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(54) Title: AURANOFIN AND AURANOFIN ANALOGS USEFUL TO TREAT PROLIFERATIVE DISEASE AND DISORDERS

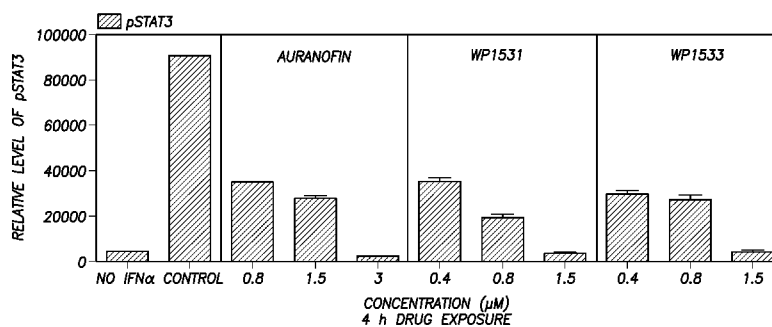


FIG. 11

(57) Abstract: Auranofin analogs and pharmaceutical compositions which inhibit p-STAT3 are provided together methods of synthesizing and methods of using the compounds. Also provided are methods of treating p-STAT3 diseases and disorders in a patient in need thereof by administering a therapeutically effective amount of one or more of these compounds, alone or in combination with another drug therapy. The compounds and pharmaceutical compositions disclosed are useful to treat proliferative diseases and disorders including, but not limited to, cancer.

**AURANOFIN AND AURANOFIN ANALOGS
USEFUL TO TREAT PROLIFERATIVE DISEASE AND DISORDERS**

FIELD OF THE INVENTION

[0001] The present disclosure is directed to compounds that modulate p-STAT3, their synthesis, and their application as a pharmaceutical for the treatment of disease.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] This application claims priority to U.S. Pat. App. Ser. No. 61/475,600 filed April 14, 2011, incorporated herein by reference in its entirety.

**STATEMENT REGARDING FEDERALLY
SPONSORED RESEARCH OR DEVELOPMENT**

[0003] None.

THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT

[0004] None.

REFERENCE TO SEQUENCE LISTING

[0005] None.

BACKGROUND OF THE INVENTION

[0006] Persistently activated STAT3 plays a central role in cellular transformation. It induces target genes which promote tumor cell proliferation, survival and invasion, regulates the communication between tumor cells and normal cells and thus contributes to the evasion of tumors.

[0007] STAT3 has been shown to be constitutively activated in cancer including, but not limited to, cancers of the brain, head, neck, breast, prostate, lung, ovary, pancreas, leukemia, multiple myeloma, and lymphoma. *See e.g.*, Song, J.I., et al., *STAT Signaling in Head and Neck Cancer, Oncogene*, 19, 2489-2495 (2000); Garcia, R., et al., *Constitutive Activation of STAT3 in Fibroblasts Transformed By Diverse Oncoproteins and in Breast Carcinoma Cells*, *Cell Growth* Duff., 812, 1267-76 (1997); Schaefer, L.K., et al., *Constitutive Activation of STAT3 in Brain*

Tumors: Localization to Tumor Endothelial Cells and Activation by the Endothelial Tyrosine Kinase Receptor (VEGFR-2), *Oncogene*, 21, 2058-2065 (2002); Dhir, R., et al., *STAT3 Activation in Prostatic Carcinomas*, *Prostate*, 51, 241-246 (2002); Seki Y.; et al., *STAT3 and MAPK in Human Lung Cancer Tissues and Suppression Of Oncogenic Growth by JAB and Dominant Negative STAT3*, *Int. J. Oncology*, 24, 931-934 (2004); Huang, M., et al., *Constitutive Activation of STAT3 Oncogene Product in Human Ovarian Carcinoma Cells*, *Gynecol. Oncol.*, 79, 67-73 (2000); Scholz, A., et al., *Activated Signal Transducer and Activator of Transcription 3 (STAT3) Supports the Malignant Phenotype of Human Pancreatic Cancer*, *Gastroenterology*, 125, 891-905 (2003); Benekti, M., et al., *Signal Transducer and Activator of Transcription Proteins in Leukemias*, *Blood*, 101, 2940-2954 (2003); Weber-Nordt, R.M., et al., *Constitutive Activation of STAT Proteins in Primary Lymphoid and Myeloid Leukemia Cells and in Epstein-Barr Virus (EBV)-Related Lymphoma Cell Lines*, *Blood*, 88, 809-816 (1996a); Bowman, T., et al., *STATs In Oncogenesis*, *Oncogene*, 19, 2474-2488 (2000); Yu, H.; Jove, R. *The STATs of cancer--new molecular targets come of age*. *Nat Rev Cancer* 4, 97-105, (2004).

[0008] Currently, different classes of compounds are being investigated as STAT3 modulators to treat proliferative diseases and disorders. Anti-cancer drugs under investigation include small molecular weight compounds, metal complexes, oligonucleotides, cell permeable peptides and peptidomimetics. Indeed, the medicinal use of metal-containing compounds has become increasingly of interest. For example, compounds that contain platinum has become one of the most widely used groups of anti-cancer drugs and includes drugs such as cisplatin, carboplatin and oxaliplatin. Recently, ependymoma, an aggressive form of brain cancer has been shown to partially respond to platinum compounds.

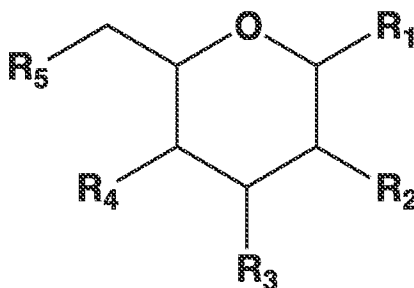
[0009] A need exists therefore to understand and develop compounds containing other metals such as gold that can treat aggressive cancers like ependymomas, and other proliferative diseases and disorders.

BRIEF SUMMARY OF THE INVENTION

[0010] Gold containing compounds and pharmaceutical compositions which inhibit p-STAT3 are provided together methods of synthesizing and methods of using the compounds. Also provided are methods of treating p-STAT3 diseases and disorders in a patient in need thereof by administering a therapeutically effective amount of one or more of these compounds,

alone or in combination with another drug therapy. The compounds and pharmaceutical compositions disclosed are useful to treat proliferative diseases and disorders including, but not limited to, cancer of the brain, head, neck, breast, prostate, lung, ovary, pancreas, leukemia, multiple myeloma, lymphoma and others.

[0011] The present disclosure provides a class of compounds useful in treating p-STAT3-mediated disorders and conditions, defined by the structural Formula I:



wherein R₁, R₂, R₃, R₄, R₅ are each optionally substituted with H, OH, O-acyl, O-alkyl, NH₂, NHAc or SAuPR₆; and
R₆ is optionally substituted with a lower alkyl

[0012] Thus, in the broad aspect, the present disclosure provides for pharmaceutical compositions comprising one or more of the compounds presented herein together with a pharmaceutically acceptable carrier as well as methods of making and using the compounds and compositions, alone or in combination with another drug product.

[0013] Methods for treating a proliferative disease or disorder in a patient in need of such treatment are further provided. The compounds of Formula I possess useful STAT3 inhibiting or modulating activity and may be used in the treatment or prophylaxis of a disease or condition in which STAT3 plays an active role. Methods of treating disease comprise the step of administering to said patient a therapeutically effective amount of a compounds or compositions described herein. Also, the compounds disclosed herein are suitable for use in the manufacture of a medicament for the treatment of a diseases or condition ameliorated by the inhibition of STAT3.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0014] Figures 1A, 1B, and 1C provide our data that shows auranofin inhibits 58-10F ependymoma cell line growth and blocks expression of pSTAT3 in ependymoma 58-10F.

[0015] Figures 2A, 2B, 2C, and 2D provide our data that shows auranofin inhibits BT-58 ependymoma cell line growth and blocks expression of constitutively activated STAT3.

[0016] Figures 3A, B and C provide our data that shows auranofin inhibits BT-58 ependymoma cell line growth and blocks IL-6 stimulated p-STAT3.

[0017] Figure 4 teaches that ependymoma tumor cell lines (58-10F, BT-58) are more sensitive to auranofin than glioma tumor cells (U87).

[0018] Figure 5 shows that ependymoma tumor cell lines (58-10F, BT-58) were more sensitive to the compound of Example 3 than glioma tumor cells (U87).

[0019] Figure 6 shows that ependymoma tumor cell lines (58-10F, BT-58) are more sensitive to the compound of Example 6 than glioma tumor cells (U87).

[0020] Figure 7 shows that auranofin inhibits HH CTCL cell growth and blocks expression of p-STAT3.

[0021] Figures 8A, 8B and 8C provide the survival of melanoma (WM35) cells after 24 hours, 48 hours and 72 hours of exposure to auranofin at various concentrations: 1, 0.5, 1, 2, 3, 4, and 10 μ M. Figure 8B shows the relative level of pSTAT3 after 4 hours of drug exposure in different concentrations. Figure 8C is a Western blot showing the concentration of pSTAT3, tSTAT3 and β Actin.

[0022] Figure 9 shows the effects of 1 μ M auranofin in combination with 10 IU/ml IFN α or 20 ng/ml IL-6 on the proliferation of CTCL HH in normoxia or hypoxia condition for 72 hours.

[0023] Figure 10 shows the MTS of treating CTL HH, Hut78, and MJ WP1527 (0., 0.5, 1, 2, 3, 4, and 6 μ M) for 72 hours.

[0024] Figure 11 shows the effects of Auranofin, WP1531, WP1533 on pSTAT3 expression in BT-58 for 4 h with 5 IU/ml of IFN α stimulation for 30 min in 10% serum.

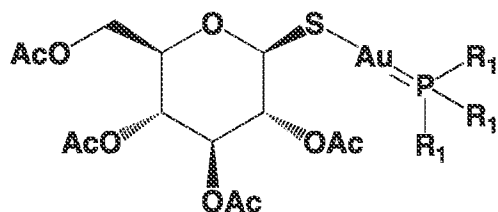
[0025] Figure 12 shows the effects of Auranofin, WP1531, and WP1533 on the proliferation of BT-58 and 58-10F for 72 h (MTS).

[0026] Figure 13 shows the effects of WP1547 on the proliferation of BT-58, 58-10F, U87, and WM35 for 72 hour (MTS).

[0027] Figure 14 shows the effects of WP1546 on the proliferation of BT-58, 58-10F, U87, and WM35 for 72h (MTS)

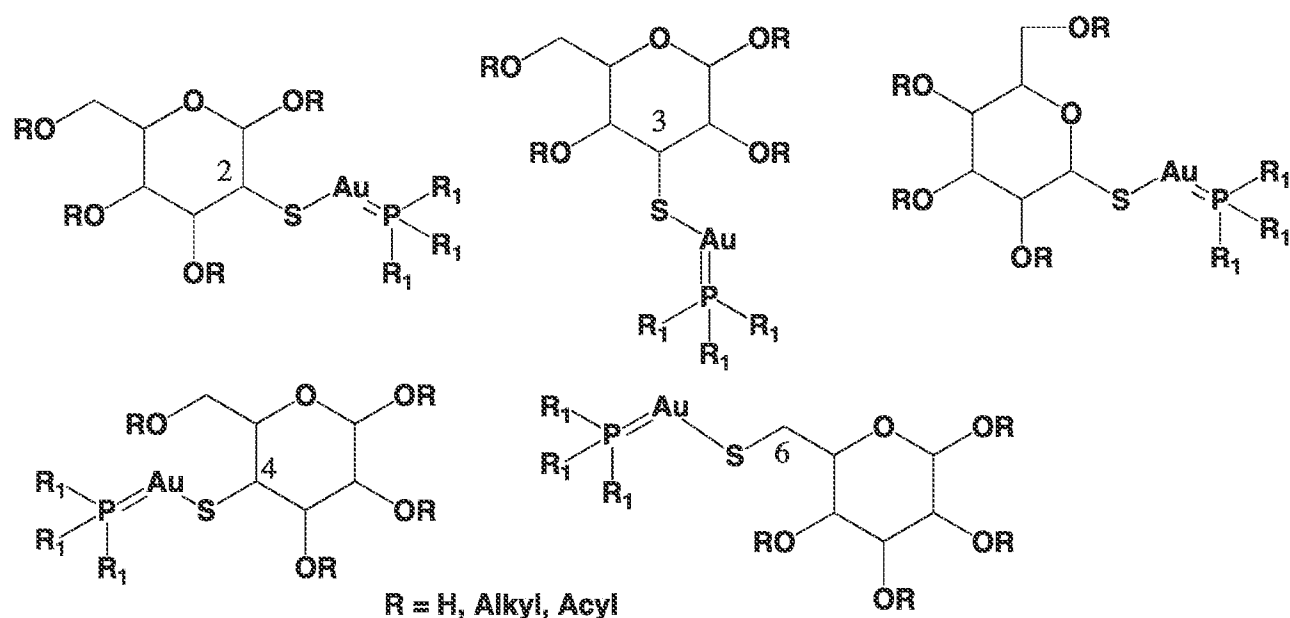
DETAILED DESCRIPTION OF THE INVENTION

[0028] Gold and its compounds have been used as medicines since ancient times. The application of gold compounds to medicine is often called "chrysotherapy" and "aurotherapy." Some of the gold compounds are currently approved for therapeutic use and are known for their ability to reduce inflammation and are used in rheumatoid arthritis. Auranofin is an example of such drug. The chemical structure of auranofin is:

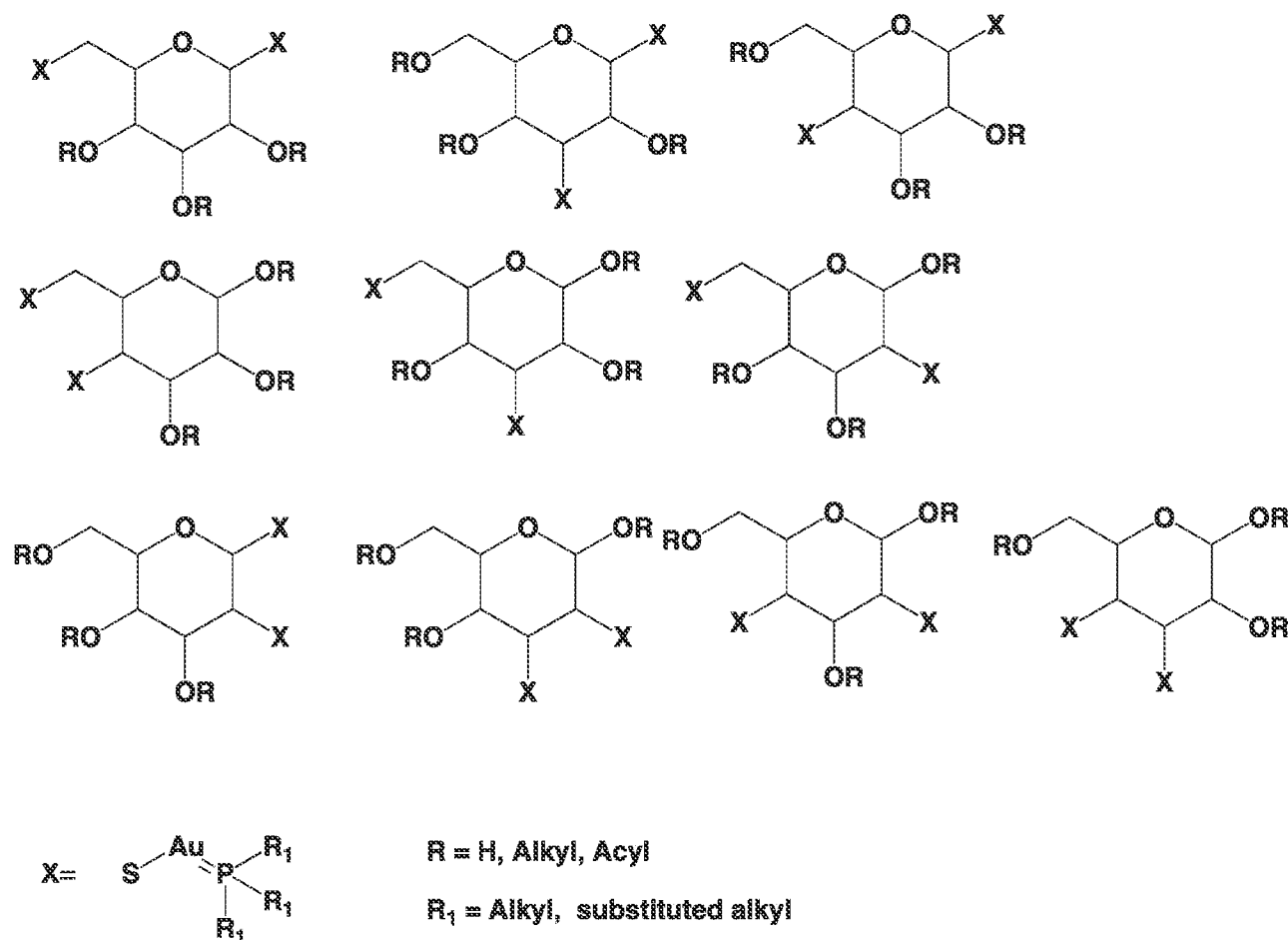


wherein Ac is acetyl or optionally substituted COCH₃ group; and R can be optionally substituted acyl (valproates and butyrates) or H.

