



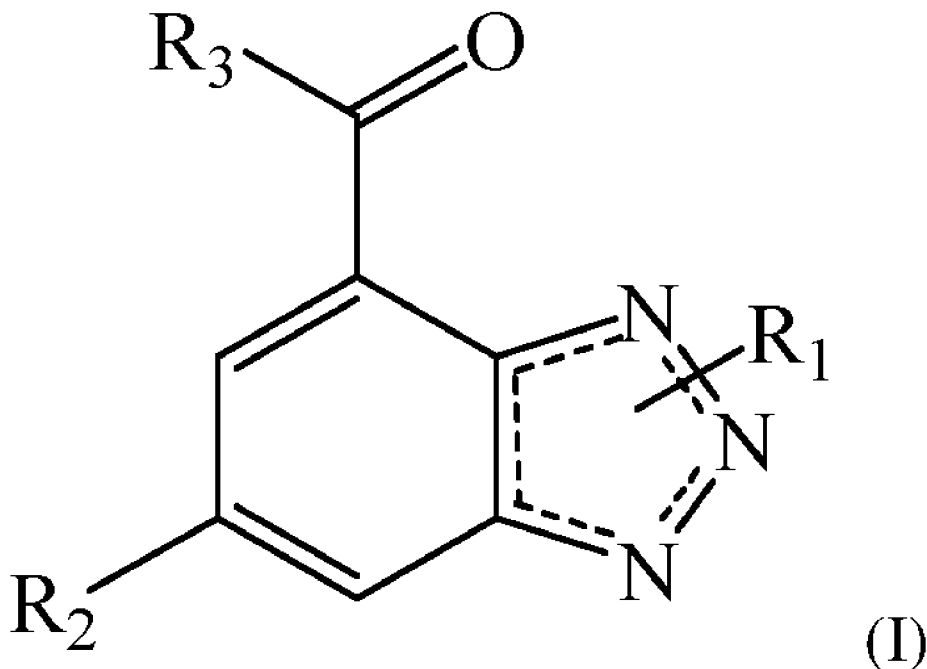
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(54) Titre : PROCÉDES D'UTILISATION DE DÉRIVÉS DE BENZOTRIAZOLE TRISUBSTITUÉS
(54) Title: METHODS OF USE FOR TRISUBSTITUTED BENZOTRIAZOLE DERIVATIVES



(57) Abrégé/Abstract:

The present invention provides methods for treating cancer in a subject with a trisubstituted benzotriazole derivative with the formula (I) or a pharmaceutically acceptable salt thereof, wherein the variables R₁, R₂ and R₃ are as defined herein.

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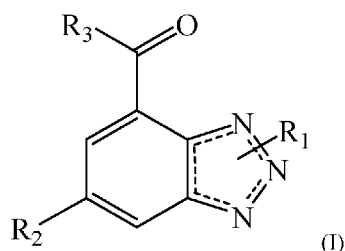
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(54) Title: METHODS OF USE FOR TRISUBSTITUTED BENZOTRIAZOLE DERIVATIVES



(57) Abstract: The present invention provides methods for treating cancer in a subject with a trisubstituted benzotriazole derivative with the formula (I) or a pharmaceutically acceptable salt thereof, wherein the variables R₁, R₂ and R₃ are as defined herein.



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METHODS OF USE FOR TRISUBSTITUTED BENZOTRIAZOLE DERIVATIVES**BACKGROUND OF THE INVENTION**5 Cross-Reference to Related Application

This application claims priority to International Patent Application No. PCT/US2018/018679, filed February 20, 2018, which is incorporated herein by reference in its entirety.

10 Field of the Invention

The present invention relates to methods of use of trisubstituted benzotriazole derivatives of formula (I), particularly methods of cancer treatment with these compounds.

Description of the Related Art

15 Lymphoma, leukemia, myeloma and myelodysplastic syndrome are the four main groups of blood or hematological cancers that are further divided into various subtypes. In the United States, it is estimated that one person in every three minutes is diagnosed with a hematological cancer and one person in every nine minutes dies from it.

Of note, acute monocytic leukemia is a distinct subtype of acute myeloid leukemia
20 (AML) with characteristic clinical features of a patient having >20% blasts in the bone marrow, of which >80% are of the monocytic lineage. Acute monocytic leukemia has been reported to have a poor prognosis compared to other subtypes of AML, and it has been shown that the disease may develop after chemotherapy exposure, particularly following epipodophyllotoxins and anthracyclines.

25 Acute lymphoblastic leukemia (ALL), another leukemia subtype, is an aggressive hematologic malignancy wherein an abnormal proliferation of lymphoblasts suppresses normal hematopoiesis resulting in progressive marrow failure and death. This particular subtype has a bimodal age distribution with an initial peak in childhood and second that increases in older adults. While outcomes for ALL in children have improved with modern
30 chemotherapy regimens, outcomes in adults remain dismal, which are attributable to a combination of increased adverse tumor biology and decreased tolerance of therapy. As a result despite a high initial remission rate most adults are destined to relapse. It has been declared that most adults with recurrent ALL “cannot be rescued with current therapies”. This

is likely the result of the fact that virtually all active therapies are used during first line treatment. There is clearly a need for additional active therapies in ALL.

A pioneering genetic evaluation of diffuse large B-cell lymphoma (DLBCL) reveals that the dual rearrangement of *MYC* and *BCL2/BCL6* occurs in approximately 5% to 7% of patients with DLBCL. This form of DLBCL has recently been re-classified as “high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements”, and is now commonly referred to as “double hit DLBCL” or “double hit lymphoma”. Sometimes, all 3 genes – *MYC*, *BCL2* and *BCL6* – are simultaneously rearranged in a phenotype termed “triple hit DLBCL” or “triple hit lymphoma”. Both double hit and triple hit lymphomas are highly proliferative and drug-resistant. Both phenotypes are also associated with an extremely poor prognosis with standard treatment, such as rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) – all of which are suboptimal. Few patients with double hit lymphoma are cured with this approach. There are retrospective reviews suggesting that a more intensive therapy, such as etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab (EPOCH-R), may be better than standard treatment. For patients who are unable to undergo transplant, or for those who relapse after a stem cell transplant, the median survival is approximately 6 months.

With non-small cell lung cancer or carcinoma (NSCLC), which accounts for about 85% of all lung cancers, surgery is the mainstay of treatment. However, only a quarter of the patients undergo successful resection, with a recurrence rate of 50%. Therapeutic approaches in advanced disease involve, following surgery, both adjuvant chemotherapy and/or adjuvant radiotherapy, whereas chemotherapy as monotherapy (first-line therapy) seems to be an approach associated with relatively poor results. In a comparison of four commonly used combination chemotherapy regimens, none was superior. Response rates varied from 15% to 22%, with 1-year survival rates of 31% to 36%. Thus, even though pre-operative chemotherapy seems to have not resulted in a prolongation of life expectancy, adjuvant chemotherapy (also if combined with radiotherapy) did show a significant increase in life expectancy.

Despite an improvement in the median overall survival for patients with advanced ovarian cancer over the decades, the disease course is one of remission and relapse requiring intermittent re-treatment. The presence of cancer cells in effusions within the serosal (peritoneal, pleural, and pericardial) cavities is a clinical manifestation of advanced stage ovarian cancer and is associated with poor survival. Unlike the majority of solid tumors,

particularly at the primary site, ovarian cancer cells in effusions are not amenable to surgical removal and failure in their eradication is one of the main causes of treatment failure.

In view of the foregoing, there remains an unmet need for new drugs that can treat aggressive lymphoma and leukemia subtypes more effectively, particularly forms of lymphoma that are refractory to standard therapy. There also exists a need for new drugs that can treat other hematological cancers that are relatively less known and understood, such as myelodysplastic syndrome and diffuse mixed cell lymphoma. In general, there is a continuing need for anti-cancer drugs with excellent potency, specificity and tolerability.

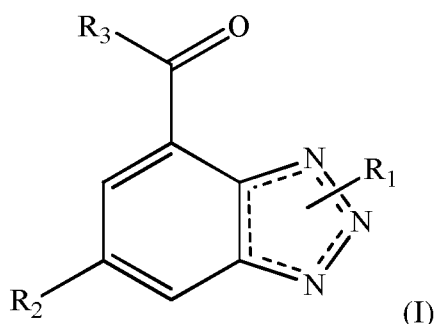
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SUMMARY OF THE INVENTION

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The present invention is directed to a method for treating a cancer selected from chemotherapy-resistant acute myeloid leukemia, cytarabine-resistant acute myeloid leukemia, acute monocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, diffuse mixed cell lymphoma, myelodysplastic syndrome, primary effusion lymphoma, erythroleukemia, chronic myeloid leukemia, chronic monocytic leukemia, double hit diffuse large B cell lymphoma, triple hit diffuse large B cell lymphoma, biliary tract cancer or cancer of the ampulla of Vater, non-small cell lung cancer, bronchoalveolar carcinoma, liver cancer, cancer of the ovary, and cancer of the upper aerodigestive tract in a subject. The method comprises the step of administering to the subject one or more times a therapeutically effective amount of a compound represented by formula (I):



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or a pharmaceutically acceptable salt thereof. In the structure, the dotted lines [...] in the ring represent an optional bond which is be present in any stable combination. R₁ is selected from hydrogen and alkyl; R₂ is -A-R₄; A is arylene or tetrasubstituted arylene; wherein the substituent is halogen; R₃ is selected from hydroxy and amino; R₄ is selected from an aryl and a heteroaryl that is optionally substituted with one or more R₅; and R₅ is selected from alkyl and -(CH₂)_nN(R_a)R_b. R_a and R_b are independently selected from hydrogen, alkyl and –

C(O)alkyl; alternatively R_a and R_b can be taken together with the nitrogen atom to which they are attached to form a 4-6 membered heterocyclyl containing 0-2 additional heteroatoms independently selected from O and N and is optionally substituted with alkyl. n is an integer selected from 0 and 1.

5

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the sensitivity of a panel of ~400 human cancer lines of hemapoietic and non-hemapoietic origin towards growth inhibition by Compound 1 of the invention.

FIG. 2 shows the sensitivity of an additional panel of human cancer lines of heme lineage towards growth inhibition by Compound 1 of the invention.

FIG. 3 shows the 4-day and 7-day relative growth curves of the THP-1 cell line treated with Compound 1.

FIG. 4 shows the 4-day and 7-day relative growth curves of the HT cell line treated with Compound 1.

FIG. 5A shows the relative growth rate vs. concentration sensitivity profiles of MV411, Kasumi-1, THP-1, DB, Toledo and WSU-DLCL2 cell lines towards varying concentrations of Compound 1.

FIG. 5B shows the relative growth rate vs. concentration sensitivity profiles of MV411, Kasumi-1, THP-1, DB, Toledo and WSU-DLCL2 cell lines towards varying concentrations of cytarabine.

FIG. 5C shows the relative growth rate vs. concentration sensitivity profiles of MV411, Kasumi-1, THP-1, DB, Toledo and WSU-DLCL2 cell lines towards varying concentrations of doxorubicin.

FIG. 6 is a curve showing the relative growth rate of OCILY18, SC-1 and CARNAVAL double hit diffuse large B cell lymphoma (DLBCL) cell lines treated with various concentrations of Compound 1 for 96 hours.

FIG. 7A shows OCILY-19 double hit diffuse large B cell lymphoma (DLBCL) tumor growth curves in CB17 SCID mice when left untreated (vehicle) or treated with 10 mg/kg of Compound 1, BID; 30 mg/kg of Compound 1, BID; 100 mg/kg of Compound 1, BID; and 200 mg/kg of Compound 1, QD, all measured over the course of 14 days.

FIG. 7B shows the pharmacokinetic profiles of Compound 1, administered at the dosages described for FIG. 7A, in the plasma of the CB17 SCID mice, at the indicated timepoints following the last dose at end of study.

5 FIG. 7C shows the DHO levels in the untreated (vehicle) OCILY-19 tumors and tumors treated with compound 1 at the indicated doses, measured over the course of 12 hours following the last dose at end of study.

FIG. 7D shows the uridine levels in the untreated (vehicle) OCILY-19 tumors and tumors treated with compound 1 at the indicated doses, measured over the course of 12 hours following the last dose at end of study.

10 FIG. 8 shows patient-derived DLBCL_1 (triple hit DLBCL) tumor growth curves in CB17 SCID mice when left untreated (vehicle) or treated with 100 mg/kg of Compound 1, BID.

DETAILED DESCRIPTION OF THE INVENTION

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The present invention further relates to a method for treating a cancer selected from chemotherapy-resistant acute myeloid leukemia, cytarabine-resistant acute myeloid leukemia, acute monocytic leukemia, acute lymphoblastic leukemia, diffuse mixed cell lymphoma, myelodysplastic syndrome, primary effusion lymphoma, erythroleukemia, 20 chronic myeloid leukemia, chronic monocytic leukemia, B-cell lymphoma, double hit diffuse large B cell lymphoma, triple hit diffuse large B cell lymphoma, biliary tract cancer or cancer of the ampulla of Vater, non-small cell lung cancer, bronchoalveolar carcinoma, liver cancer, cancer of the ovary, and cancer of the upper aerodigestive tract in a subject, comprising the step of administering to the subject a therapeutically effective amount of a compound represented by formula (I) or a pharmaceutically acceptable salt 25 thereof or a pharmaceutical composition comprising the same.

In one embodiment, the cancer treated in the method is chemotherapy-resistant acute myeloid leukemia. In one embodiment, the cancer treated in the method is cytarabine-resistant acute myeloid leukemia. In one embodiment, the cancer treated in the method is acute monocytic leukemia. In one embodiment, the cancer treated in the method is acute lymphoblastic leukemia. In one embodiment, the cancer treated in the method is diffuse mixed cell lymphoma. In one embodiment, the cancer treated in the method is myelodysplastic syndrome. In one embodiment, the cancer treated in the method is primary effusion lymphoma. In one embodiment, the cancer treated in the method is 30

erythroleukemia. In one embodiment, the cancer treated in the method is chronic myeloid leukemia. In one embodiment, the cancer treated in the method is chronic monocytic leukemia. In one embodiment, the cancer treated in the method is B-cell lymphoma. In one embodiment, the cancer treated in the method is biliary tract cancer or cancer of the ampulla of Vater. In one embodiment, the cancer treated in the method is non-small cell lung cancer. In one embodiment, the cancer treated in the method is bronchoalveolar carcinoma. In one embodiment, the cancer treated in the method is liver cancer. In one embodiment, the cancer treated in the method is cancer of the ovary. In one embodiment, the cancer treated in the method is cancer of the upper aerodigestive tract.

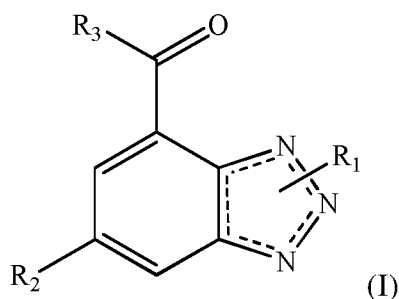
As used herein, “chemotherapy-resistant acute myeloid leukemia” refers to a form of acute myeloid leukemia that is resistant or refractory to standard chemotherapy for acute myeloid leukemia. In one embodiment, the standard chemotherapy for acute myeloid leukemia comprises one or more approved chemotherapeutic agents selected from cytarabine, doxorubicin, daunorubicin (daunomycin), idarubicin, clardribine (Leustatin[®], 2-CdA), fludarabine (Fludara[®]), topotecan, etoposide (VP-16), 6-thioguanine or 6-TG, hydroxyurea (Hydrea[®]), corticosteroids (*e.g.*, prednisone or dexamethasone (Decadron[®]), methotrexate or MTX, 6-mercaptopurine or 6-MP, azacitidine (Vidaza[®]), decitabine (Dacogen[®]).

As used herein, “cytarabine-resistant acute myeloid leukemia” refers to a form of acute myeloid leukemia that is resistant or refractory to treatment of the disease with cytarabine, alone or in combination with one or more additional therapeutic agents.

As used herein, “double hit diffuse large B cell lymphoma” refers to a form of lymphoma or diffuse large B cell lymphoma where the lymphoma cells are altered at two oncogenes which are *c-MYC* and *BCL2* or *BCL6*. In one embodiment, double hit diffuse large B cell lymphoma is treated in the method, and is characterized by gene alterations at *c-MYC* and *BCL2*. In another embodiment, double hit diffuse large B cell lymphoma is treated in the method, and is characterized by gene alterations at *c-MYC* and *BCL6*.

