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(54) Title: METHODS AND COMPOSITIONS FOR TREATMENT OF MYELODYSPLASTIC SYNDROMES AND/OR ACUTE MYELOID LEUKEMIAS

(57) Abstract: Disclosed are methods for treating a myelodysplastic syndrome (MDS) and/or an acute myeloid leukemia (AML) in an individual in need thereof. Further disclosed are compositions for use in the disclosed methods, used for treating a myelodysplastic syndrome (MDS) and/or an acute myeloid leukemia (AML) in an individual in need thereof.



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**METHODS AND COMPOSITIONS FOR TREATMENT OF  
MYELODYSPLASTIC SYNDROMES AND/OR ACUTE  
MYELOID LEUKEMIAS**

**Cross Reference to Related Applications**

**[0001]** This application claims priority to and the benefit of U.S. Provisional Patent Application Serial Number 62/429,958, filed December 5, 2016, to Starczynowski, entitled “Inhibition of UBE2N as a Therapeutic Approach in Myelodysplastic Syndromes and Acute Myeloid Leukemia,” and U.S. Provisional Patent Application Serial Number 62/414,021, filed October 28, 2016, to Starczynowski, entitled “Inhibition of UBE2N as a Therapeutic Approach in Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML),” the contents of all are incorporated by reference in their entirety.

**Background**

**[0002]** Myelodysplastic Syndromes (MDS) are malignant, potentially fatal blood diseases that arise from a defective hematopoietic stem/progenitor cell. MDS are heterogeneous diseases with few treatment options. One of the key challenges facing MDS treatment is the lack of effective medicines capable of providing a durable response.

**[0003]** MDS are hematologic malignancies defined by blood cytopenias due to ineffective hematopoiesis, and a predisposition to acute myeloid leukemia (AML) (Corey et al., 2007; Nimer, 2008). MDS is most prominent in individuals over 60 years of age, and as a result of longer life expectancies, the incidence of MDS has escalated in recent years (Sekeres, 2010b). MDS is fatal in majority of patients as a result of marrow failure, immune dysfunction, and/or transformation to overt leukemia. Current treatment options for MDS include allogeneic HSC transplantation, demethylating agents, and immunomodulatory therapies (Ebert, 2010). At present, the only curative treatment for

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MDS is (hemopoietic stem cell) HSC transplantation, an option unavailable to many of the older patients. Instead, these patients receive supportive care and transfusions to ameliorate their disease complications. Unfortunately, even with this treatment, the MDS clones persist in the marrow and the disease invariably advances (Tehranchi et al., 2010). For advanced disease or high-risk MDS, patients may also receive immunosuppressive therapy, epigenetic modifying drugs, and/or chemotherapy (Greenberg, 2010). Despite recent progress, most MDS patients exhibit treatment-related toxicities or relapse (Sekeres, 2010a). Overall the efficacy of these treatments is variable, and generally life expectancies are only slightly improved as compared to supportive care.

**[0004]** Approximately 30% of MDS patients also develop aggressive Acute Myeloid leukemia (AML) due to acquisition of additional mutations in the defective hematopoietic stem/progenitor cell (HSPC) (Greenberg et al., 1997). AML is a cancer of the myeloid line of blood cells, characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells. AML is the most common acute leukemia affecting adults, and its incidence increases with age. Although AML is a relatively rare disease, accounting for approximately 1.2% of cancer deaths in the United States, its incidence is expected to increase as the population ages. Several risk factors and chromosomal abnormalities have been identified, but the specific cause is not clear. As an acute leukemia, AML progresses rapidly and is typically fatal within weeks or months if left untreated. The prognosis for AML that arises from MDS has a worse as compared to other types of AML.

**[0005]** Consequently, there is an urgent need to develop targeted therapies capable of eliminating the MDS-initiating clones, and for treatments and method of treating MDS and AML. Identification of molecular

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targets is essential to improve outcome and eliminate the MDS-causing clones and/or AML. Herein, therapeutic targets and agents for treating MDS and/or AML are described.

### **Brief Summary**

**[0006]** Disclosed are methods for treating a myelodysplastic syndrome (MDS) and/or an acute myeloid leukemia (AML) in an individual in need thereof. Further disclosed are compositions for use in the disclosed methods, used for treating a myelodysplastic syndrome (MDS) and/or an acute myeloid leukemia (AML) in an individual in need thereof.

### **Brief Description of the Drawings**

**[0007]** The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

**[0008]** FIG 1. Knockdown of UBE2N with lentivirally expressed shRNAs abrogates AML cell clonogenic potential.

**[0009]** FIG 2. Knockdown of UBE2N with lentivirally expressed shRNAs abrogates engraftment of AML cells in NSG mice.

**[0010]** FIG 3. Pharmacological inhibition of UBE2N with NSC23 inhibits NKkB and interferon signaling in AML/MDS cells

**[0011]** FIG 4. Pharmacological inhibition of UBE2N with NSC23 inhibits NFkB and interferon signaling in AML/MDS cells.

**[0012]** FIG 5. Pharmacological inhibition of UBE2N with NSC23 inhibits TLR mediated NFkB activity.

**[0013]** FIG 6. Pharmacological inhibition of UBE2N with NSC23 inhibits NFkB and interferon signaling in AML/MDS cells.

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- [0014]** FIG 7. Pharmacological inhibition of UBE2N with NSC23 reduces proliferation and clonogenic potential of AML/MDS cells.
- [0015]** FIG 8. Pharmacological inhibition of UBE2N with NSC23 reduces proliferation and clonogenic potential of AML/MDS cells.
- [0016]** FIG 9. Pharmacological inhibition of UBE2N with NSC23 induces cell cycle arrest in mitosis and cell death of AML/MDS cells.
- [0017]** FIG 10. Differential protein ubiquitination in MDSL cells upon NSC23 treatment.
- [0018]** FIG 11. Pharmacological inhibition of UBE2N with NSC23 induces DNA damage, cell cycle arrest in mitosis and cell death of AML/MDS cells.
- [0019]** FIG 12. Pharmacological inhibition of UBE2N with NSC23 induces DNA damage, cell cycle arrest in mitosis and cell death of AML/MDS cells.
- [0020]** FIG 13. Schematic of structure based in silico library screening to identify cysteine-reactive inhibitors of UBE2N
- [0021]** FIG 14. UC 64 and UC 65 directly bind UBE2N, through a Michael-Addition reaction.
- [0022]** FIG 15. Pharmacological inhibition of UBE2N with UC64 and UC65 inhibits NFkB signaling in AML cells.
- [0023]** FIG 16. Pharmacological inhibition of UBE2N with UC64 and UC65 inhibits TLR mediated NFkB signaling in AML cells.
- [0024]** FIG 17. Treatment of AML cells with UC64 and UC65 reduces their proliferation.
- [0025]** FIG 18. Treatment of AML cells with UC64 and UC65 reduces their viability.

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- [0026] FIG 19. Treatment of AML cells with UC64 and UC65 reduces their clonogenic potential.
- [0027] FIG 20. UC65 is effective against targeting MDS/AML cells in vivo.
- [0028] FIG 21. Treatment of primary MDS stem cells with UC65/65 reduces their clonogenic potential.
- [0029] FIG 22. Treatment of MOLM-13 and THP-1 cells with UC64/65 does not cause DNA damage.
- [0030] FIG 23. UC64/65 reduces UBE2N ubiquitination at Lysine (K)-92
- [0031] FIG 24. UBE2N active site mutant is less sensitive to UC64/65 and NSC23 mediated inhibition of NFkB.
- [0032] FIG 25. DDB1 is differentially ubiquitinated following inhibition of UBE2N with UC64/65 and NSC23.
- [0033] FIG 27. UBE2N inhibition enhances the cytotoxic effects of lenalidomide in MDS/AML cells
- [0034] FIG 28. UBE2N inhibition does not affect the function of normal CD34+ cells in the presence of lenalidomide.
- FIG 29. Schematic of the forms of ubiquitination.

### **Detailed Description**

- [0035] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. In case of conflict, the present document, including definitions, will control. Preferred methods and materials are described below, although methods and materials similar or equivalent to those described herein can be used in practice or testing of the present invention. All publications, patent applications, patents and other

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references mentioned herein are incorporated by reference in their entirety. The materials, methods, and examples disclosed herein are illustrative only and not intended to be limiting.

**[0036]** The terms and expressions used herein have the ordinary meaning as is accorded to such terms and expressions with respect to their corresponding respective areas of inquiry and study except where specific meanings have otherwise been set forth herein.

**[0037]** The terms and expressions used herein have the ordinary meaning as is accorded to such terms and expressions with respect to their corresponding respective areas of inquiry and study except where specific meanings have otherwise been set forth herein.

**[0038]** As used herein and in the appended claims, the singular forms “a,” “and,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a method” includes a plurality of such methods and reference to “a dose” includes reference to one or more doses and equivalents thereof known to those skilled in the art, and so forth.

**[0039]** The term “about” or “approximately” means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, e.g., the limitations of the measurement system. For example, “about” can mean within 1 or more than 1 standard deviation, per the practice in the art. Alternatively, “about” can mean a range of up to 20%, or up to 10%, or up to 5%, or up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value. Where particular values are described in the application and claims, unless

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otherwise stated the term “about” meaning within an acceptable error range for the particular value should be assumed.

**[0040]** The terms “individual,” “host,” “subject,” and “patient” are used interchangeably to refer to an animal that is the object of treatment, observation and/or experiment. Generally, the term refers to a human patient, but the methods and compositions may be equally applicable to non-human subjects such as other mammals. In some embodiments, the terms refer to humans. In further embodiments, the terms refer to children.

**[0041]** “Therapeutically effective amount” relates to the amount or dose of an active compound or composition described herein that will lead to one or more therapeutic effect, in particular, a desired beneficial effect. A therapeutically effective amount of a substance can vary according to factors such as the disease state, age, sex, and weight of the subject, and the ability of the substance to elicit a desired response in the subject. Dosage regime may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

**[0042]** The phrase “pharmaceutically acceptable,” as used in connection with compositions of the disclosure, refers to molecular entities and other ingredients of such compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a subject (e.g., human). In certain embodiments, as used herein, the term “pharmaceutically acceptable” means approved by a regulatory agency of a Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals (e.g., humans).



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**[0043]** The terms “pharmaceutically acceptable salts” or “a pharmaceutically acceptable salt thereof” refer to salts prepared from pharmaceutically acceptable, non-toxic acids or bases. Suitable pharmaceutically acceptable salts include metallic salts, e.g., salts of aluminum, zinc, alkali metal salts such as lithium, sodium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts; organic salts; salts of free acids and bases; inorganic salts, e.g., sulfate, hydrochloride, and hydrobromide; and other salts which are currently in widespread pharmaceutical use and are listed in sources well known to those of skill in the art, such as The Merck Index. Any suitable constituent can be selected to make a salt of an active drug discussed herein, provided that it is non-toxic and does not substantially interfere with the desired activity. In addition to salts, pharmaceutically acceptable precursors and derivatives of the compounds can be employed. Pharmaceutically acceptable amides, lower alkyl esters, and protected derivatives of the disclosed actives can also be suitable for use in the compositions and methods disclosed herein. A salt of a compound of this disclosure may be formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt. Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as

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related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate,  $\beta$ -hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

**[0044]** The terms “treat,” “treating” or “treatment,” as used herein, refers to methods of alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

**[0045]** The term “carrier” applied to pharmaceutical compositions of the disclosure refers to a diluent, excipient, or vehicle with which an active compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water, saline solutions, aqueous dextrose solutions,

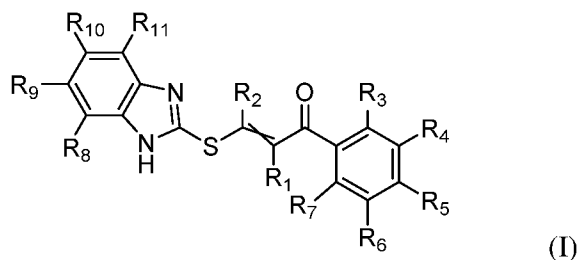
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aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" (any edition).

**[0046]** The term "compound," as used herein, is also intended to include any salts, solvates, or hydrates thereof.

**[0047]** Applicant has discovered novel methods of treating a myelodysplastic syndrome (MDS) and/or an acute myeloid leukemia (AML), which may include administration of one or more of the disclosed compounds/compositions to an individual in need thereof.

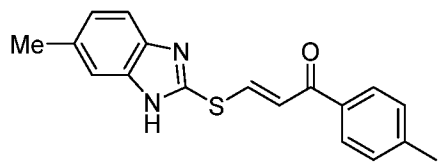
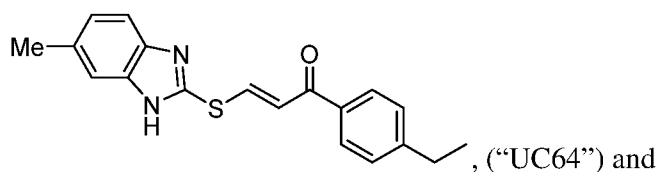
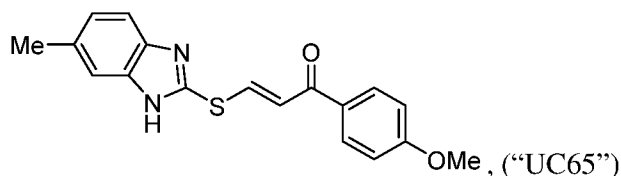
**[0048]** In some embodiments, the method of treating a myelodysplastic syndrome (MDS) and/or an acute myeloid leukemia (AML) may comprise the step of administering one or more compounds selected from:



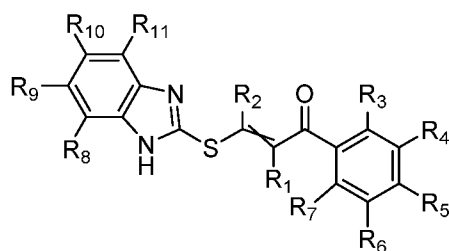
wherein  $R_1$  is selected from H, F, Cl, Br, nitrile,  $CH_3$ , and  $CH_2CH_3$ ;  $R_2$  is selected from H, F, Cl, and  $C_1$ - $C_4$  alkyl;  $R_3$ - $R_7$  are independently selected from H, F, Cl, Br, nitrile,  $NHCOCH_3$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy; and  $R_4$  with either  $R_3$  or  $R_5$  are a substituted or unsubstituted benzo fused ring; and  $R_8$ - $R_{10}$  are independently selected from H, F, Cl, Br, nitrile  $NHCOCH_3$ ,  $C_1$ - $C_4$  alkyl,  $C_1$ - $C_4$  alkoxy. Compound (I) is an alpha, beta unsaturated ketone with a 2-mercaptobenzimidazole at the beta position. The double bond may be cis or trans. In some embodiments, the double bond is trans.

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**[0049]** In some embodiments, for Compound 1, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>10</sub>, and R<sub>11</sub> are H; and R<sub>5</sub> and R<sub>9</sub> are independently selected from H, F, Cl, Br, nitrile NHC(O)CH<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy. Examples include, but are not limited to:



**[0050]** In one aspect, the method of treating a myelodysplastic syndrome (MDS) and/or an acute myeloid leukemia (AML) may comprise the step of administering one or more compounds selected from:

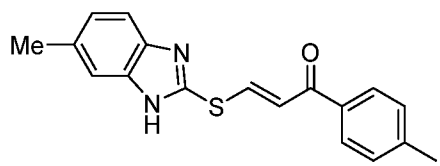


(Compound I)

wherein R<sub>1</sub> is selected from H, F, Cl, Br, nitrile, CH<sub>3</sub>, and CH<sub>2</sub>CH<sub>3</sub>; R<sub>2</sub> is selected from H, F, Cl, and C<sub>1</sub>-C<sub>4</sub> alkyl; R<sub>3</sub>-R<sub>7</sub> are independently selected from H, F, Cl, Br, nitrile, NHC(O)CH<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy; and R<sub>4</sub> with either R<sub>3</sub> or R<sub>5</sub> are a substituted or unsubstituted benzo fused ring; and R<sub>8</sub>-R<sub>10</sub> are independently selected from H, F, Cl,

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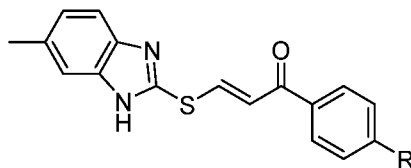
Br, nitrile  $\text{NHCOCH}_3$ ,  $\text{C}_1\text{-C}_4$  alkyl,  $\text{C}_1\text{-C}_4$  alkoxy, wherein Compound I



does not include

**[0051]** In some embodiments, for Compound 1,  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$ ,  $\text{R}_6$ ,  $\text{R}_7$ ,  $\text{R}_8$ ,  $\text{R}_{10}$ , and  $\text{R}_{11}$  are H; and  $\text{R}_5$  and  $\text{R}_9$  are independently selected from H, F, Cl, Br, nitrile  $\text{NHCOCH}_3$ , methyl, ethyl, methoxy and ethoxy.