[0029] Auranofin analogs useful in treating proliferative disease have the structural Formula I above. More particularly, certain compounds may have the following structure:



[0030] Also, certain compounds may have the following structure:



[0031] Specific novel auranofin analog compounds (also referred to herein as “auranofin analogs”) are provided in Examples 1 to 8.

[0032] The term “optionally substituted” means the antecedent group may be substituted or unsubstituted. When substituted, the substituents of an “optionally substituted” group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, carboxyl, lower alkylcarbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, nitro, thiol, lower alkylthio,

arylthio, lower alkylsulfinyl, lower alkylsulfonyl, arylsulfinyl, arylsulfonyl, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N₃, SH, SCH₃, C(O)CH₃, CO₂CH₃, CO₂H, pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Two substituents may be joined together to form a fused five-, six-, or seven-membered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (e.g., -CH₂CH₃), fully substituted (e.g., -CF₂CF₃), monosubstituted (e.g., -CH₂CH₂F) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., -CH₂CF₃). Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended. Additionally, different sets of optional substituents to a particular moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, "optionally substituted with."

[0033] The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety selected from the group consisting of hydrogen, alkyl, acyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and Rⁿ where n = (1, 2, 3, ...n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (e.g. aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence. One of skill in the art will further recognize that certain groups may be attached to a parent molecule or may occupy a position in a chain of elements from either end as written. Thus, by way of example only, an unsymmetrical group such as -C(O)N(R)- may be attached to the parent moiety at either the carbon or the nitrogen.

[0034] Proliferative disease means and includes, but is not limited to, psoriasis, skin cancer, CNS cancer including brain cancer and cancer metastatic to CNS, ovarian cancer, head cancer, neck cancer, prostate cancer, hematological malignancies including leukemia, lymphoma and myeloma, breast cancer, skin cancer including squamous cell carcinomas, basal cell cancers,

cutaneous T-cell lymphomas, primary cutaneous B cell lymphomas, Dermatofibrosarcoma protuberans, Merkel cell carcinoma, Kaposi's sarcoma, keratoacanthoma, and melanoma.

[0035] Additional proliferative diseases include for example, breast cancer; lung cancer, including non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC), gastrointestinal cancer, including esophageal, gastric, small bowel, large bowel, rectal and colon cancer, CNS melanoma, Leptomeningeal disease (LMD), cancer metastatic to CNS, sarcoma, such as those involving bone, cartilage, soft tissue, muscle, blood and lymph vessels, ovarian cancer; female cervical cancer, endometrial cancer, mesothelioma, renal cancer, uteran, bladder and urethral cancers.

[0036] Where a tumor, a carcinoma or a cancer is mentioned, metastasis in the original organ or tissue and/or in any other location is implied alternatively or in addition, whatever the location of the tumor.

[0037] In another aspect of any of these methods, the proliferative disease may be refractory to one or more existing cancer treatments. By "refractory" in this context is meant that the proliferative disease does not respond to treatment. The proliferative disease may be resistant at the beginning of treatment or it may become resistant during treatment.

[0038] The compounds described herein may be useful for the treatment of a wide variety of disorders or conditions where inhibition or modulation of the STAT3 pathway is needed. The compounds decrease and can therapeutically treat proliferative disease conditions. Uses for these compounds include the compounds as agents to: decrease STAT3 activity; STAT3 phosphorylation; and the expression of proteins controlled by transcriptional activation by activated STAT3. Along these lines, the compounds can be specifically used as agents to decrease VEGF, MMP9, MMP2, survivin, c-Myc, MMP-1, MEK-5, c-FOS, COX-2, Bcl-xl, MMP-10, HSP-27 and Jmjdla.

[0039] As described throughout this disclosure, disorders or conditions that can be prevented or treated by compounds and methods described herein include the prevention or treatment of cancer, such as cutaneous T-cell leukemia, head and neck tumors, pancreatic cancer, bladder cancer, high grade gliomas, ependymomas, brain metastasis, melanoma, skin cancer, lung cancer, breast cancer, prostate cancer, colon cancer, leukemia, myelodysplastic syndrome (a pre-leukemia condition), and multiple myeloma. In general, metastasis of any cancer can be

prevented or treated with the compounds and methods described herein. The compounds can also be used to prevent or treat proliferative angiogenic conditions including telangiectasia, venous angiomas, hemangioblastoma.

[0040] Hence, methods of preventing or treating proliferative diseases or disorders of the skin, including topical dermatitis, psoriasis, and rosacea, comprise the step of administering to a patient in need thereof a therapeutically effective amount of a compound described herein.

[0041] Furthermore, the compounds and methods that are described herein can be used to prevent or treat Central Nervous System ("CNS") diseases and conditions such as CNS inflammatory and conditions, *e.g.*, multiple sclerosis and progressive multifocal leukoencephalopathy.

[0042] Moreover, the compounds described herein can be used to prevent or treat inflammatory diseases and conditions, such as osteoarthritis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, and auto-immune diseases such as lupus and mixed auto-immune disease by administering a therapeutically effective amount of the compound to a patient in need thereof.

[0043] Diseases and conditions such as telangiectasia, venous angiomas, hemangioblastoma, and polycythemia vera may also be advantageously prevented or treated with the compounds described herein.

[0044] The compounds provided herein can affect stem cell survival and differentiation by maintaining stem cell stemness, *e.g.*, preventing the differentiation of stem cells. The compounds taught herein may also be used for the augmentation of immune response, particularly where the augmentation of the immune response leads to the expression of co-stimulatory molecules on the peripheral macrophages and tumor-infiltrating microglia. These compounds are also useful when the immune response leads to proliferation of effector T cells and/or up-regulation of several key intracellular signaling molecules that critically regulate T-cell and monocyte activation. The compounds are useful when the immune responses leads to up-regulation of several key intracellular signaling molecules that critically regulate T-cell and monocyte activation, particularly phosphorylation of Syk (Tyr(352)) in monocytes and ZAP-70 (Tyr (319)) in T cells.

[0045] Generally, inhibitors of STAT3 (also referred to herein as inhibitors of p-STAT3, phosphorylated or activated STAT3) are useful in treating a wide variety of cancers because these inhibitors provide tumor cytotoxic effects - whether acting directly or indirectly on the activation of STAT3 and/or whether the inhibitor prevents activation of STAT3, upstream or downstream in its pathway.

[0046] However, while these inhibitors can have a significant impact on patients with primary and metastatic tumors, STAT3 blockade agents (also referred to sometimes as a “STAT3 inhibitors”) have multiple mechanisms of activity and potentially conflicting effects. In short, the various targets of STAT3 blockade agents (even if selective) include molecules in the STAT3 activation pathway of both tumor cells and immune cells. As such, this effect can adversely impact the potential wide spread uses of STAT3 inhibitors.

[0047] The activation of the p-STAT3 pathway is useful to prevent anti-tumor immune activity as inflammatory conditions can initiate or promote oncogenic transformation. Yu, H. et al, *STATs in Cancer Inflammation and Immunity: a Leading Role for STAT3*, Nature, Vol. 9, 798-809 (Nov. 2009) (where signalling between STAT3 and NF- κ B signalling is noted as interconnected). As discussed by Yu, overexpression or persistent activation of growth factor receptors together with oncogenic mutations in the receptor associated JAK family members may cause some types of cancer. Yu, H. et al, *STATs in Cancer Inflammation and Immunity: a Leading Role for STAT3*, *supra*, discussed in detail at pages 799 to 807, incorporated herein by reference. The tyrosine kinase receptors and non-receptor tyrosine kinases such as SRC can be activated by extrinsic pathways such as factors associated with inflammation such as UV radiation or sunlight, chemical carcinogens, infection, stress and cigarette smoke. In turn, the tyrosine kinases induced by both extrinsic and intrinsic pathways phosphorylate STAT3 which in turn forms dimers that translocate to the nucleus where gene expression is directly regulated. In addition to upregulating genes, STAT3 will induce the expression of many cytokines, chemokines and other mediators such as IL-6 and cyclooxygenase 2 that are associated with cancer-promoting inflammation. Most importantly, the receptors for many of the cytokines further activate STAT3.

[0048] Novel analogs of auranofin (also referred to herein as “auranofin analogs”) which can act as inhibitors of STAT3 are disclosed in Examples 1 to 8 of the present application.

[0049] Additional inhibitors of STAT3 that may be useful in connection with the methods provided herein include direct and indirect inhibitors of STAT3. Potential indirect inhibitors of STAT3 phosphorylation include inhibitors of upstream activators like growth factors, cytokines, src, Tyk2 and Janus kinases (this includes Jak2, Jak3, and Tyk2 inhibitors). Key activators of STAT3 include IL-6, IL-10, IL-23, IL-11 and OSM. Molecules upregulated by STAT3 which may be modulated by a STAT3 inhibitor include but are not limited to BCL-X_L, MYC, BIRC5, MMP9, MMP2, HIF α , ICAM1, TWIST1, VIM, MCL1, HSP70 and HSP90, IL-10, VEGF, FGF2 (also known as BFGF), COX2 CXCL12 (also known as SDF1), IL-11, IL-23, IL-17, and IL6. Molecules downregulated by STAT3 include IL-6, IL-12A (also known as P35), CD80, CD86, CXCL10 (also known as IP-10), IFN α , IFN β , CCL5, NOS2, IL-8, IL-1 β , and CCL2 (also known as MCP1).

[0050] More specifically potential indirect inhibitors of STAT3 include the Jak2 inhibitors currently under clinical trials such as: INCB018424 by Incyte; TG101348 by TargeGen; CEP-701 (lestaurtinib) by Cephalon; AZD1480 by AstraZeneca; XL019 by Exelixis; CYT-387 by Cytopia; SGI-1252 by SuperGen; and SB1518 by S*BIO. The Jak2 Inhibitors in preclinical development can also be useful as an indirect inhibitor of STAT3 and include: AG490; Tkip; Z3; TG101209; and C7. Furthermore, non-specific inhibitors of Jak2 can be useful and currently including: Go6976; Erlotinib; Atiprimod; CP-690,550; AT9283; and MK-0457.

[0051] While it may be possible for the compounds of the subject invention to be administered as the raw chemical, it is also possible to present them as a pharmaceutical formulation. Accordingly, the subject invention provides a pharmaceutical formulation comprising a compound or a pharmaceutically acceptable salt, ester, prodrug or solvate thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences. The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of

conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0052] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of the subject invention or a pharmaceutically acceptable salt, ester, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0053] It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0054] The compounds of the invention may be administered orally or via injection at a dose of from 0.1 to 500 mg/kg per day. The dose range for adult humans is generally from 5 mg to 2 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

[0055] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

[0056] The compounds of the subject invention can be administered in various modes, *e.g.* orally, topically, or by injection. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any particular

patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. Also, the route of administration may vary depending on the condition and its severity.

[0057] In one aspect, the compounds taught herein are administered alone or in combination with cytokines IL-6 or IFN α to treat a patient with a proliferative disease. The term “proliferative disease” refers to a cancer, (and/or any metastases) or hyperproliferative condition, such as a leukemia, lymphoma or multiple myeloma. The term also includes benign tumors, malignant tumors, rheumatoid arthritis, psoriasis, ocular angiogenesis diseases, Osler-Webber Syndrome, myocardial angiogenesis, plaque neovascularization, graft and post-angioplasty stenosis, telangiectasia, hemophiliac joints, angiofibroma, wound granulation, intestinal adhesions, atherosclerosis, scleroderma, hypertrophic scars, cat scratch disease, and *Helicobacter pylori* ulcers or metastasis.

[0058] In any case, the multiple therapeutic agents (at least one of which is a compound of the present invention) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may be any duration of time ranging from a few minutes to four weeks.

[0059] Thus, in another aspect, the present invention provides methods for treating STAT3-mediated disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of the present invention effective to reduce or prevent said disorder in the subject in combination with at least one additional agent for the treatment of said disorder that is known in the art. In a related aspect, the present invention provides therapeutic compositions comprising at least one compound of the present invention in combination with one or more additional agents for the treatment of STAT3.

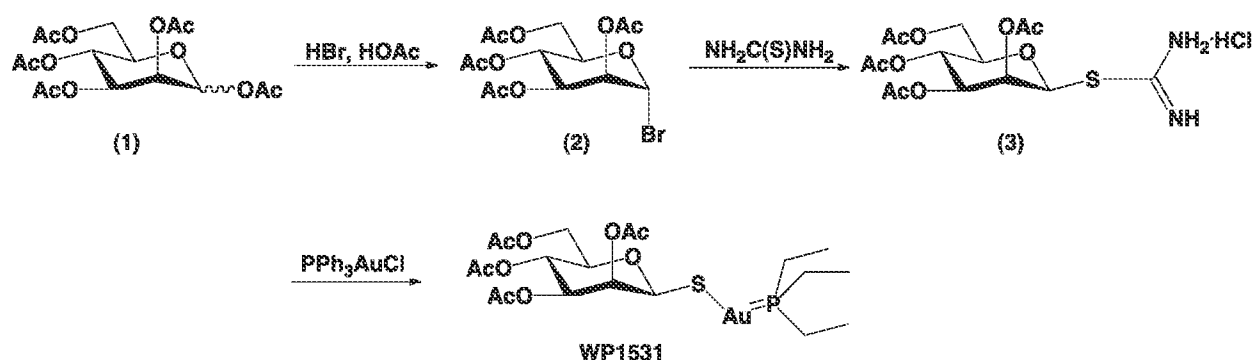
[0060] As noted above, the compounds of the subject invention may be useful for the treatment or disorders of a wide variety of condition where inhibition or modulation of STAT3 is

useful. Disorders or conditions advantageously treated by the compounds of the subject invention include the prevention or treatment of cancer, such as colorectal cancer, and cancer of the breast, lung, prostate, bladder, cervix and skin. Compounds of the invention may be used in the treatment and prevention of neoplasias including but not limited to brain cancer, bone cancer, a leukemia, a lymphoma, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. The neoplasia can be selected from gastrointestinal cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamous cell and basal cell cancers.

