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(54) Title: METHODS FOR TREATING HEMATOLOGICAL MALIGNANCIES

(57) Abstract: The invention provides methods and pharmaceutical compositions for treating certain hematological cancers.



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METHODS FOR TREATING HEMATOLOGICAL MALIGNANCIES
RELATED APPLICATION DATA

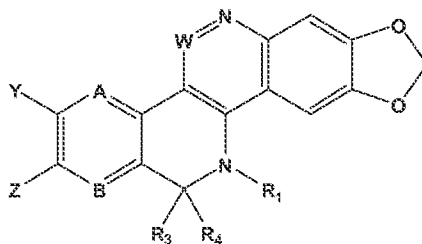
- [01] This application claims the benefit of US Provisional Application No. 61/368,478 filed July 28, 2010 hereby incorporated by reference in its entirety.

BACKGROUND

- [02] DNA-topoisomerases are enzymes which are present in the nuclei of cells where they catalyze the breaking and rejoining of DNA strands, which control the topological state of DNA. Recent studies also suggest that topoisomerases are also involved in regulating template supercoiling during RNA transcription. There are two major classes of mammalian topoisomerases. DNA-topoisomerase-I catalyzes changes in the topological state of duplex DNA by performing transient single-strand breakage-union cycles. In contrast, mammalian topoisomerase II alters the topology of DNA by causing a transient enzyme bridged double-strand break, followed by strand passing and resealing. Mammalian topoisomerase II has been further classified as Type II α and Type II β . The antitumor activity associated with agents which are topoisomerase poisons is associated with their ability to stabilize the enzyme-DNA cleavable complex. This drug-induced stabilization of the enzyme-DNA cleavable complex effectively converts the enzyme into a cellular poison.
- [03] Several antitumor agents in clinical use have potent activity as mammalian topoisomerase II poisons. These include adriamycin, actinomycin D, daunomycin, VP-16, and VM-26 (teniposide or epipodophyllotoxin). In contrast to the number of clinical and experimental drugs which act as topoisomerase II poisons, there are currently only a limited number of agents which have been identified as topoisomerase I poisons. Camptothecin and its structurally-related analogs are among the most extensively studied topoisomerase I poisons. Bi- and terbenzimidazoles (Chen et al., Cancer Res. 1993, 53, 1332-1335; Sun et al., J. Med. Chem. 1995, 38,

3638-3644; Kim et al., J. Med. Chem. 1996, 39, 992-998), certain benzo[c]phenanthridine and protoberberine alkaloids and their synthetic analogs (Makhey et al., Med. Chem. Res. 1995, 5, 1-12; Janin et al., J. Med. Chem. 1975, 18, 708-713; Makhey et al., Bioorg. & Med. Chem. 1996, 4, 781-791), as well as the fungal metabolites, bulgarein (Fujii et al., J. Biol. Chem. 1993, 268, 13160-13165) and saintopin (Yamashita et al., Biochemistry 1991, 30, 5838-5845) and indolocarbazoles (Yamashita et al., Biochemistry 1992, 31, 12069-12075) have been identified as topoisomerase I poisons. Other topoisomerase poisons have been identified including certain benzo[j]phenanthridine and cinnoline compounds (see LaVoie et al., U.S. Pat. No. 6,140,328, and WO 01/32631. While these compounds are useful they are somewhat limited due to low solubility.

- [04] F.D.A. approved Topoisomerase I inhibitors are camptothecin derivatives and include CAMPTOSAR® (irinotecan) and HYCAMTIN® (topotecan). CAMPTOSAR® (irinotecan) is indicated as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum. CAMPTOSAR® (irinotecan) is also indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy. SN-38 is a well known active metabolite of irinotecan. HYCAMTIN® (topotecan) is indicated for treatment of patients with relapsed small cell lung cancer in patients with a prior complete or partial response and who are at least 45 days from the end of first-line chemotherapy. As mentioned above, these camptothecin derivatives suffer from low solubility.
- [05] There thus is a need for non-camptothecin based Topoisomerase I inhibitors that are therapeutically effective against cancers.
- [06] International patent application number PCT/US02/36901 discusses compounds of formula I:

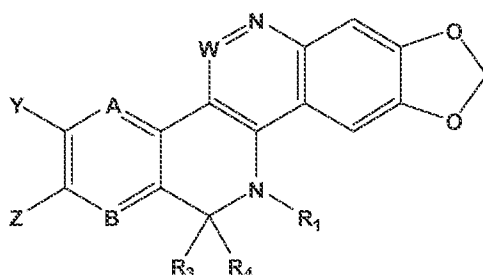


Formula I

that are reported to have topoisomerase inhibiting activity. The compounds of formula I are non-camptothecin derivatives, and as such, are not burdened with certain shortcomings of camptothecin based derivatives. Applicant has discovered that compounds of formula I are particularly active against hematological cancers including leukemia and lymphoma. Hematological malignancies within the scope of the present disclosure include blood cancers such as acute lymphoblastic leukemia, adult; acute lymphoblastic leukemia, childhood; acute myeloid leukemia, adult; acute myeloid leukemia, childhood; AIDS-related lymphoma; Burkitt lymphoma; central nervous system lymphoma, primary; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloproliferative disorders; cutaneous T-cell lymphoma; hairy cell leukemia; Hodgkin lymphoma, adult; Hodgkin lymphoma, childhood; leukemia, acute lymphoblastic, adult; leukemia, acute lymphoblastic, childhood; leukemia, acute myeloid, adult; leukemia, acute myeloid, childhood; leukemia, chronic lymphocytic; leukemia, chronic myelogenous; leukemia, hairy cell; lymphoma, AIDS-related; lymphoma, Burkitt; lymphoma, Hodgkin, adult; lymphoma, Hodgkin, childhood; lymphoma, Non-Hodgkin, adult; lymphoma, Non-Hodgkin, childhood; lymphoma, primary central nervous system; mycosis fungoides; myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; myelogenous leukemia, chronic; myeloid leukemia, adult acute; myeloid leukemia, childhood acute; myeloproliferative disorders, chronic; Non-Hodgkin lymphoma, adult; Non-Hodgkin lymphoma, childhood; primary central nervous system lymphoma; Sézary syndrome; and Waldenström macroglobulinemia. Certain hematological malignancies, such as cancers include monocytic leukemia, acute erythroleukemia, acute monocytic leukemia, B myelomonocytic leukemia, non-Hodgkin's lymphoma, acute promyelocytic leukemia, Burkitt's lymphoma, B cell

lymphoma, and B lymphoblastoid. Particularly preferred compounds include 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N,N-diethylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; and 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N-methylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; and pharmaceutically acceptable salts, prodrugs and metabolites thereof.

[07] Accordingly, in one embodiment the invention provides a method for treating a hematological cancer in a mammal comprising administering to the mammal an effective amount of a compound of formula I:



Formula I

wherein:

A and B are independently N or CH;

W is N or CH;

R₃ and R₄ are each independently H, (C₁-C₆)alkyl, or substituted (C₁-C₆)alkyl, or R₃ and R₄ together are =O, =S, =NH or =N-R₂;

Y and Z are independently hydroxy, (C₁-C₆)alkoxy, substituted (C₁-C₆)alkoxy, (C₁-C₆)alkanoyloxy, substituted (C₁-C₆) alkanoyloxy, -O-P(=O)(OH)₂, or -O-C(=O)NR_cR_d; or Y and Z together with the ring carbon atoms to which they are attached form an alkylendioxy ring with from 5 to 7 ring atoms;

R₁ is a -(C₁-C₆)alkyl substituted with one or more solubilizing groups;

R₂ is (C₁-C₆)alkyl or substituted (C₁-C₆)alkyl; and

R_c and R_d are each independently (C₁-C₆) alkyl or substituted (C₁-C₆) alkyl; or R_c and R_d together with the nitrogen to which they are attached form a N'-{(C₁-C₆)alkyl}piperazino,

pyrrolidino, or piperidino ring, which ring can optionally be substituted with one or more aryl, heteroaryl, or heterocycle;

or a pharmaceutically acceptable salt, prodrug or metabolite thereof.

[008] The invention also provides pharmaceutical compositions for the treatment of a hematological cancer comprising a compound of formula I or a pharmaceutically acceptable salt, prodrug or metabolite thereof and a pharmaceutically acceptable excipient. In certain embodiments, the compound of formula I is 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N,N-diethylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; or 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N-methylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; or a pharmaceutically acceptable salt, prodrug or metabolite thereof.

[009] The invention also provides a compound of formula I or a pharmaceutically acceptable salt, prodrug or metabolite thereof for use in the prophylactic or therapeutic treatment of hematological cancer in a mammal.

[010] The invention also provides for the use of a compound of formula I or a pharmaceutically acceptable salt, prodrug or metabolite thereof for the manufacture of a medicament useful for the treatment of a hematological cancer in a mammal.

[011] The invention also provides a pharmaceutical composition for use in a method to treat a hematological cancer in a mammal, wherein the pharmaceutical composition comprises a compound of formula I or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

[012] The foregoing and other features and advantages of the present invention will be more fully understood from the following detailed description of illustrative embodiments taken in conjunction with the accompanying drawings. It will be recognized that the results and examples in the figures are only illustrative and other

examples and illustrations will be readily recognized by the person of ordinary skill in the art, given the benefit of this disclosure.