**[0052]** In some embodiments, the compound is selected from:



wherein R is selected from ethyl and methoxy.

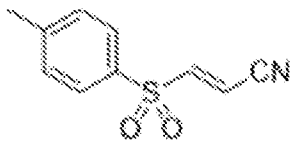
**[0053]** The term “alkyl” includes straight, branched chain, or cyclic alkyl groups, such as, but not limited to, methyl, ethyl, propyl, butyl, trifluoromethyl, and tetradecyl.

**[0054]** The term “alkoxy” includes straight, branched chain, or cyclic alkoxy groups, such as, but not limited to, methoxy, ethoxy, propoxy, butoxy, 2-methoxyethoxy, sec-butoxy, hexyloxy, and 2-ethylhexyloxy, tetradecyloxy groups.

**[0055]** The term “group” is used, it is intended to encompass not only the substituent's unsubstituted form, but also its form further substituted with any substituent group or groups as herein mentioned, so long as the substituent does not destroy properties necessary for utility. Suitably, a substituent group may be halogen or may be bonded to the remainder of the molecule by an atom of carbon, nitrogen, oxygen, or sulphur.

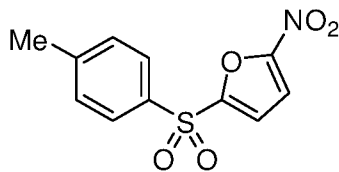
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**[0056]** In one aspect, the method of treating a myelodysplastic syndrome (MDS) and/or an acute myeloid leukemia (AML) may comprise the step of administering the compound



(“Bay 11-7082”), alone or in combination with a compound described herein, to an individual in need thereof.

**[0057]** In one aspect, the method of treating a myelodysplastic syndrome (MDS) and/or an acute myeloid leukemia (AML) may comprise the step of administering the compound



(NSC697923), alone or in combination with a compound described herein, to an individual in need thereof.

**[0058]** In one aspect, the one or more compounds may be administered in an amount sufficient to activate TRAF6 and/or NF kappa beta.

**[0059]** In one aspect, the one or more compounds may be administered in an amount sufficient to slow or prevent growth of AML and/or MDS cells, reduce clonogenic potential of AML and/or MDS cells, reduce AML and/or MDS cell viability; promote apoptosis of AML and/or MDS cells, or combinations thereof.

**[0060]** In one aspect, the one or more compounds may be co-administered with lenalidomide (“LEN”), wherein said administration is in an amount sufficient to reduce/inhibit MDS/AML cell function.

**[0061]** In one aspect, the one or more compounds may be co-administered with a chemotherapeutic agent selected from a taxane, a platinum-based agent, an anthracycline, an alkylating agent, a vinca alkaloid, an

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epothilone, a histone deacetylase inhibitor, a topoisomerase I and II inhibitor, a kinase inhibitor, a nucleotide analog, a precursor analog, a peptide antibiotic, and combinations thereof

- [0062]** In one aspect, a method of treating a non-del(5q) MDS patient is disclosed, in which an individual is administered a compound or compositions as disclosed herein.
- [0063]** In one aspect, an article of manufacture is disclosed, in which the article of manufacture may comprise a container, a composition or compound as disclosed herein in a dosage form, and instructions for administering said dosage form to an individual diagnosed or suspected of having a myelodysplastic syndrome (MDS) and/or an acute myeloid leukemia (AML). The dosage form may be any disclosed herein, for example, an oral dosage form, a form suitable for bronchial administration, or an intravenous form. The article of manufacture may further comprise a means for delivery of said dosage form.
- [0064]** Dosage
- [0065]** In one aspect, an agent disclosed herein may be present in an amount of from about 0.5% to about 95%, or from about 1% to about 90%, or from about 2% to about 85%, or from about 3% to about 80%, or from about 4%, about 75%, or from about 5% to about 70%, or from about 6%, about 65%, or from about 7% to about 60%, or from about 8% to about 55%, or from about 9% to about 50%, or from about 10% to about 40%, by weight of the composition.
- [0066]** The compositions may be administered in oral dosage forms such as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous,

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intralesional, or intramuscular forms all utilizing dosage forms well known to those of ordinary skill in the pharmaceutical arts. The compositions may be administered by intranasal route via topical use of suitable intranasal vehicles, or via a transdermal route, for example using conventional transdermal skin patches. A dosage protocol for administration using a transdermal delivery system may be continuous rather than intermittent throughout the dosage regimen.

**[0067]** In one aspect, the compounds may be administered at the rate of 100 µg to 1000 mg per day per kg of body weight. Orally, the compounds may be suitably administered at the rate of about 100, 150, 200, 250, 300, 350, 400, 450, or 500 µg to about 1, 5, 10, 25, 50, 75, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 mg per day per kg of body weight. The required dose can be administered in one or more portions. For oral administration, suitable forms are, for example, tablets, gel, aerosols, pills, dragees, syrups, suspensions, emulsions, solutions, powders and granules; one method of administration includes using a suitable form containing from 1 mg to about 500 mg of active substance. In one aspect, administration may comprise using a suitable form containing from about 1, 2, 5, 10, 25, or 50 mg to about 100, 200, 300, 400, 500 mg of active substance.

**[0068]** A dosage regimen will vary depending upon known factors such as the pharmacodynamic characteristics of the agents and their mode and route of administration; the species, age, sex, health, medical condition, and weight of the patient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, the route of administration, the renal and hepatic function of the patient, and the desired effect. The effective amount of a drug required to prevent, counter, or arrest progression of a symptom or effect of a muscle contracture can be readily determined by an ordinarily skilled physician



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**[0069]** The pharmaceutical compositions may include suitable dosage forms for oral, parenteral (including subcutaneous, intramuscular, intradermal and intravenous), transdermal, sublingual, bronchial or nasal administration. Thus, if a solid carrier is used, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form, or in the form of a troche or lozenge. The solid carrier may contain conventional excipients such as binding agents, fillers, tableting lubricants, disintegrants, wetting agents and the like. The tablet may, if desired, be film coated by conventional techniques. Oral preparations include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with a filler or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers. If a liquid carrier is employed, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule, sterile vehicle for injection, an aqueous or non-aqueous liquid suspension, or may be a dry product for reconstitution with water or other suitable vehicle before use. Liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, wetting agents, non-aqueous vehicle (including edible oils), preservatives, as well as flavoring and/or coloring agents. For parenteral administration, a vehicle normally will comprise sterile water, at least in large part, although saline solutions, glucose solutions and like may be utilized. Injectable suspensions also may be used, in which case conventional suspending agents may be employed. Conventional preservatives, buffering agents and the like also may be added to the parenteral dosage forms. For topical or nasal administration, penetrants or permeation agents that are appropriate to the particular barrier to be

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permeated are used in the formulation. Such penetrants are generally known in the art. The pharmaceutical compositions are prepared by conventional techniques appropriate to the desired preparation containing appropriate amounts of the active ingredient, that is, one or more of the disclosed active agents or a pharmaceutically acceptable salt thereof according to the invention.

**[0070]** The dosage of an agent disclosed herein used to achieve a therapeutic effect will depend not only on such factors as the age, weight and sex of the patient and mode of administration, but also on the degree of inhibition desired and the potency of an agent disclosed herein for the particular disorder or disease concerned. It is also contemplated that the treatment and dosage of an agent disclosed herein may be administered in unit dosage form and that the unit dosage form would be adjusted accordingly by one skilled in the art to reflect the relative level of activity. The decision as to the particular dosage to be employed (and the number of times to be administered per day) is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect.

**[0071]** Routes of Administration

**[0072]** Any suitable route of administration can be employed for providing the patient with an effective dosage of the disclosed compositions. For example, oral, rectal, transdermal, parenteral (subcutaneous, intramuscular, intravenous), intrathecal, topical, inhalable, and like forms of administration can be employed. Suitable dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, and the like. Administration of medicaments prepared from the compounds described herein can be by any suitable method capable of introducing the compounds into the bloodstream. In some embodiments, the formulations can contain a mixture of active

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compounds with pharmaceutically acceptable carriers or diluents known to those of skill in the art.

**[0073]** The compositions can be prepared in any desired form, for example, tables, powders, capsules, injectables, suspensions, sachets, cachets, patches, solutions, elixirs, and aerosols. Carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like can be used in oral solid preparations. In certain embodiments, the compositions are prepared as oral solid preparations (such as powders, capsules, and tablets). In certain embodiments, the compositions are prepared as oral liquid preparations. In some embodiments, the oral solid preparations are tablets. If desired, tablets can be coated by standard aqueous or non-aqueous techniques.

**[0074]** In addition to the dosage forms set out above, one or more disclosed compounds may also be administered by sustained release, delayed release, or controlled release compositions and/or delivery devices.

**[0075]** Pharmaceutical compositions suitable for oral administration can be provided as discrete units such as capsules, cachets, sachets, patches, injectables, tablets, and aerosol sprays, each containing predetermined amounts of the active ingredients, as powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions can be prepared by any of the conventional methods of pharmacy, and may include the step of bringing into association the active ingredients with a carrier which constitutes one or more ingredients. In general, the compositions may be prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then, optionally, shaping the product into the desired presentation.

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- [0076]** For example, a tablet can be prepared by compression or molding, optionally, with one or more additional ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets can be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.
- [0077]** A composition or formulation may be administered to a subject continuously or periodically.
- [0078]** The compositions or fractions thereof typically comprise suitable pharmaceutical diluents, excipients, vehicles, or carriers selected based on the intended form of administration, and consistent with conventional pharmaceutical practices. The carriers, vehicles etc. may be adapted to provide an additive, synergistically effective or therapeutically effective amount of the active compounds. Suitable pharmaceutical diluents, excipients, vehicles, and carriers are described in the standard text, Remington: The Science and Practice of Pharmacy, and in The United States Pharmacopeia: The National Formulary (USP 24 NF 19) published in 1999. By way of example, for oral administration in the form of a capsule or tablet, the active components can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, methyl cellulose, magnesium stearate, glucose, calcium, sulfate, dicalcium phosphate, mannitol, sorbitol, and the like. For oral administration in a liquid form, the agents may be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Suitable binders (e.g. gelatin, starch, corn sweeteners, natural sugars including glucose; natural and synthetic gums, and waxes), lubricants (e.g. sodium oleate, sodium stearate,

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magnesium stearate, sodium benzoate, sodium acetate, and sodium chloride), disintegrating agents (e.g. starch, methyl cellulose, agar, bentonite, and xanthan gum), flavoring agents, and coloring agents may also be combined in the compositions or components thereof.

**[0079]** In one aspect, a pharmaceutical composition may have pH from about 7 to 10.

**[0080]** Formulations for parenteral administration of a composition may include aqueous solutions, syrups, aqueous or oil suspensions and emulsions with edible oil such as cottonseed oil, coconut oil or peanut oil. Dispersing or suspending agents that can be used for aqueous suspensions include synthetic or natural gums, such as tragacanth, alginate, acacia, dextran, sodium carboxymethylcellulose, gelatin, methylcellulose, and polyvinylpyrrolidone.

**[0081]** Compositions for parenteral administration may include sterile aqueous or non-aqueous solvents, such as water, isotonic saline, isotonic glucose solution, buffer solution, or other solvents conveniently used for parenteral administration of therapeutically active agents. A composition intended for parenteral administration may also include conventional additives such as stabilizers, buffers, or preservatives.

**[0082]** In an embodiment, a solid form pharmaceutical composition is provided (e.g. tablets, capsules, powdered, or pulverized form) comprising one or more disclosed compounds or salt thereof.

**[0083]** After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of a composition, such labeling would include amount, frequency, and method of administration.

**[0084]** Kits

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**[0085]** Kits are also provided. In one aspect, a kit may comprise or consist essentially of agents or compositions described herein. The kit may be a package that houses a container which may contain a composition comprising an oxime or pharmaceutically acceptable salt thereof as disclosed herein, and also houses instructions for administering the agent or composition to a subject. In one aspect, a pharmaceutical pack or kit is provided comprising one or more containers filled with one or more composition as disclosed herein. Associated with such container(s) can be various written materials such as instructions for use, or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use, or sale for human administration.

**[0086]** As there may be advantages to mixing a component of a composition described herein and a pharmaceutically acceptable carrier, excipient or vehicle near the time of use, kits in which components of the compositions are packaged separately are disclosed. For example, the kit can contain an active ingredient in a powdered or other dry form in, for example, a sterile vial or ampule and, in a separate container within the kit, a carrier, excipient, or vehicle, or a component of a carrier, excipient, or vehicle (in liquid or dry form). In one aspect, the kit can contain a component in a dry form, typically as a powder, often in a lyophilized form in, for example, a sterile vial or ampule and, in a separate container within the kit, a carrier, excipient, or vehicle, or a component of a carrier, excipient, or vehicle. Alternatively, the kit may contain a component in the form of a concentrated solution that is diluted prior to administration. Any of the components described herein, any of the carriers, excipients or vehicles described herein, and any combination of components and carriers, excipients or vehicles can be included in a kit.

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**[0087]** Optionally, a kit may also contain instructions for preparation or use (e.g., written instructions printed on the outer container or on a leaflet placed therein) and one or more devices to aid the preparation of the solution and/or its administration to a patient (e.g., one or a plurality of syringes, needles, filters, tape, tubing, alcohol swabs, or the like). Compositions which are more concentrated than those administered to a subject can be prepared. Accordingly, such compositions can be included in the kits with, optionally, suitable materials (e.g., water, saline, or other physiologically acceptable solutions) for dilution. Instructions included with the kit can include, where appropriate, instructions for dilution.

**[0088]** In other embodiments, the kits can include pre-mixed compositions and instructions for solubilizing any precipitate that may have formed during shipping or storage. Kits containing solutions of one or more of the aforementioned active agents, or pharmaceutically acceptable salts thereof, and one or more carriers, excipients or vehicles may also contain any of the materials mentioned above (e.g., any device to aid in preparing the composition for administration or in the administration per se). The instructions in these kits may describe suitable indications (e.g., a description of patients amenable to treatment) and instructions for administering the solution to a patient.

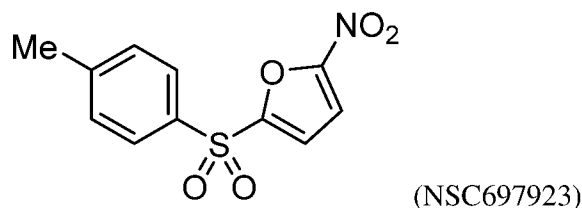
**[0089]** **Examples**

**[0090]** Applicant has found that UBE2N inhibition achieves reduction of TRAF6 protein levels, abrogation of TRAF6 signaling in AML/MDS cell lines and primary cells, AML/MDS cell cycle arrest (leading to cell death); alteration of ubiquitination of DDDDB1 (a component of the CRBN complex), and cooperation with lenalidomide to reduce AML/MDS cell function. Net, the data reveals that UBE2N, an E2 ubiquitin conjugating enzyme, as a novel therapeutic target in MDS/AML.

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**[0091]** Hematopoietic stem and progenitor cells (HSPC) from MDS and AML patients exhibit overexpression of TRAF6 and related innate immune pathway genes, suggesting a dependency of leukemic HSPC on activated innate immune signaling. Unfortunately, inhibiting TRAF6 directly has proven difficult, as few binding pockets on TRAF6 exist for targeting small molecules. UBE2N/Ubc13, a cofactor of TRAF6 and key enzyme in innate immune signaling, is a ubiquitin-conjugating E2 enzyme that catalyzes lysine 63 (K63)-linked ubiquitin chains on TRAF6 and its substrates. Importantly, a commercially available compound and a chemical series of UBE2N inhibitors are available. Applicant evaluated the cellular and molecular effects of pharmacologic and genetic inhibition of UBE2N in MDS and AML cells.