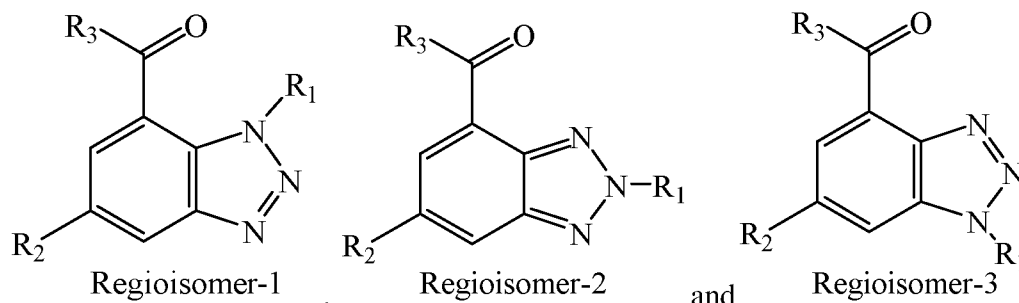
As used herein, “triple hit diffuse large B cell lymphoma” refers to a form of lymphoma or diffuse large B cell lymphoma where the lymphoma cells are altered at three oncogenes which are *c-MYC*, *BCL2* and *BCL6*. In one embodiment, triple hit diffuse large B cell lymphoma is treated in the method.

In accordance with the present invention, the compound used in the method of treatment is represented by formula (I):



or a pharmaceutically acceptable salt, wherein the dotted lines [...] in the ring represent an optional bond which is present in any stable combination R_1 is selected from hydrogen and alkyl; R_2 is $-A-R_4$; A is arylene or tetrasubstituted arylene; wherein the substituent is halogen; R_3 is selected from hydroxy and amino; R_4 is selected from an aryl and a heteroaryl that is optionally substituted with one or more R_5 ; and R_5 is selected from alkyl and $-(CH_2)_nN(R_a)R_b$. R_a and R_b are independently selected from hydrogen, alkyl and $-C(O)alkyl$; alternatively R_a and R_b can be taken together with the nitrogen atom to which they are attached to form a 4-6 membered heterocyclyl containing 0-2 additional heteroatoms independently selected from O and N and is optionally substituted with alkyl. n is an integer selected from 0 and 1.

The compound represented by formula (I) described herein includes a regioisomer having any one of the following structures:

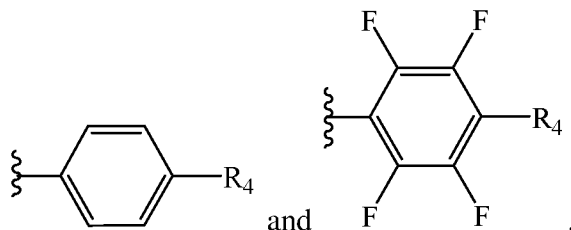


Since the pharmaceutical activity of the regioisomers may differ, it may be desirable to use a specific regioisomer or a mixture of regioisomers. In such cases, a regioisomer can be separated at any of the possible stage either as an intermediate or as an end product by one or more processes well known to the person skilled in the art or even employed as such in the synthesis.

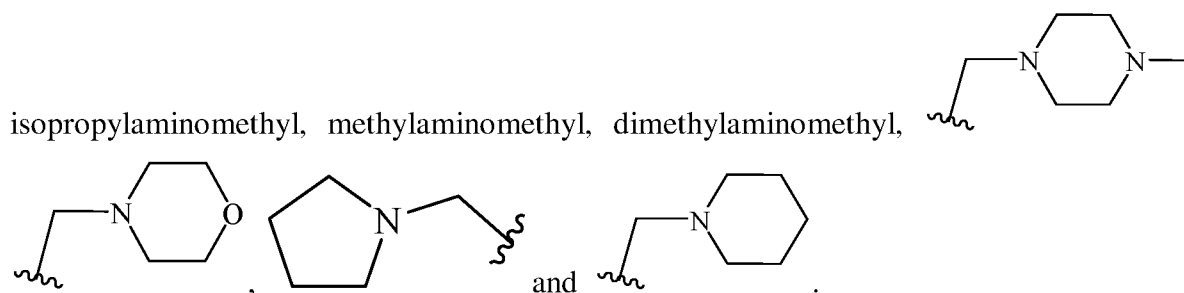
According to one embodiment, provided is a compound represented by formula (I), or a pharmaceutically acceptable salt thereof, in which R_1 is alkyl; in particular alkyl is methyl.

According to another embodiment, provided is a compound represented by formula (I), in which R_2 is $-A-R_4$; in which $-A-$ is selected from arylene and tetrasubstituted arylene.

According to another embodiment, provided is a compound represented by formula (I), or a pharmaceutically acceptable salt thereof, in which R₂ is selected from



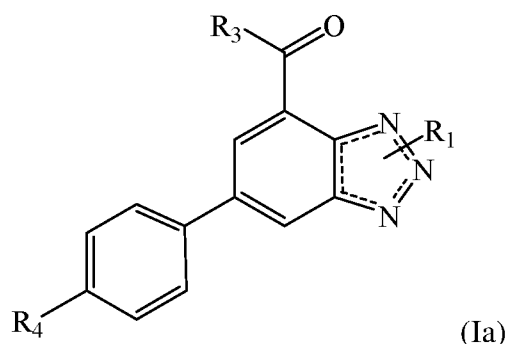
5 According to another embodiment, provided is a compound represented by formula (I), or a pharmaceutically acceptable salt thereof, in which R₄ is selected from optionally substituted phenyl; in which optional substituents are selected from methyl, acetylamino,



10 According to another embodiment, provided is a compound represented by formula (I), or a pharmaceutically acceptable salt thereof, in which R₄ is selected from 2,5-dimethyl-1H-pyrrole.

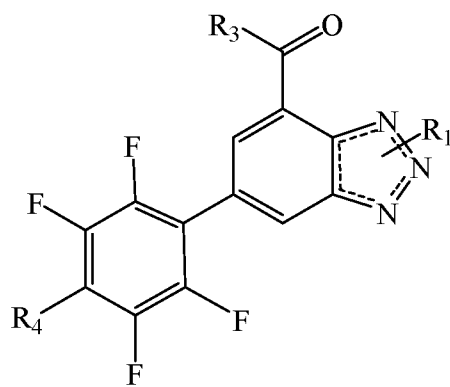
According to another embodiment, provided is a compound represented by formula (I), or a pharmaceutically acceptable salt thereof, in which R₃ is -OH and -NH₂.

15 According to yet another particular embodiment, a compound of the present invention is a compound represented by formula (Ia):



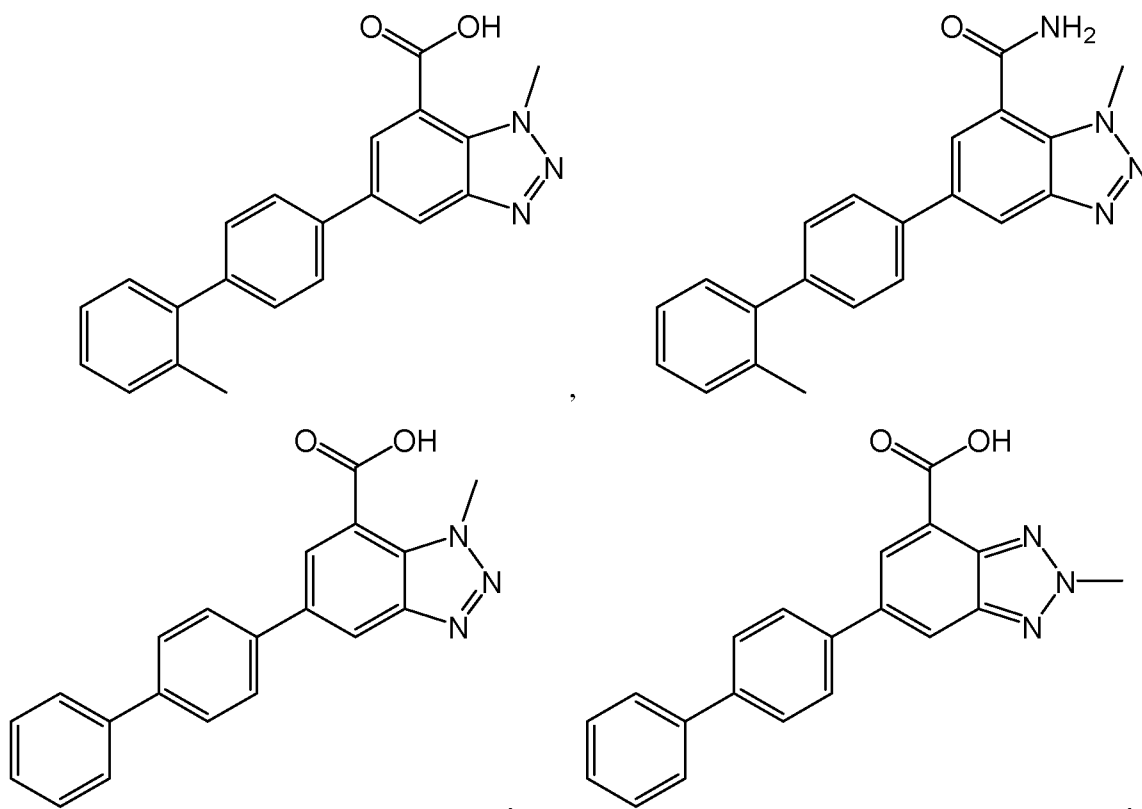
or a pharmaceutically acceptable salt thereof, wherein the dotted line [---], R₁, R₃ and R₄ are same as defined for formula (I).

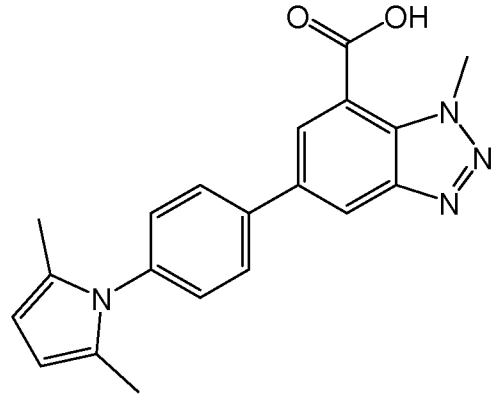
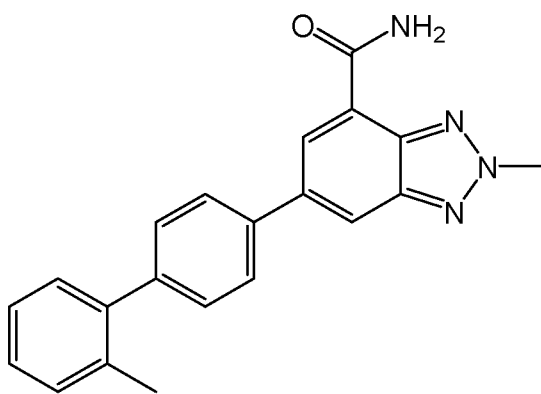
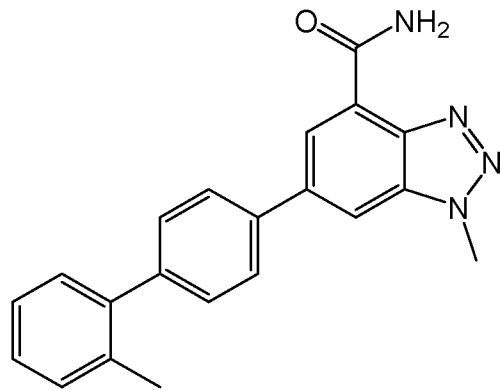
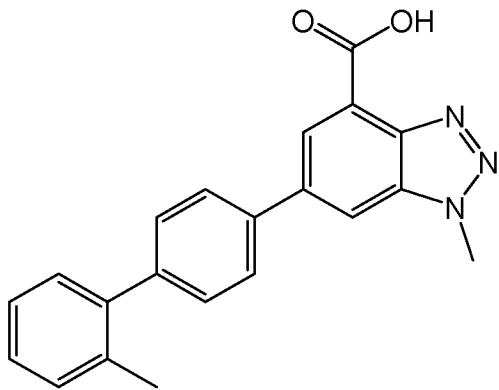
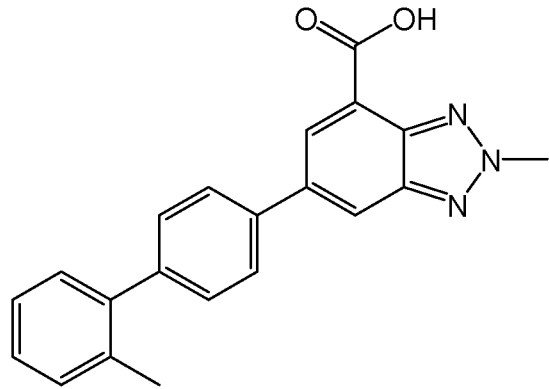
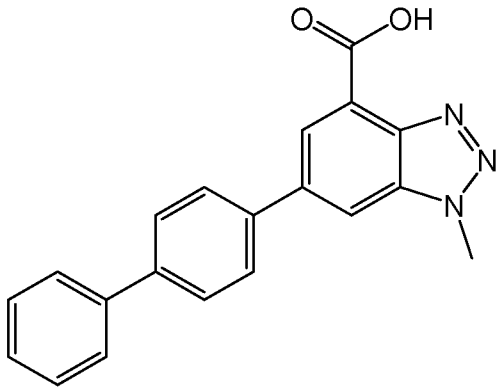
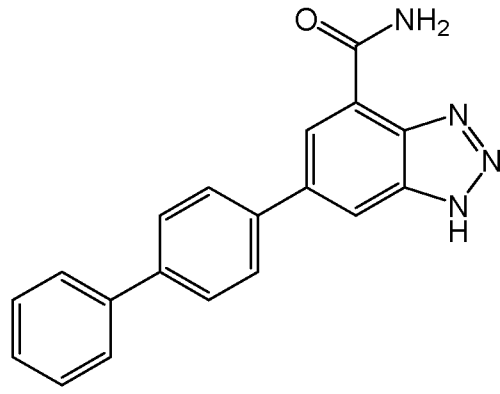
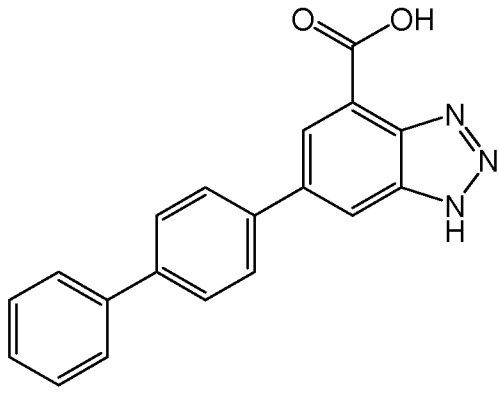
20 According to yet another particular embodiment, a compound of the present invention is a compound represented by formula (Ib):

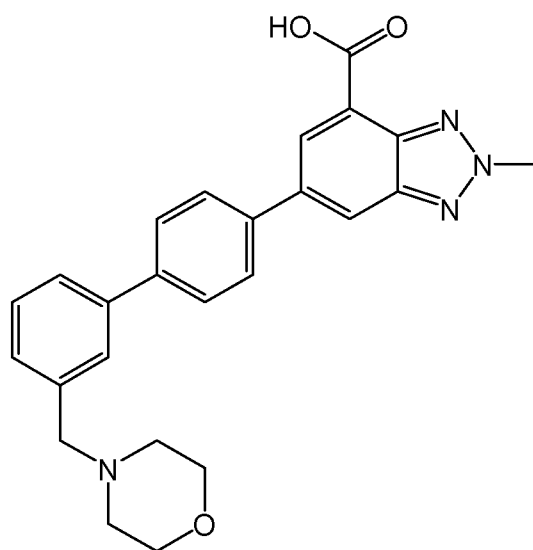
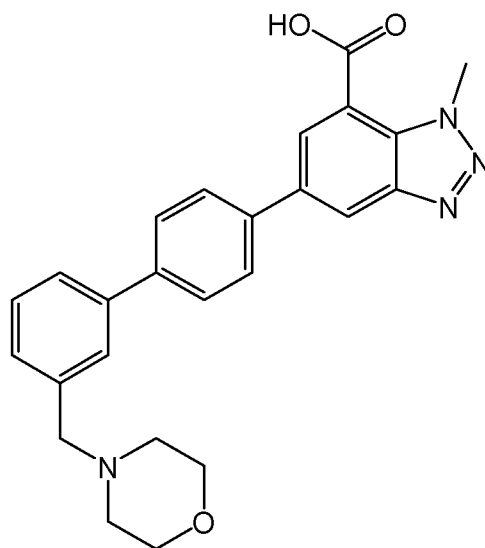
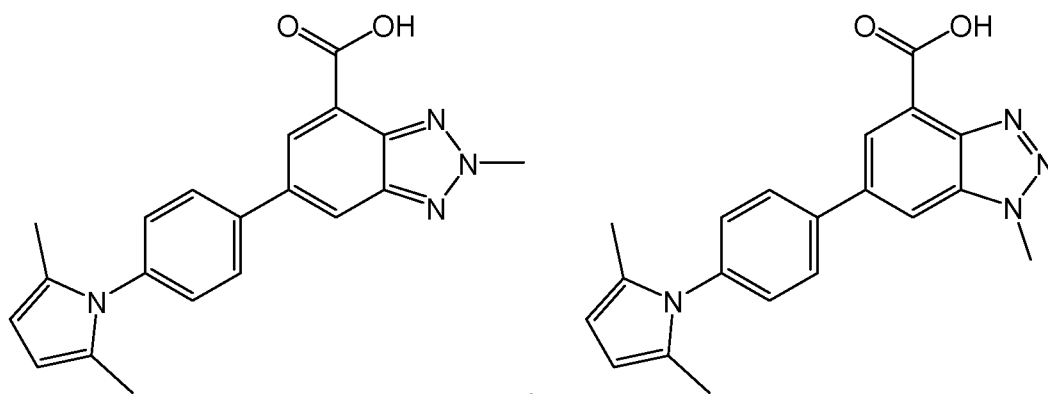