- [13] Figure 1 shows the human tumor cell IC_{50} values for Compound 2 in nanomolar concentrations for human tumor cell lines representing hematological malignancies.
- [14] Figure 2 shows the human tumor cell IC_{90} values for Compound 2 in nanomolar concentrations for human tumor cell lines representing hematological malignancies.
- [15] Figure 3 shows the surviving fraction versus concentration of Compound 2 for human tumor cell lines representing hematologic malignancies.
- [16] Figure 4 shows the surviving fraction versus concentration of Compound 2 for human tumor cell lines representing hematologic malignancies.
- [17] Figure 5 shows the mean tumor volume of mice treated with Compound 2 versus vincristine in MOLM-13 human acute myeloid leukemia.
- [18] Figure 6 shows the percent change in body weight of mice treated with Compound 2 versus vincristine in MOLM-13 human acute myeloid leukemia.
- [19] Figure 7 shows the mean tumor volume of mice treated with Compound 2 versus vincristine in Karpas 299 human lymphoma tumor.
- [20] Figure 8 shows the percent change in body weight of mice treated with Compound 2 versus vincristine in Karpas 299 human lymphoma tumor.

DETAILED DESCRIPTION

- [21] The following definitions are used, unless otherwise described.
- [22] “(C₁-C₆)alkyl” denotes both straight and branched carbon chains with one or more, for example, 1, 2, 3, 4, 5, or 6, carbon atoms, but reference to an individual radical such as “propyl” embraces only the straight chain radical, a branched chain isomer such as “isopropyl” being specifically referred to. Specifically, (C₁-C₆)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, pentyl, 3-pentyl, or hexyl.

- [23] "Substituted (C₁-C₆)alkyl" is an alkyl group of the formula (C₁-C₆)alkyl as defined above wherein one or more (e.g. 1 or 2) carbon atoms in the alkyl chain have been replaced with a heteroatom independently selected from -O-, -S- and NR- (where R is hydrogen or C₁-C₆alkyl) and/or wherein the alkyl group is substituted with from 1 to 5 substituents independently selected from cycloalkyl, substituted cycloalkyl, (C₁-C₆)alkoxycarbonyl (e.g. -CO₂Me), cyano, halo, hydroxy, oxo (=O), carboxy (COOH), aryloxy, heteroaryloxy, heterocyclooxy, nitro, and -NR^aR^b, wherein R^a and R^b may be the same or different and are chosen from hydrogen, alkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic. Substituted (C₁-C₆)alkyl groups are exemplified by, for example, groups such as hydroxymethyl, hydroxyethyl, hydroxypropyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-dimethylaminopropyl, 2-carboxyethyl, hydroxylated alkyl amines, such as 2-hydroxyaminoethyl, and like groups. Specific substituted (C₁-C₆)alkyl groups are (C₁-C₆)alkyl groups substituted with one or more substituents of the formula-NR_aR_b where R_a and R_b together with the nitrogen to which they are attached form of nitrogen containing heterocyclic ring. Specific examples of such heterocyclic rings include piperazino, pyrrolidino, piperidino, morpholino, or thiomorpholino. Other specific substituted (C₁-C₆)alkyl groups are (C₁-C₆)alkyl groups substituted with one or more carbon-linked oxygen containing heterocyclic rings. Specific examples of such oxygenated heterocyclic rings are, for example, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, and like groups.
- [24] "(C₁-C₆)alkoxy" refers to groups of the formula (C₁-C₆)alkyl-O-, where (C₁-C₆)alkyl is as defined herein. Specific alkoxy groups include, by way of example, methoxy, ethoxy, propoxy, iso-propoxy, butoxy, iso-butoxy, sec-butoxy, n-butoxy, tert-butoxy, pentoxy, 3-pentoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, and like groups.
- [25] "Substituted (C₁-C₆)alkoxy" refers to a substituted (C₁-C₆)alkyl-O- group wherein substituted (C₁-C₆)alkyl is as defined above. Substituted (C₁-C₆)alkoxy is exemplified by groups such as O-CH₂CH₂-NR_aR_b, O-CH₂CH₂-CHR_aR_b, or O-CH₂-CHOH-CH₂-OH, and like groups. Specific substituted (C₁-C₆)alkoxy groups are (C₁-C₆)alkyl substituted with one or more substituents of the formula-NR_aR_b where R_a

and R_b together with the nitrogen to which they are attached form of a heterocyclic ring. Specific examples of such heterocyclic rings include piperazino, pyrrolidino, piperidino, morpholino, or thiomorpholino. Other specific substituted (C₁-C₆)alkoxy groups are (C₁-C₆)alkoxy groups substituted with one or more carbon-linked oxygen containing heterocyclic rings. Specific examples of specific oxygenated heterocyclic ring substituents are, for example, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, and like groups. Specific examples of such oxygenated heterocyclic rings are, for example, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, and like groups.