**[0092]** Pharmacological inhibition of UBE2N with NSC697923 (available from Sigma Aldrich, Tocris, Cayman, and other vendors), having the following structure:



**[0093]** or genetic inhibition with shRNAs reduced the clonogenic capacity of MDSL/AML cell lines and primary cells while not significantly affecting normal HSPC. Treatment of MDS/AML cells with NSC697923 reduced the cellular metabolic activity, induced a G2/M cell cycle arrest, and increased cell death. Moreover, xenotransplantation of an MDS-derived patient cell line (MDSL) into immunodeficient mice (NSG-SGM3) showed a 50-70% reduced graft upon UBE2N knockdown relative to a non-silencing control. The cellular effects of UBE2N inhibition correspond with suppression of



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TRAF6-induced NF-kappa beta activation of target genes. In addition, applicant found that NSC697923 treatment results in a dramatic loss of TRAF6 protein expression, which is rescued by inhibition of the proteasome. Intriguingly, the molecular analysis revealed that UBE2N inhibition shifts the stoichiometry of TRAF6 ubiquitin chains from K63-lined to K48-linked ubiquitin, resulting in proteasome-mediated degradation.

**[0094]** To identify the molecular basis of UBE2N inhibition, Applicant performed a global ubiquitin screen for changes in ubiquitinated substrates and gene expression profiling by RNA sequencing. For the ubiquitin screen, K63 ubiquitinated proteins were immunoprecipitated from MDSL cells upon pharmacologic inhibition of UBE2N, followed by mass spectrometry analysis. UBE2N inhibition significantly altered the ubiquitination of about 200 proteins involved in innate immune signaling, glycolysis, cell survival, RNA splicing, and DNA damage response. In parallel, RNA sequencing of MDSL cells treated with NSC697923 revealed expression changes in genes involved in mRNA processing, cell cycle, and glycolysis. Several components of the E3 ligase anaphase-promoting complex APC/CDC20 were downregulated after UBE2N inhibition. As expected, increased expression of APC/CDC20 substrates (i.e., cyclin B1) were observed following treatment with NSC697923, suggesting that UBE2N inhibition in MDS/AML blocks degradation of APC/CDC20 targets and leads to mitotic alteration and apoptosis.

**[0095]** One substrate identified in NSC697923-treated MDSL cells by the ubiquitin screen is DDB1, a component of the CUL4-CRBN E3 ligase complex targeted by Lenalidomide (LEN). Lenalidomide has been shown to be effective for treatment of myelodysplastic syndromes (MDS) and has significantly improved overall survival in myeloma (which formerly carried a poor prognosis), although toxicity remains

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an issue for users. LEN has shown encouraging results in del(5q) MDS patients (“deletion 5q (del 5q) MDS” in which part of chromosome 5 is missing), but its effects are limited in other cytogenetic subtypes of MDS or AML. Therefore, the identification of molecular targets that can enhance or extend the use of LEN in a broader spectrum of patients is desired. Applicant explored the possibility of a cooperative effect of LEN and NSC697923 on MDS/AML cells. As compared to individual treatments, the combination of LEN and NSC697923 or UBE2N shRNAs significantly suppressed the function and viability of MDS/AML cell lines and patient samples in vitro. More striking, treatment of LEN and NSC697923 impaired MDS/AML cells that are refractory to treatment of LEN or NSC697923 alone. As such, UBE2N is a promising target for extending the use of LEN to other subtypes of MDS/AML.

- [0096]** Net, Applicant has identified a novel therapeutic target, an E2 ubiquitin conjugating enzyme (UBE2N) in MDS/AML. UBE2N inhibition suppresses the function and viability of MDS/AML cell lines and patient samples, due in part to degradation of TRAF6, suppressing innate immune signaling, and inducing mitotic alterations. Applicant has also found that inhibition of UBE2N alters ubiquitination of DDB1, a component of the CRBN complex, and cooperates with LEN to target MDS/AML cells.
- [0097]** All percentages and ratios are calculated by weight unless otherwise indicated.
- [0098]** All percentages and ratios are calculated based on the total composition unless otherwise indicated.
- [0099]** It should be understood that every maximum numerical limitation given throughout this specification includes every lower numerical limitation, as if such lower numerical limitations were expressly

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written herein. Every minimum numerical limitation given throughout this specification will include every higher numerical limitation, as if such higher numerical limitations were expressly written herein. Every numerical range given throughout this specification will include every narrower numerical range that falls within such broader numerical range, as if such narrower numerical ranges were all expressly written herein.

**[00100]** The dimensions and values disclosed herein are not to be understood as being strictly limited to the exact numerical values recited. Instead, unless otherwise specified, each such dimension is intended to mean both the recited value and a functionally equivalent range surrounding that value. For example, a dimension disclosed as “20 mm” is intended to mean “about 20 mm.”

**[00101]** Every document cited herein, including any cross referenced or related patent or application, is hereby incorporated herein by reference in its entirety unless expressly excluded or otherwise limited. The citation of any document is not an admission that it is prior art with respect to any invention disclosed or claimed herein or that it alone, or in any combination with any other reference or references, teaches, suggests or discloses any such invention. Further, to the extent that any meaning or definition of a term in this document conflicts with any meaning or definition of the same term in a document incorporated by reference, the meaning or definition assigned to that term in this document shall govern.

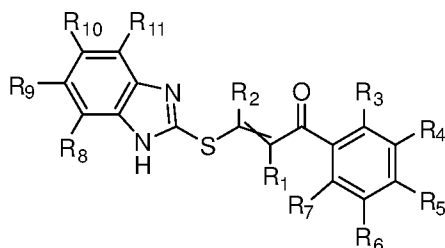
**[00102]** While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

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## Claims

What is claimed is:

1. A method of treating a myelodysplastic syndrome (MDS) and/or an acute myeloid leukemia (AML) comprising the step of administering one or more compounds selected from:

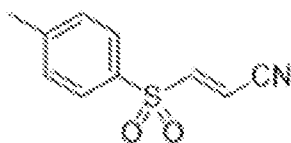


wherein R<sub>1</sub> is selected from H, F, Cl, Br, nitrile, CH<sub>3</sub>, and CH<sub>2</sub>CH<sub>3</sub>;

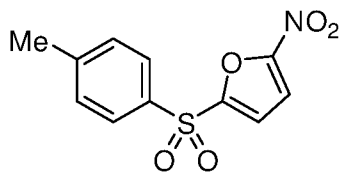
R<sub>2</sub> is selected from H, F, Cl, and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>3</sub>-R<sub>7</sub> are independently selected from H, F, Cl, Br, nitrile, NHCOCH<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy; and R<sub>4</sub> with either R<sub>3</sub> or R<sub>5</sub> are a substituted or unsubstituted benzo fused ring; and

R<sub>8</sub>-R<sub>10</sub> are independently selected from H, F, Cl, Br, nitrile NHCOCH<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy;



("Bay 11-7082"); and

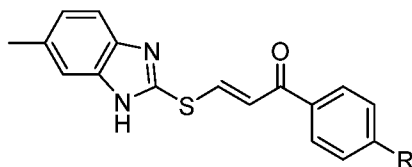


(NSC697923).

2. The method of claim 1, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>10</sub>, and R<sub>11</sub> are H; R<sub>5</sub> and R<sub>9</sub> are independently selected from H, F, Cl, Br, nitrile NHCOCH<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy.

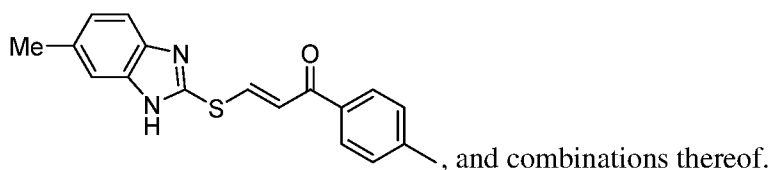
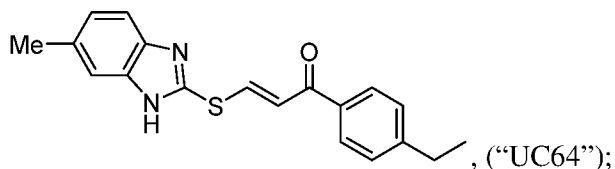
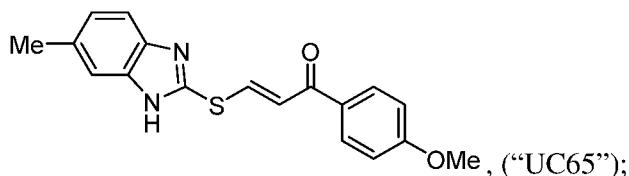
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3. The method of claim 1 or 2, wherein R<sub>5</sub> and R<sub>9</sub> are independently selected from H, F, Cl, Br, nitrile NHCOCH<sub>3</sub>, methyl, ethyl, methoxy and ethoxy.
4. The method of any preceding claim, wherein the compound is selected from:



wherein R is selected from ethyl and methoxy.

5. The method of claim 1, wherein the compound is selected from



6. The method of any preceding claim wherein said one or more compounds is administered in an amount sufficient to activate TRAF6 and/or NF kappa beta.
7. The method of any preceding claim wherein said one or more compounds is administered in an amount sufficient to slow or prevent growth of AML and/or MDS cells, reduce clonogenic potential of AML and/or MDS cells, reduce AML and/or MDS cell viability; promote apoptosis of AML and/or MDS cells, or combinations thereof.

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8. The method of any preceding claim, wherein said one or more compounds is co-administered with lenalidomide ("LEN"), wherein said administration is in an amount sufficient to reduce/inhibit MDS/AML cell function.
9. The method of any preceding claim, wherein said one or more compounds is co-administered with a chemotherapeutic agent selected from a taxane, a platinum-based agent, an anthracycline, an alkylating agent, a vinca alkaloid, an epothilone, a histone deacetylase inhibitor, a topoisomerase I and II inhibitor, a kinase inhibitor, a nucleotide analog, a precursor analog, a peptide antibiotic, and combinations thereof
10. A composition comprising a compound according to any preceding claim and a pharmaceutically acceptable carrier.
11. The composition of claim 10, wherein said composition is in the form of a tablet, capsule, or intravenous form.
12. The composition of claim 10 or 11, wherein said one or more compound is present in an amount of from about 5 mg to about 1000 mg.
13. The composition of any of claims 10 through 12, wherein said pharmaceutically acceptable carrier is a saline solution, preferably comprising a buffer.
14. A method of treating a non-del(5q) MDS patient, comprising the step of administering a compound or composition according to any preceding claim.
15. An article of manufacture comprising a container, a composition or compound of any preceding claim in a dosage form, and instructions for administering said dosage form to an individual diagnosed or suspected of having a myelodysplastic syndrome (MDS) and/or an acute myeloid leukemia (AML).

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16. The article of manufacture of claim 15, wherein said dosage form is selected from an oral dosage form, a form suitable for bronchial administration, or an intravenous form.
17. The article of manufacture of claim 15 or 16, further comprising a means for delivery of said dosage form.