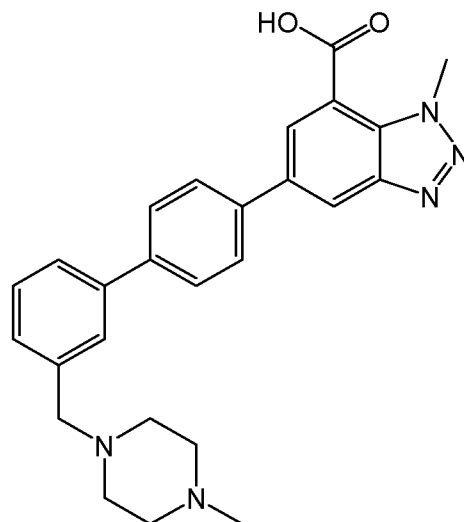
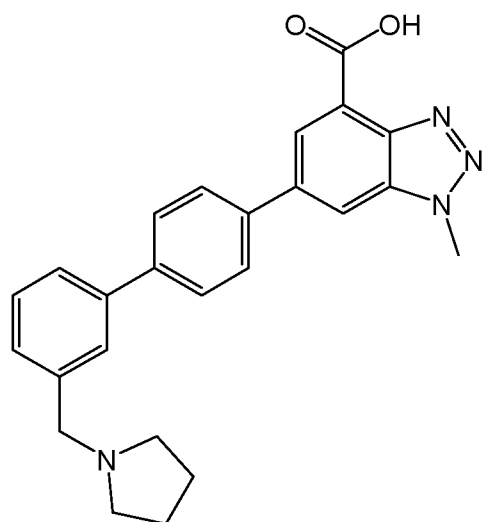
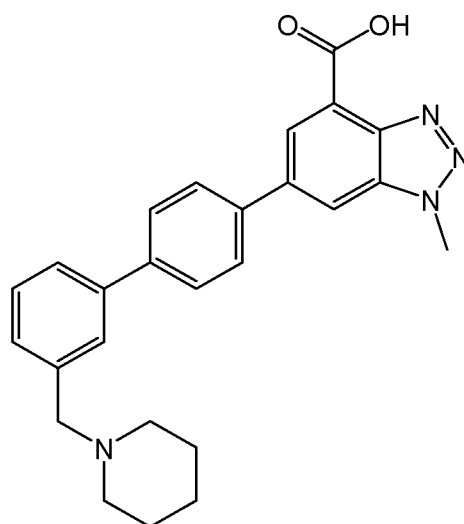
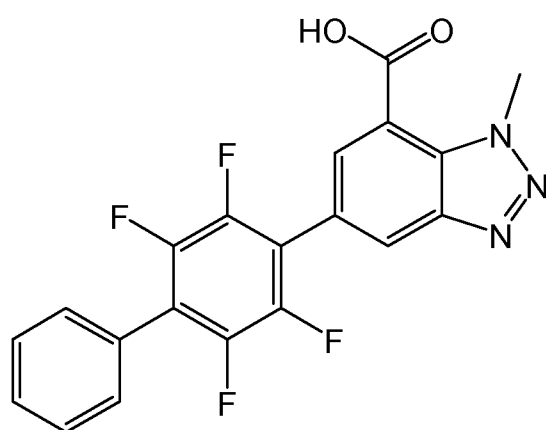
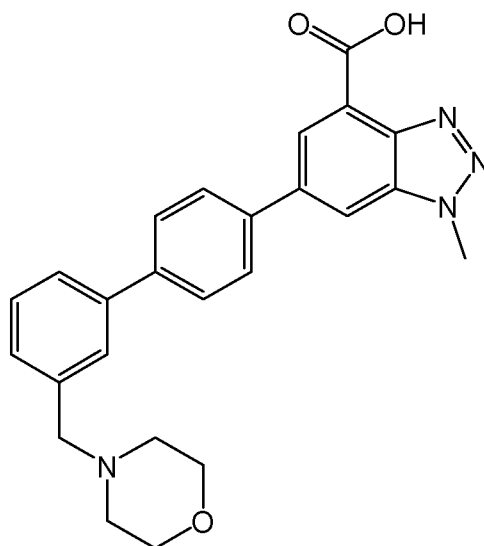
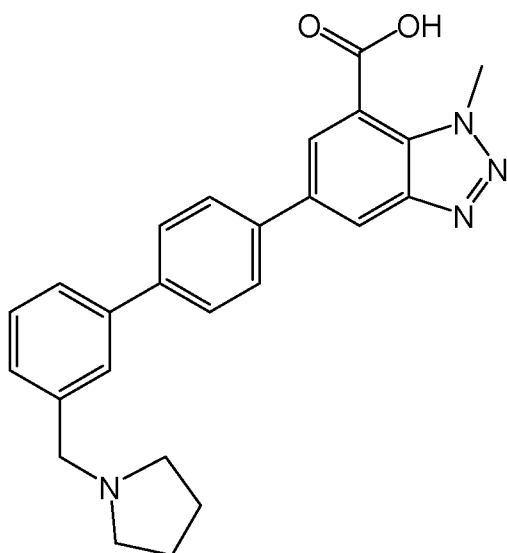
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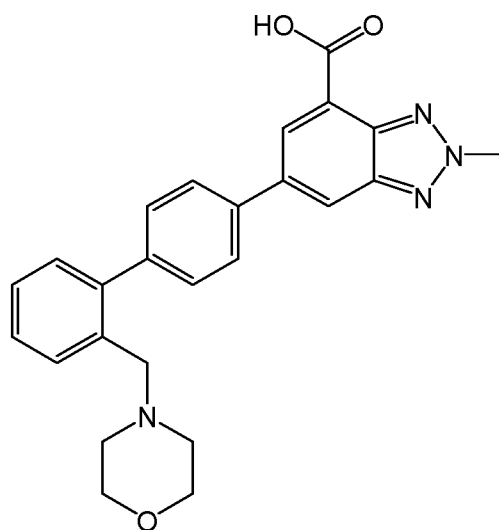
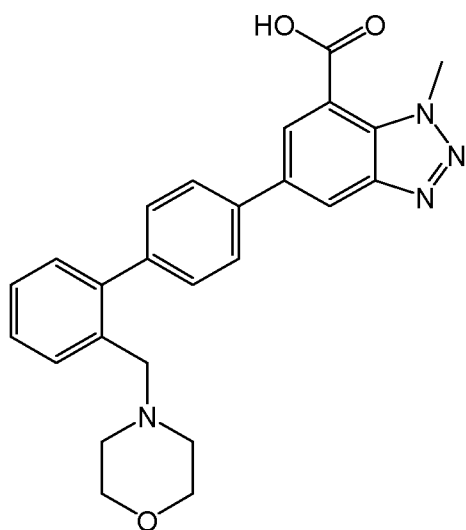
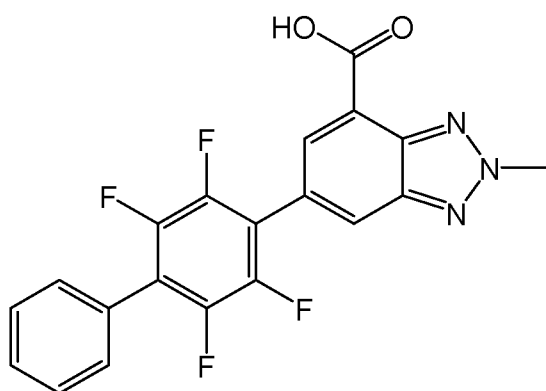
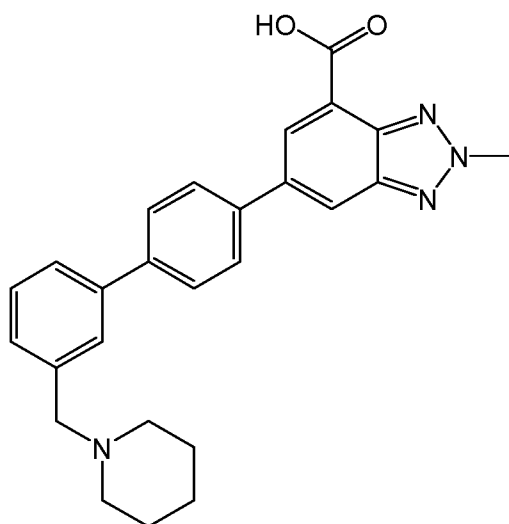
5 Examples of compounds that can be used in the disclosed treatment methods include:

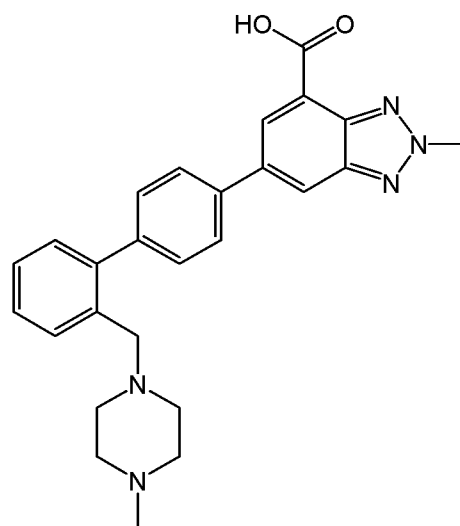
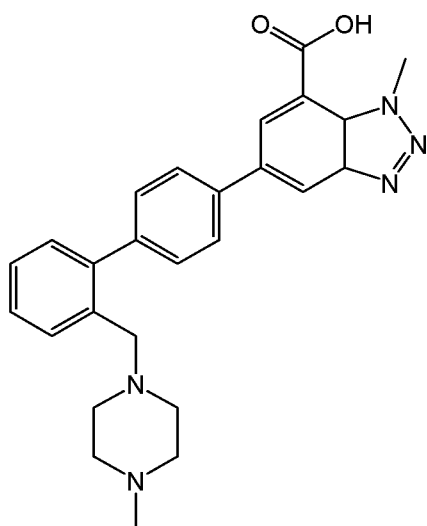
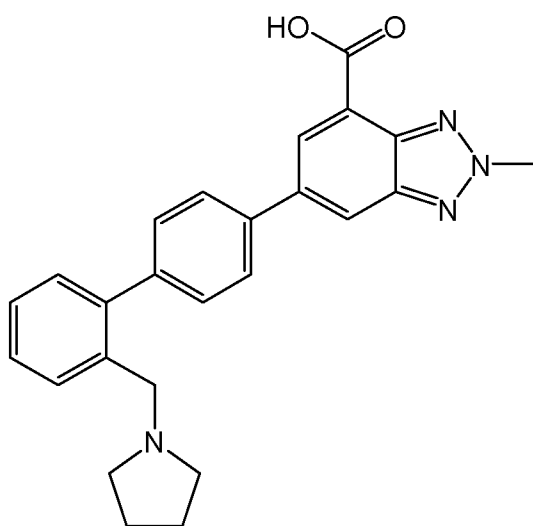
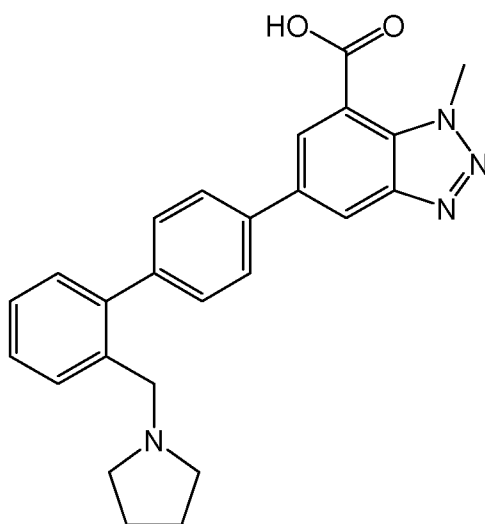


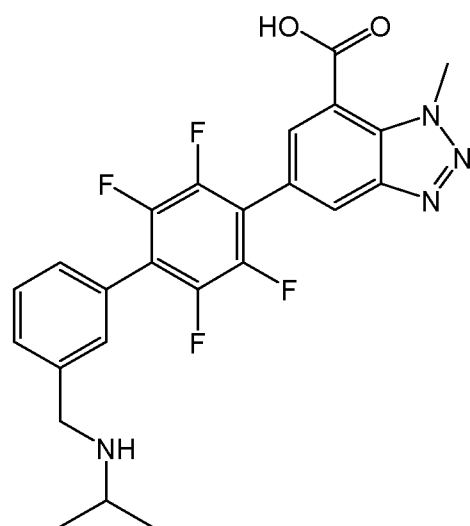
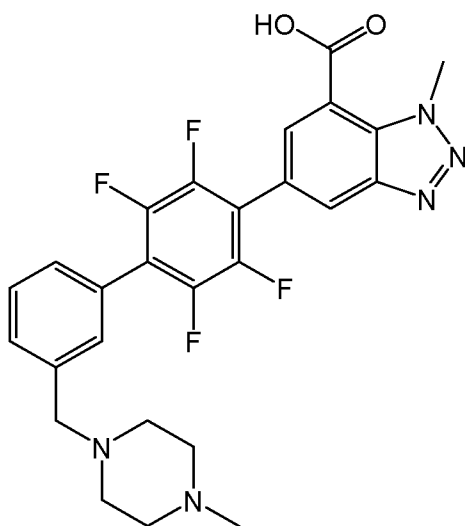
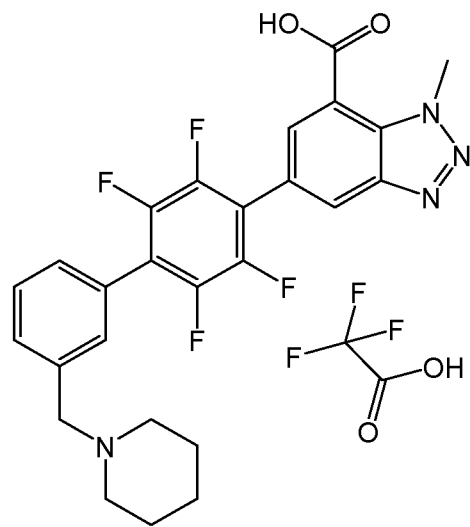
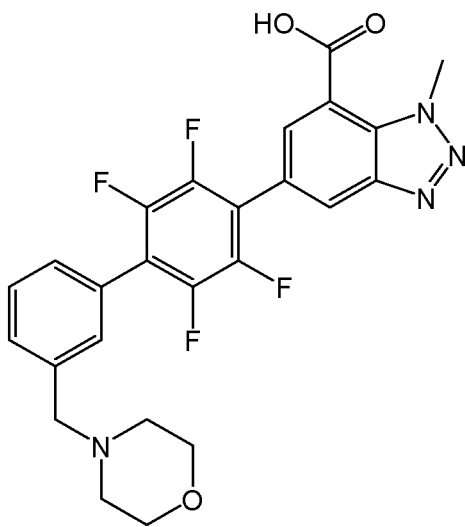
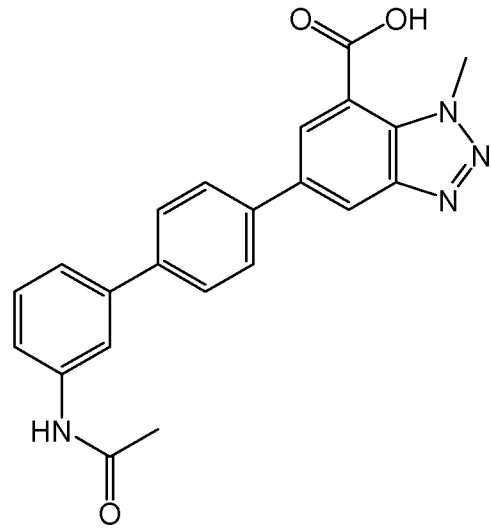
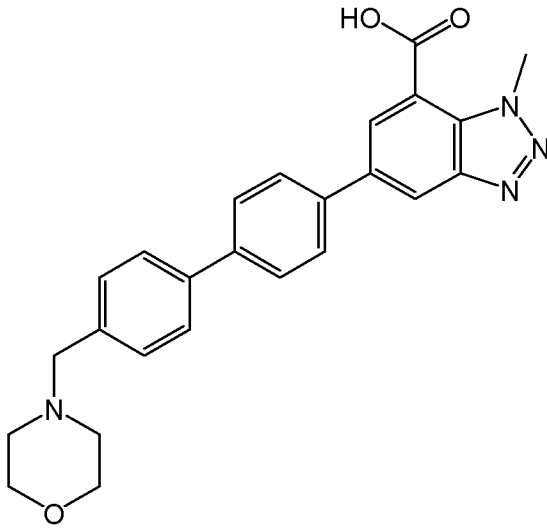


