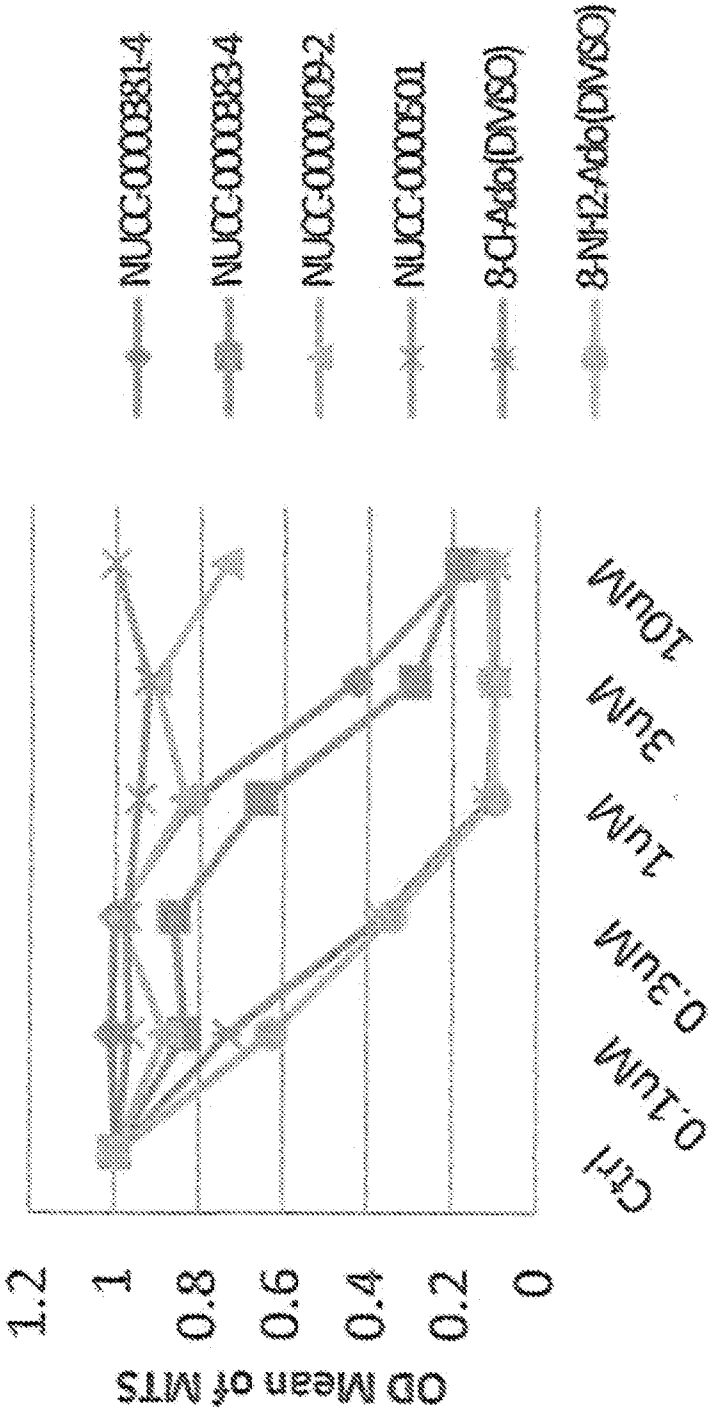


FIG. 13

U937 with 8Cl/8NH and NUCCs 3d

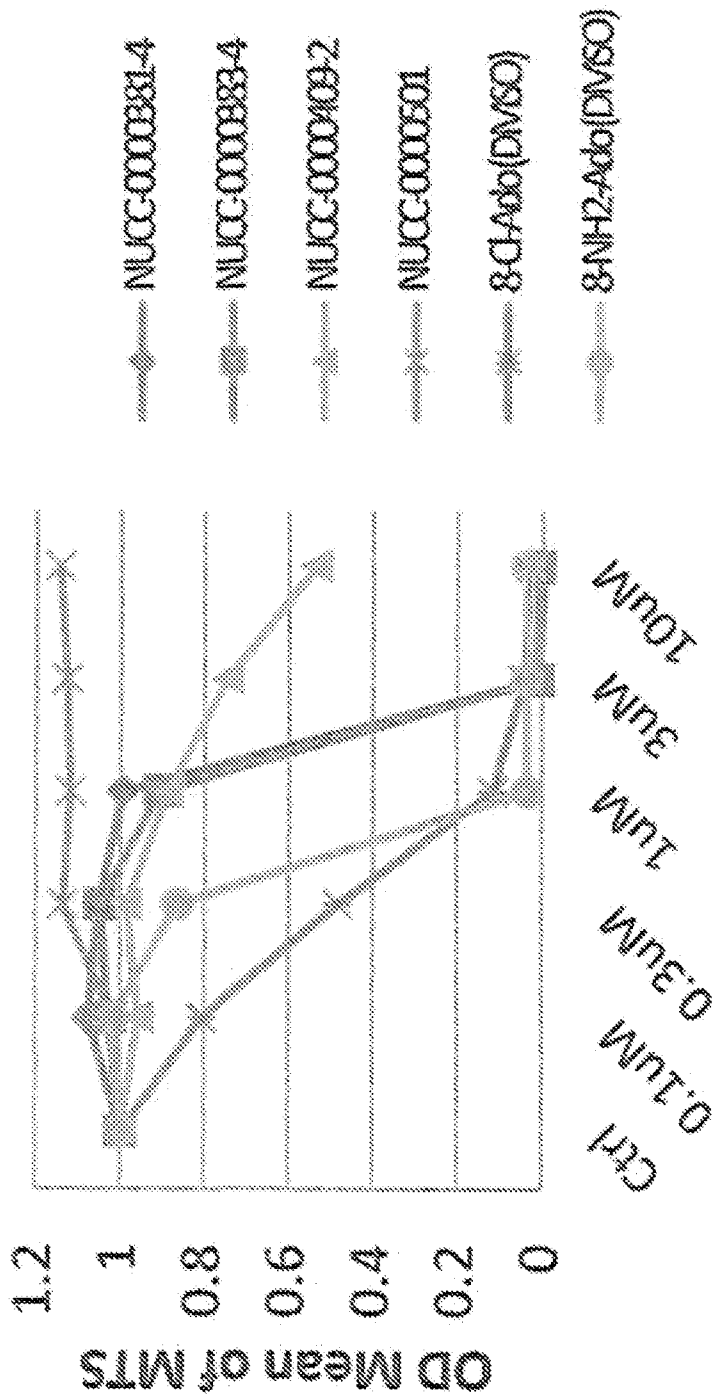