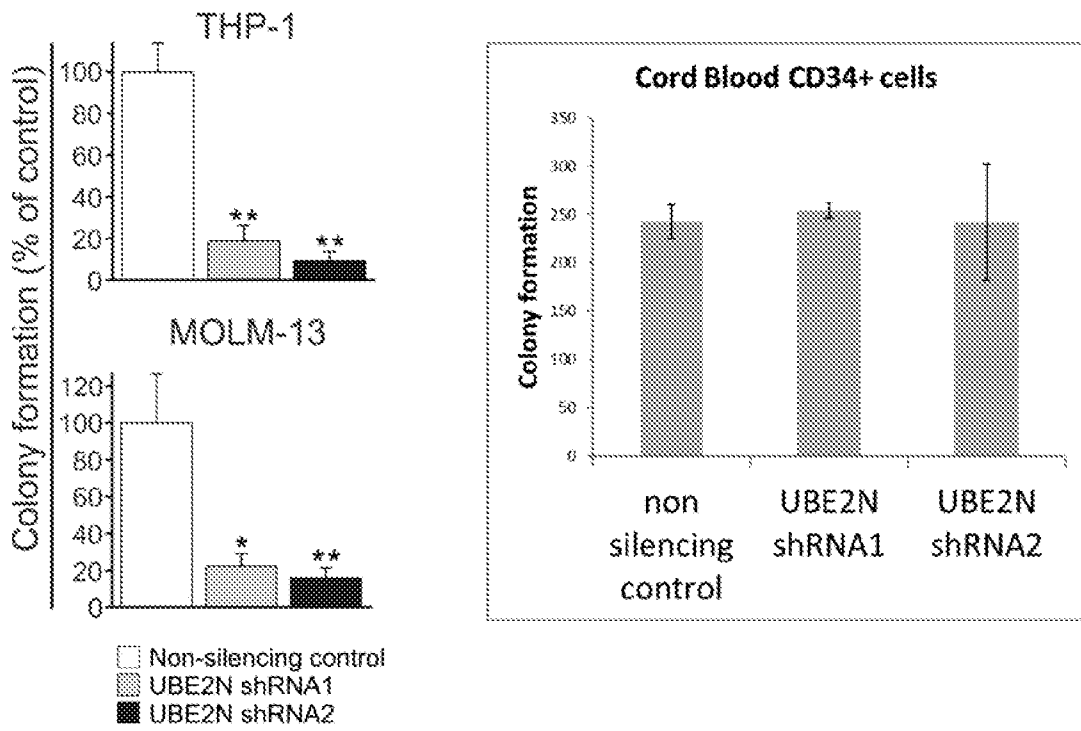


FIG. 1



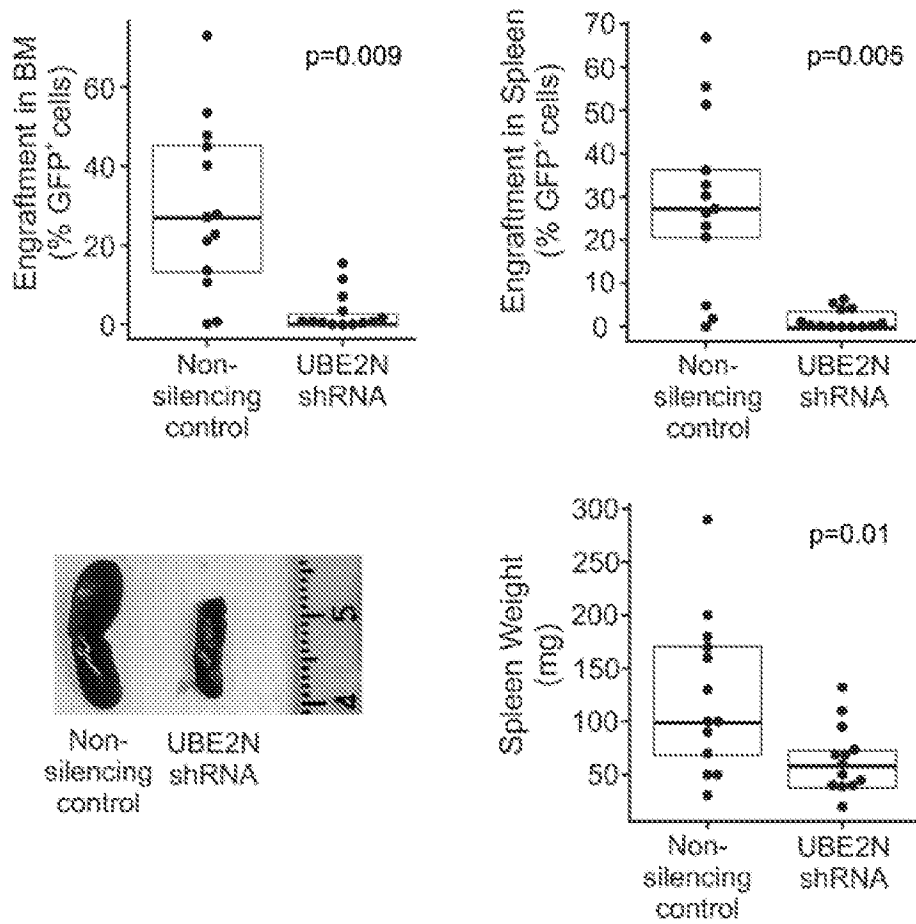


FIG. 2

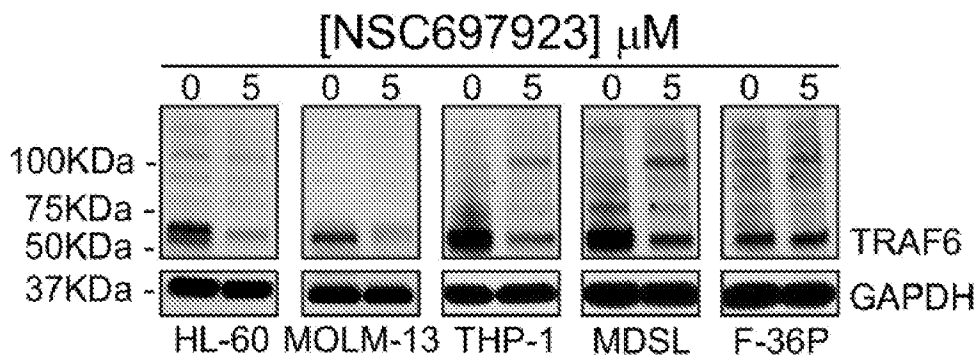


FIG. 3

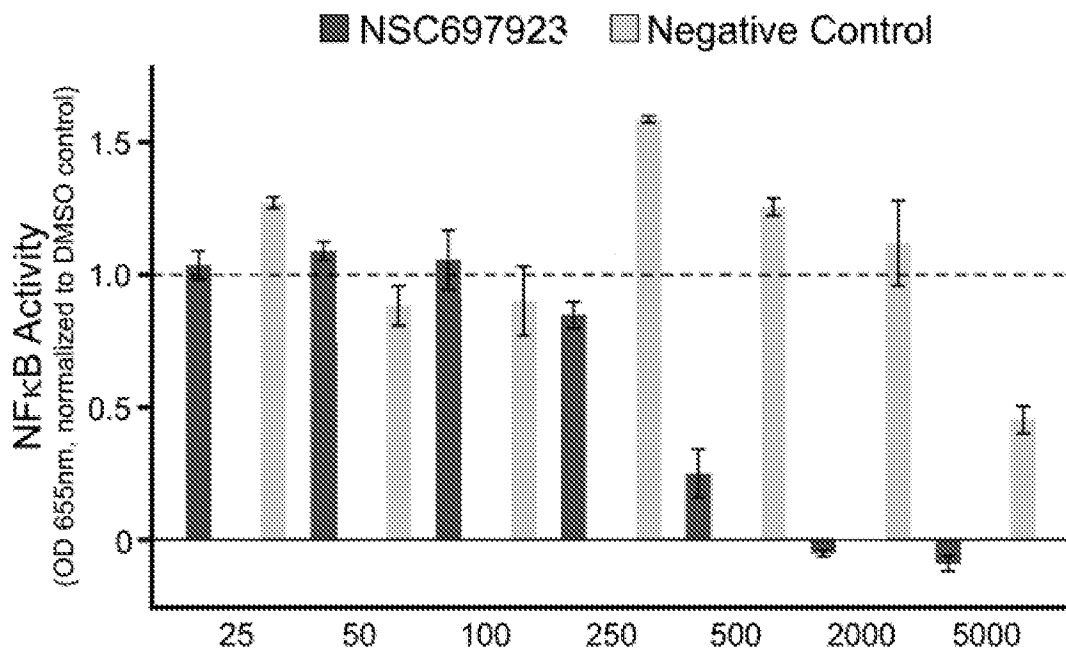
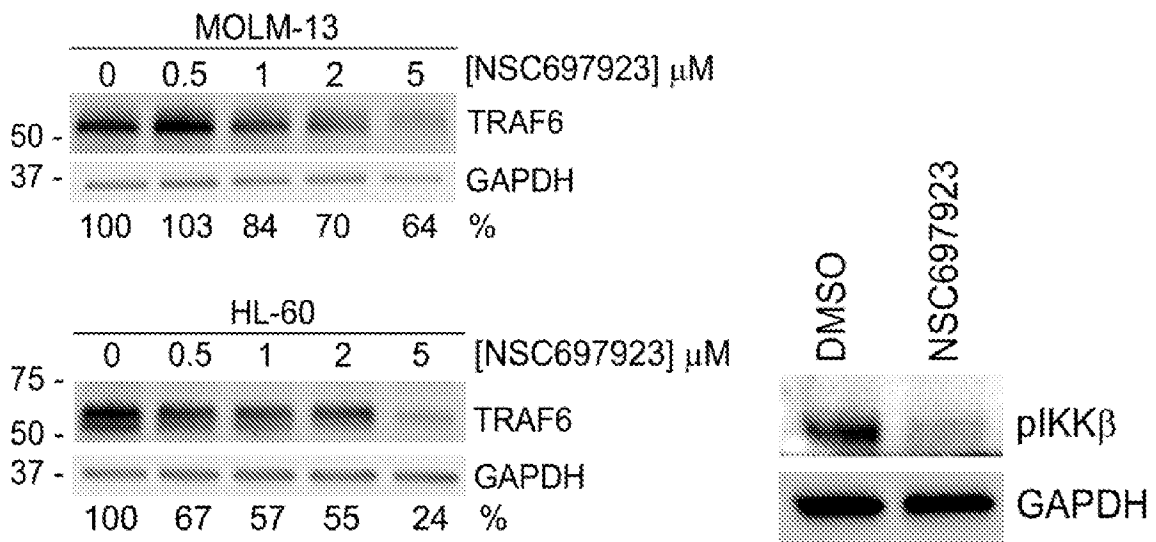


FIG. 4

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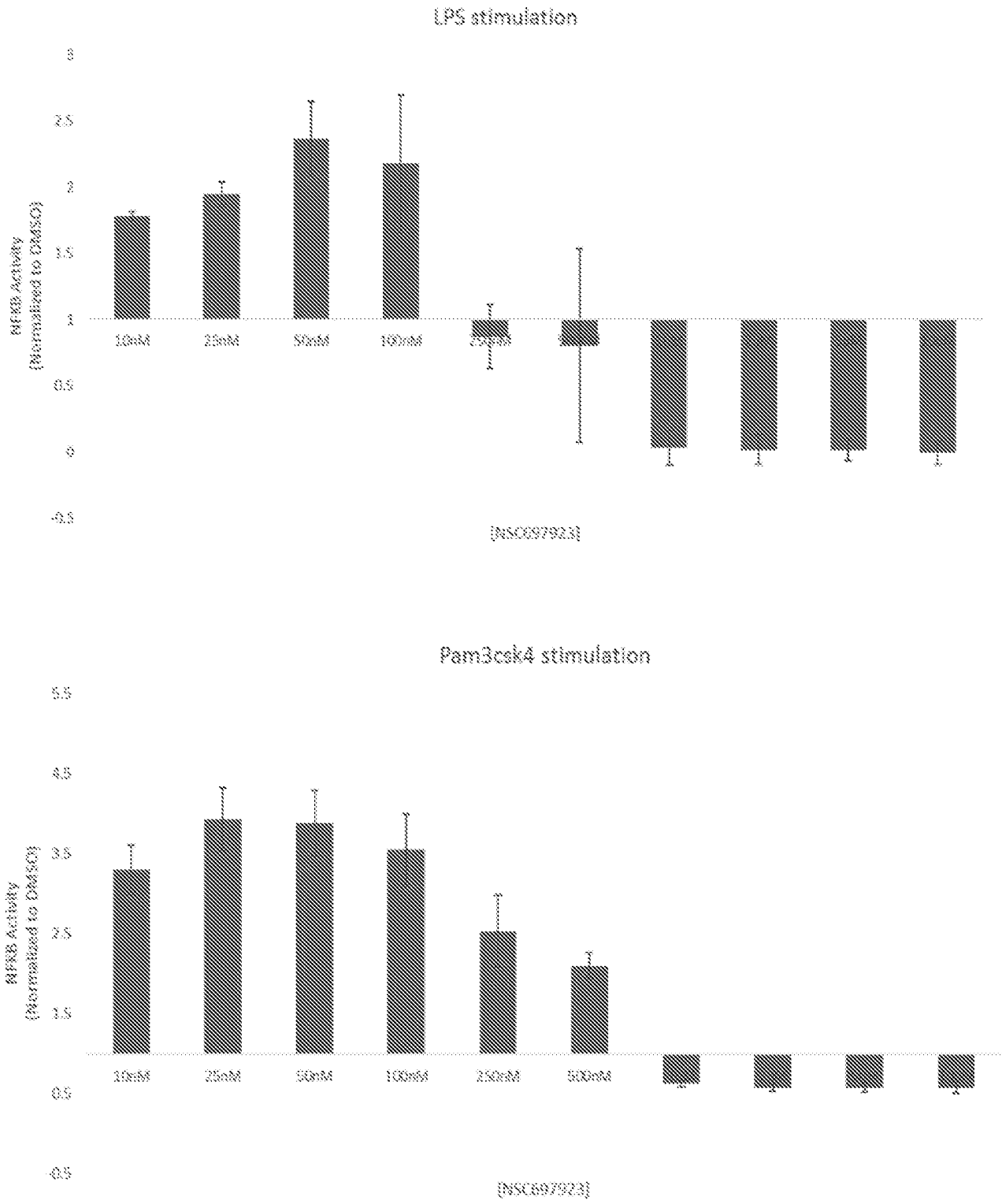