[0061] Besides being useful for human treatment, the compounds and formulations of the present invention are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

[0062] GENERAL SYNTHETIC METHODS FOR PREPARING COMPOUNDS

[0063] Examples 1 to 8 can be synthesized using the following general and exemplary synthetic procedure:



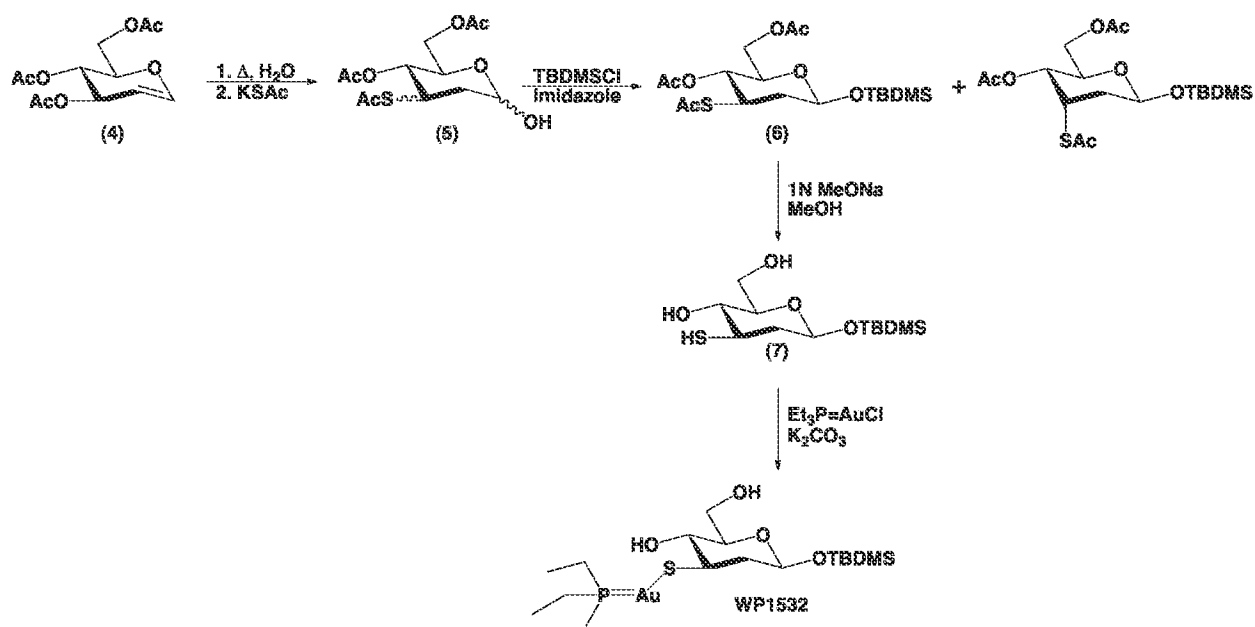
[0064] General synthetic procedure is exemplified below by synthesis of D-mannose analog, the compound of Example 5, WP1531 as follows:

[0065] **Synthesis of 2, 3, 4, 6-tetra-O-acetyl-1-pseudothiourea- β -D-mannose (3):** 33% HBr / AcOH solution (3.5 mmol) was added to the solution of penta-O-acetyl-D-mannose (1) (1 mmol) in mixture of AcOH and Ac₂O (1:1, v/v) (4 mL). The reaction mixture was stirred at room temperature until reaction was completed (TLC control). Then the reaction mixture was diluted with dichloromethane (40 mL) and washed with sat. NaCO₃ aqueous solution and subsequently with water until neutral. The organic layer was dried over Na₂SO₄. Drying agent and solvent were removed to give the oily 2,3,4,6-tetra-O-acetyl-D-mannosyl bromide (2), which was used in the next step without purification. Bromide 2 (1 mmol) was dissolved in acetone (5 mL) and thiourea (3.0 mmol) was added and such obtained mixture was refluxed until starting material was converted (TLC monitored) into the 2,3,4,6-tetra-O-acetyl-1-pseudothiourea- β -D-mannose (3). The final product was then crystallized from acetone (yield 64%).

[0066] **Synthesis of 2, 3, 4, 6-tetra-O-acetyl-1-thio(triethylphosphine)gold- β -D-mannopyranoside (WP1531).** Solution of triethylphosphine gold chloride (0.64 mmol) in the ethanol (1ml) was added to previously prepared solution of 2,3,4,6-tetra-O-acetyl-1-pseudothiourea- β -D-mannose (3) (0.64 mmol) the 10% solution of K₂CO₃ in water (2 mL) at 0°C. The mixture was stirred at 0°C for 1 hr then cooling was removed to allow the temperature to rise to the room temperature. The stirring continued until compound 3 was completely converted to product (TLC monitored progress of the reaction). The reaction mixture was then extracted with dichloromethane (3 times) and combined the organic layers were dried over Na₂SO₄. Drying agent and solvent were removed to give oily product WP531 that solidified upon adding of pentane.

[0067] The synthetic procedure described immediately above can be used to make the compounds WP1527, WP1528, WP1529, WP1533, the compounds of Examples 1, 2, 3 and 7 below.

[0068] General synthetic procedure is further exemplified immediately below by synthesis of 2-deoxy-3-thio(triethylphosphine)gold-1-tert-butyl dimethyl- β -D-glucopyranoside (WP1532), the compound of Example 6:



[0069] The suspension of 3, 4, 6-tri-O-acetyl-D-glucal (4) (10 mmol) in water (100 mL) was heated to 70°C while stirring continues vigorously until substrate was hydrolyzed. Then reaction mixture was cooled down to room temperature and potassium thioacetate (30 mmol) followed by dichloromethane (DCM) (25 mL) was added. Stirring continued and after 12 hrs (overnight). Water and organic layers were separated. Water layer was extracted with dichloromethane (DCM) (25 mL). Combined organic extracts were washed with water until neutral then dried over Na_2SO_4 . Solvent was partially removed (to the volume of ~10 mL) and imidazole (20 mmol) followed by TBDMCl (15 mmol) were added. Obtained thick solution was stirred at room temperature until all substrate was consumed (TLC control). After reaction was completed the reaction mixture was diluted with DCM (100 mL) and washed with 10% water solution of Na_2CO_3 , then with water until neutral pH, and then dried over Na_2SO_4 . Drying agent and solvent were removed and reaction mixture was separated by column chromatography to give 4, 6-di-O-acetyl-3-thio-acetyl-2-deoxy-1-O-tertbutyldimethylsilyl- β -D-glucopyranoside (6) as a main product.

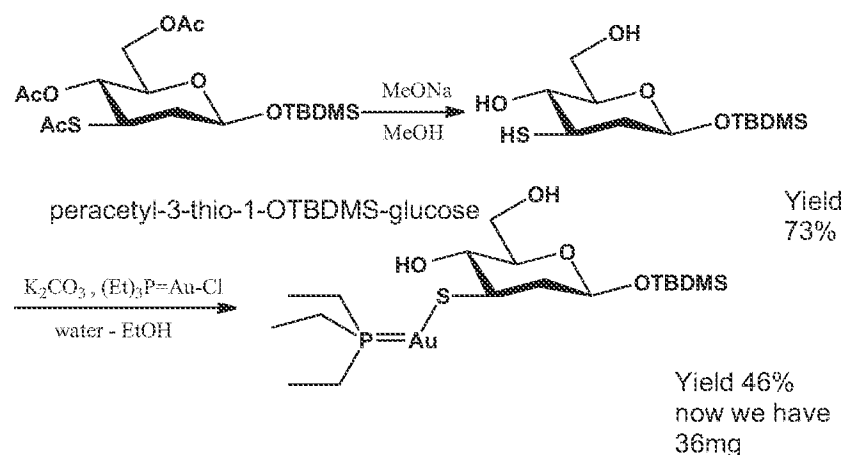
[0070] 1N $MeONa$ solution in methanol (1 mL, 1 mmol) was added to the solution of 4,6-di-O-acetyl-3-thio-acetyl-2-deoxy-1-O-tertbutyldimethylsilyl- β -D-glucopyranoside (6) (1 mmol) in methanol (25 mL). Obtained mixture was stirred at room temperature until substrate was converted into product (TLC monitored progress of the reaction). Acetic acid (1 mmol) was added and the reaction mixture was evaporated to dryness. Product was purified by column

chromatography to give 0.73 mmol of 2-deoxy-3-thio-1-O-tertbutyldimethylsilyl- β -D-glucopyranoside (7).

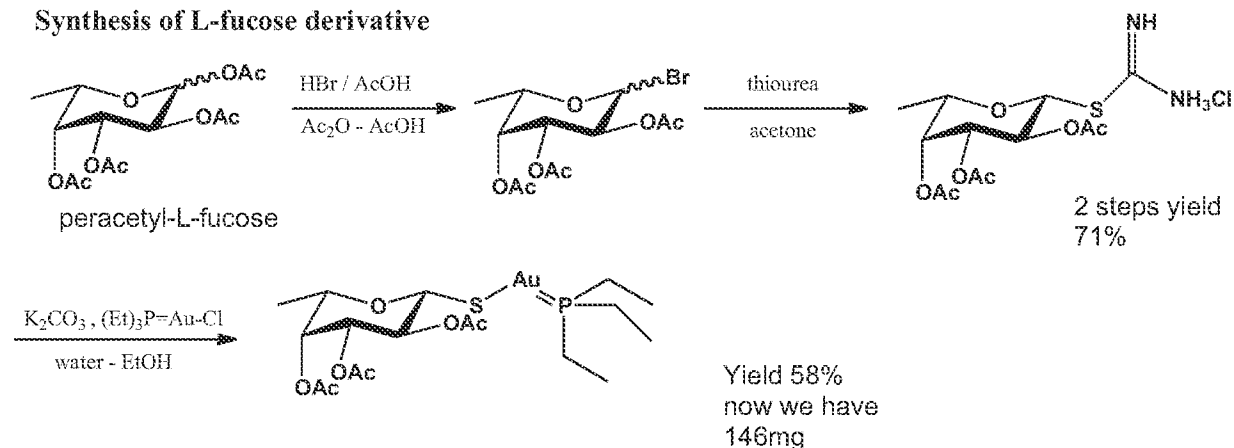
[0071] Then solution of triethylphosphine gold chloride (0.73 mmol) in the ethanol (1.5 mL) was added to previously prepared solution of 2-deoxy-3-thio-1-O-tertbutyldimethylsilyl- β -D-glucopyranoside (7)(0.73 mmol) the 10% solution of K_2CO_3 in water (2 mL) at $0^\circ C$. The mixture was stirred at $0^\circ C$ for 1 hr then temperature was brought to room temperature. The stirring continued until compound 7 was converted (TLC monitored) into the final product WP1532. The reaction mixture was then extracted with DCM (3 times), then combined the organic layers were dried over Na_2SO_4 . Drying agent and solvent were removed to give oily product WP1532 (0.46 mmol) that solidified upon treatment with pentane.

[0072] A general a synthesis of 3-thio sugar derivative is shown immediately below:

Synthesis of 3-thio sugar derivative



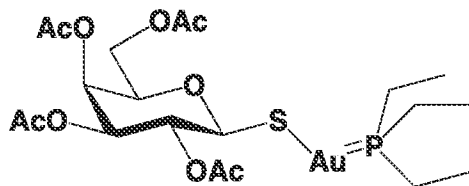
Synthesis of L-fucose derivative



[0073] The disclosure provided is further illustrated by the following examples:

EXAMPLE 1

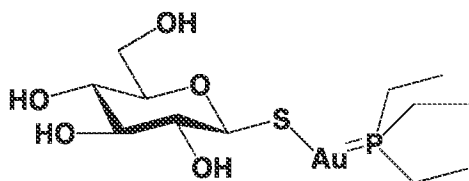
2,3,4,6-tetra-O-acetyl-1-thio(triethylphosphine)gold- β -D-galactopyranoside
WP1527



^1H NMR (CDCl_3 , 300 MHz) δ 5.41 (dd, $J = 3.4$ Hz, $J = 1.1$ Hz, H-4), 5.20 (dd, 1H, $J = J = 9.4$ Hz, H-2), 5.14 (d, 1H, $J = 9.4$ Hz, H-1), 4.97 (dd, 1H, $J = 9.4$ Hz, $J = 3.4$ Hz, H-3), 4.18-4.08 (m, 2H, H-6, H-6), 3.95 (dd, $J = J = 6.6$ Hz, $J = 1.1$ Hz, H-5), 2.11, 2.09, 2.03, 1.97 (4s, 3H ea, OAc), 1.86 (q, 3H, $J = 7.5$ Hz, CH_3), 1.83 (q, 3H, $J = 7.5$ Hz, CH_3), 1.22 (t, 2H, $J = 7.5$ Hz, CH_2), 1.16 (t, 2H, $J = 7.5$ Hz, CH_2)

EXAMPLE 2

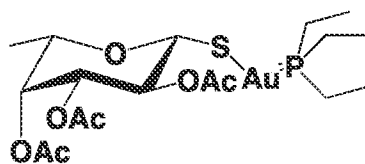
1-thio(triethylphosphine)gold- β -D-glucopyranoside
WP1528



^1H NMR ($\text{DMSO}-d_6 + \text{D}_2\text{O}$), 300 MHz) δ 4.53 (d, 1H, $J = 8.9$ Hz, H-1), 3.53 (dd, 1H, $J = 11.7$ Hz, $J = 1.5$ Hz, H-6), 3.23 (dd, 1H, $J = 11.7$ Hz, $J = 5.7$ Hz, H-6), 3.00 – 2.85 (m, 3H, H-3, H-4, H-5), 2.78 (dd, 1H, $J = 8.8$ Hz, $J = 8.7$ Hz, H-2), 1.76 (q, 3H, $J = 7.7$ Hz, CH_3), 1.73 (q, 3H, $J = 7.7$ Hz, CH_3), 1.12 (t, 2H, $J = 7.7$ Hz, CH_2), 1.06 (t, 2H, $J = 7.7$ Hz, CH_2)

EXAMPLE 3

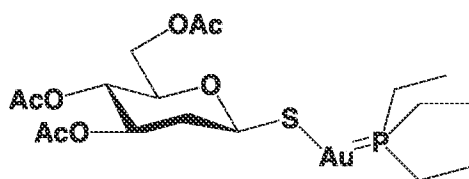
2,3,4-tri-O-acetyl-1-thio(triethylphosphine)gold- β -L-fucopyranoside
WP1529



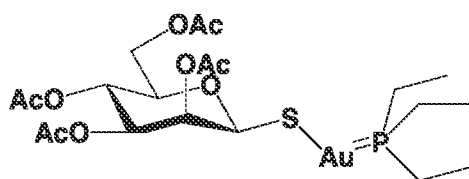
$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 5.25 (dd, 1H, $J = 3.4$ Hz, $J = 0.8$ Hz, H-4), 5.18 (dd, 1H, $J = J = 9.3$ Hz, H-2), 5.12 (d, 1H, $J = 9.3$ Hz, H-1), 4.97 (dd, 1H, $J = 9.3$ Hz, $J = 3.4$ Hz, H-3), 3.83 (dq, 1H, $J = 6.5$ Hz, $J = 0.9$ Hz, H-5), 2.13, 2.08, 1.96 (3s, 3H ea, OAc), 1.86 (q, 3H, $J = 7.5$ Hz, CH_3), 1.83 (q, 3H, $J = 7.5$ Hz, CH_3), 1.24 (t, 2H, $J = 7.5$ Hz, CH_2), 1.21 (d, 1H, $J = 6.5$ Hz, H-6), 1.20 (t, 2H, $J = 7.5$ Hz, CH_2), 2.07, 2.01, 1.98 (4s, 3H ea, OAc), 1.87 (q, 3H, $J = 7.5$ Hz, CH_3), 1.83 (q, 3H, $J = 7.5$ Hz, CH_3), 1.26 (t, 2H, $J = 7.5$ Hz, CH_2), 1.20 (t, 2H, $J = 7.5$ Hz, CH_2)

EXAMPLE 4

3,4,6-tri-O-acetyl-2-deoxy-1-thio(triethylphosphine)gold- β -D-glucopyranoside
WP1530

EXAMPLE 5

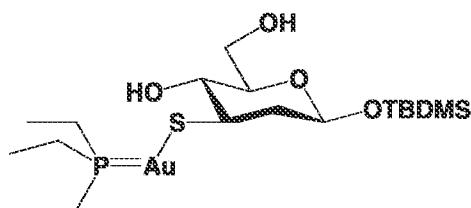
2,3,4,6-tetra-O-acetyl-1-thio(triethylphosphine)gold- β -D-mannopyranoside
WP1531