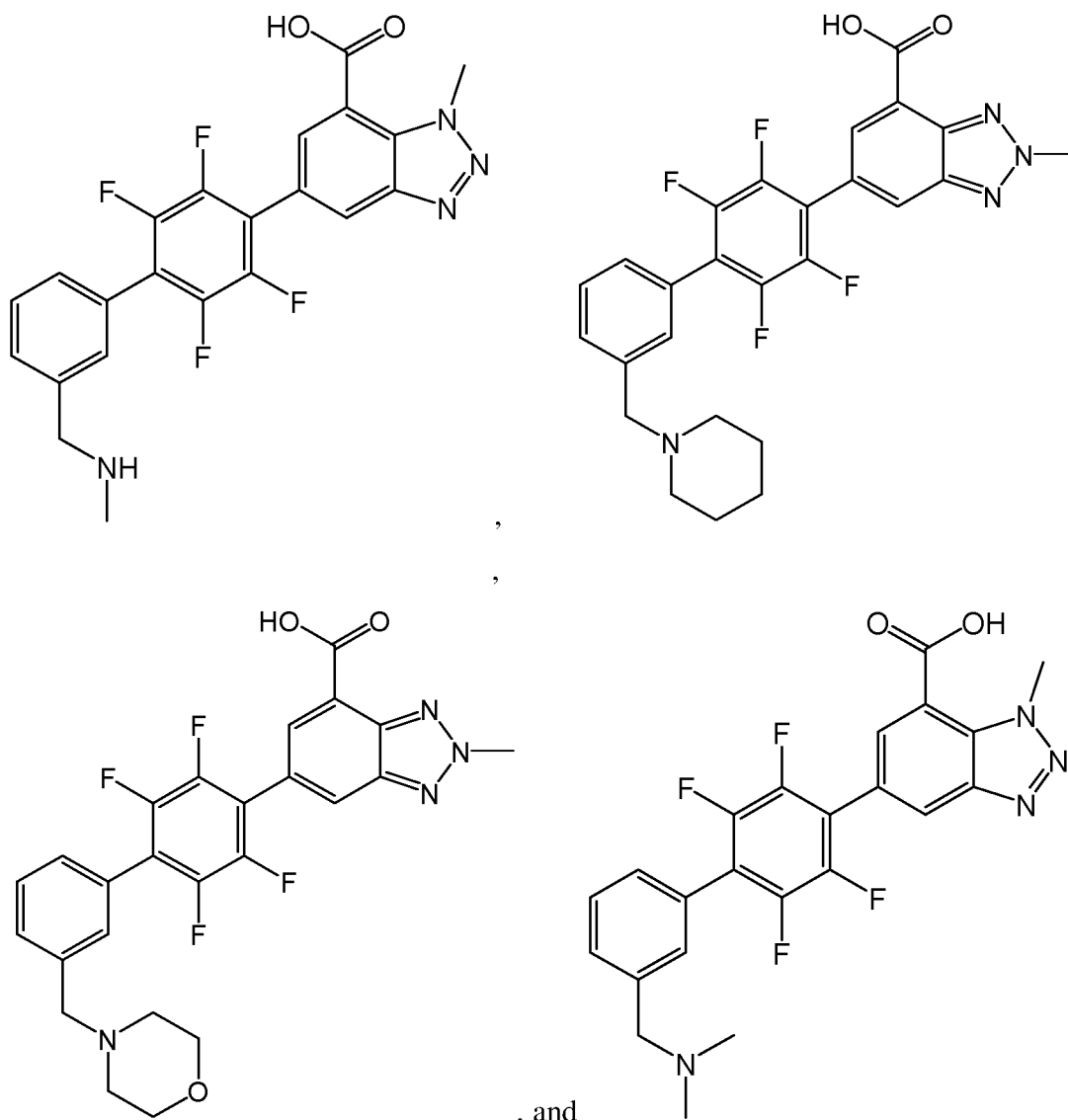












or a pharmaceutically acceptable salt thereof.

5 As used herein, “alkyl” refers to a hydrocarbon chain that may be a linear or branched chain, containing the indicated number of carbon atoms, for example, a C₁-C₆ alkyl group may have from 1 to 6 (inclusive) carbon atoms in it. Examples of C₁-C₄ and C₁-C₆ alkyl groups include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl, and isohexyl. An alkyl group
10 can be unsubstituted or substituted with one or more suitable groups.

As used herein, “amino” refers to an -N- group, the nitrogen atom of said group being attached to a hydrogen, alkyl, cycloalkyl, aryl, heterocyclyl or any suitable groups. Representative examples of an amino group include, but are not limited to -NH₂, -NHCH₃ and -NH-cyclopropyl. An amino group can be unsubstituted or substituted with one or more
15 of the suitable groups.

As used herein, "aryl" refers to an optionally substituted monocyclic, bicyclic or polycyclic aromatic carbocyclic ring system of about 6 to 14 carbon atoms. Examples of a C₆-C₁₄ aryl group include, but are not limited to phenyl, naphthyl, biphenyl, anthryl, tetrahydronaphthyl, fluorenyl, indanyl, biphenylenyl, and acenaphthyl. Aryl group which can
5 be unsubstituted or substituted with one or more suitable groups.

As used herein, "arylene" denotes a divalent monocyclic or bicyclic, saturated, unsaturated or aromatic carbocyclic ring having 6 to 14 carbon atoms which may be unsubstituted or substituted with one or more suitable groups.

As used herein, "halogen" or "halo" includes fluorine, chlorine, bromine or iodine.

10 As used herein, "hydroxy" refers to -OH group.

As used herein, "heterocyclyl" includes the definitions of "heterocycloalkyl" and "heteroaryl". The term "heterocycloalkyl" refers to a non-aromatic, saturated or partially saturated, monocyclic or polycyclic ring system of 3 to 10 member having at least one heteroatom or heterogroup selected from O, N, S, S(O), S(O)₂, NH and C(O). Exemplary
15 heterocycloalkyl groups include piperdiny, piperaziny, morpholiny, thiomorpholiny, 1,3-dioxolany, 1,4-dioxany and the like. A heterocycloalkyl group can be unsubstituted or substituted with one or more suitable groups.

As used herein, "heteroaryl" refers to an unsaturated, monocyclic, bicyclic, or polycyclic aromatic ring system containing at least one heteroatom selected from oxygen,
20 sulphur and nitrogen. Examples of C₅-C₁₀ heteroaryl groups include furan, thiophene, indole, azaindole, oxazole, thiazole, thiadiazole, isoxazole, isothiazole, imidazole, N-methylimidazole, pyridine, pyrimidine, pyrazine, pyrrole, N-methylpyrrole, pyrazole, N-methylpyrazole, 1,3,4-oxadiazole, 1,2,4-triazole, 1-methyl-1,2,4-triazole, 1H-tetrazole, 1-methyltetrazole, benzoxazole, benzothiazole, benzofuran, benzisoxazole, benzimidazole, N-
25 methylbenzimidazole, azabenzimidazole, indazole, quinazoline, quinoline, and isoquinoline. Bicyclic heteroaryl groups include those where a phenyl, pyridine, pyrimidine or pyridazine ring is fused to a 5 or 6-membered monocyclic heterocyclyl ring having one or two nitrogen atoms in the ring, one nitrogen atom together with either one oxygen or one sulfur atom in the ring, or one O or S ring atom. A heteroaryl group can be unsubstituted or substituted with one
30 or more suitable groups.

As used herein, "heteroatom" refers to a sulfur, nitrogen or oxygen atom.

"Optionally substituted or substituted" as used herein means that at least one hydrogen atom of the optionally substituted group has been substituted with suitable substitutions as exemplified but not limited to halogen, nitro, cyano, hydroxy, oxo (=O), thio (=S), -N(C₁-

C₃alkyl)C(O)(C₁-C₆alkyl), -NHC(O)(C₁-C₆alkyl), -NHC(O)(cycloalkyl), -NHC(O)(aryl), -NHC(O)(heterocyclyl), -NHC(O)(heteroaryl), -NHC(O)H, -C(O)NH₂, -C(O)NH(C₁-C₆alkyl), -C(O)NH(cycloalkyl), -C(O)NH(heterocyclyl), -C(O)NH(heteroaryl), -C(O)N(C₁-C₆alkyl)(C₁-C₆alkyl), -S(O)NH(C₁-C₆alkyl), -S(O)₂NH(C₁-C₆alkyl), -S(O)NH(cycloalkyl), -S(O)₂NH(cycloalkyl), carboxy, -C(O)O(C₁-C₆alkyl), -C(O)(C₁-C₆alkyl), =N-OH, substituted or unsubstituted alkyl, substituted or unsubstituted haloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted haloalkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring.

As used herein, “pharmaceutically acceptable salt” is taken to mean an active ingredient, which comprises a compound of the formula (I) in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic properties on the active ingredient compared with the free form of the active ingredient or any other salt form of the active ingredient used earlier. The pharmaceutically acceptable salt form of the active ingredient can also provide this active ingredient for the first time with a desired pharmacokinetic property which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active ingredient with respect to its therapeutic efficacy in the body.

As used herein, the term “subject” and “patient” may be used interchangeably, and means a mammal in need of treatment, e.g., companion animals (e.g., dogs, cats and the like), farm animals (e.g., cows, pigs, horses, sheep, goats and the like) and laboratory animals (e.g., rats, mice, guinea pigs and the like). Typically, the subject is a human in need of treatment.

As used herein, the term “treating” or “treatment” refers to obtaining desired pharmacological and/or physiological effect. The effect can be therapeutic, which includes achieving, partially or substantially, one or more of the following results: partially or totally reducing the extent of the disease, disorder or syndrome; ameliorating or improving a clinical symptom or indicator associated with the disorder; and delaying, inhibiting or decreasing the likelihood of the progression of the disease, disorder or syndrome.

The term “a therapeutically effective amount” means an amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof, e.g., 0.1 mg to 1000 mg/kg body weight, when administered to a subject, which results in beneficial or desired results,

including clinical results, i.e., reversing, alleviating, inhibiting, reducing or slowing the progression of a disease or condition treatable by a compound of formula (I), or a pharmaceutically acceptable salt thereof, reducing the likelihood of recurrence of a disease or condition treatable by a compound of formula (I), or a pharmaceutically acceptable salt thereof or one or more symptoms thereof, e.g., as determined by clinical symptoms, compared to a control. The expression “therapeutically effective amount” also encompasses the amounts which are effective for increasing normal physiological function.

The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” refers to a non-toxic carrier, diluent, adjuvant, vehicle or excipient that does not adversely affect the pharmacological activity of the compound with which it is formulated, and which is also safe for human use. Pharmaceutically acceptable carriers that may be used in the compositions of this disclosure include, but are not limited to, ion exchangers, alumina, aluminum stearate, magnesium stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances (e.g., microcrystalline cellulose, hydroxypropyl methylcellulose, lactose monohydrate, sodium lauryl sulfate, and crosscarmellose sodium), polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

Pharmaceutical formulations can be adapted for administration via any desired suitable method, for example by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) methods. Such formulations can be prepared using all processes known in the pharmaceutical art by, for example, combining the active ingredient with the excipient(s) or adjuvant(s).

Pharmaceutical formulations adapted for oral administration can be administered as separate units, such as, for example, capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or foam foods; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For example, in the case of oral administration as tablet or capsule, the active-ingredient component can be combined with an oral, non-toxic and pharmaceutically acceptable inert excipient, such as, for example, ethanol, glycerol, water and the like.

Powders are prepared by comminuting the compound to a suitable fine size and mixing it with a pharmaceutical excipient comminuted in a similar manner, such as, for example, an edible carbohydrate, such as, for example, starch or mannitol. A flavour, preservative, dispersant and dye may likewise be present.

5 Capsules are produced by preparing a powder mixture as described above and filling shaped gelatine shells therewith. Glidants and lubricants, such as, for example, highly disperse silicic acid, talc, magnesium stearate, calcium stearate or polyethylene glycol in solid form can be added to the powder mixture before the filling operation. A disintegrant or solubiliser, such as, for example, agar-agar, calcium carbonate or sodium carbonate, may
10 likewise be added in order to improve the availability of the medica-ment after the capsule has been taken.

In addition, if desired or necessary, suitable binders, lubricants and disintegrants as well as dyes can likewise be incorporated into the mixture. Suitable binders include starch, gelatine, natural sugars, such as, for example, glucose or beta-lactose, sweeteners made from
15 maize, natural and synthetic rubber, such as, for example, acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. The lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. The disintegrants include, without being restricted thereto, starch, methylcellulose, agar, bentonite, xanthan gum and the
20 like. The tablets are formulated by, for example, preparing a powder mixture, granulating or dry-pressing the mixture, adding a lubricant and a disintegrant and pressing the entire mixture to give tablets. A powder mixture is prepared by mixing the compound comminuted in a suitable manner with a diluent or a base, as described above, and optionally with a binder, such as, for example, carboxymethylcellulose, an alginate, gelatine or polyvinyl-pyrrolidone,
25 a dissolution retardant, such as, for example, paraffin, an absorption accelerator, such as, for example, a quaternary salt, and/or an absorbant, such as, for example, bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting it with a binder, such as, for example, syrup, starch paste, acacia mucilage or solutions of cellulose or polymer materials and pressing it through a sieve. As an alternative to granulation, the powder mixture
30 can be run through a tableting machine, giving lumps of non-uniform shape which are broken up to form granules. The granules can be lubricated by addition of stearic acid, a stearate salt, talc or mineral oil in order to prevent sticking to the tablet casting moulds. The lubricated mixture is then pressed to give tablets. The active ingredients can also be combined with a free-flowing inert excipient and then pressed directly to give tablets without carrying out the

granulation or dry-pressing steps. A transparent or opaque protective layer consisting of a shellac sealing layer, a layer of sugar or polymer material and a gloss layer of wax may be present. Dyes can be added to these coatings in order to be able to differentiate between different dosage units.

5 Oral liquids, such as, for example, solution, syrups and elixirs, can be prepared in the form of dosage units so that a given quantity comprises a pre-specified amount of the compounds. Syrups can be prepared by dissolving the compounds in an aqueous solution with a suitable flavour, while elixirs are prepared using a non-toxic alcoholic vehicle. Suspensions can be for-mulated by dispersion of the compounds in a non-toxic vehicle.

10 Solubilisers and emulsifiers, such as, for example, ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavour additives, such as, for example, peppermint oil or natural sweeteners or saccharin, or other artificial sweeteners and the like, can likewise be added.

The dosage unit formulations for oral administration can, if desired, be encapsulated

15 in microcapsules. The formulation can also be prepared in such a way that the release is extended or retarded, such as, for example, by coating or embedding of particulate material in polymers, wax and the like.

Compounds represented by formula (I) or a pharmaceutically acceptable salt thereof may be prepared using the methods and procedures described in U.S. Patent No. 9,630,932,

20 which is incorporated herein by reference in its entirety.

Although the invention is illustrated by certain of the following examples, it is not to be construed as being limited thereby; but rather, the invention encompasses the generic area as hereinbefore disclosed. Various modifications and embodiments can be made without departing from the spirit and scope thereof.

25

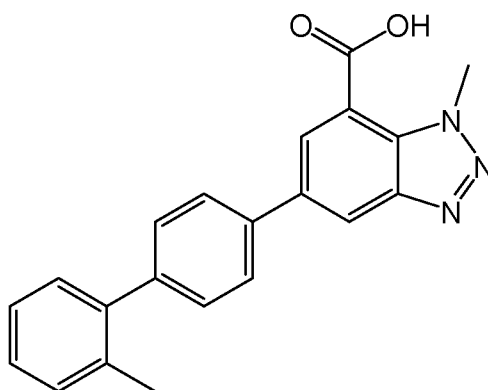
EXAMPLES

Example 1

In vitro growth inhibition of multiple human cancer cell lines by Compound 1

A tumor cell line panel screen aimed at identifying tumor cell subsets that were

30 particularly sensitive to inhibition of DHODH with Compound 1 was performed. Compound 1 is represented by the following structural formula:



These cell lines were treated with Compound 1 for a total of 72 hrs.