FIG. 5

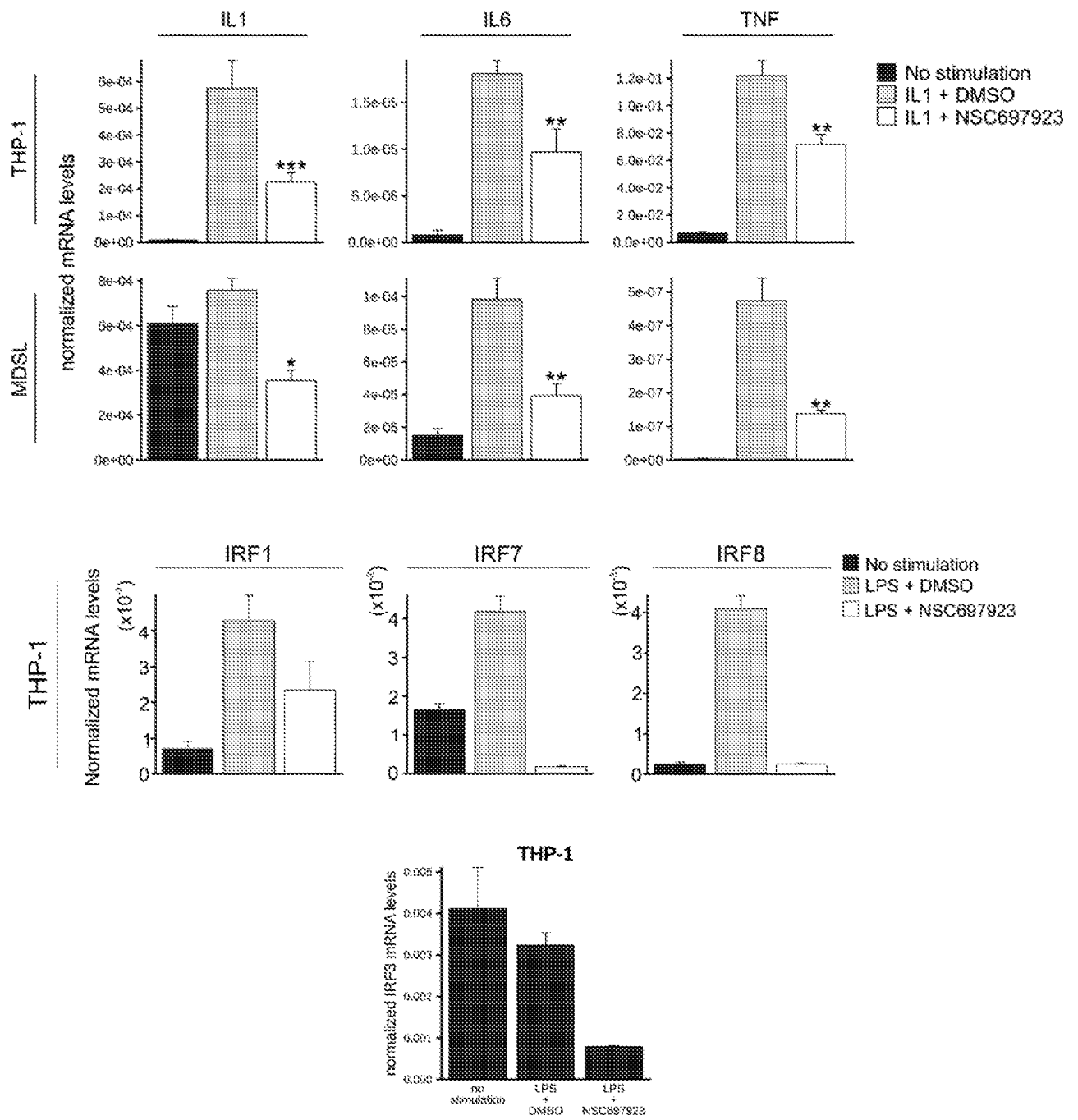


FIG. 6

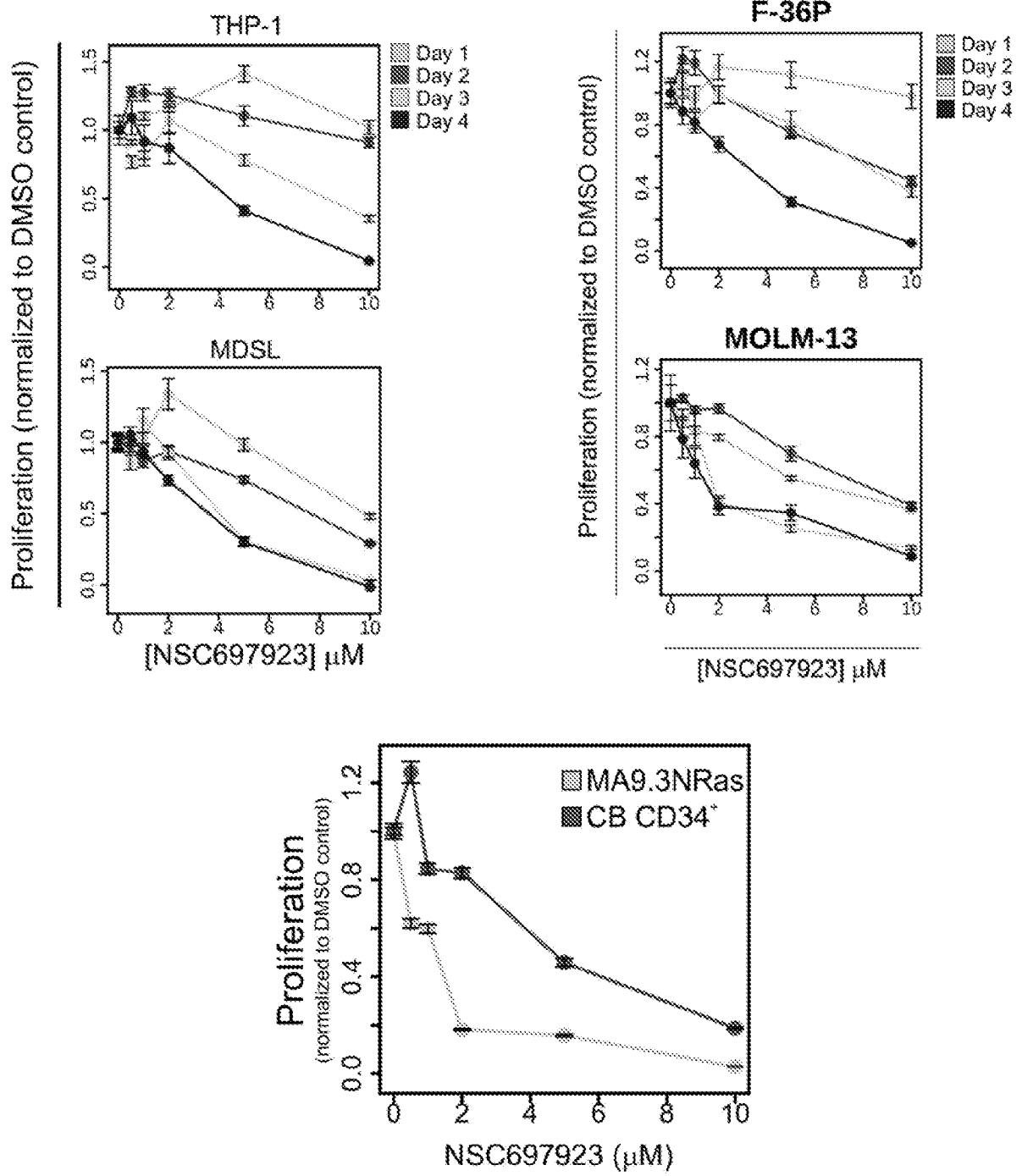


FIG. 7

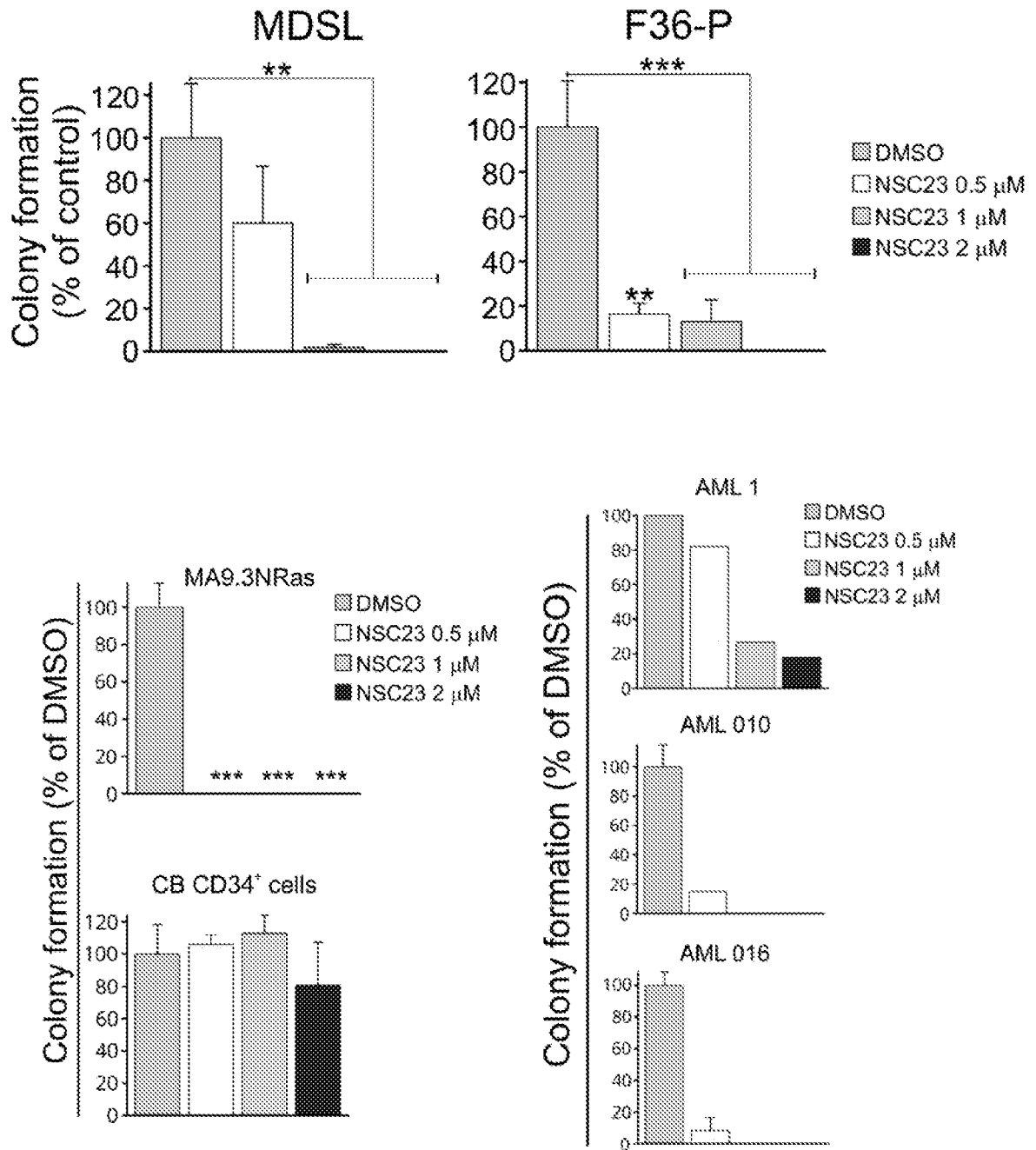


FIG. 8

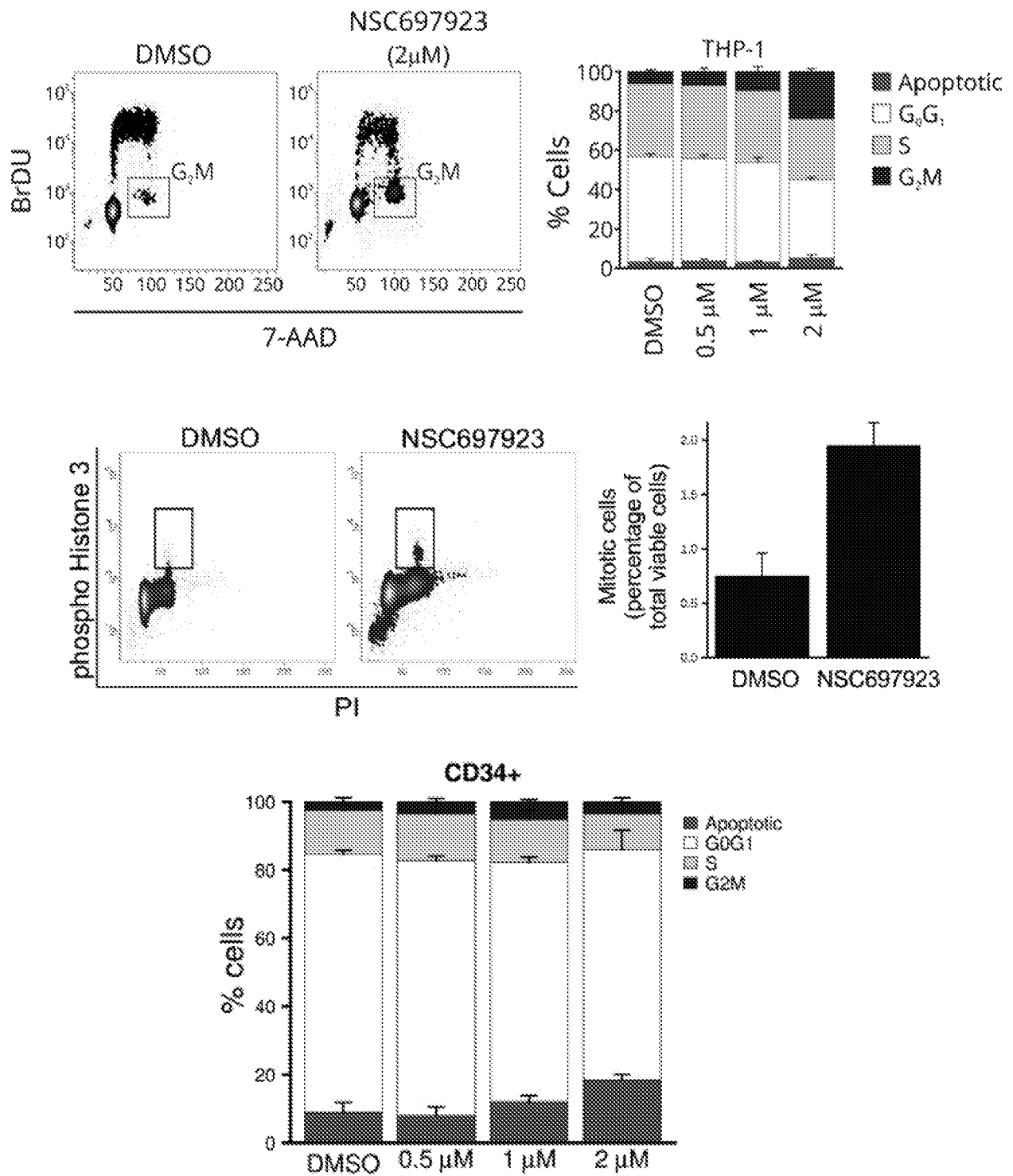


FIG. 9

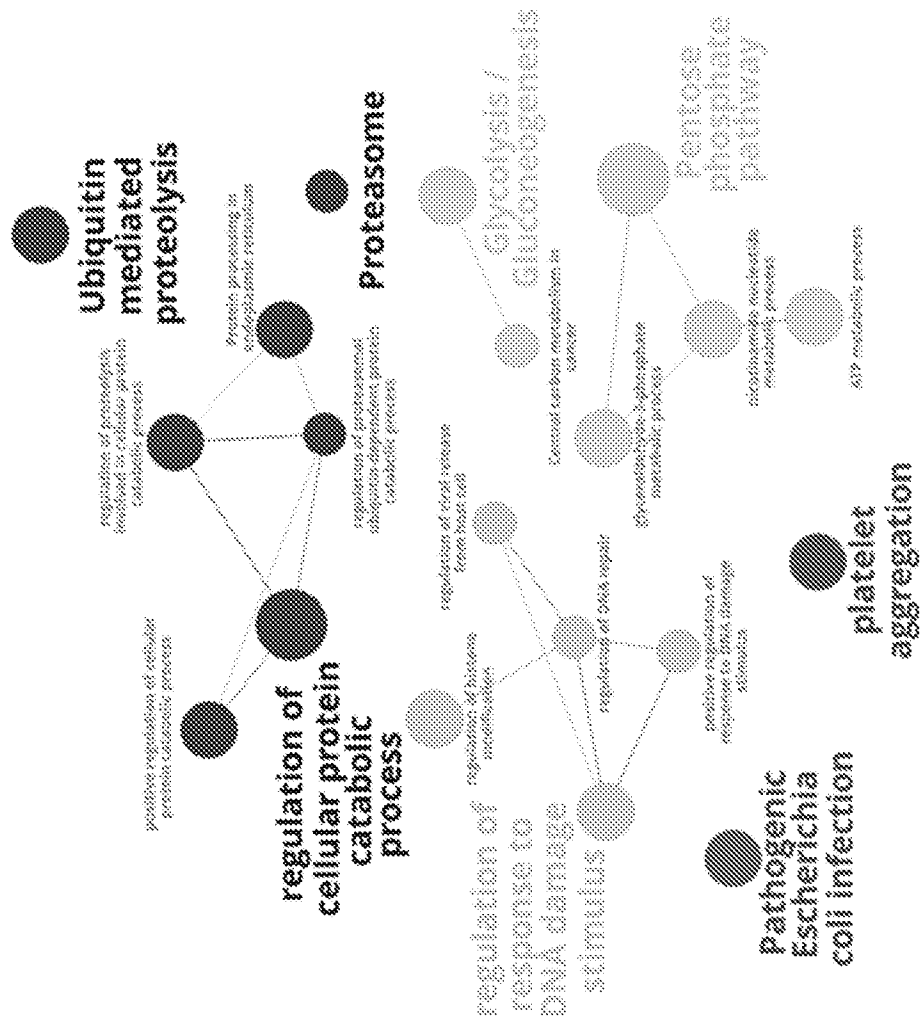
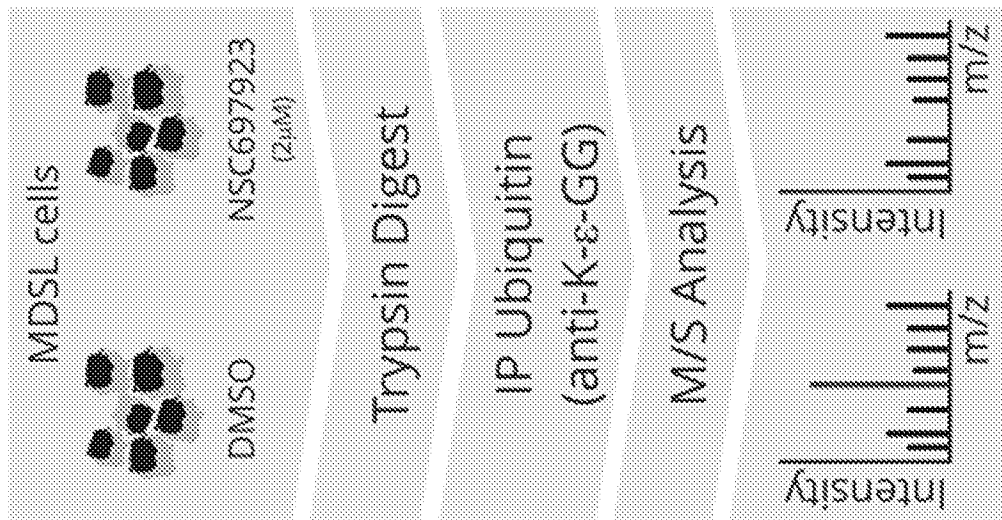


FIG. 10



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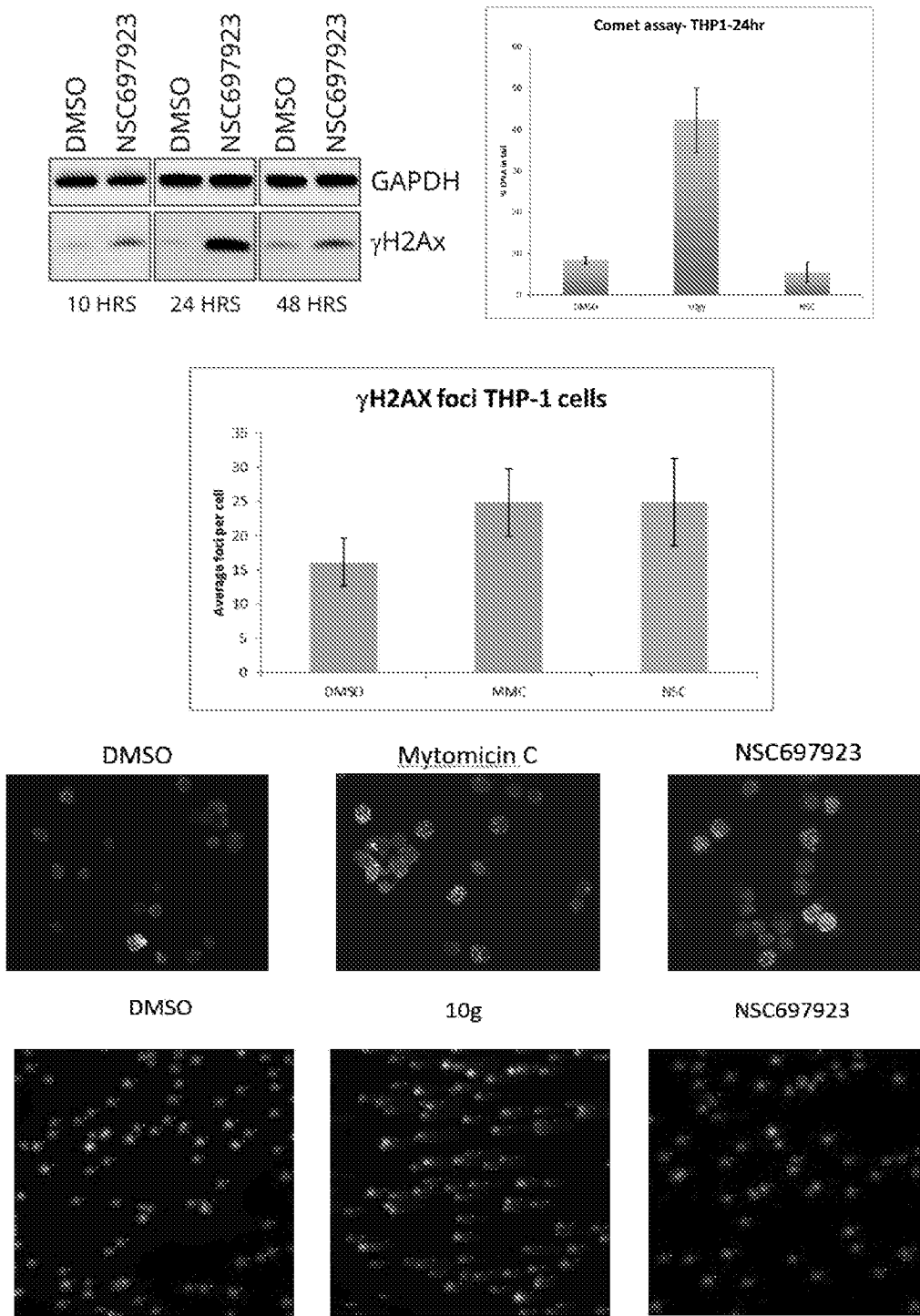