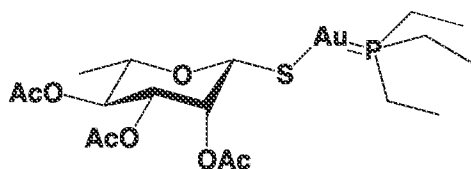
$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 6.00 (dd, 1H, $J = 9.9$ Hz, $J = 3.5$ Hz, H-3), 5.84 (d, 1H, $J = 1.4$ Hz, H-1), 5.47 (dd, 1H, $J = 3.5$ Hz, $J = 1.4$ Hz, H-2), 5.32 (dd, 1H, $J = J = 9.9$ Hz, H-4), 4.77 (ddd, 1H, $J = 9.9$ Hz, $J = 4.0$ Hz, $J = 2.3$ Hz, H-5), 4.37 (dd, 1H, $J = 12.3$ Hz, $j = 4.0$ Hz, H-6), 4.05 (dd, 1H, $J = 12.3$ Hz, $J = 2.3$ Hz, H-6), 2.14, 2.11, 2.03, 1.97 (4s, 3H ea, OAc), 1.87 (q, 3H, $J = 7.5$ Hz, CH_3), 1.83 (q, 3H, $J = 7.5$ Hz, CH_3), 1.23 (t, 2H, $J = 7.5$ Hz, CH_2), 1.18 (t, 2H, $J = 7.5$ Hz, CH_2)

EXAMPLE 6

2-deoxy-3-thio(triethylphosphine)gold-1-tert-butylidimethyl- β -D-glucopyranoside
WP 1532

EXAMPLE 7

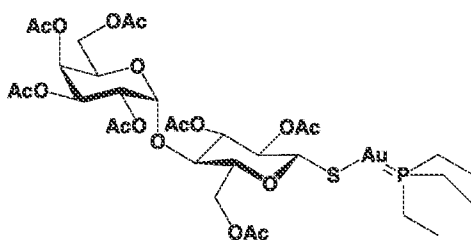
2,3,4-tri-O-acetyl-1-thio(triethylphosphine)gold- β -L-rhamnopyranoside
WP1533



^1H NMR (CDCl_3 , 300 MHz) δ 5.96 (dd, 1H, $J = 10.0$ Hz, $J = 3.4$ Hz, H-3), 5.76 (d, 1H, $J = 1.7$ Hz, H-1), 5.47 (dd, 1H, $J = 3.4$ Hz, $J = 1.8$ Hz, H-2), 5.06 (dd, 1H, $J = 10.0$ Hz, H-4), 4.60 (dq, 1H, $J = 6.0$ Hz, $J = 10.0$ Hz, H-5), 2.13, 2.04, 1.96 (3s, 3H ea, OAc), 1.87 (q, 3H, $J = 7.6$ Hz, CH_3), 1.84 (q, 3H, $J = 7.6$ Hz, CH_3), 1.23 (t, 2H, $J = 7.6$ Hz, CH_2), 1.20 (t, 2H, $J = 7.5$ Hz, CH_2), 1.16 (d, 1H, $J = 6.0$ Hz, H-6),

EXAMPLE 8

2,3,6,2',3',4',6'-hepta-O-acetyl-1-thio(triethylphosphine)gold- β -D-lactoside
WP1534



[0074] **Biological Activity Assays**

[0075] Figure 9 the effects of 1 μM auranofin in combination with 10 IU/ml IFN α or 20 ng/ml IL-6 on the proliferation of CTCL HH in normoxia or hypoxia condition for 72 hours. In

this experiment, 30,000 cells/well of CTCL HH were plated in each well of a 96-well plate containing 100 μ l of RPMI with 10% FBS and 1% pen/strep at 37°C and 5% CO₂. The cells were treated with 1 μ M auranofin, 10 IU/ml IFN α , 20 ng/ml IL-6, 1 μ M auranofin and 10 IU/ml IFN α , or 20 ng/ml IL-6 and 1 μ M auranofin for 72 hours. Promega's MTS reagent were added to the cells according to manufacturer's instructions and incubated for 1.5 hours. The plates were read at 490 nm and the resulting data graphed with GraphPad Prism 5 software.

[0076] Figure 10 shows the results of treating CTL HH, Hut78, and MJ cells with different concentrations of the compound of Example I and after being incubated for 72 hours. In this experiment, 60,000 cells/well of CTCL HH, 30,000 cells/ well of HuT78, and 30,000 cells/well of MJ were plated in each well of a 96-well plate containing 100 μ l of RPMI with 10% FBS and 1% pen/strep and allowed to grow for 24 hours at 37°C 5% CO₂. The cells were treated with different concentrations of drugs and incubated for 72 hours. Promega's MTS reagent were added to the cells according to manufacturer's instructions and incubated for 1.5 hours. The plates were read at 490 nm and the resulting data graphed with GraphPad Prism 5 software.

[0077] Figure 11 shows the effects of Auranofin, WP1531, WP1533 on pSTAT3 expression in BT-58 for 4 h with 5 IU/ml of IFN α stimulation for 30 min in 10% serum. Specifically, 500,000 cells of BT-58 were seeded in 2 ml of DMEM/F12 supplemented 10 ng/ml of EGF and bFGF and 10% FBS. Cells were allowed to grow for 16 h then treated with 0.8, 1.5, 3 μ M of Auranofin and 0.4, 0.8, and 1.5 μ M of WP1531, and WP1533 for 4h. Cells were then stimulated with 5 IU/ml of IFN α for 30 min. Lysates were collected and protein concentration was determined. 40 μ g were ran out on each lane on MSD plate detecting pSTAT3.

[0078] Figure 12 shows the effects of Auranofin, WP1531, and WP1533 on the proliferation of BT-58 and 58-10F for 72 h (MTS). Specifically, 4,000 cells/well of BT-58, and 58-10F were seeded in each well of a 96-well plate containing 100 μ l of DMEM/F12 media. The cells were then treated with different concentrations of drugs and incubated for 72 h at 37° C in 5% CO₂. Promega's MTS reagent were added to the cells according to manufacture's instructions and incubated for 1.5 h. The plates were read at 490 nm and resulting data graphed with GraphPad Prism 5 software.

[0079] Figure 13 shows the effects of WP1547 on the proliferation of BT-58, 58-10F, U87, and WM35 for 72 hour (MTS). Specifically, 5,000, 4000, 10000, 7000 cells per well of

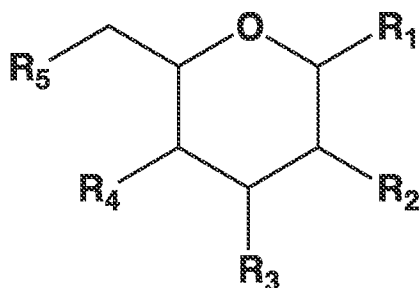
BT-58, 58-10F, U87, and WM35 respectively were plated in each well of a 96 well plate containing 100 μ l media appropriate to each cell line. The cells were allowed to grow for 24 hr at 37° C in 5% CO₂. The cells were then treated with different concentration of drugs and incubated for 72 hr Promega's MTS reagent were added to the cells according to manufacture's instructions and incubated for 1.5 hr. The plate were read at 490 nm and resulting data graphed with GraphPad Prism 5 software.

[0080] Figure 14 shows the effects of WP1546 on the proliferation of BT-58, 58-10F, U87, and WM35 for 72h (MTS). Specifically, 5,000, 4000, 10000, 7000 cells per well of BT-58, 58-10F, U87, and WM35 respectively were plated in each well of a 96 well plate containing 100 μ l media appropriate to each cell line. The cells were allowed to grow for 24 hr at 37° C in 5% CO₂. The cells were then treated with different concentration of drugs and incubated for 72 hr Promega's MTS reagent were added to the cells according to manufacture's instructions and incubated for 1.5 hr. The plate were read at 490 nm and resulting data graphed with GraphPad Prism 5 software.

CLAIMS

We claim:

1. A compound of structural Formula I



wherein R₁, R₂, R₃, R₄, R₅ are each selected from H, OH, O-acyl, O-alkyl, NH₂, NHAc or SAuPR₆; and

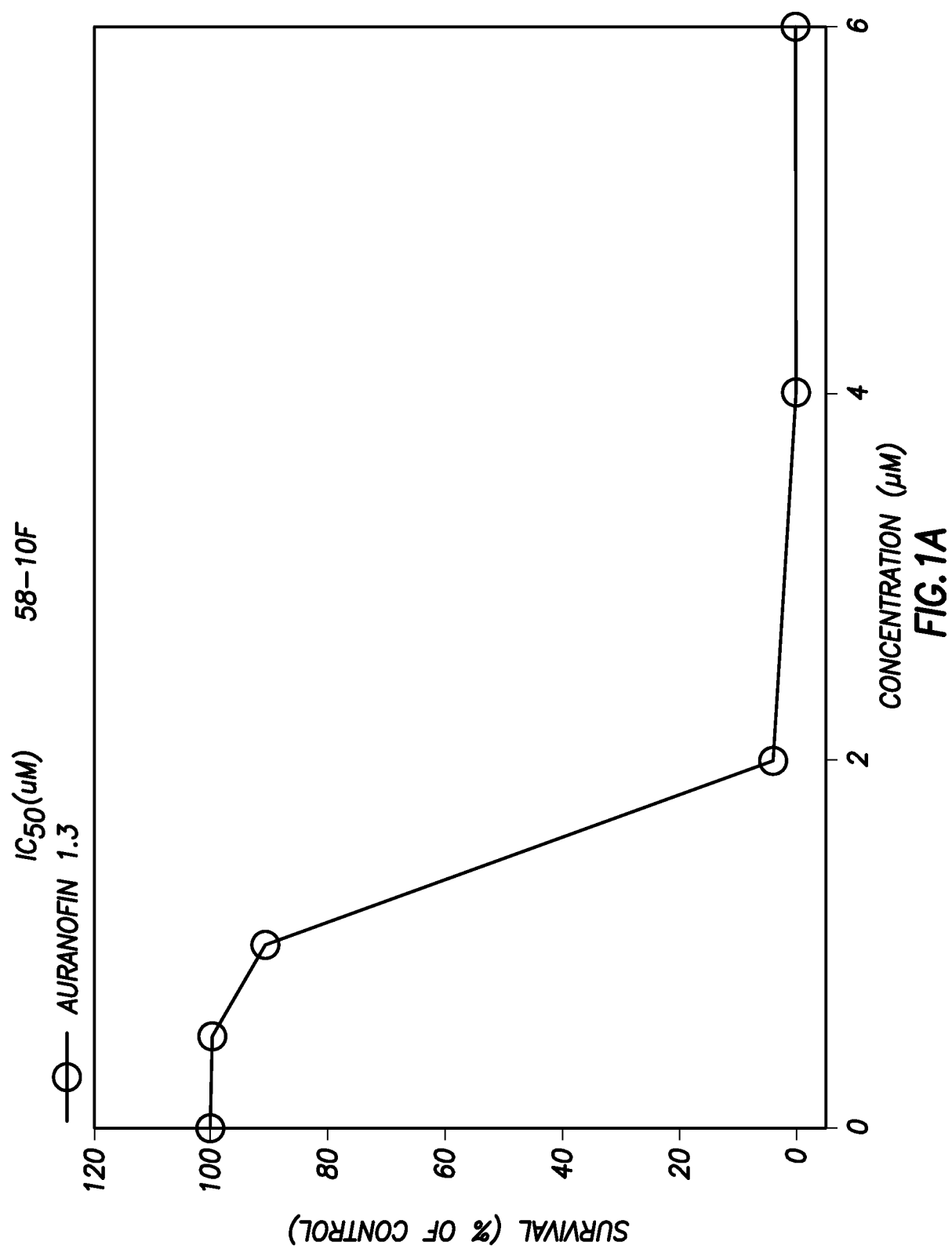
R₆ is lower alkyl.

2. A compound selected from the group consisting of Example 1 to Example 8.
3. A pharmaceutical composition as recited in claim 1 or claim 2 useful for the treatment or prevention of a proliferative disease or disorder.
4. Compound according to any one of claims 1 or 2 as a medicament for the treatment and prevention of cancer.
5. A compound or composition as recited in claims 1 or 2 for use in the manufacture of a medicament for the prevention or treatment of a disease or condition ameliorated by the modulation of p-STAT3.
6. A method of inhibition of STAT3 comprising contacting STAT3 with a compound as recited in Claims 1 or Claim 2.

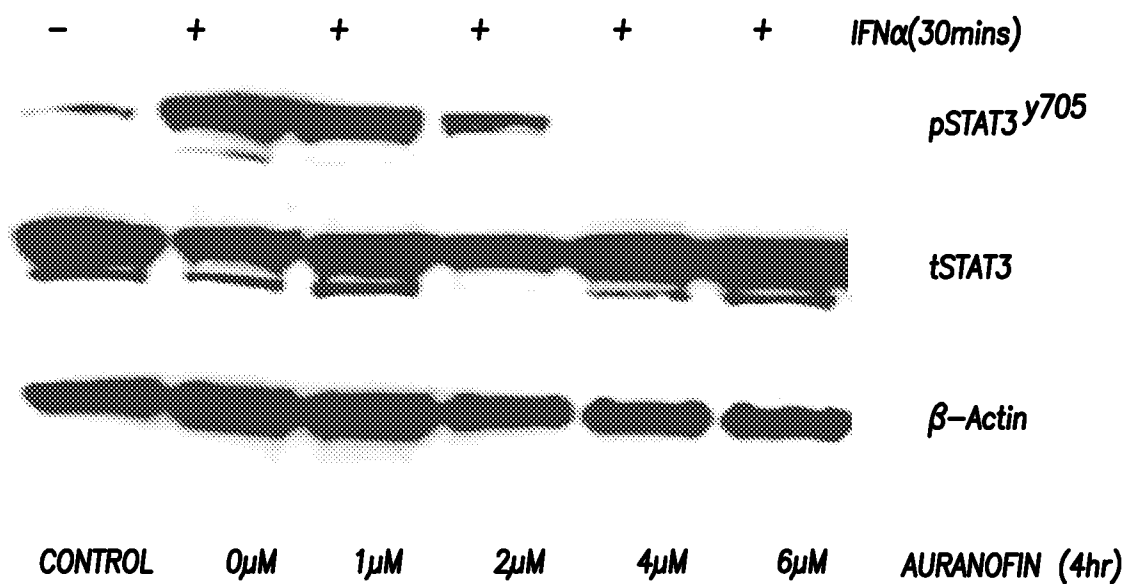
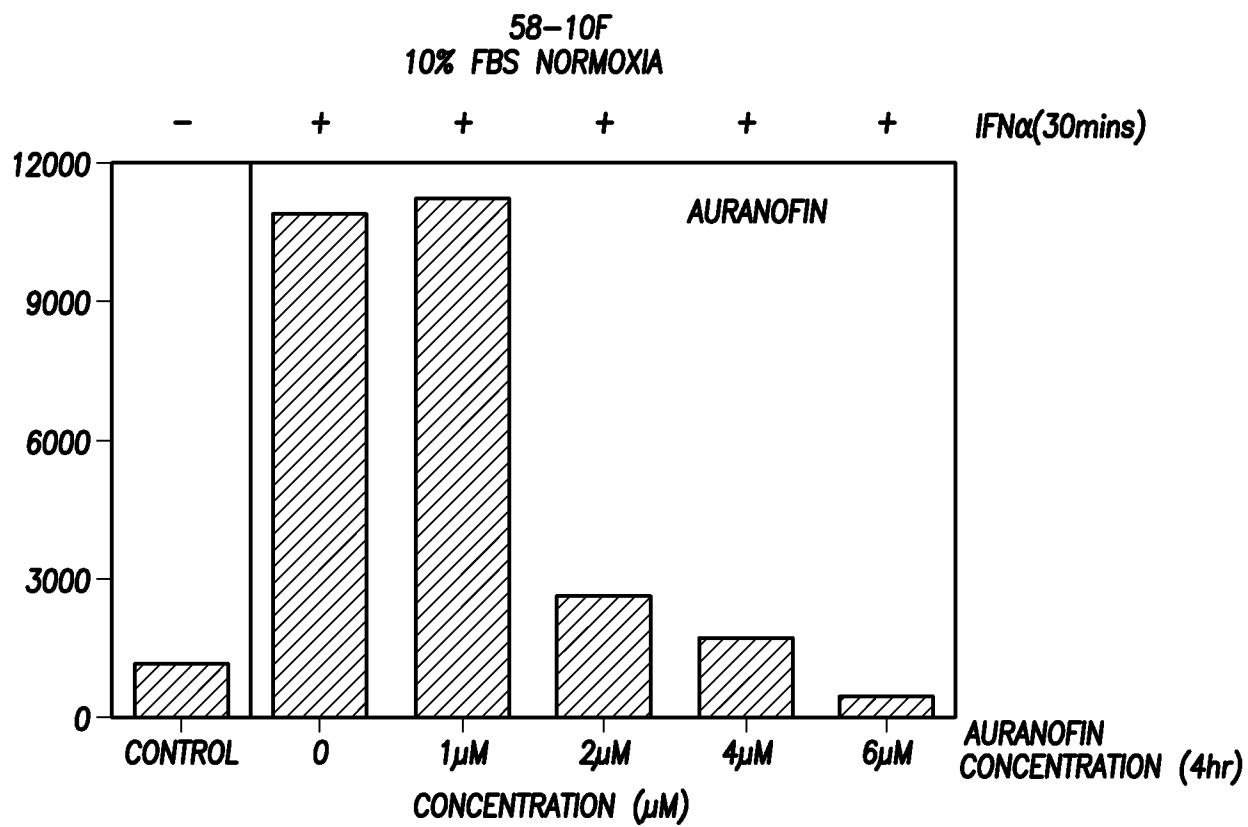
7. A method of treatment of a proliferative disease or disorder comprising the administration of a therapeutically effective amount of the compound as recited in Claims 1 or Claim 2 to a patient in need thereof.