FIG. 14

U937: Inhibition of DNA Synthesis

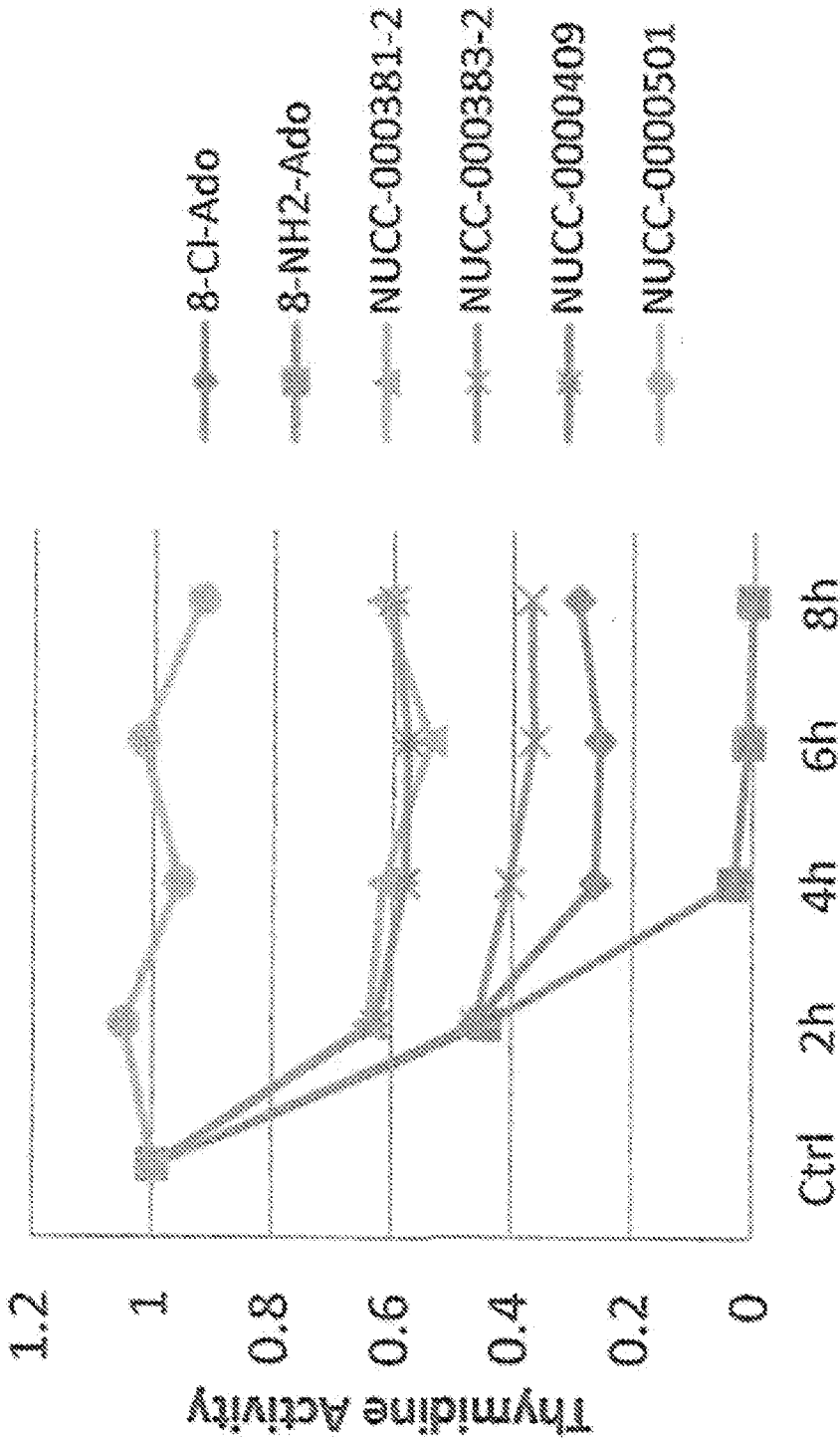