FIG. 11

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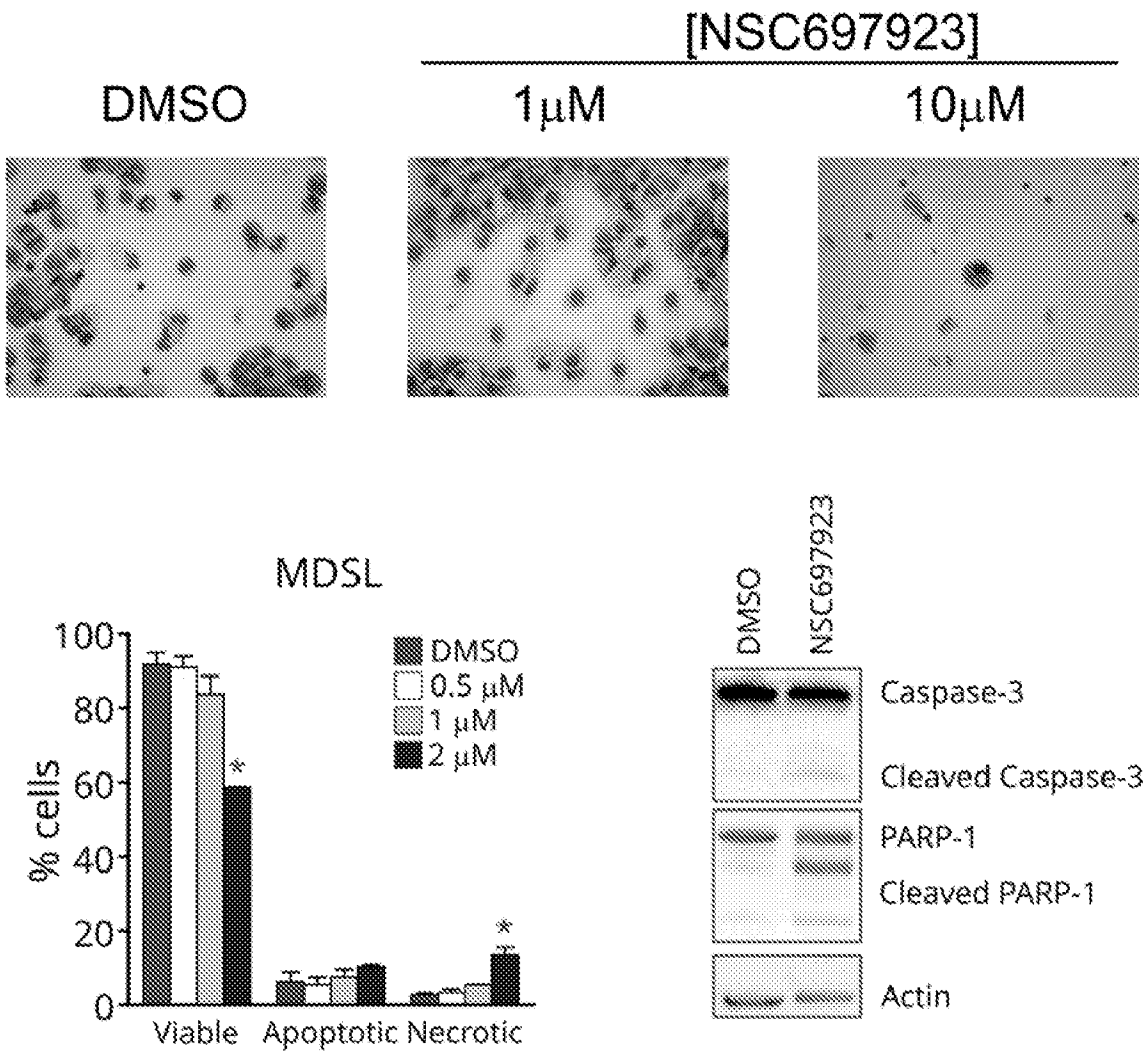


FIG. 12

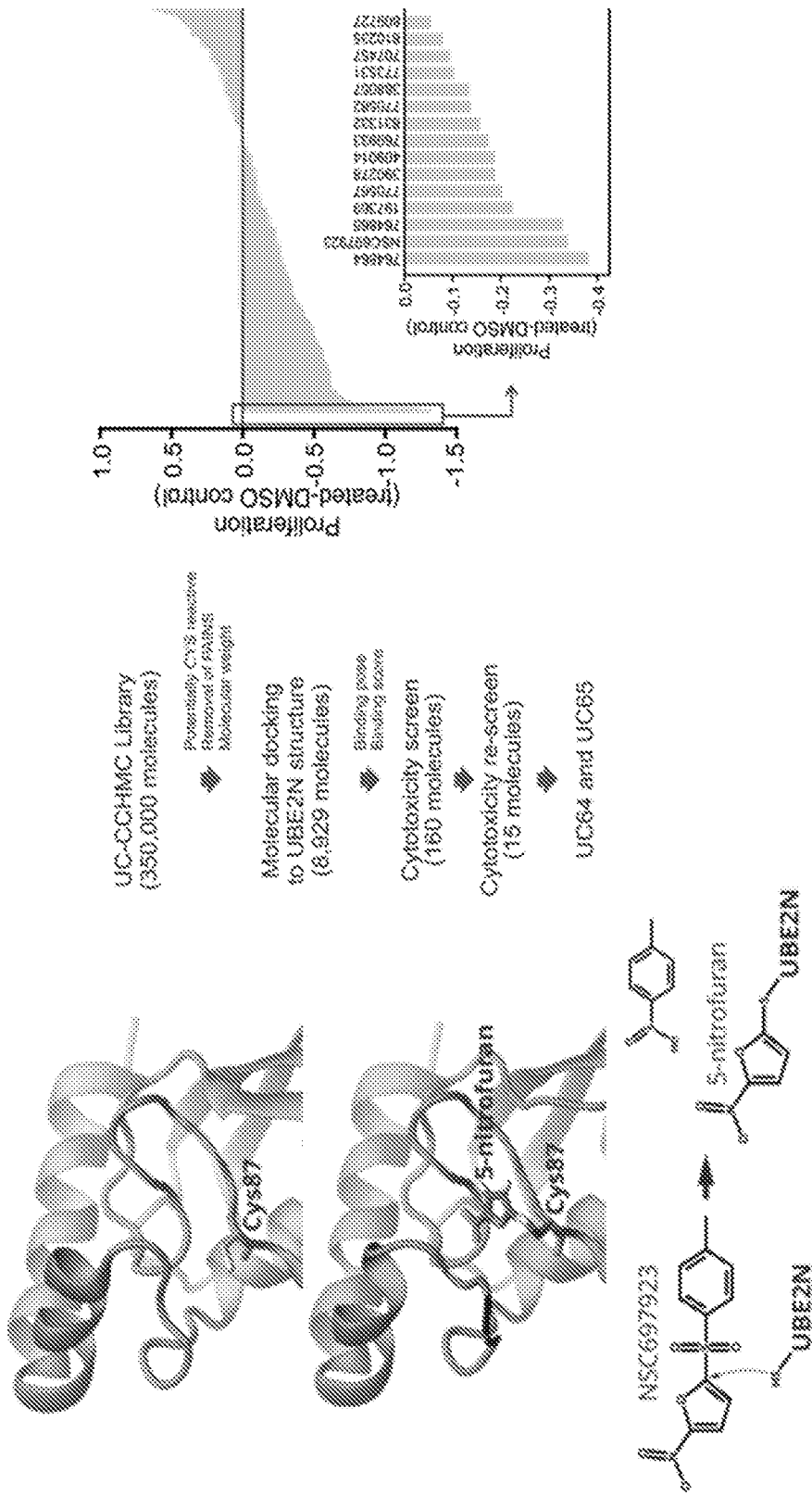


FIG. 13

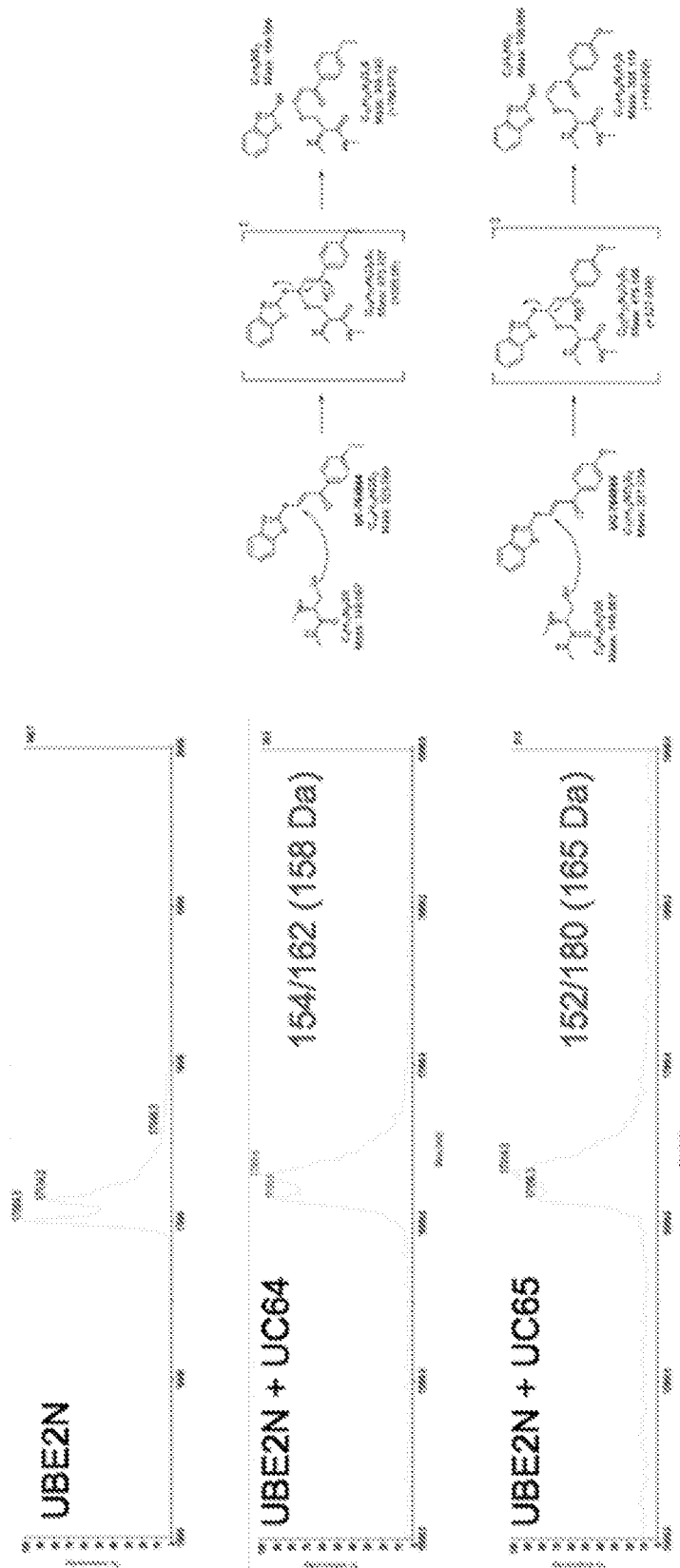


FIG. 14

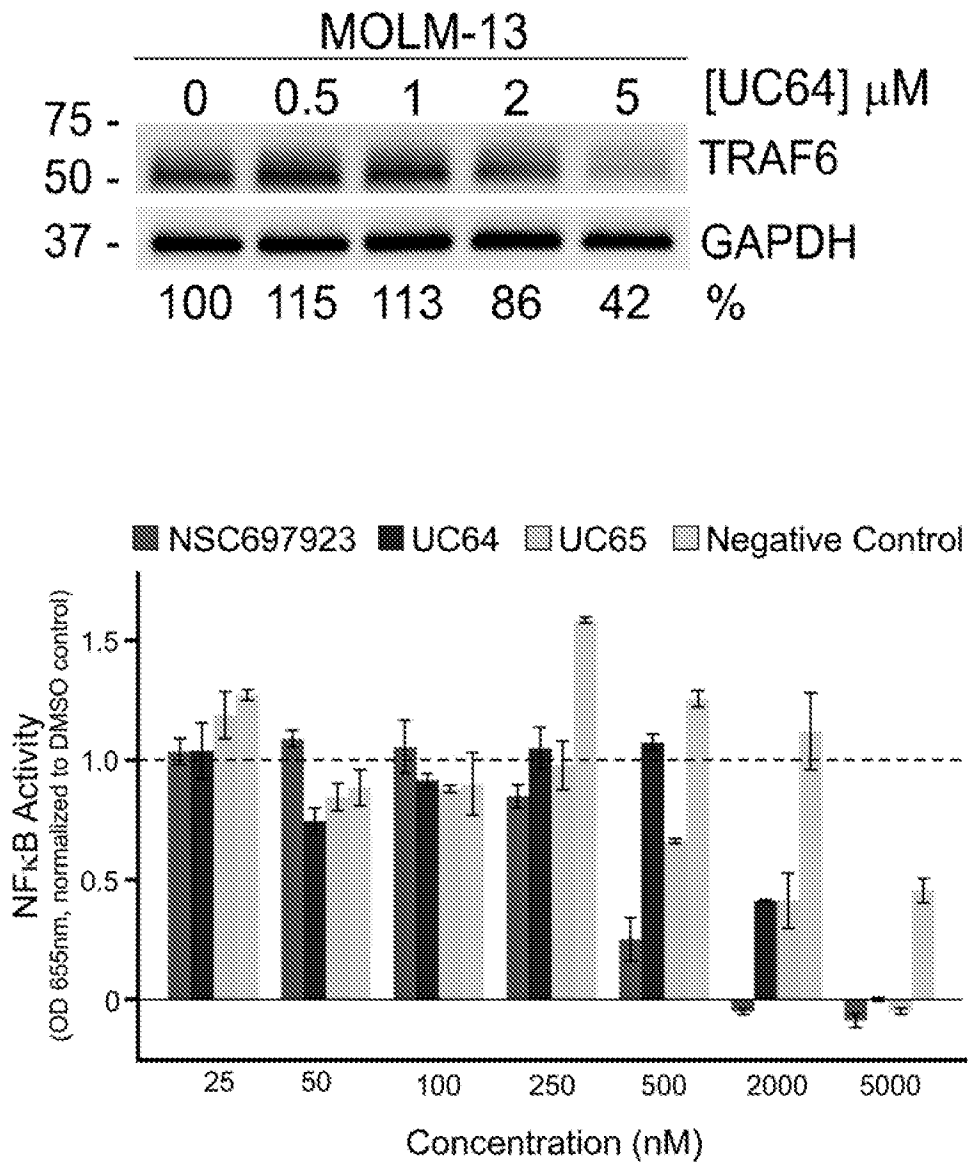
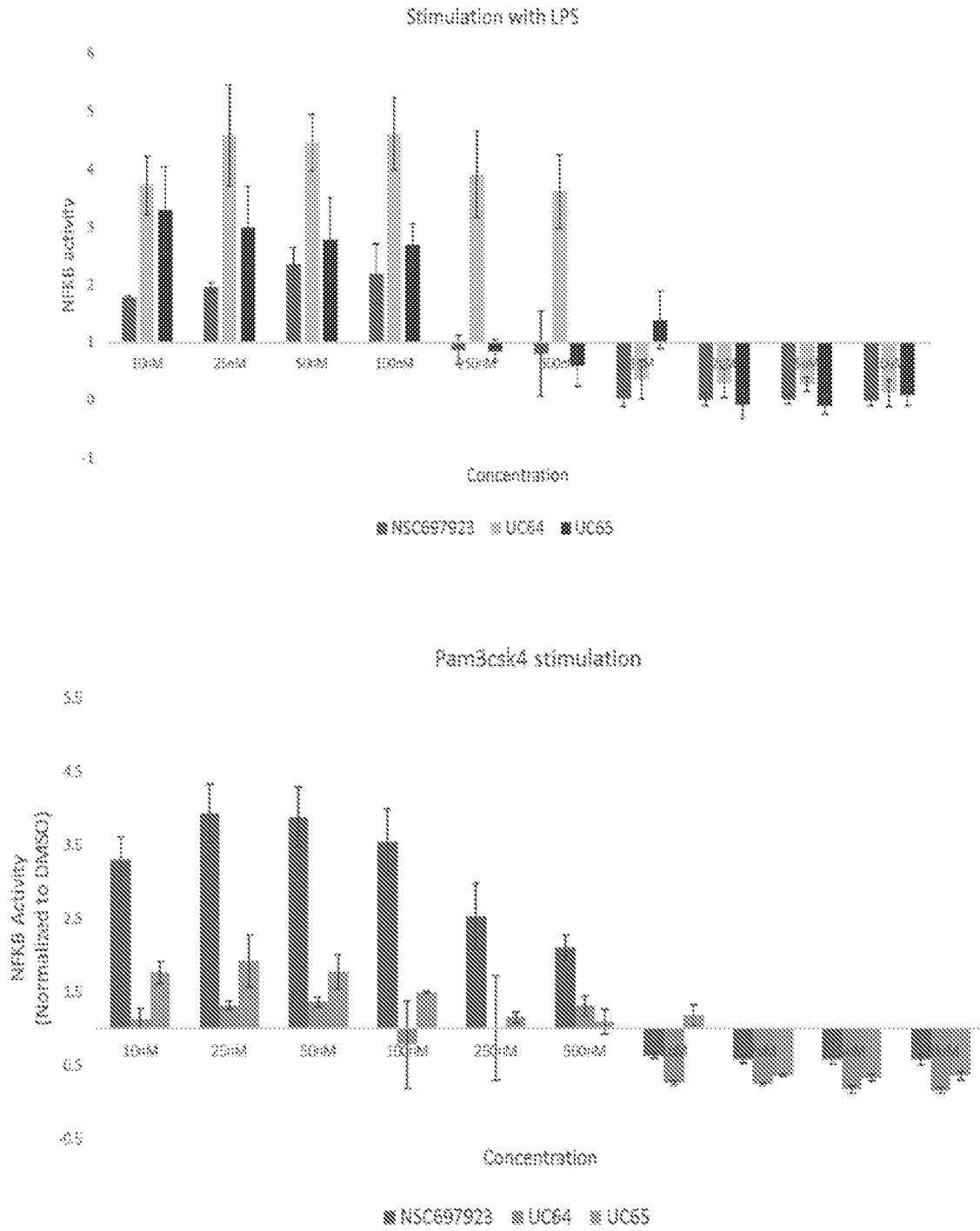