8. The method as recited in Claim 3 above wherein the disease is cancer.

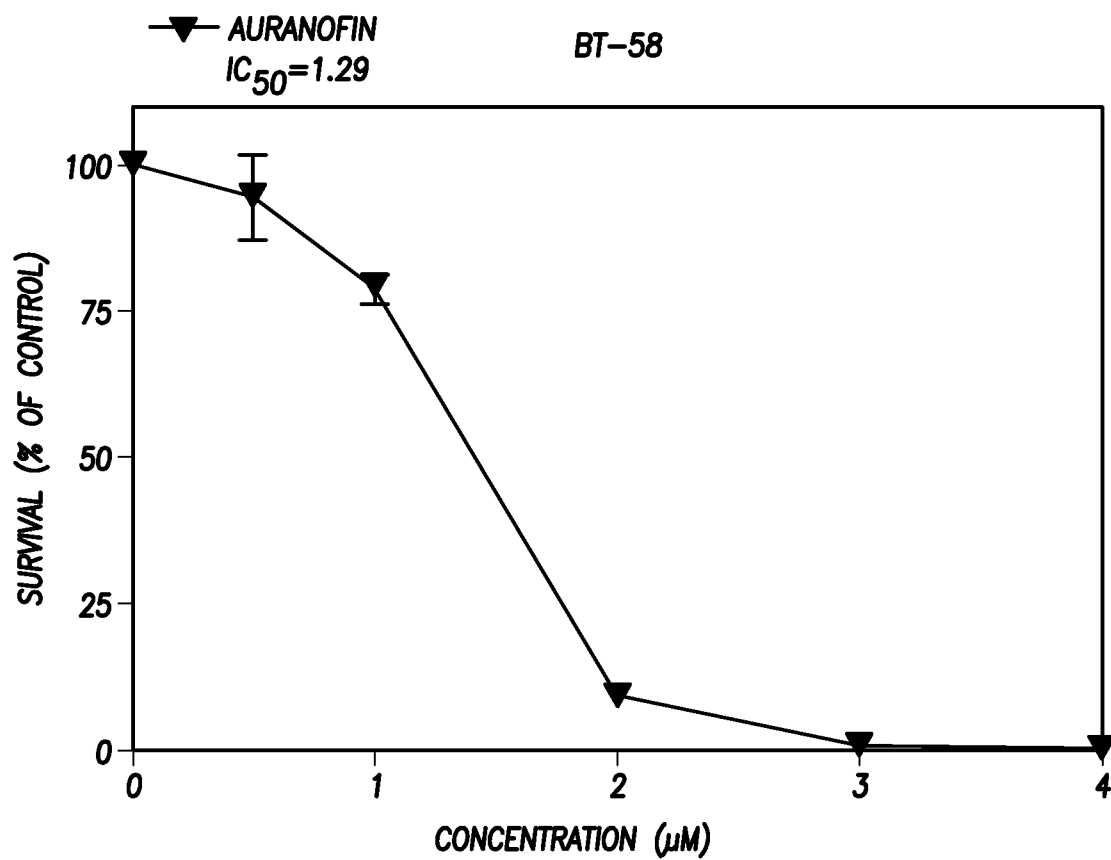
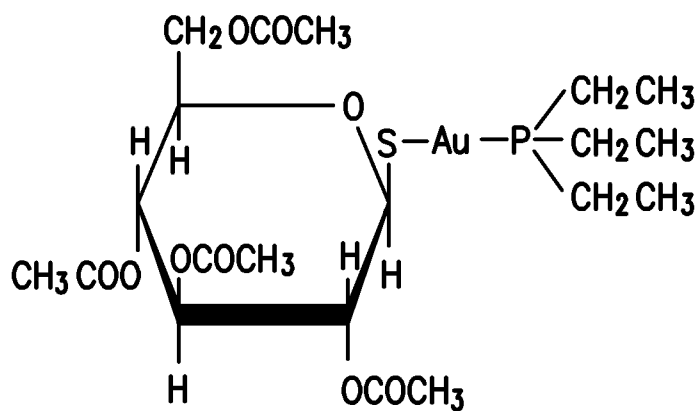
1/19



2/19



3/19

**FIG.2A****FIG.2C**

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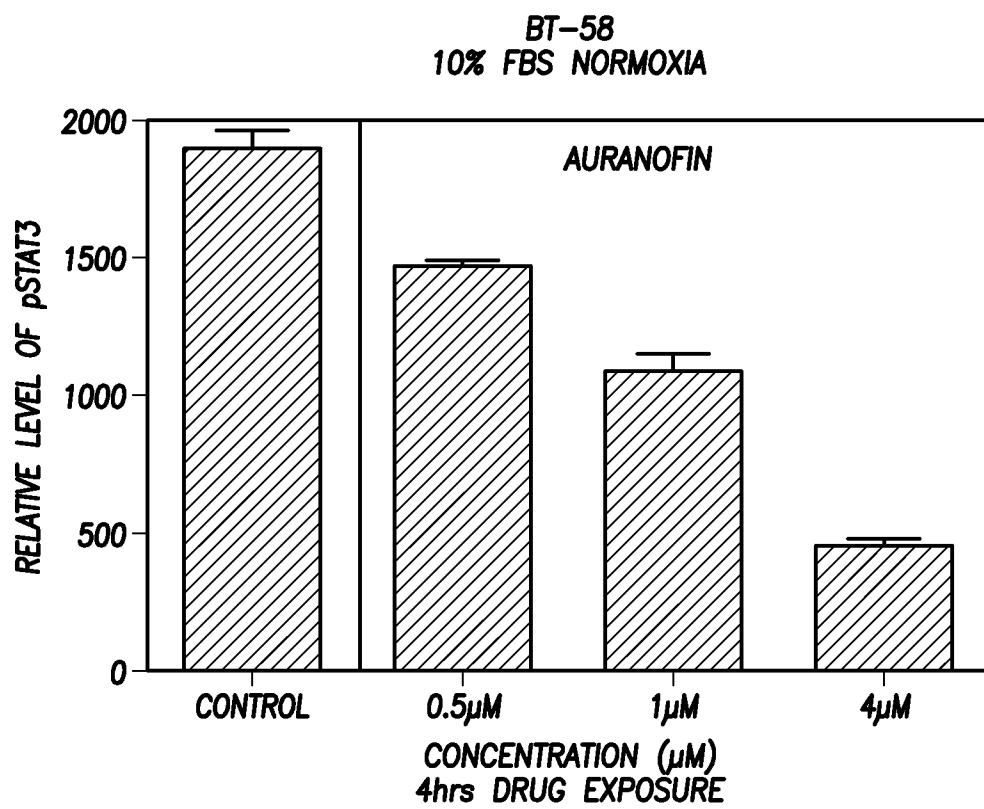


FIG.2B

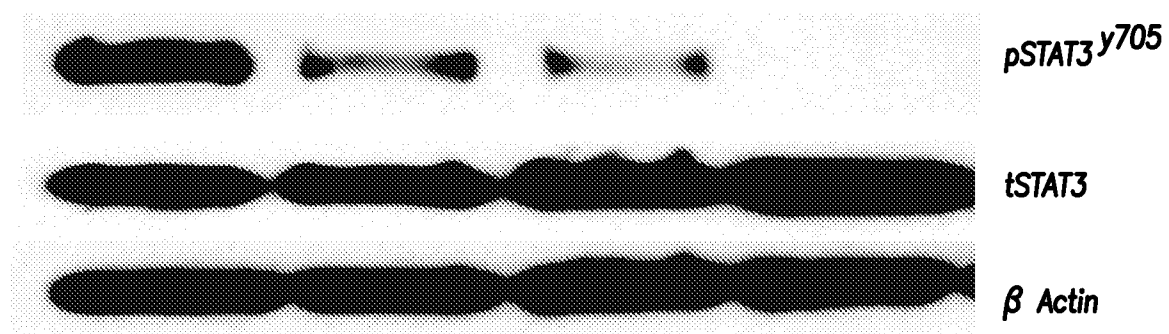
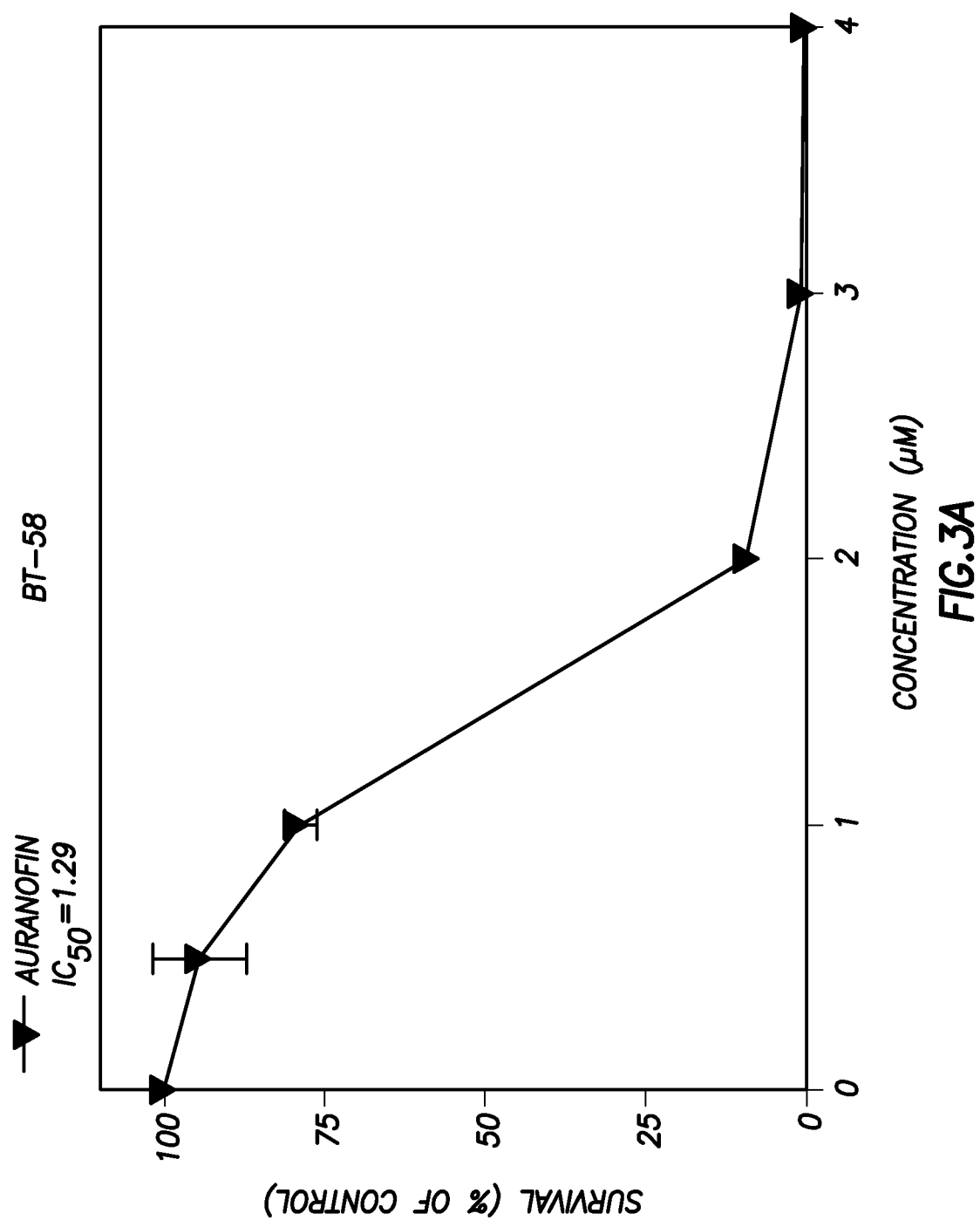