Assessment of tumor growth rates after the 72-hour treatment, as shown in FIG. 1 and Table 1, revealed that a distinct subset of cell lines (depicted by grey dots in FIG. 1) were sensitive to Compound 1. The majority of the cell lines exhibiting high sensitivity to Compound 1 are of hematopoietic origin though some solid tumor lines also exhibited high sensitivity (Table 1). For purposes of generating FIG. 1, sensitive cell lines were defined as exhibiting $\geq 75\%$ maximal growth inhibition and a log GI_{50} value of $< 1.5 \mu\text{M}$. In Table 1, a maximum inhibition of 100 represents complete growth inhibition; a max inhibition value > 100 represents cell killing.

A follow-up screen was performed on an expanded panel of cell lines of heme lineage in a 4-day growth assay. Growth was assessed by Cell-Titer Glo measurements on day 0 and day 4. As shown in FIG. 2, 25% of the heme lines screened (20/80) exhibited sensitivity to Compound 1. A subset of the heme lines that were of intermediate sensitivity (defined as $> 50\%$ and $< 75\%$ growth rate inhibition) or insensitive (defined as $< 50\%$ growth rate inhibition) to Compound 1 in this follow-up screen were subjected to extended growth assays to evaluate if increased treatment time modulated their sensitivity profile. Specifically, these heme lines were pretreated with Compound 1 for three days at the indicated concentrations and then re-plated for a standard 4-day growth assay in fresh media/drug. The vast majority of re-tested heme lines exhibited strong sensitivity to Compound 1 following 7 days of treatment (Table 2. FIGS. 3 and 4 show 4-day and 7-day relative growth curves of THP-1 and HT cell lines treated with Compound 1, respectively. Growth rates were calculated using the formula: $\ln(T_{96}/T_0)/\text{time}(\text{hrs})$ and plotted relative to DMSO treated cells. The strong sensitivity of THP-1 cells to Compound 1 in this assay is of particular interest given their resistance to the AML standard of care drug cytarabine (Ara-C), reportedly due to high expression of SAMHD1, which inactivates the active metabolite Ara-CTP. In other words, THP-1 cells highly express SAMHD1, which correlates to a mechanism of resistance to

cytarabine (Schneider et al., *Nature Medicine*, 2017, 23(2), 250-254; Herold et al., *Cell Cycle*, 2017, 16(11):1029-1038). Yet, the cell line was shown to be sensitive to Compound 1 in the 7-day assay. Thus, Compound 1 may have particular benefit in treating AML patients that have developed resistance to standard chemotherapeutic agents.

5

Table 1. GI₅₀ and maximum growth inhibition of various cell lines treated with Compound 1.

Cell line	Primary site	Disease	GI ₅₀ (μM)	Maximum growth inhibition
SNU478	Biliary tract	Biliary cancer or cancer of the ampulla of Vater	0.05	75.4
NCIH460	Lung	Non-small cell lung cancer/carcinoma	0.07	96.6
NCIH1155	Lung	Non-small cell lung cancer/carcinoma	0.11	171.4
NCIH1666	Lung	Non-small cell lung cancer/carcinoma	0.13	118.7
BICR22	Upper aerodigestive tract	Cancer of the upper aerodigestive tract (tongue)	0.21	78.9
HLF	Liver	Liver cancer (hepatocellular carcinoma)	0.36	85.8
LCLC103H	Lung	Non-small cell lung cancer/carcinoma	0.64	87.8
NCIH1581	Lung	Non-small cell lung cancer/carcinoma	1.13	94.4
NCIH1435	Lung	Non-small cell lung cancer/carcinoma	1.25	117.0
OAW42	Ovary	Cancer of the ovary	1.31	77.6

Table 2. 4-day and 7-day sensitivity of various heme cell lines treated with Compound 1.

10

Cell line	Disease	Sensitivity	
		4-day	7-day
NALM-1	Chronic myeloid leukemia (chronic monocytic leukemia)	**	***
HT	B-cell lymphoma/Diffuse mixed cell lymphoma	*	***
F36P	Acute myeloid leukemia (secondary to myelodysplastic syndrome)	**	***
THP-1	Acute myeloid leukemia/Acute	**	***

Cell line	Disease	Sensitivity	
		4-day	7-day
	monocytic leukemia		
AML-193	Acute myeloid leukemia/Acute monocytic leukemia	**	***
NALM-16	Acute lymphoblastic leukemia (childhood B acute lymphoblastic leukemia)	**	***
BCP-1	B-cell lymphoma/Primary effusion lymphoma	*	***
TF1	Acute myeloid leukemia/Erythroleukemia	*	***
HEL	Acute myeloid leukemia/Erythroleukemia	**	***
* - insensitive ** - intermediate *** - sensitive			

Example 2

Comparison of Compound 1 sensitivity profiles against cytarabine and doxorubicin sensitivity profiles

5 The sensitivity profile of Compound 1 against a subset of heme lines was compared to the sensitivity profiles other agents that are used as standard of care (SOC) in heme malignancies. Compound 1 displayed a sensitivity profile (FIG. 5A) distinct from cytarabine (FIG. 5B) and doxorubicin (FIG. 5C) sensitivity profiles, thereby suggesting that the mechanism of action of Compound 1 is different from those of cytarabine and doxorubicin.

10

Example 3

In vitro growth inhibition of double hit diffuse large B cell lymphoma human cancer cell lines by Compound 1

15 Three patient-derived DLBCL lymphoma cell lines classified as double-hit DLBCL, namely OCILY18, SC-1 and CARNAVAL, were found to be highly sensitive to inhibition by Compound 1 in a 96-hr growth assay (FIG. 6).

Example 4

Compound 1 effectively blocks tumor growth in patient-derived double hit DLBCL xenograft model

20

A strong block in *in vivo* tumor growth was observed with Compound 1 in the OCILY-19 double hit diffuse large B-cell lymphoma (DLBCL) xenograft model. 7×10^6

OCILY-19 cells were implanted subcutaneously into CB17 SCID mice. Mice (n = 15-18/group) were treated with vehicle or Compound 1 at the indicated dose/frequency once tumors reached an average of ~150 mm³. Tissues were collected at the indicated timepoints post-last dose for PK and biomarker analyses.

5 Degree of pathway modulation and tumor growth inhibition was demonstrated to be dose and schedule dependent (FIG. 7A). The 100 mg/kg BID dosing regimen resulted in superior efficacy compared to the 10 and 30 mg/kg BID dose arms and this correlated with a larger increase in tumor DHO (FIG. 7C) as well as a decrease in total tumor uridine pools (FIG. 7D). The 200 mg/kg QD regimen was less efficacious than the 100mg/kg BID dosing
10 regimen due to the short half-life of Compound 1 in mice, resulting in lower trough drug concentrations with QD dosing (see FIG. 7B).

Example 5

Compound 1 effectively blocks tumor growth in patient-derived triple hit DLBCL xenograft
15 model

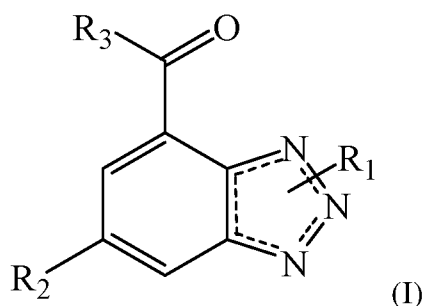
Efficacy of Compound 1 in a triple hit DLBCL patient-derived xenograft model (DLBCL_1) was assessed as part of a larger screen for sensitivity in PDX models of hematologic origin. Tumor-bearing mice (n = 3/group) were treated with vehicle or Compound 1 at 100 mg/kg BID PO.

20 As shown in FIG. 8, anti-tumor activity of Compound 1 was observed in the DLBCL_1 model tested, with >70% TGI.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating a cancer selected from chemotherapy-resistant acute myeloid leukemia, cytarabine-resistant acute myeloid leukemia, acute monocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, diffuse mixed cell lymphoma, myelodysplastic syndrome, primary effusion lymphoma, erythroleukemia, chronic myeloid leukemia, chronic monocytic leukemia, double hit diffuse large B cell lymphoma, triple hit diffuse large B cell lymphoma, biliary tract cancer or cancer of the ampulla of Vater, non-small cell lung cancer, bronchoalveolar carcinoma, liver cancer, cancer of the ovary, and cancer of the upper aerodigestive tract in a subject, comprising administering to the subject a therapeutically effective amount of a compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof; wherein:

the dotted lines [...] in the ring represent an optional bond which may be present in any stable combination;

R_1 is selected from hydrogen and alkyl;

R_2 is -A- R_4 ;

A is arylene or tetrasubstituted arylene; wherein the substituent is halogen;

R_3 is selected from hydroxy and amino;

R_4 is selected from an aryl and a heteroaryl that is optionally substituted with one or more R_5 ;

R_5 is selected from alkyl and $-(CH_2)_nN(R_a)R_b$;

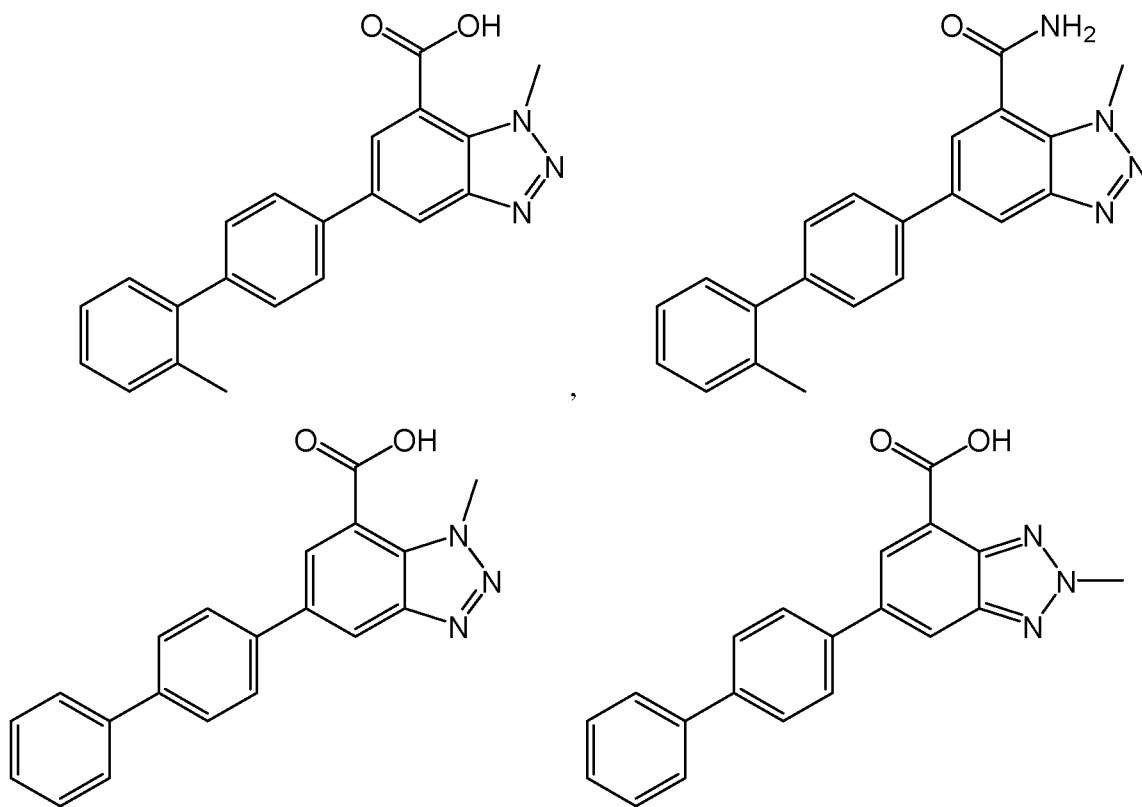
R_a and R_b are independently selected from hydrogen, alkyl and $-C(O)alkyl$;

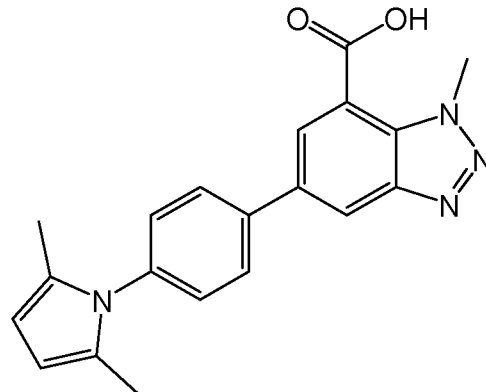
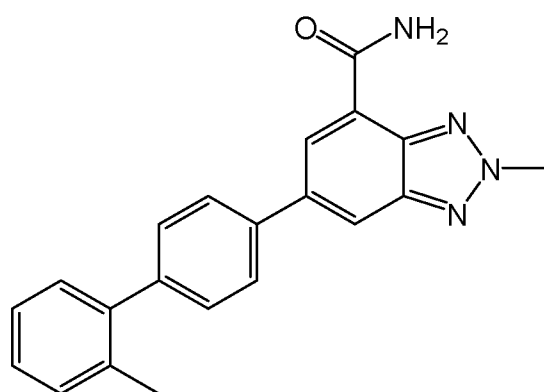
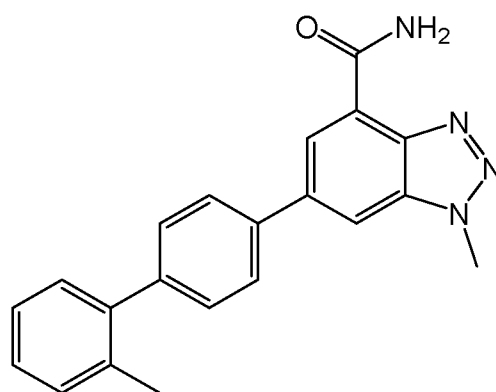
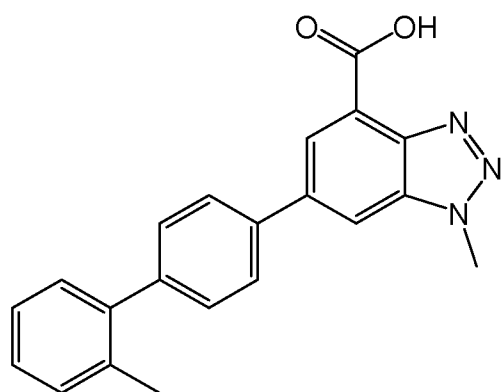
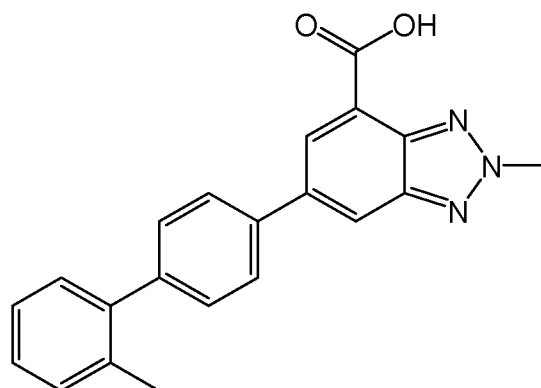
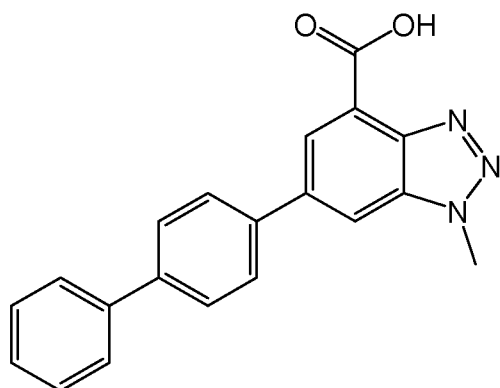
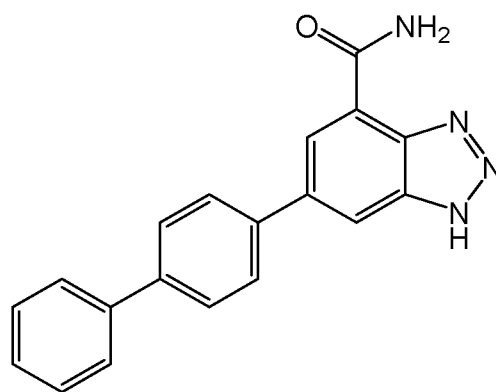
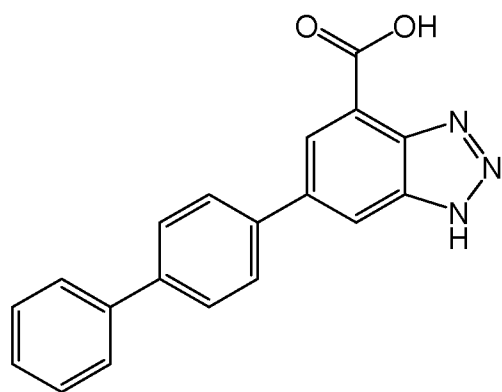
alternatively R_a and R_b can be taken together with the nitrogen atom to which they are attached to form a 4-6 membered heterocyclyl containing 0-2 additional heteroatoms independently selected from O and N and is optionally substituted with alkyl; and