FIG. 15

U937: Inhibition of RNA Synthesis

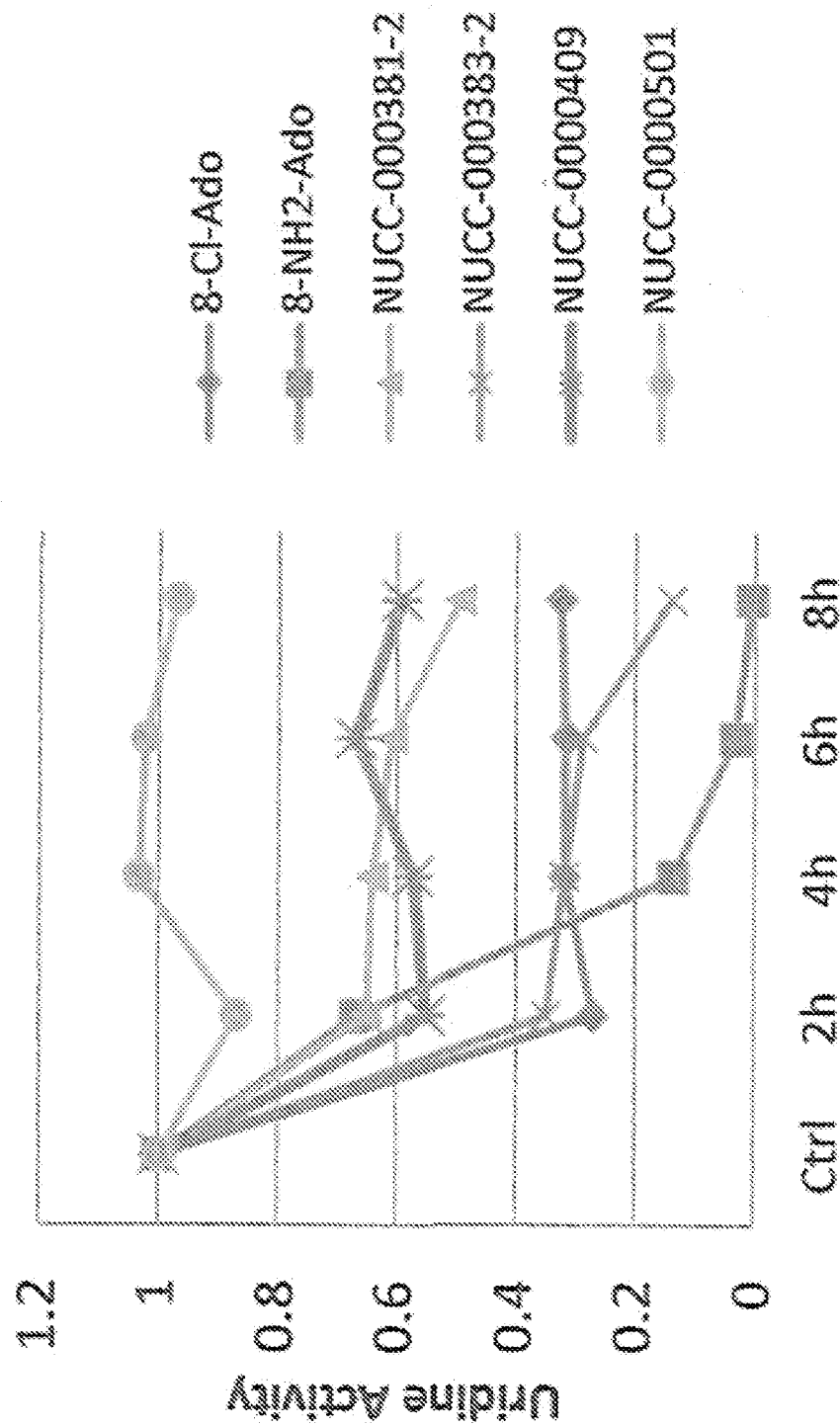


FIG. 16

FIG. 17