FIG.2D

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6/19

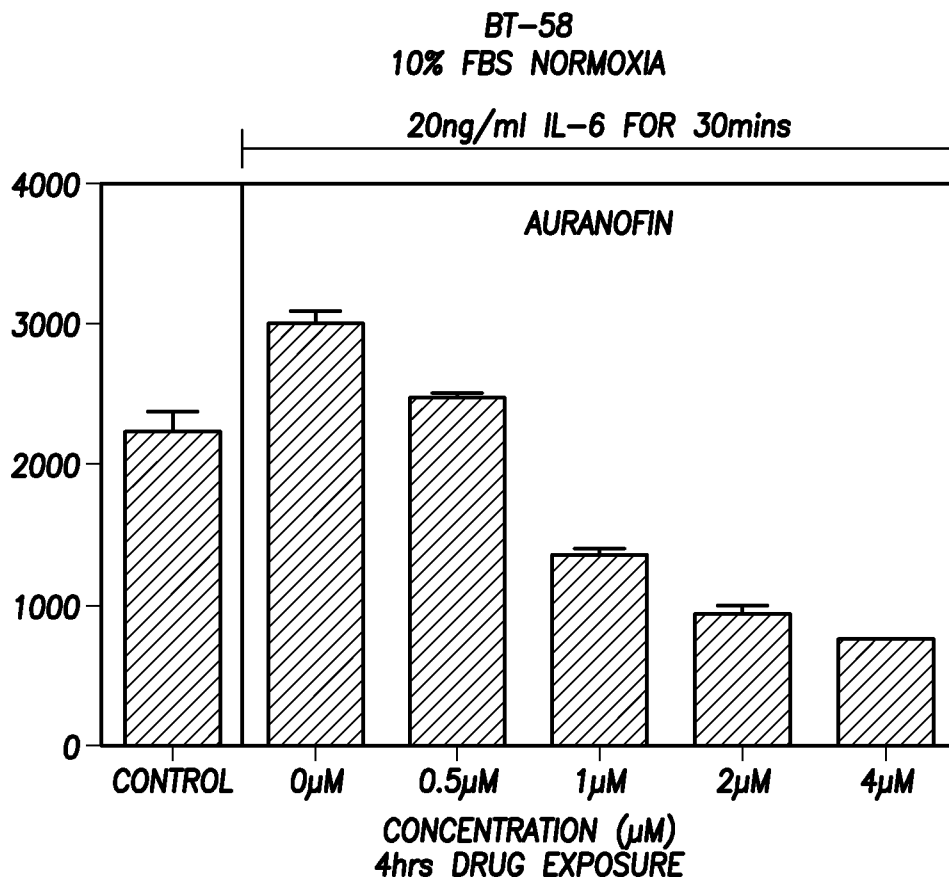


FIG.3B

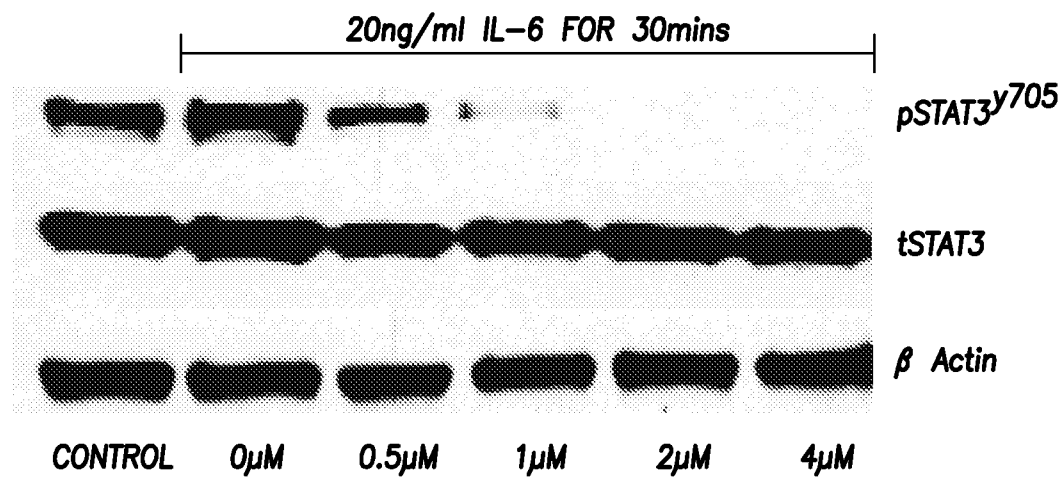
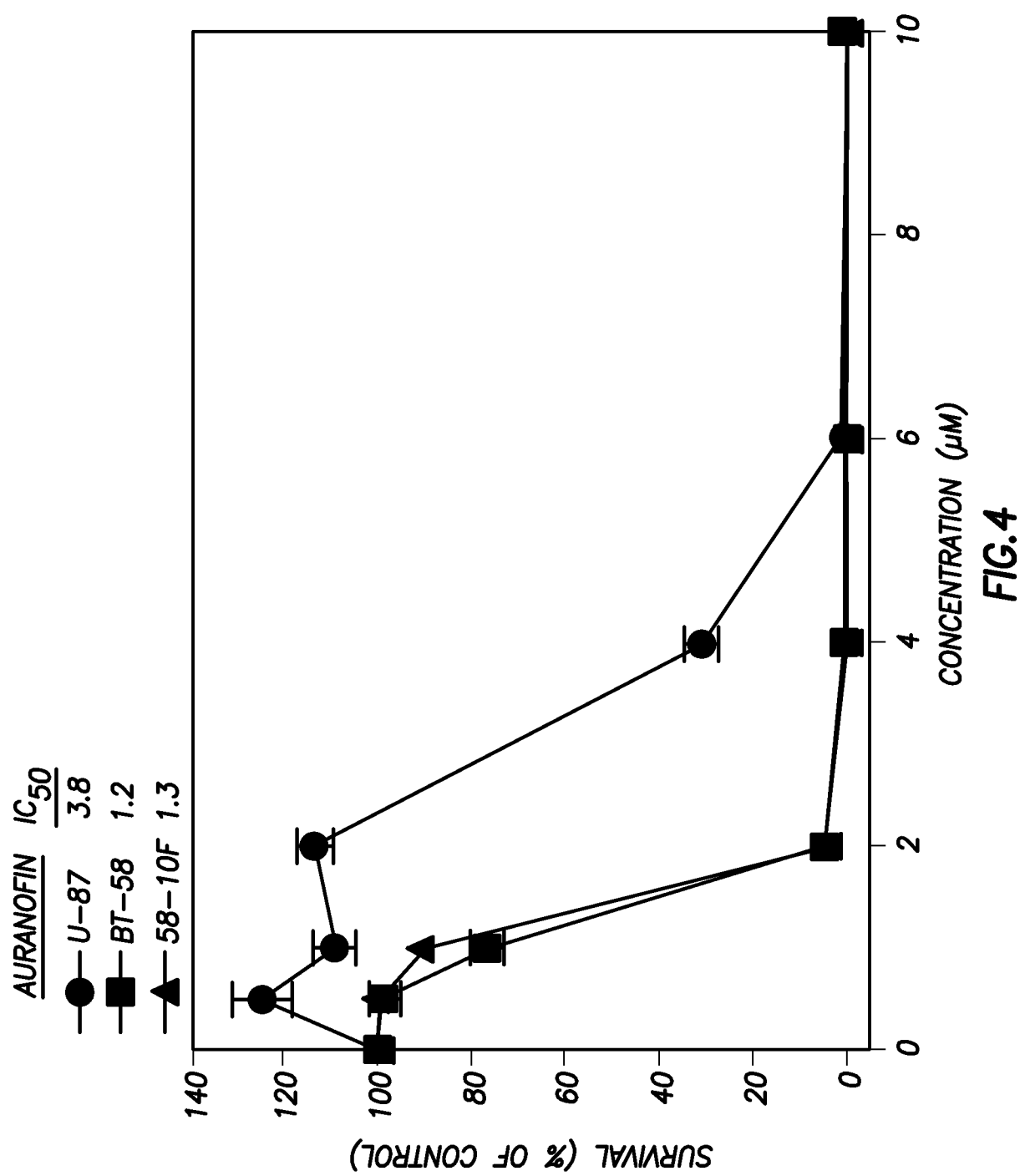


FIG.3C



8/19

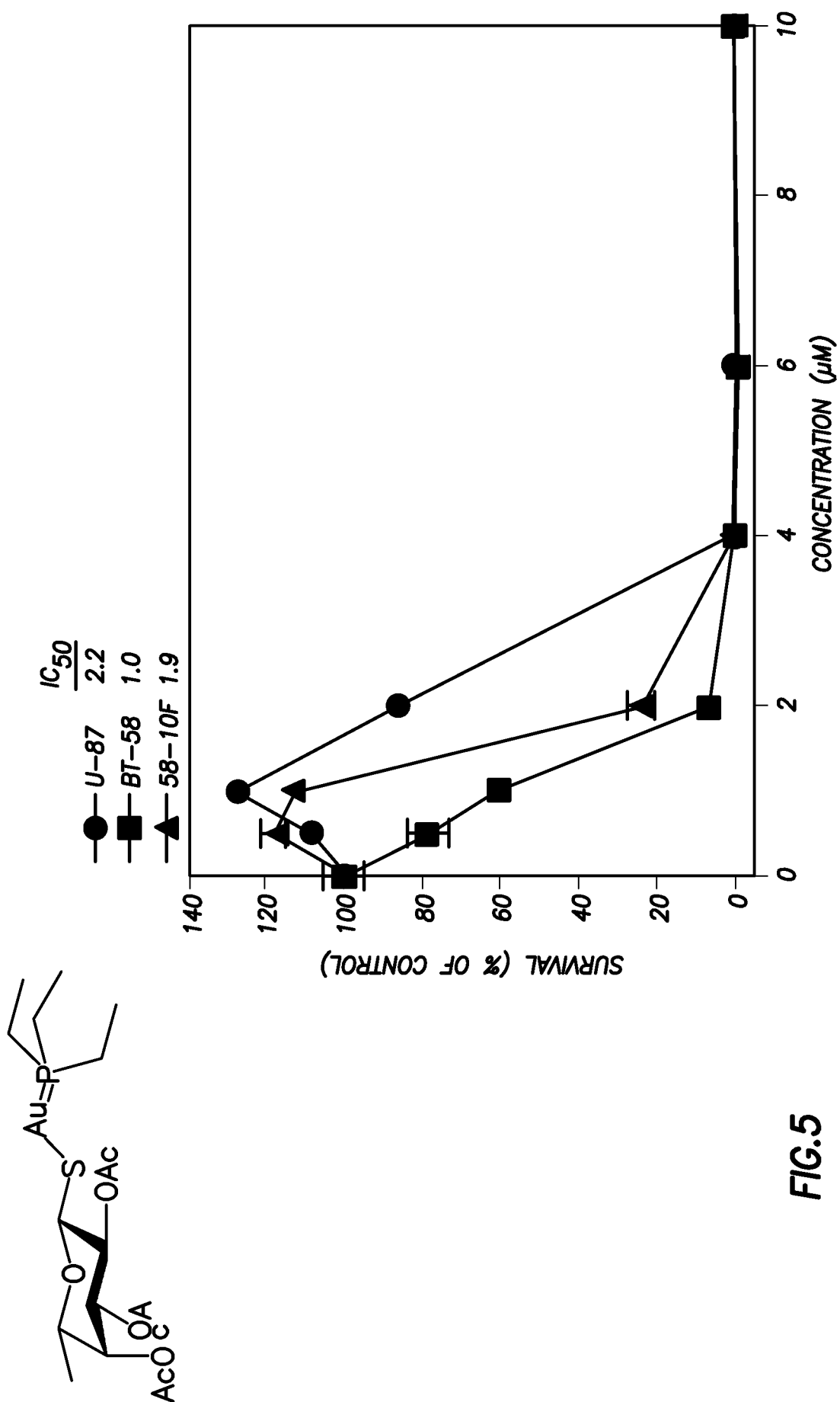


FIG.5

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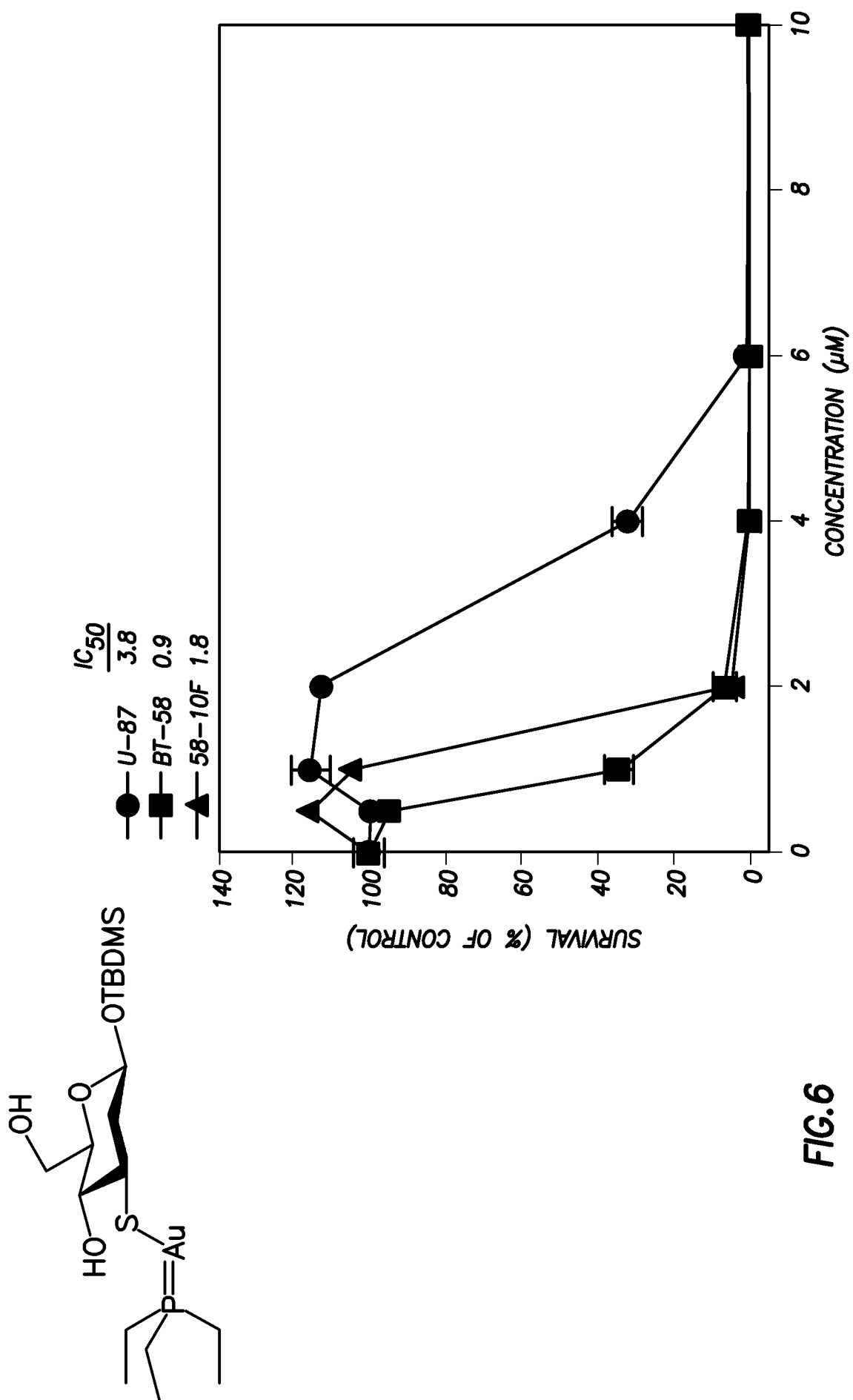