FIG. 15



**FIG. 16**

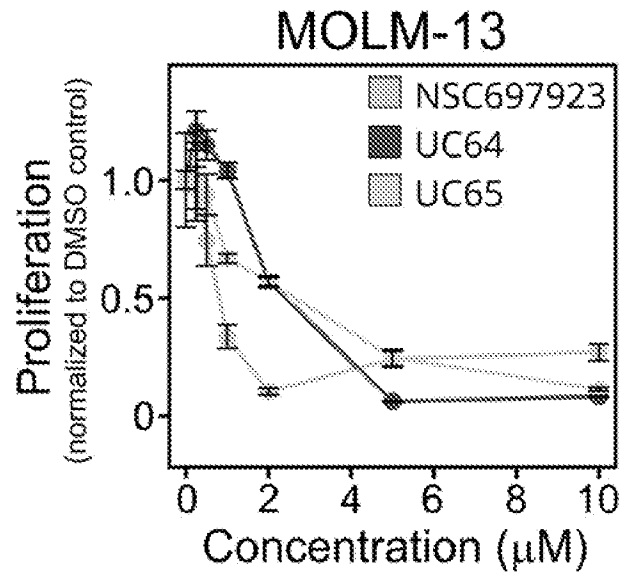


FIG. 17

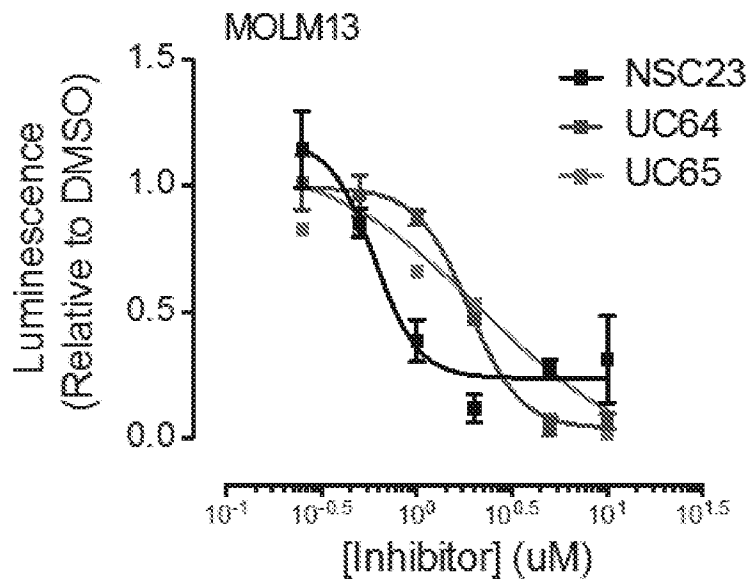


FIG. 18

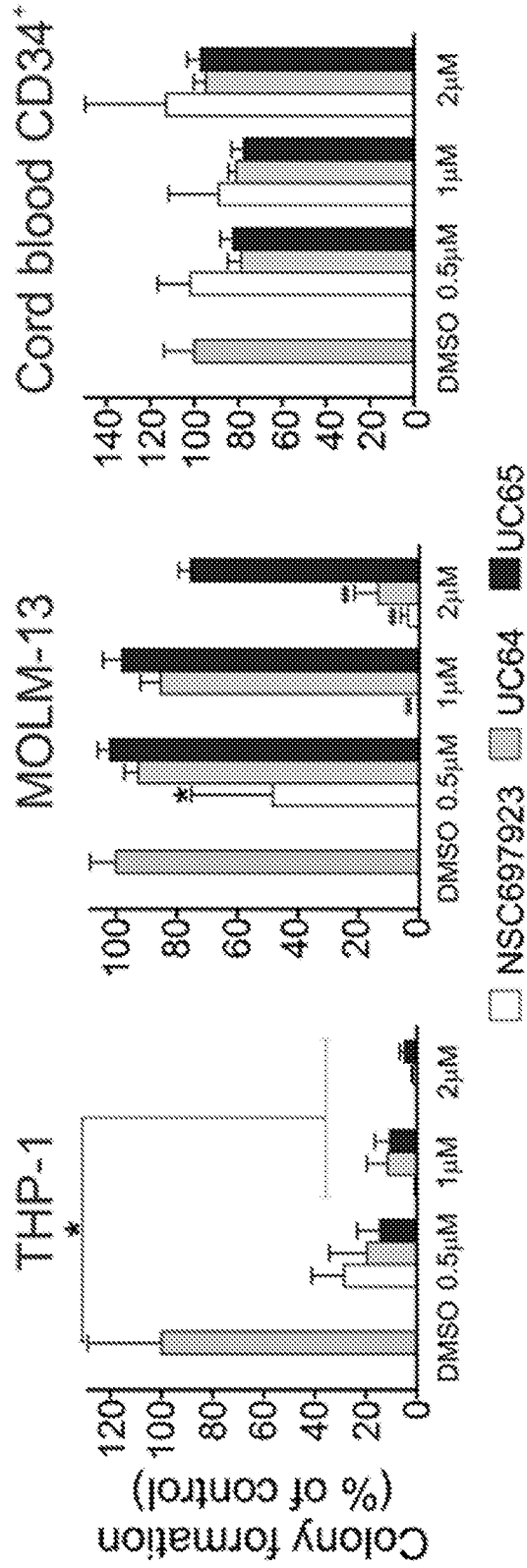


FIG. 19



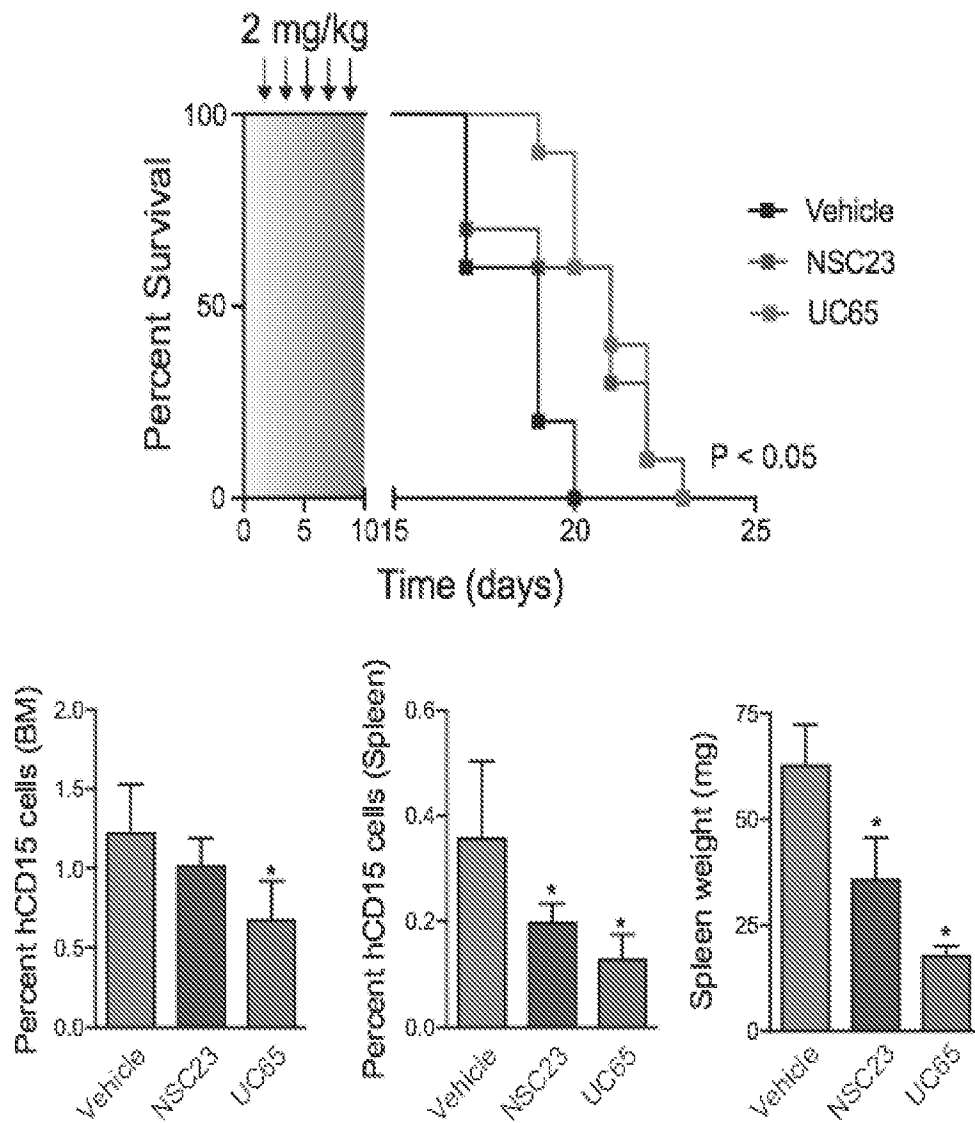


FIG. 20

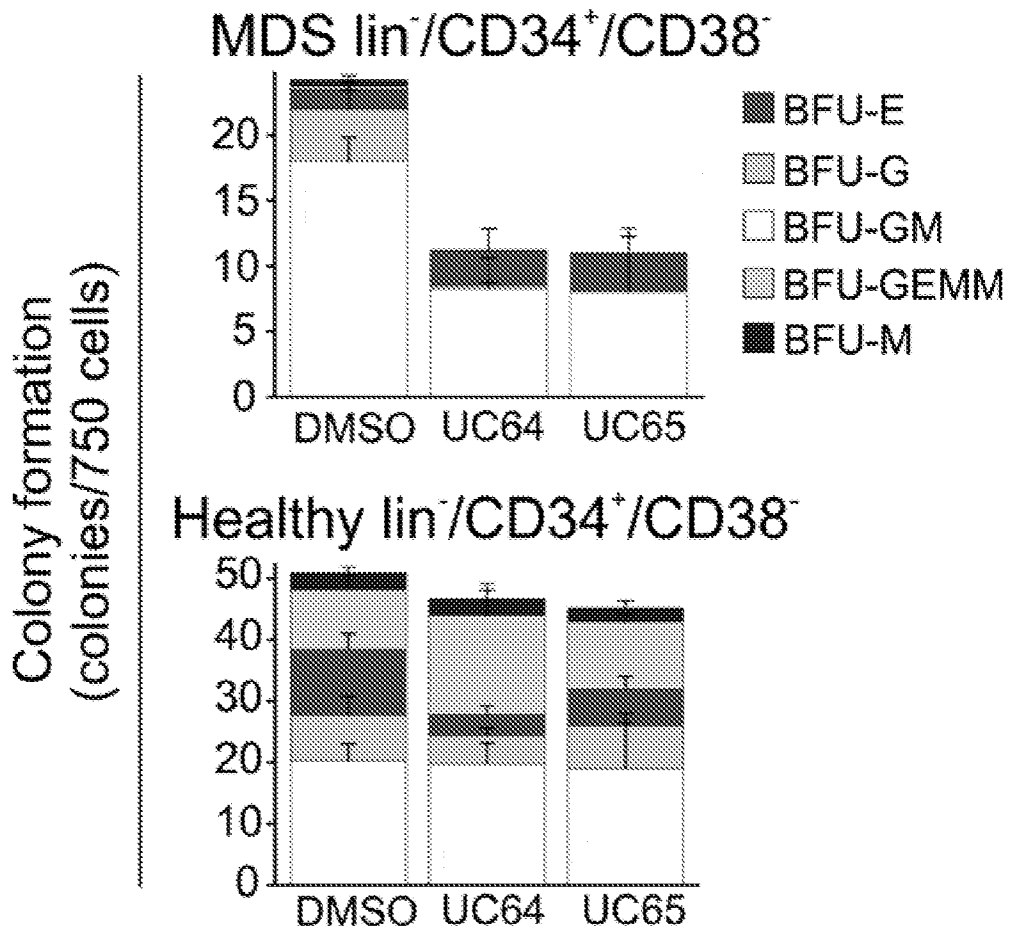
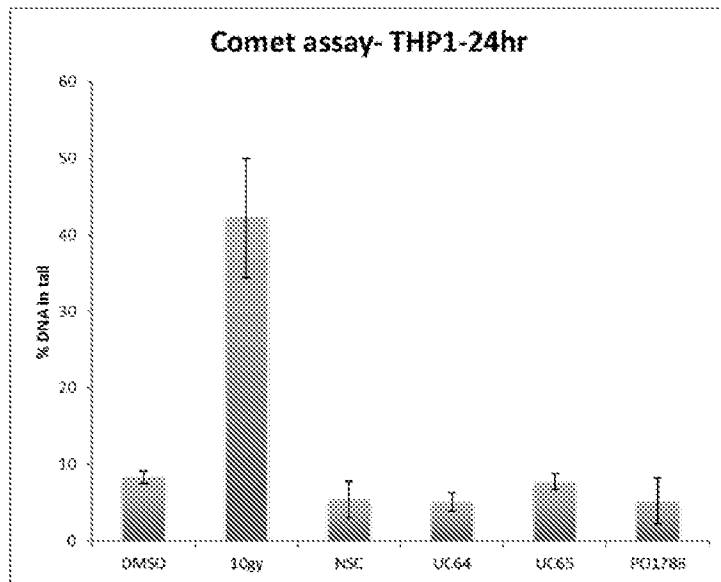
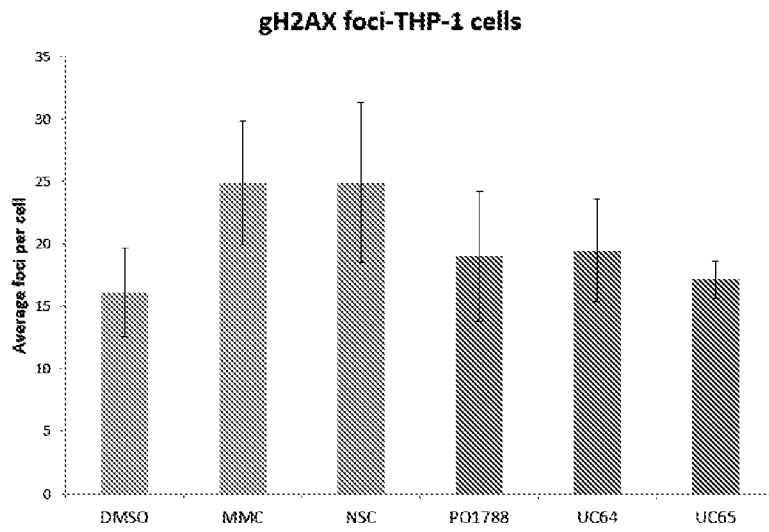
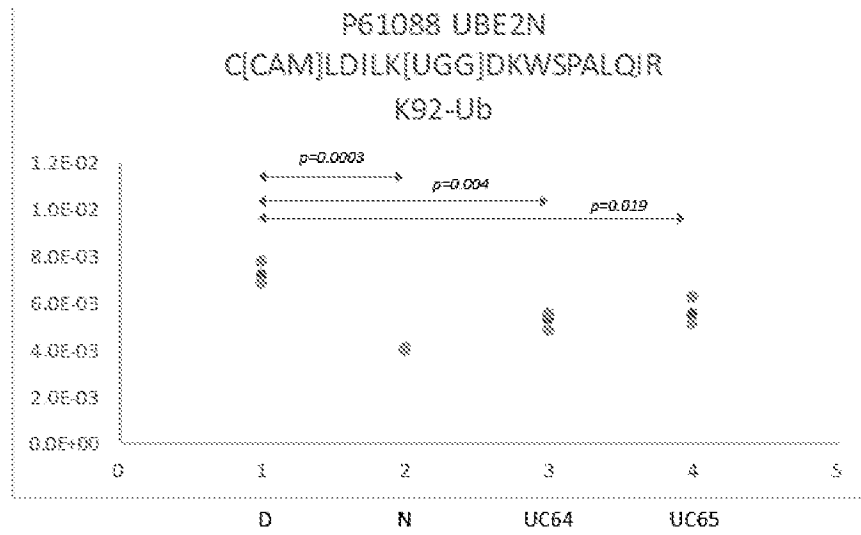