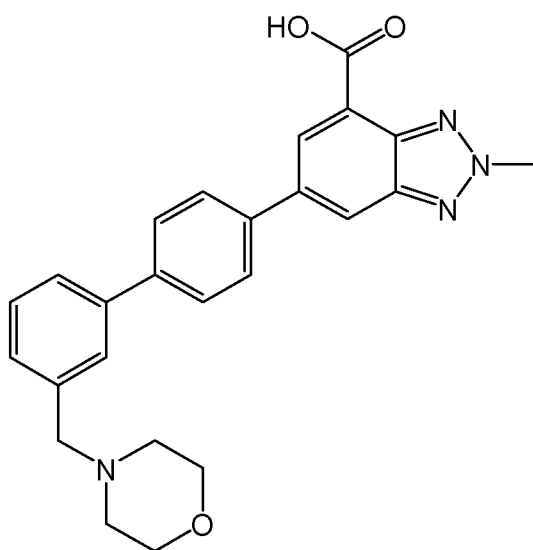
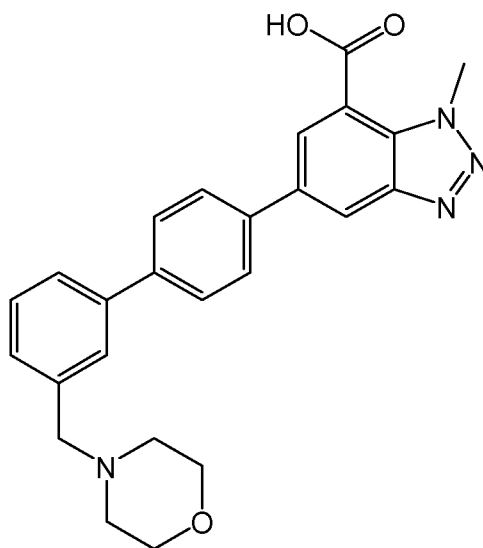
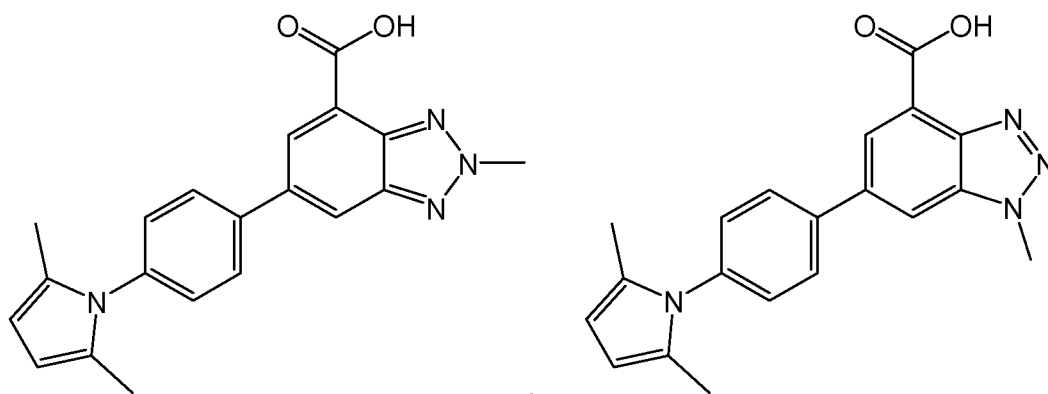
n is an integer selected from 0 and 1.

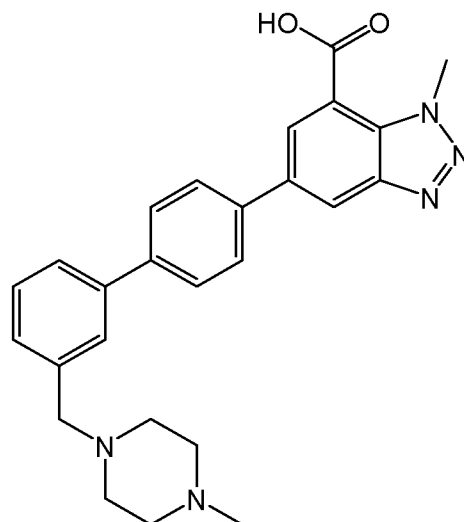
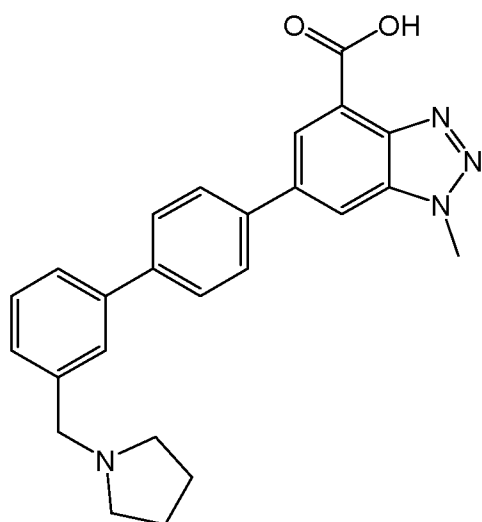
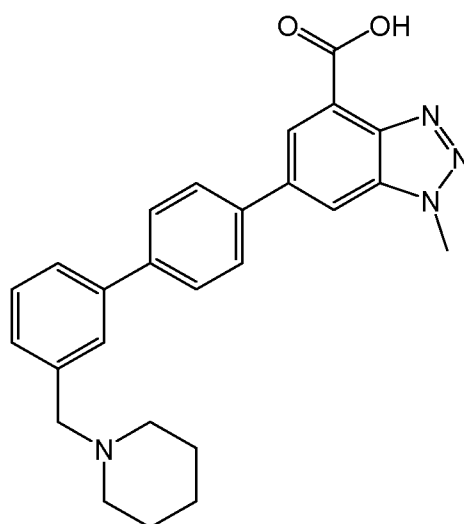
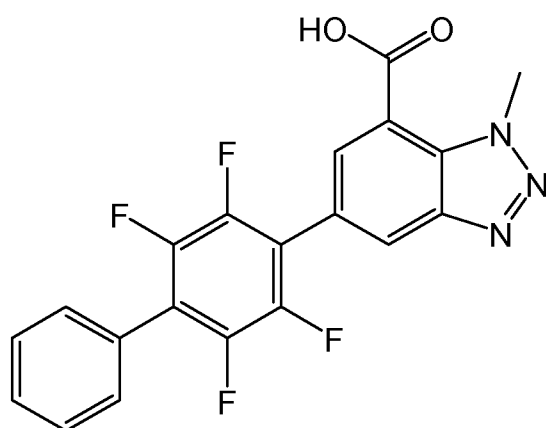
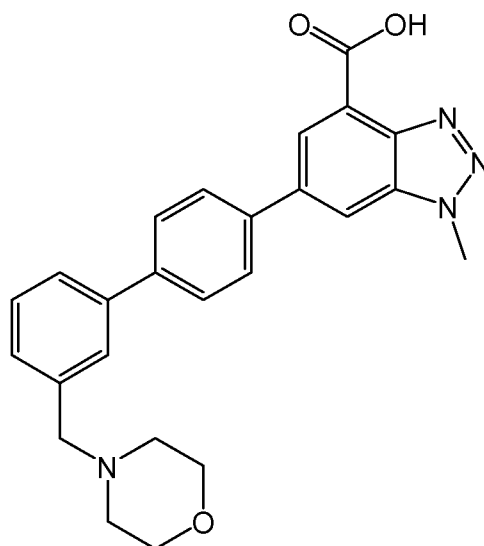
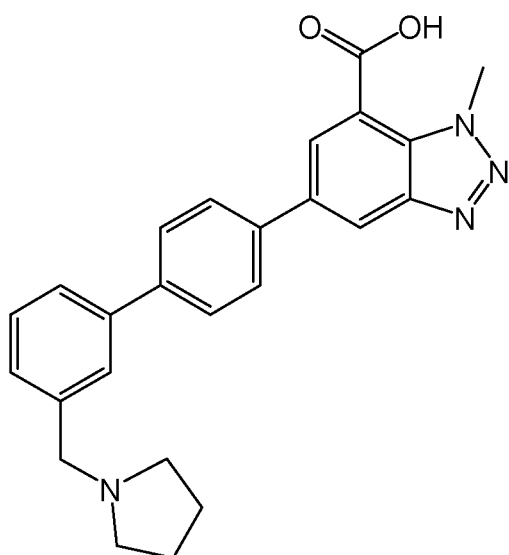
2. The method according to claim 1, wherein the cancer is chemotherapy-resistant acute myeloid leukemia.
3. The method according to claim 1, wherein the cancer is cytarabine-resistant acute myeloid leukemia.
4. The method according to claim 1, wherein the cancer is acute monocytic leukemia.
5. The method according to claim 1, wherein the cancer is acute lymphoblastic leukemia.
6. The method according to claim 1, wherein the cancer is B-cell lymphoma.
7. The method according to claim 1, wherein the cancer is diffuse mixed cell lymphoma.
8. The method according to claim 1, wherein the cancer is myelodysplastic syndrome.
9. The method according to claim 1, wherein the cancer is primary effusion lymphoma.
10. The method according to claim 1, wherein the cancer is erythroleukemia.
11. The method according to claim 1, wherein the cancer is chronic myeloid leukemia.
12. The method according to claim 1, wherein the cancer is chronic monocytic leukemia.
13. The method according to claim 1, wherein double hit diffuse large B cell lymphoma is treated and is characterized by gene alterations at *c-MYC* and *BCL2*.
14. The method according to claim 1, wherein double hit diffuse large B cell lymphoma is treated and is characterized by gene alterations at *c-MYC* and *BCL6*.
15. The method according to claim 1, wherein triple hit diffuse large B cell lymphoma is treated.

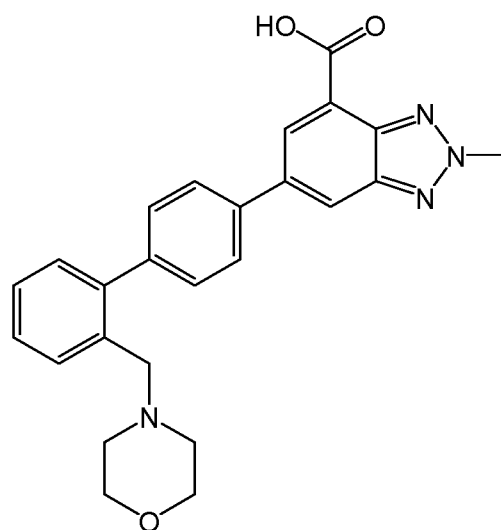
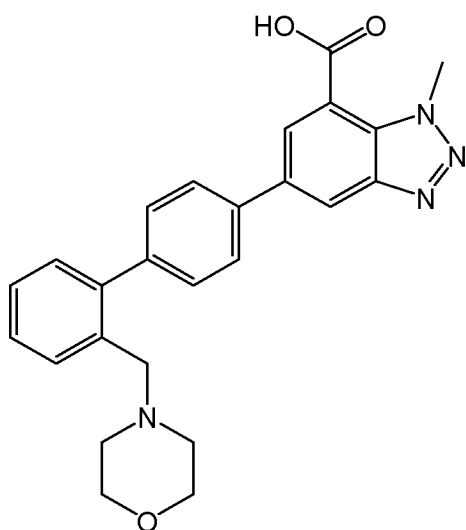
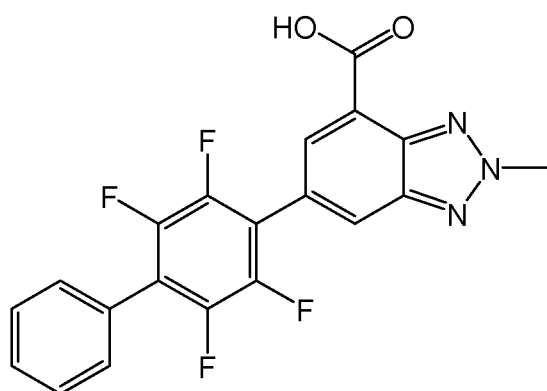
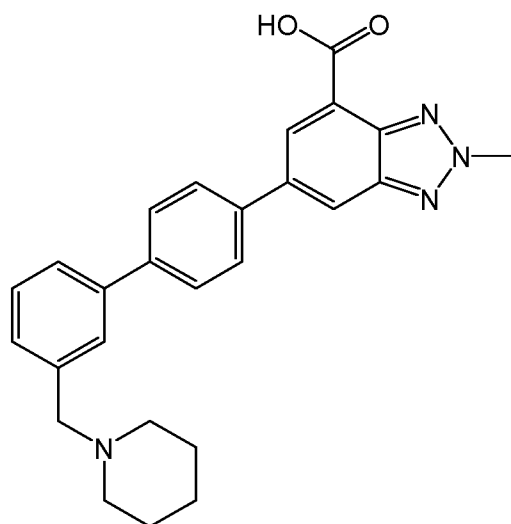
16. The method according to claim 1, wherein the cancer is biliary tract cancer or cancer of the ampulla of Vater.
17. The method according to claim 1, wherein the cancer is non-small cell lung cancer.
18. The method according to claim 1, wherein the cancer is bronchoalveolar carcinoma.
19. The method according to claim 1, wherein the cancer is liver cancer.
20. The method according to claim 1, wherein the cancer is cancer of the ovary.
21. The method according to claim 1, wherein the cancer is cancer of the upper aerodigestive tract.
22. The method according to any one of claims 1-21, wherein the compound is selected from:

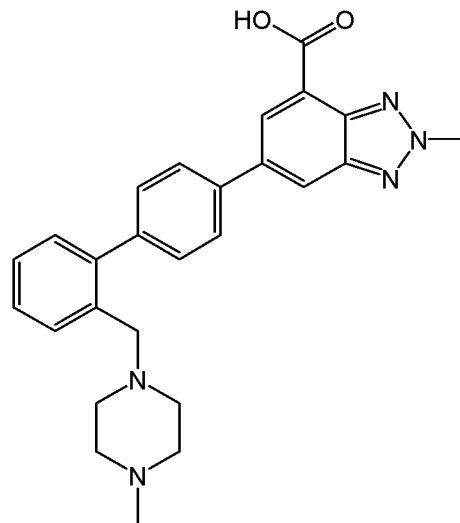
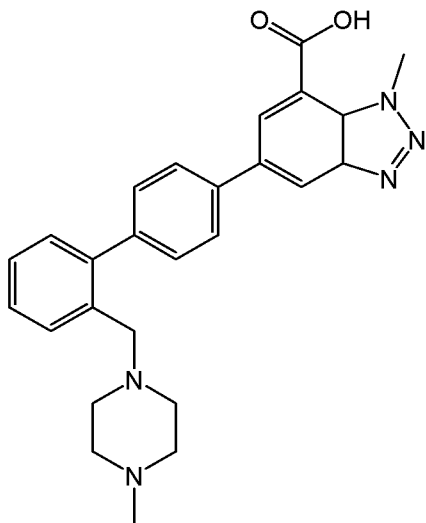
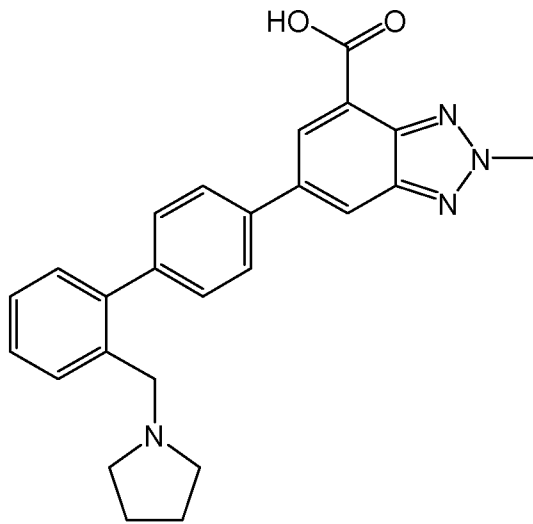
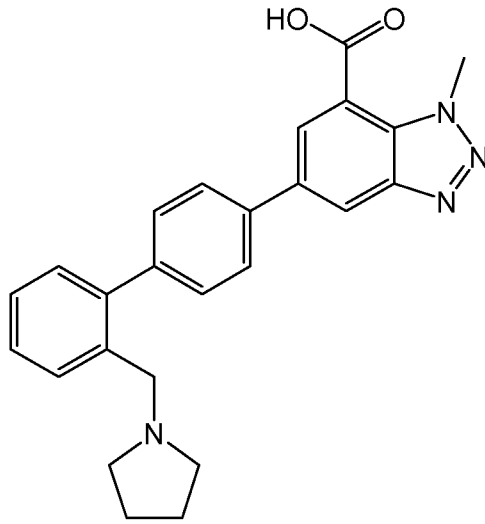