FIG.6

10/19

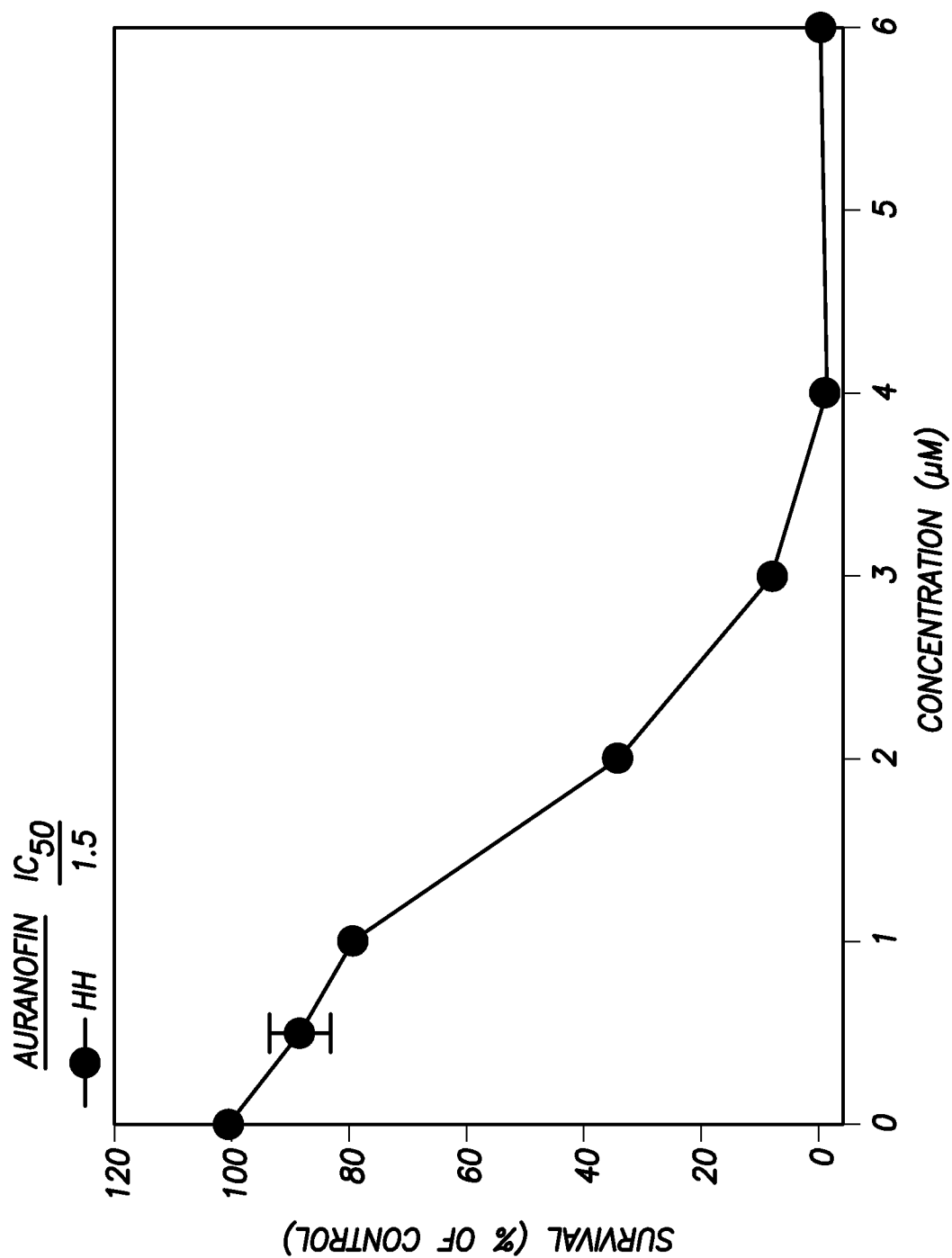


FIG. 7A

11/19

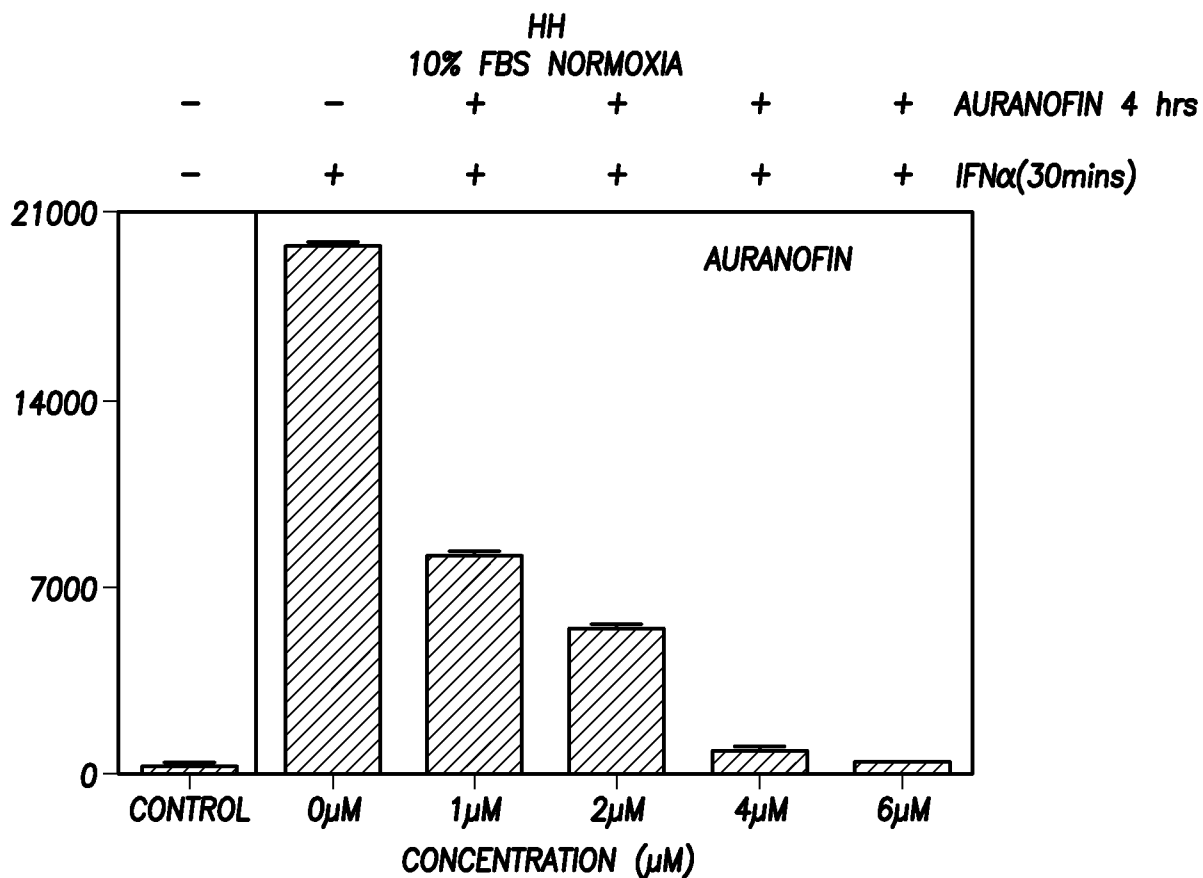


FIG. 7B

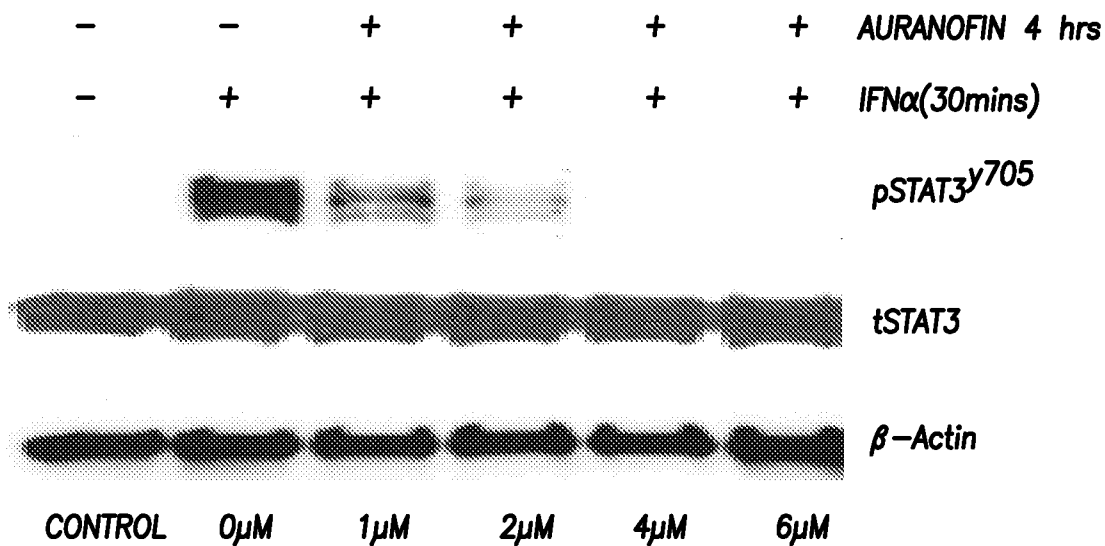
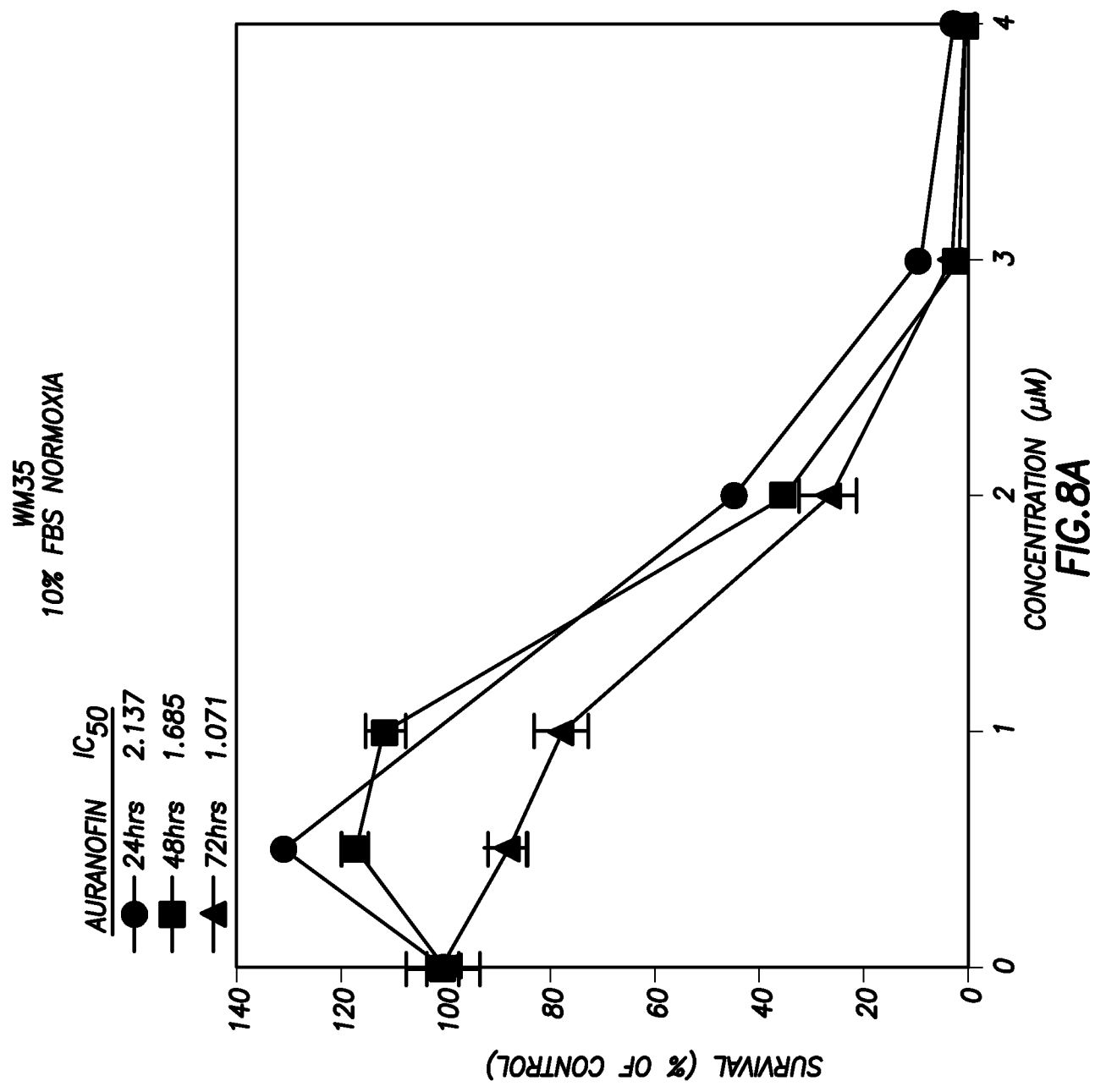