FIG. 21



**FIG. 22**

**UBE2N**  
DDB1  
HTRA2  
RL30  
ATX3  
UBC12  
TM205  
HNRPD  
PPIA  
HMOX1



**FIG. 23**

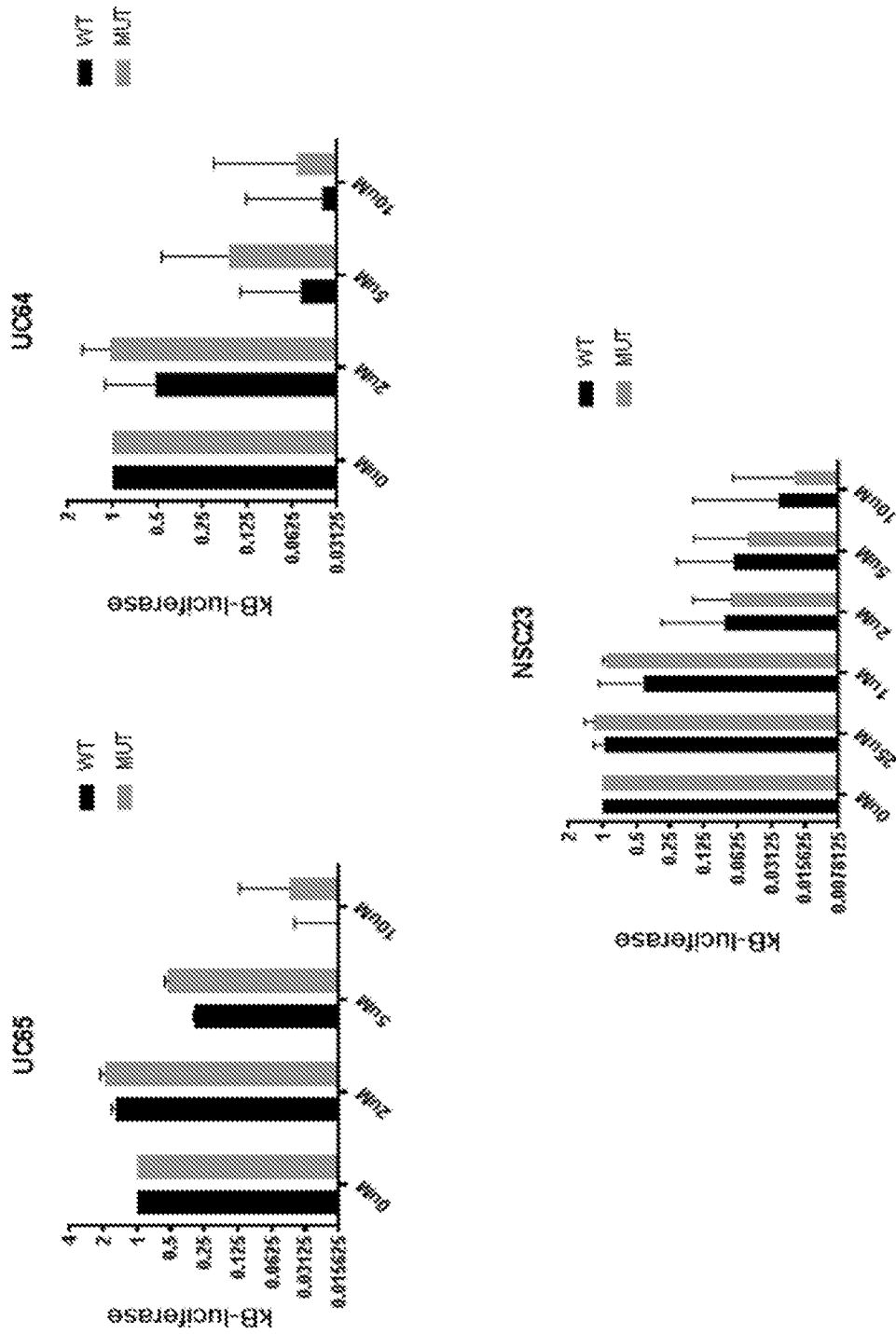


FIG. 24

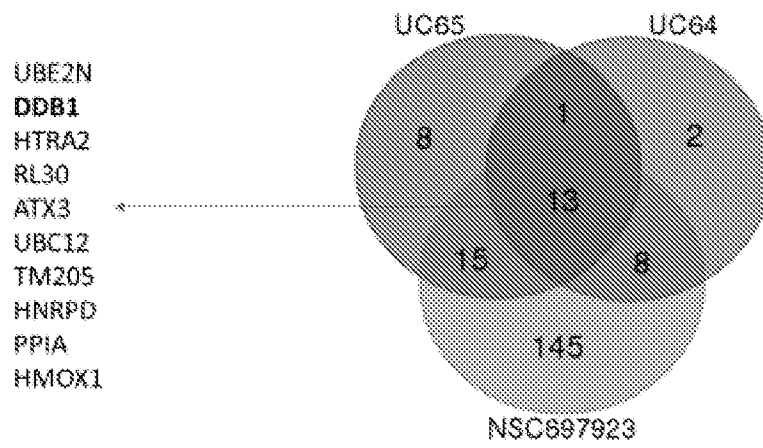


FIG. 25

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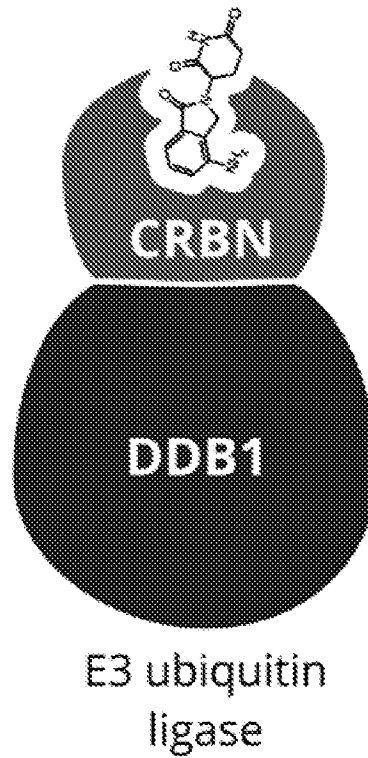


FIG. 26

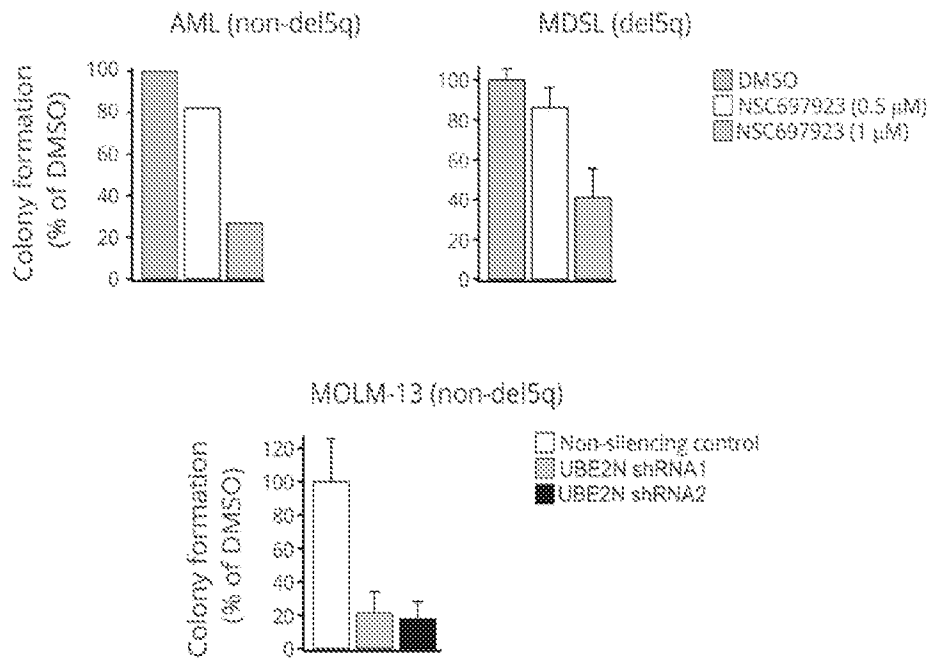


FIG. 27

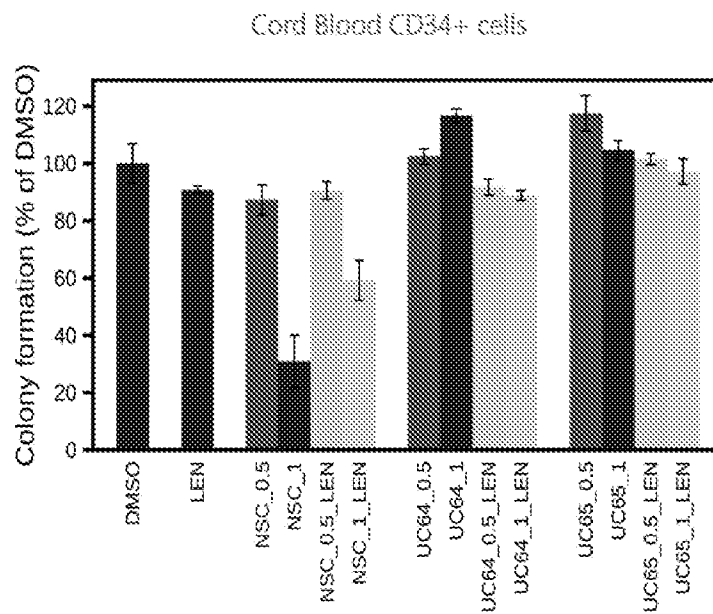


FIG. 28

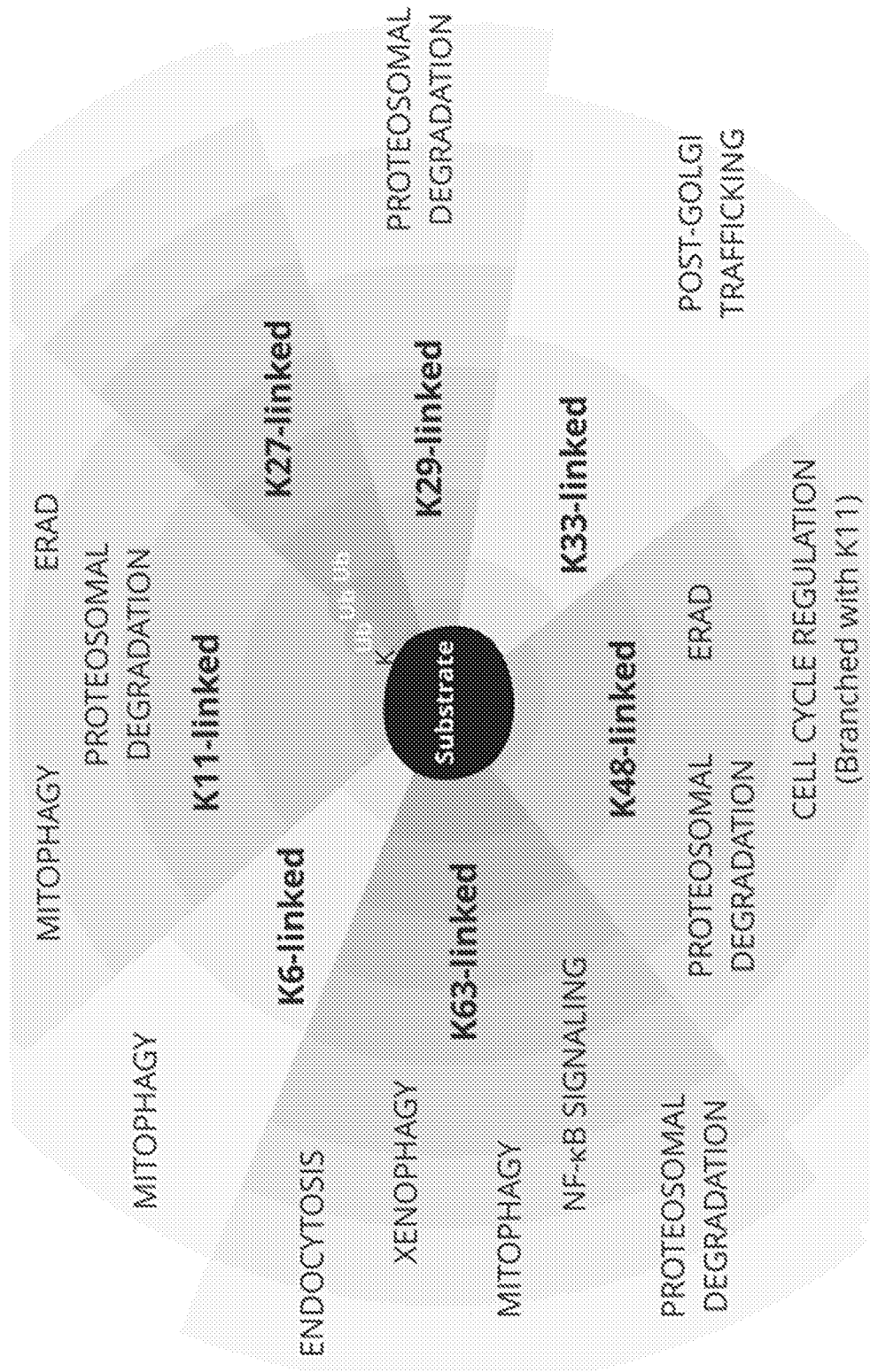


FIG. 29



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/58435

**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.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
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:
  
3.  Claims Nos.: 4; 6-17  
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 additional fees, this Authority did not invite payment of 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.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/58435

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC(8) - C07D 417/04; A61P 35/00 ; C07D 417/04 (2017.01)  
 CPC - C07D 417/04; A61K 9/5078, A61K 31/4439

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)

See Search History Document

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

See Search History Document

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

See Search History Document

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PUBCHEM 5375132 deposited on 27 March 2005 (27.03.2005) pp 1-14. pg 4	1-3; 5
Y	US 2006/0084687 A1 (BOYCE et.al.) 20 April 2006 (20.04.2006) para [0107];[0231]; pg 7, Table 1	1-3; 5
A	US 2010/0179147 A1 (CHANG et.al.) 15 July 2010 (15.07.2010) ENTIRE DOCUMENT	1-3; 5
A	US 6,900,235 B1 (AGYIN et.al.) 31 May 2005 (31.05.2005) ENTIRE DOCUMENT	1-3; 5
A	BUCKLEY et.al. 'IRAK-4 inhibitors. Part 1: A series of amides in Bioorganic and Medicinal Letter', Bioorganic & Medicinal Chemistry Letters 18 (2008) 321173214	1-3; 5

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

"&" document member of the same patent family

Date of the actual completion of the international search

14 DECEMBER 2017

Date of mailing of the international search report

03 JAN 2018

Name and mailing address of the ISA/US

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