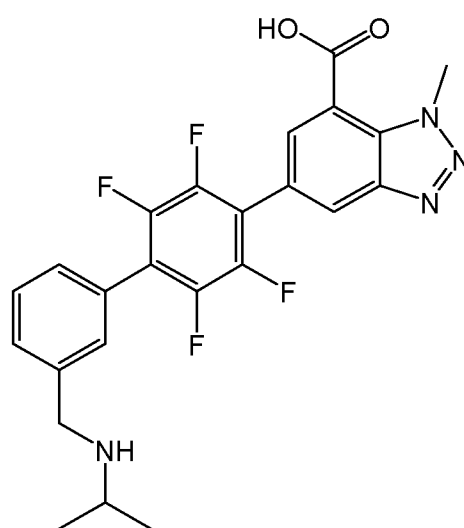
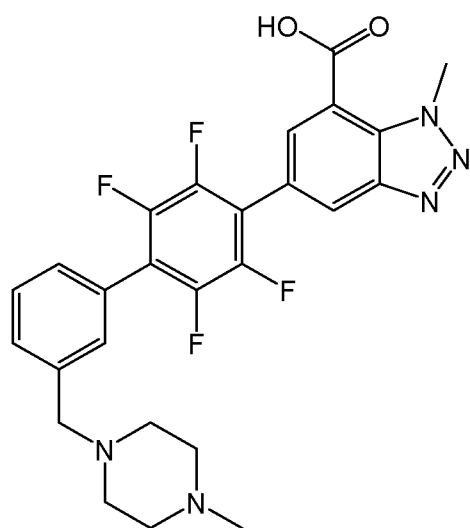
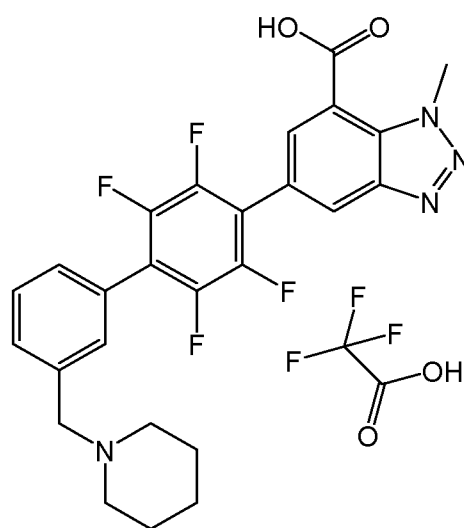
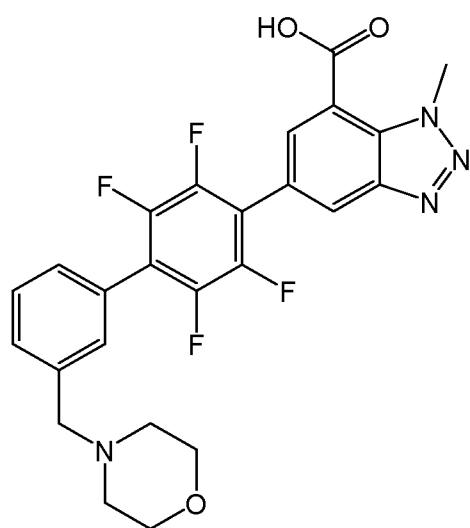
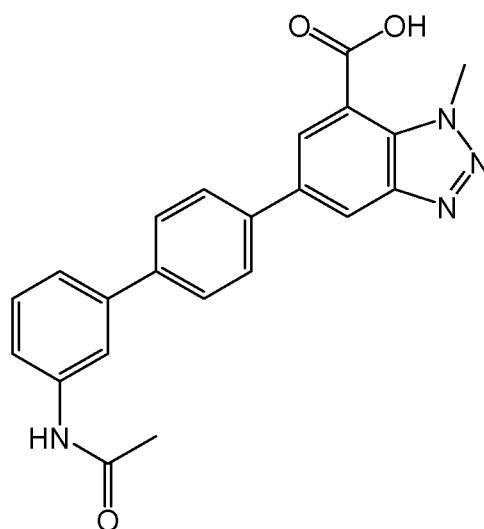
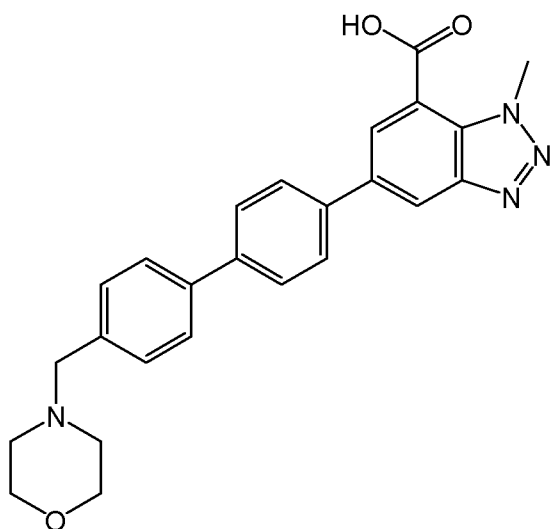


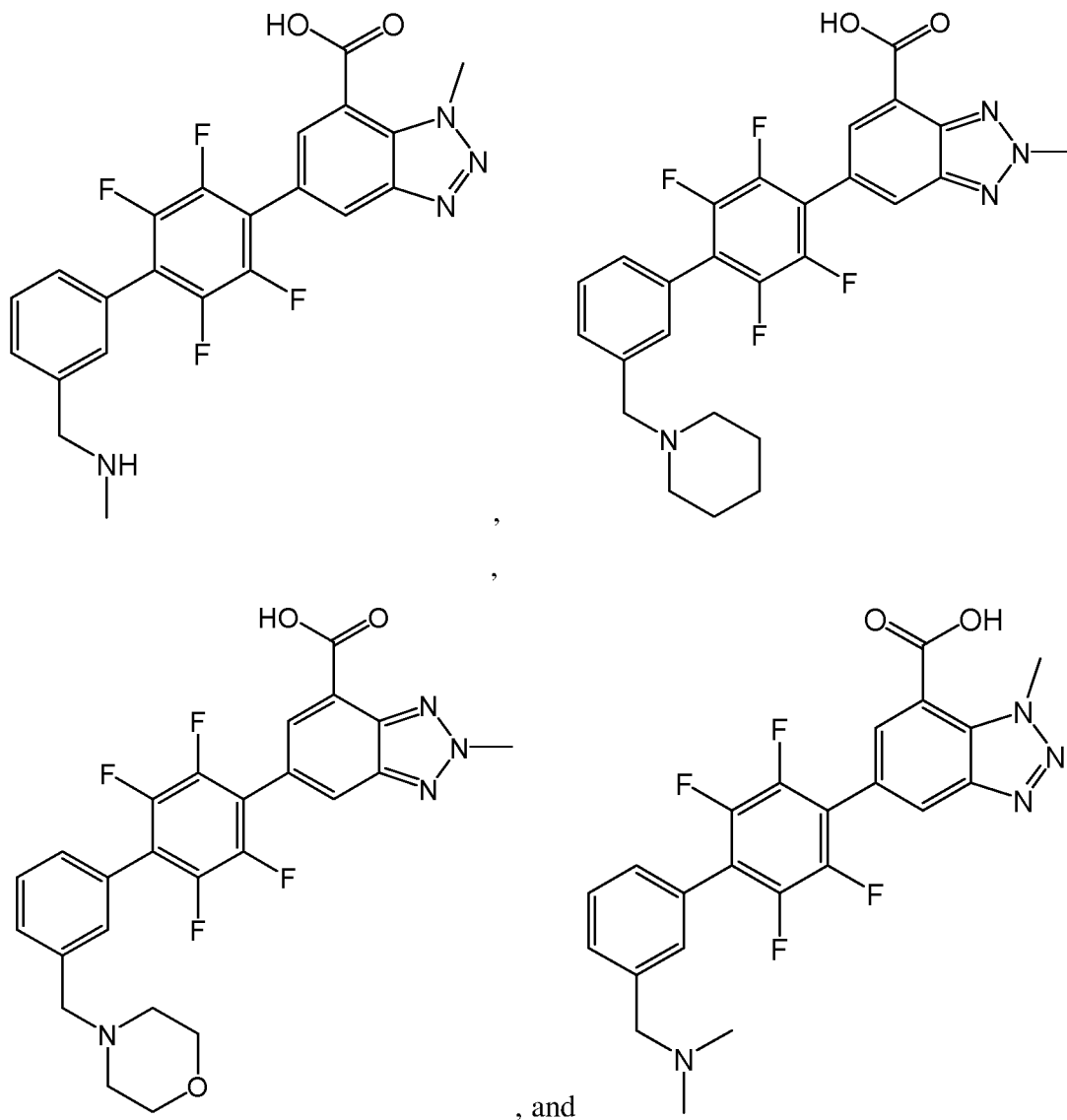






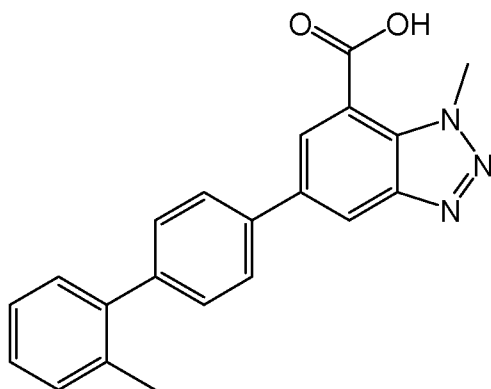






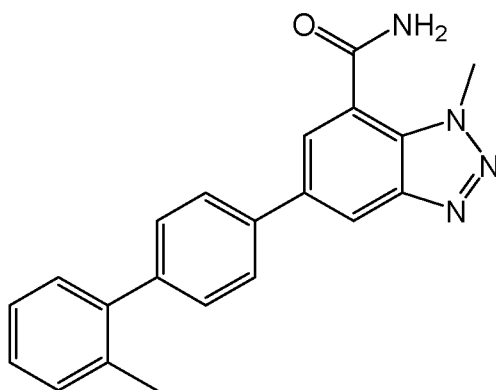
or a pharmaceutically acceptable salt thereof.

23. The method according to any one of claims 1-22, wherein the compound is



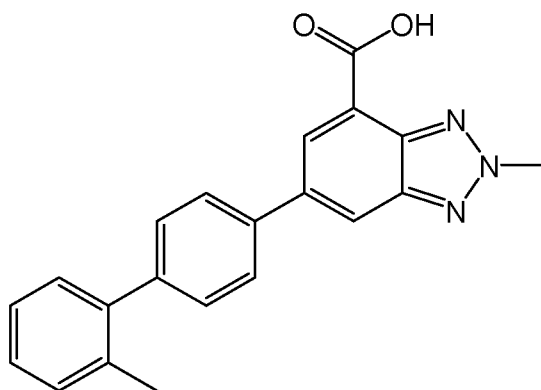
or a pharmaceutically acceptable salt thereof.

24. The method according to any one of claims 1-22, wherein the compound is



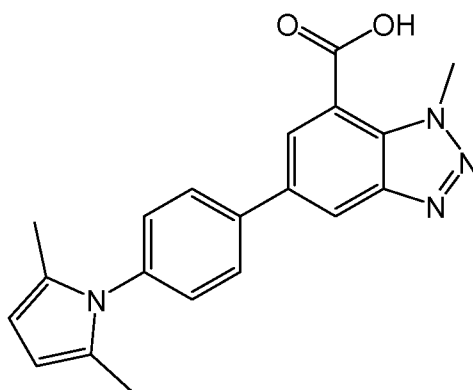
or a pharmaceutically acceptable salt thereof.

25. The method according to any one of claims 1-22, wherein the compound is



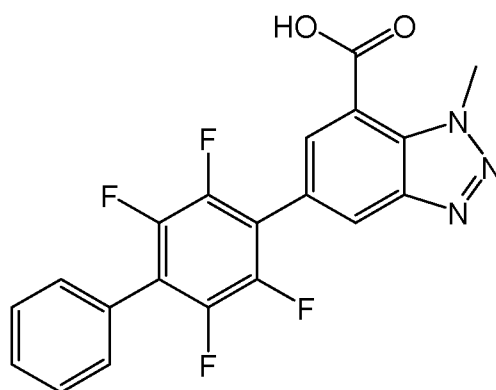
or a pharmaceutically acceptable salt thereof.

26. The method according to any one of claims 1-22, wherein the compound is



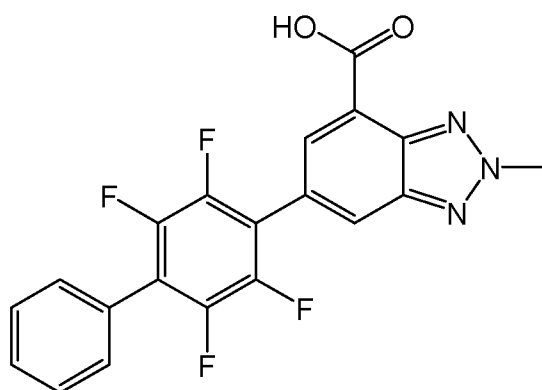
or a pharmaceutically acceptable salt thereof.

27. The method according to any one of claims 1-22, wherein the compound is



or a pharmaceutically acceptable salt thereof.

28. The method according to any one of claims 1-22, wherein the compound is



or a pharmaceutically acceptable salt thereof.