FIG. 7C

12/19



13/19

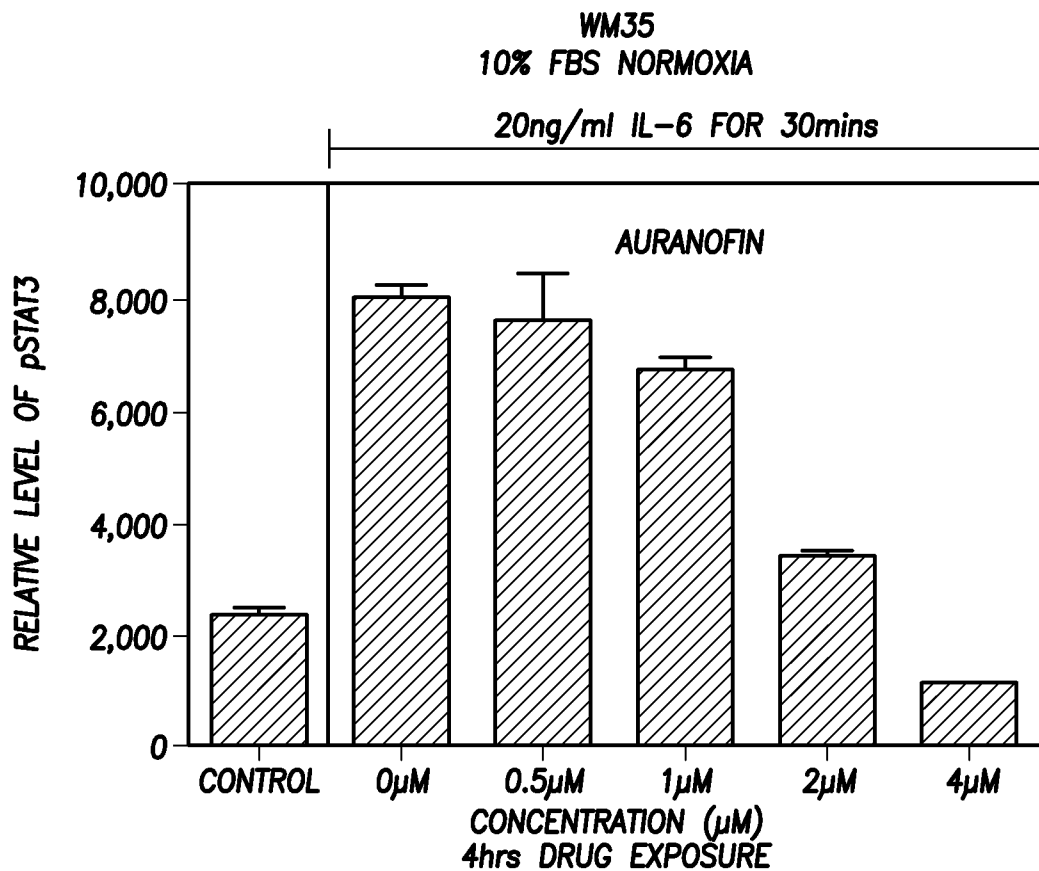


FIG.8B

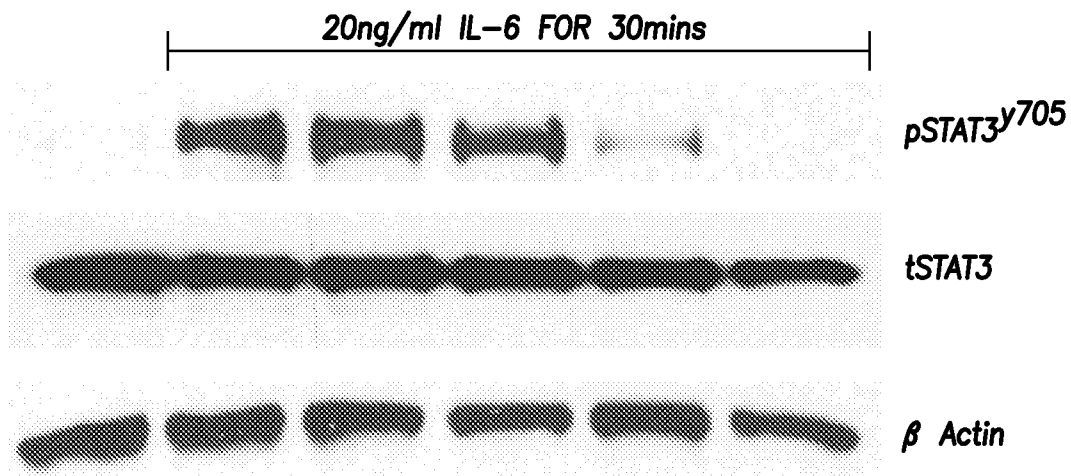


FIG.8C

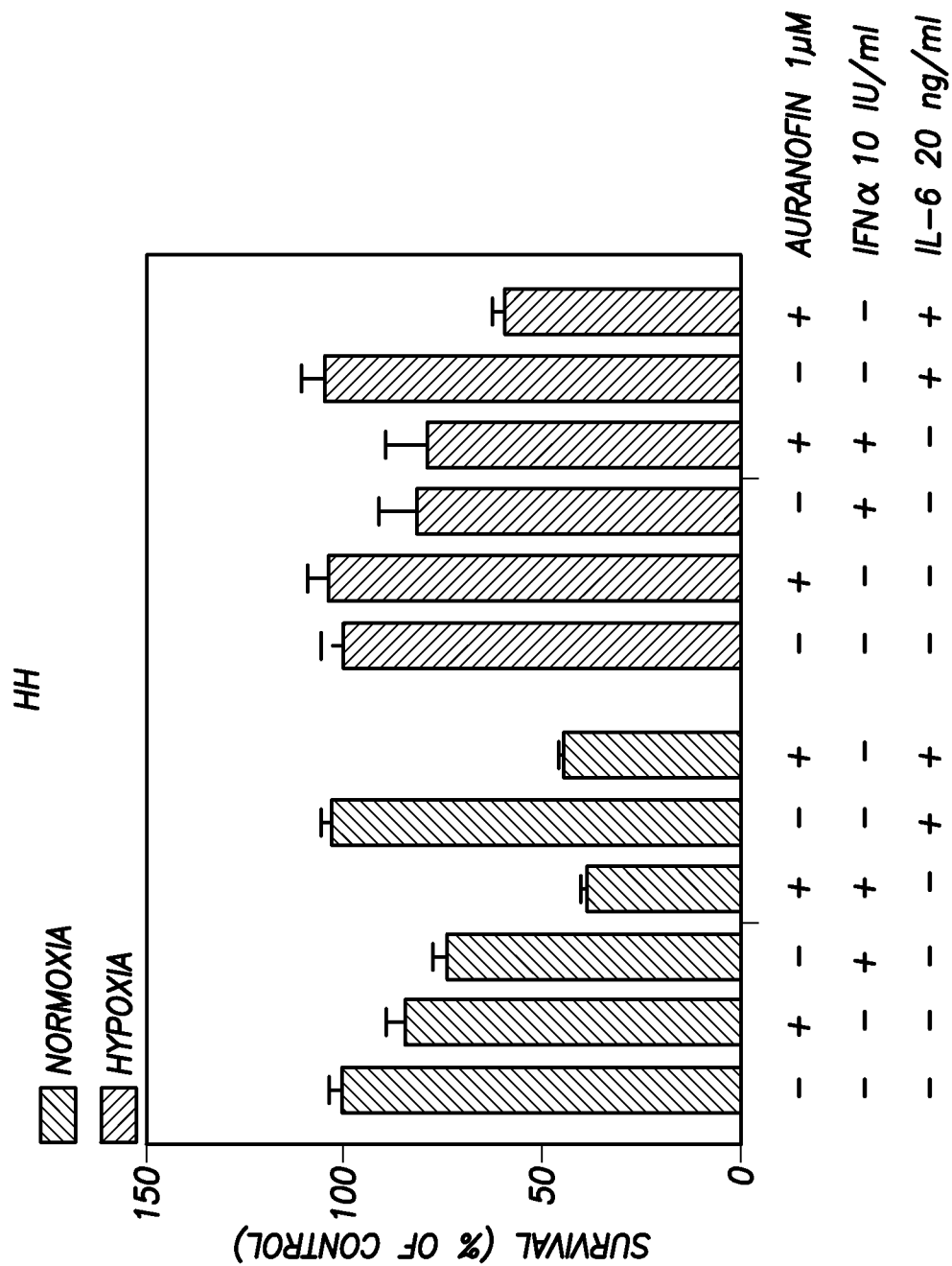


FIG.9

15/19

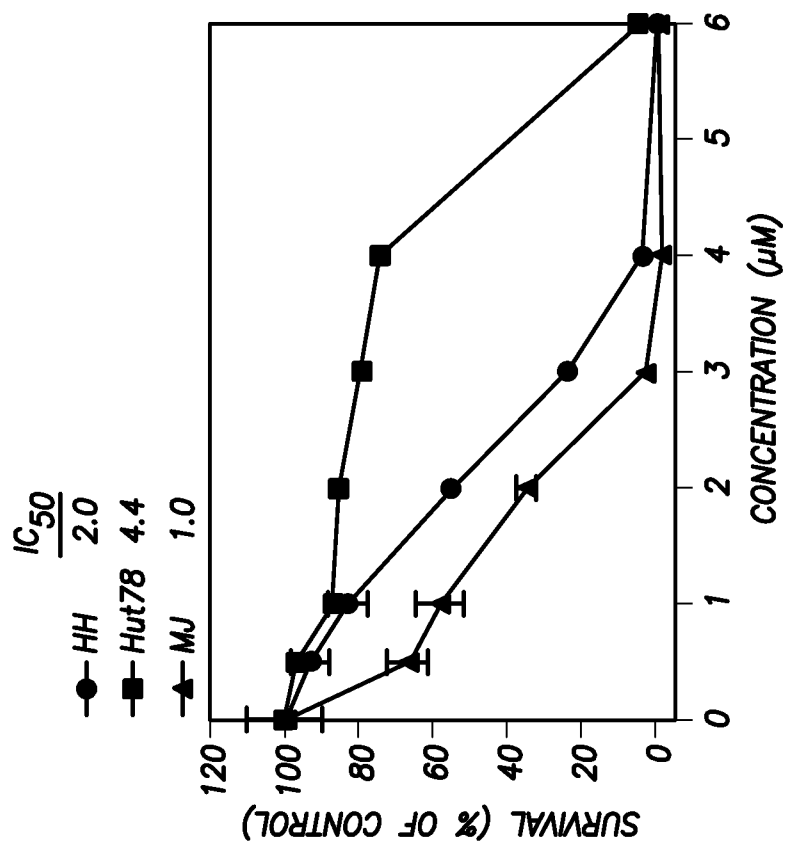
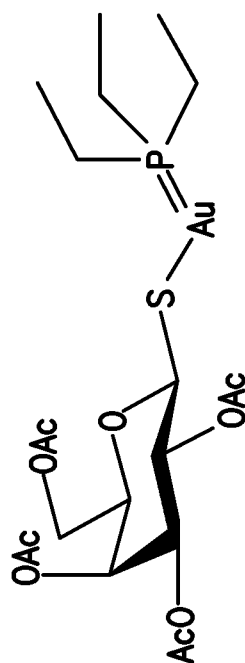


FIG.10

GALACTOSE DERIVATIVE (TK-1-79)
MW=678.48



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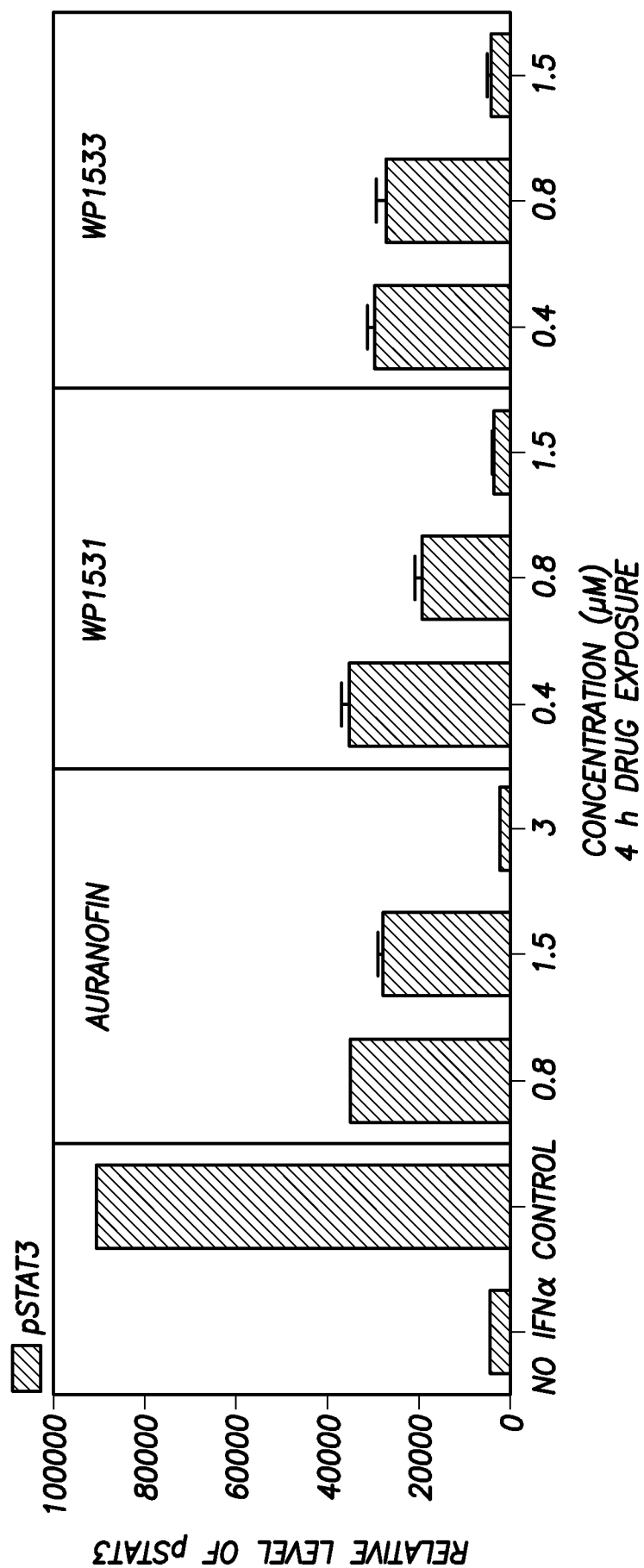
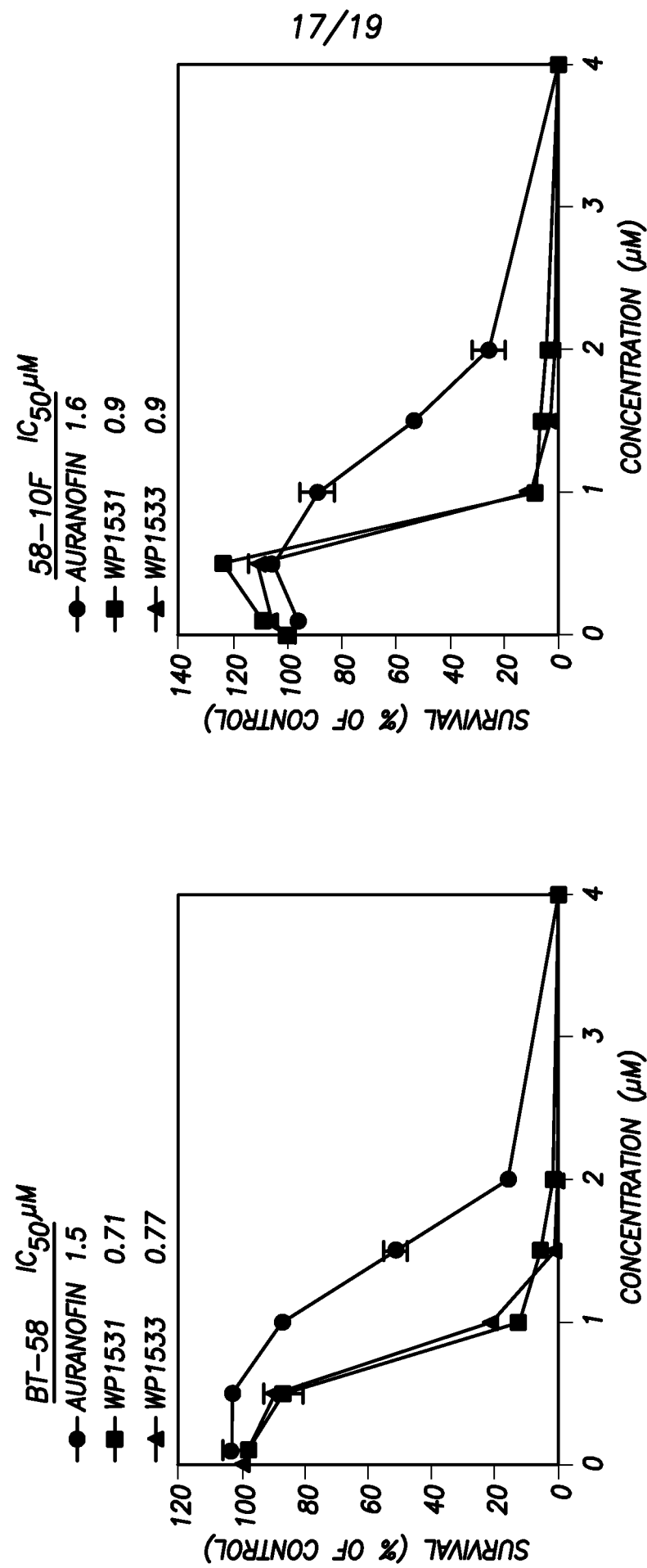


FIG.11



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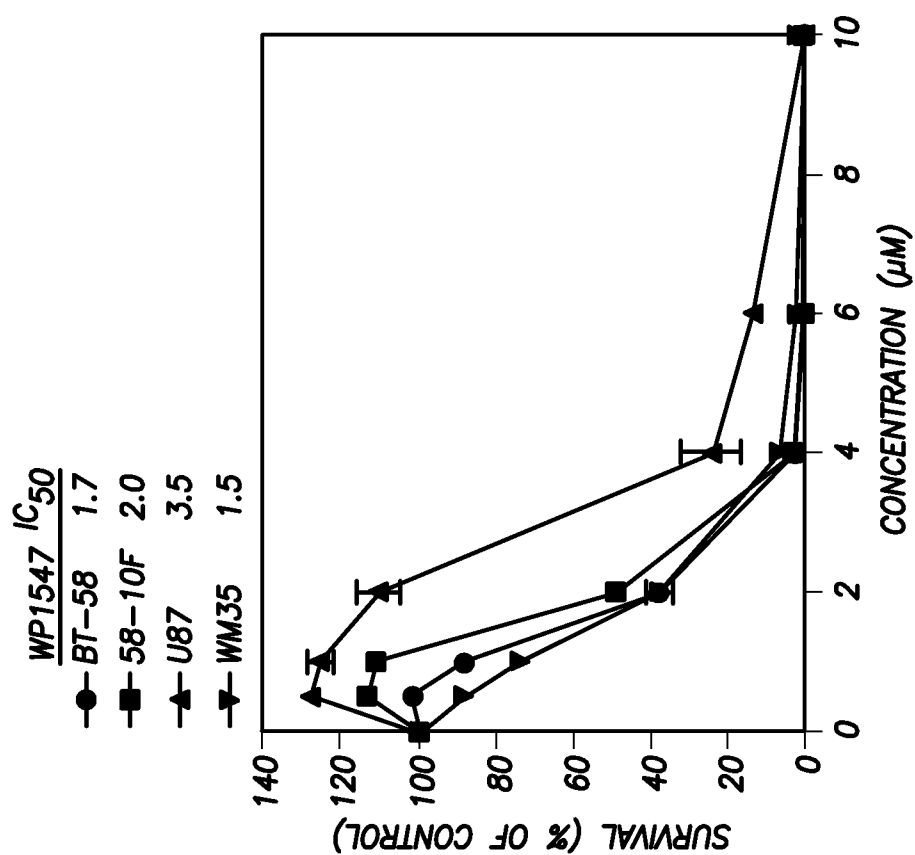
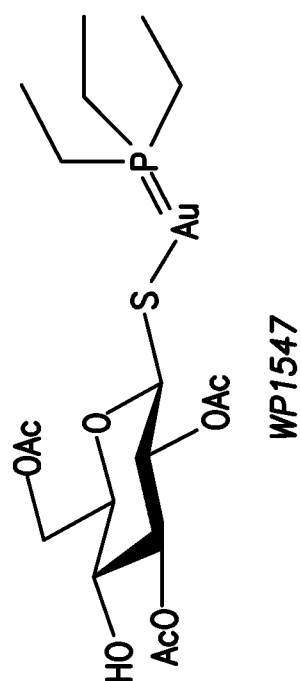


FIG.13



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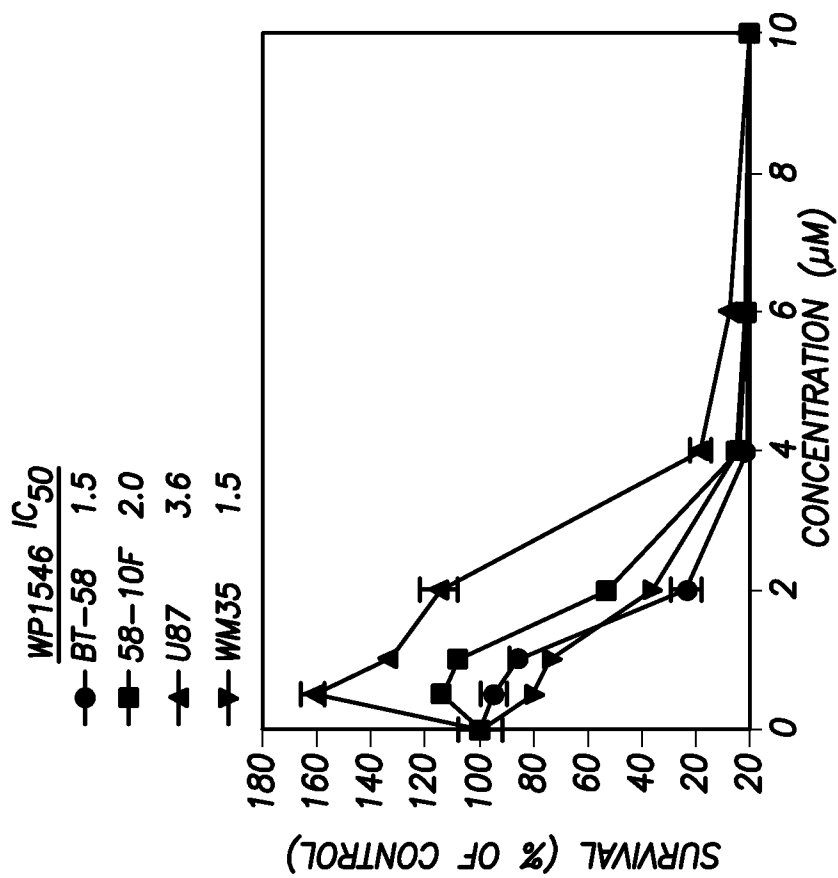


FIG.14