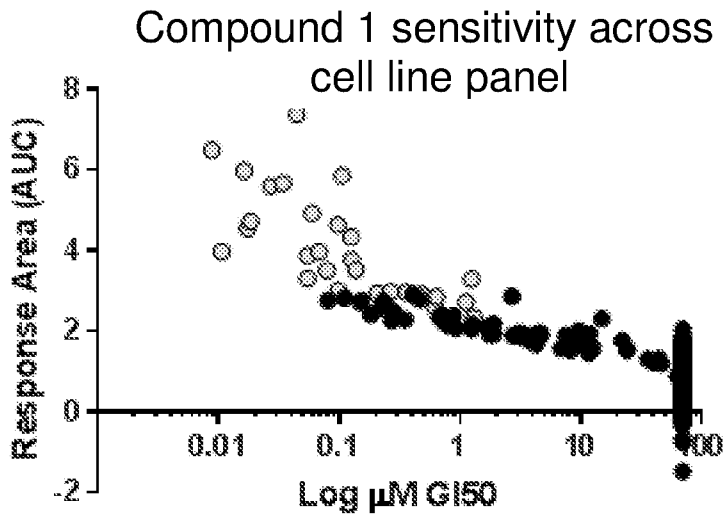


FIG. 1

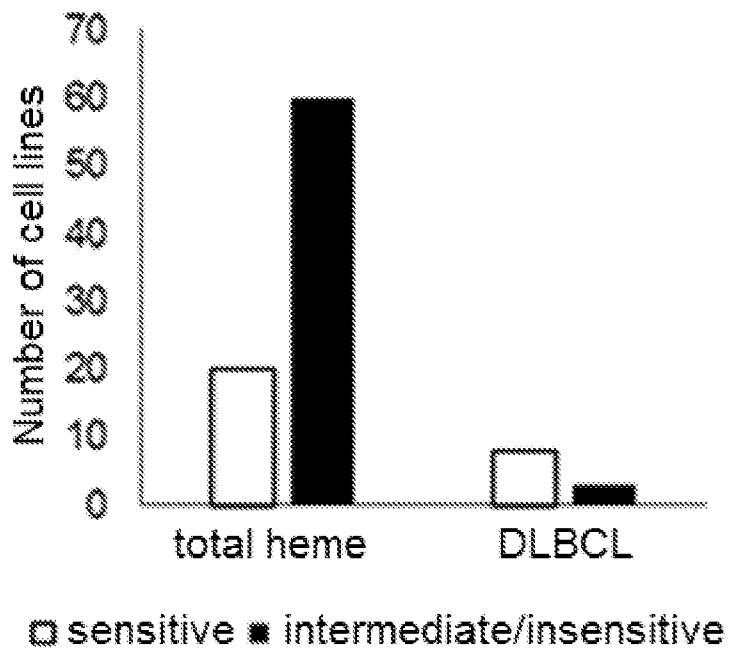
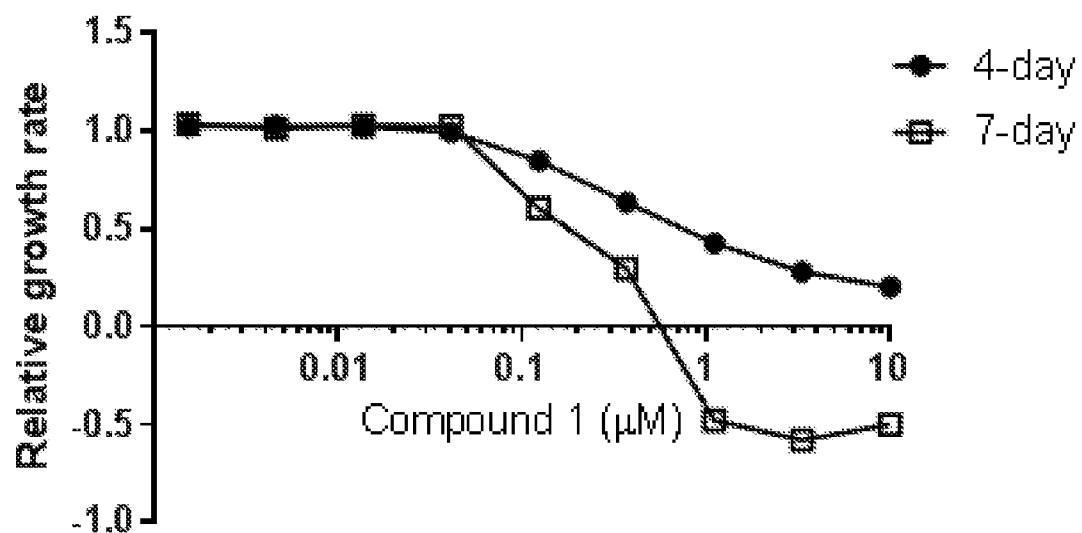
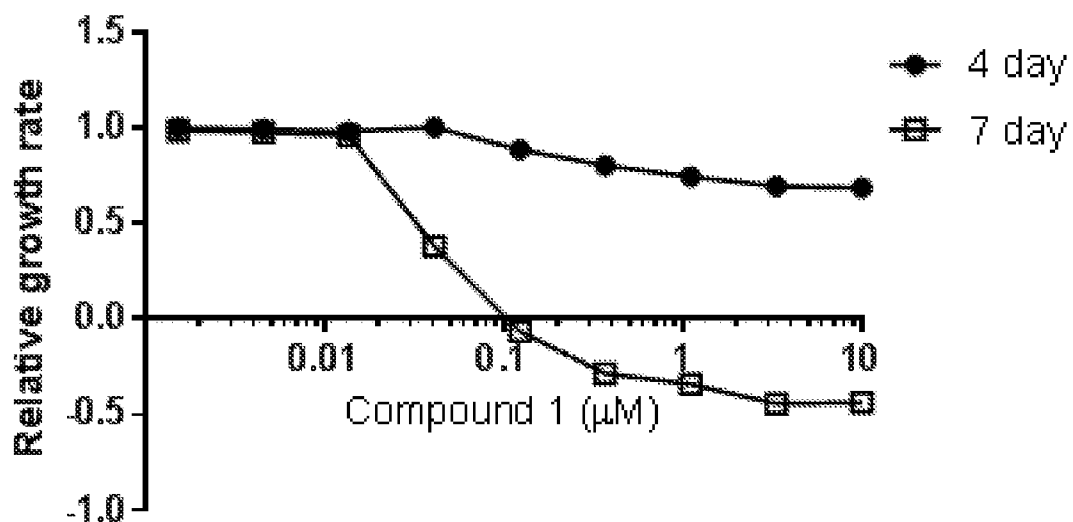


FIG. 2

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THP-1 cell line**FIG. 3****HT cell line****FIG. 4**

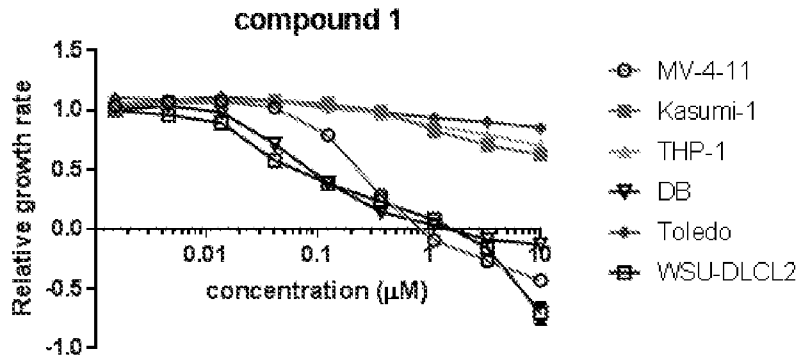


FIG. 5A

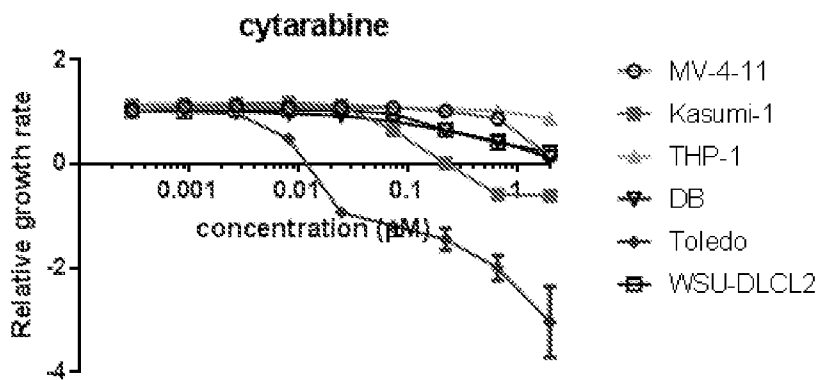


FIG. 5B

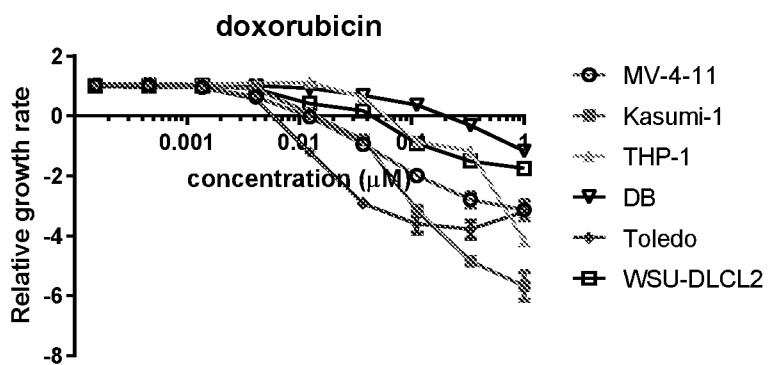


FIG. 5C

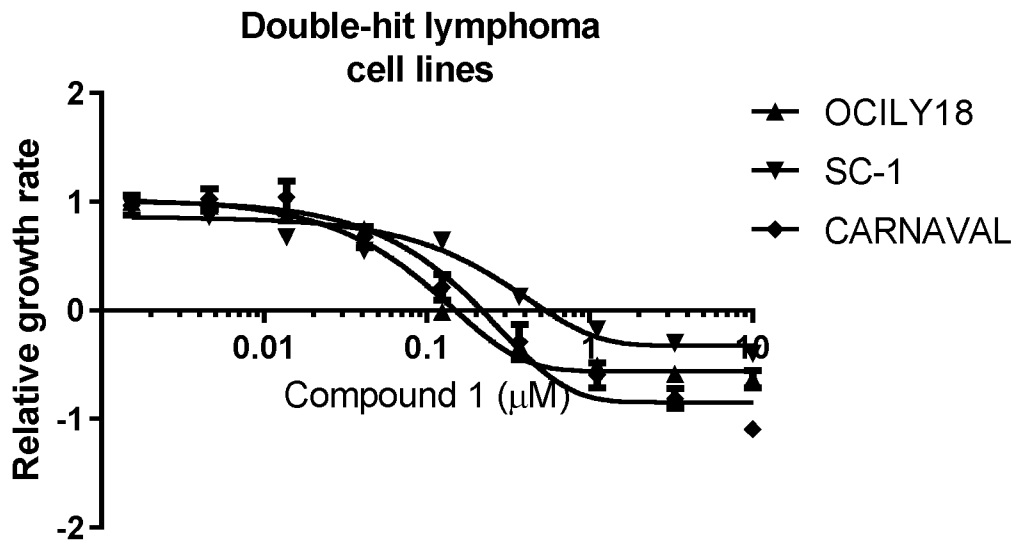


FIG. 6

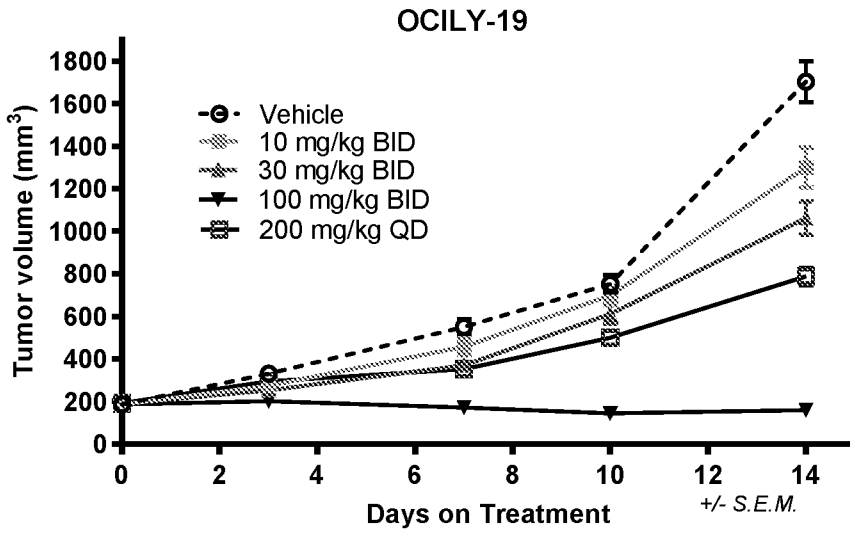


FIG. 7A

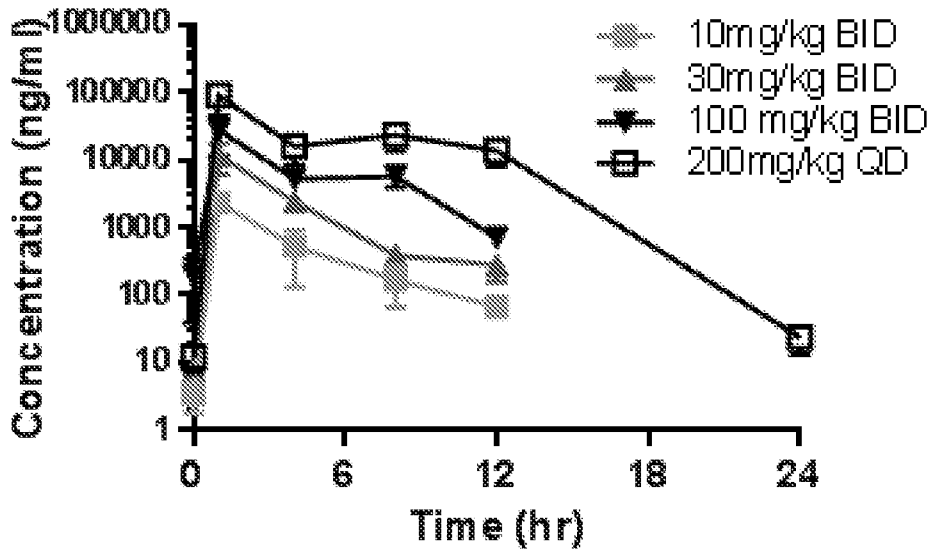


FIG. 7B

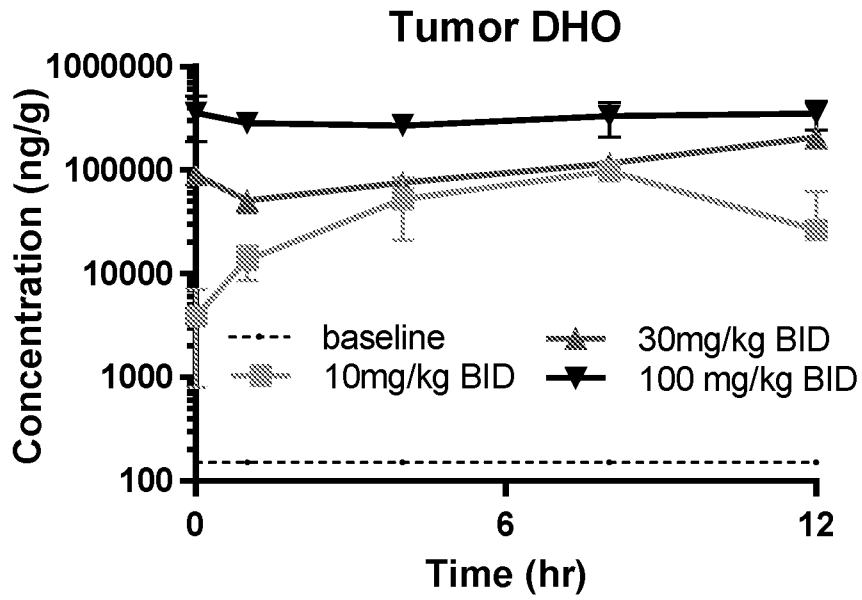


FIG. 7C

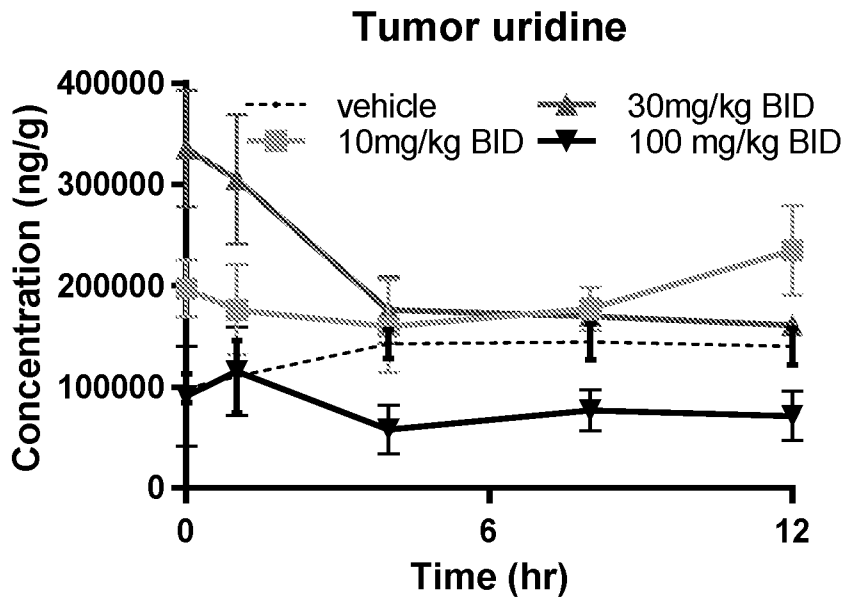


FIG. 7D

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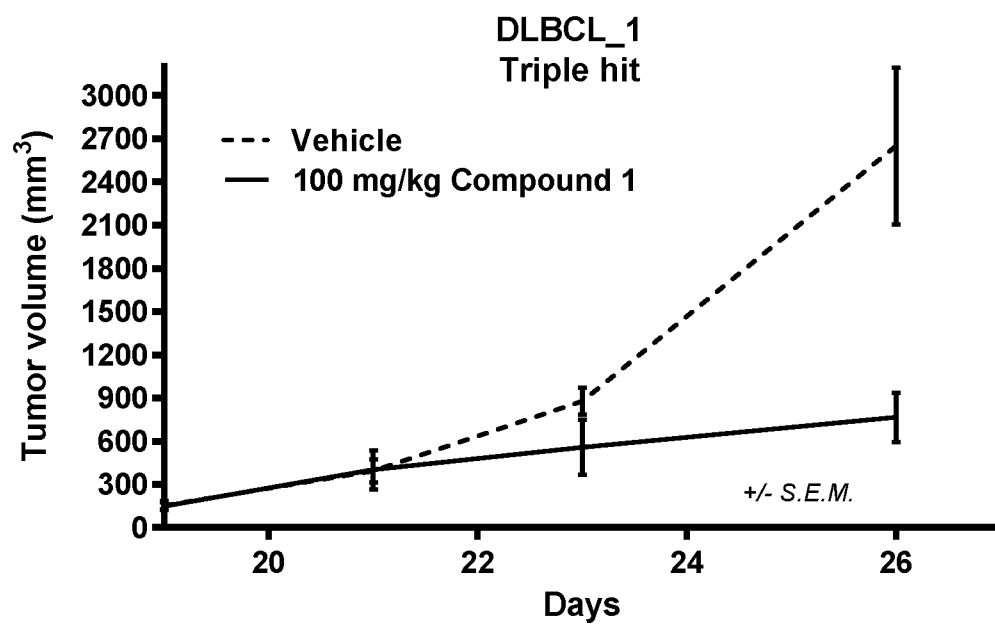


FIG. 8