- [26] “(C₁-C₆)alkanoyloxy” includes, by way of example, formyloxy, acetoxy, propanoyloxy, iso-propanoyloxy, n-butanoyloxy, *tert*-butanoyloxy, *sec*-butanoyloxy, n-pentanoyloxy, n-hexanoyloxy, 1,2-dimethylbutanoyloxy, and like groups.
- [27] “Substituted (C₁-C₆)alkanoyloxy” refers to a (C₁-C₆)alkanoyloxy group wherein one or more (e.g. 1 or 2) carbon atoms in the alkyl chain have been replaced with a heteroatom independently selected from -O-, -S- and NR- (where R is hydrogen or C₁-C₆alkyl) and/or wherein the alkyl group is substituted with from 1 to 5 substituents independently selected from cycloalkyl, substituted cycloalkyl, (C₁-C₆)alkoxycarbonyl (e.g. -CO₂Me), cyano, halo, hydroxy, oxo (=O), carboxy (COOH), aryloxy, heteroaryloxy, heterocyclooxy, nitro, and -NR^aR^b, wherein R^a and R^b may be the same or different and are chosen from hydrogen, alkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic. Substituted (C₁-C₆)alkanoyloxy is exemplified by groups such as -O-C(=O)CH₂-NR_aR_b, and O-C(=O)-CHOH-CH₂-OH. Specific substituted (C₁-C₆)alkanoyloxy groups are groups wherein the alkyl group is substituted with one or more nitrogen and oxygen containing heterocyclic rings such as piperazino, pyrrolidino, piperidino, morpholino, thiomorpholino, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, and like groups.
- [28] Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Examples of aryl include phenyl, indenyl, and naphthyl.

- [29] Heteroaryl encompasses a radical attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(X) wherein X is absent or is H, O, (C₁-C₄)alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto. Examples of heteroaryl include furyl, imidazolyl, triazolyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazoyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) and quinolyl (or its N-oxide).
- [30] The term "heterocycle" refers to a monovalent saturated or partially unsaturated cyclic non-aromatic group which contains at least one heteroatom, preferably 1 to 4 heteroatoms, selected from nitrogen (NR_x, wherein R_x is hydrogen, alkyl, or a direct bond at the point of attachment of the heterocycle group), sulfur, phosphorus, and oxygen within at least one cyclic ring and which may be monocyclic or multi-cyclic. Such heterocycle groups preferably contain from 3 to 10 atoms. The point of attachment of the heterocycle group may be a carbon or nitrogen atom. This term also includes heterocycle groups fused to an aryl or heteroaryl group, provided the point of attachment is on a non-aromatic heteroatom-containing ring. Representative heterocycle groups include, by way of example, pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, morpholinyl, indolin-3-yl, 2-imidazoliny, 1,2,3,4-tetrahydroisoquinolin-2-yl, quinuclidinyl and the like.
- [31] "Aryloxy" refers to a group of the formula aryl-O-, where aryl is as defined herein. Examples of aryloxy groups include, phenoxy and 1-naphthyloxy.
- [32] "Heteroaryloxy" refers to a group of the formula heteroaryl-O-, where heteroaryl is as defined herein. Examples of heteroaryloxy groups include, 3-piperidyloxy, 3-furyloxy, and 4-imidazoyloxy.

- [33] "Heterocyclooxy" refers to a group of the formula heterocycle-O-, where heterocycle is as defined herein. Examples of heterocyclooxy groups include, 4-morpholinooxy and 3-tetrahydrofuranyloxy.
- [34] "Arylalkyl" refers to a group of the formula aryl-(C₁-C₆)alkyl-, where aryl and (C₁-C₆)alkyl are as defined herein.
- [35] "Heteroarylalkyl" refers to a group of the formula heteroaryl-(C₁-C₆)alkyl -, where heteroaryl and (C₁-C₆)alkyl are as defined herein.
- [36] "Heterocycloalkyl" refers to a group of the formula heterocycle-(C₁-C₆)alkyl -, where heterocycle and (C₁-C₆)alkyl are as defined herein.
- [37] "Effective amount" or "therapeutically effective amount" of a compound refers to a nontoxic but sufficient amount of the compound to provide the desired therapeutic or prophylactic effect to most patients or individuals. In the context of treating cancer, a nontoxic amount does not necessarily mean that a toxic agent is not used, but rather means the administration of a tolerable and sufficient amount to provide the desired therapeutic or prophylactic effect to a patient or individual. The effective amount of a pharmacologically active compound may vary depending on the route of administration, as well as the age, weight, and sex of the individual to which the drug or pharmacologically active agent is administered. Those of skill in the art given the benefit of the present disclosure can easily determine appropriate effective amounts by taking into account metabolism, bioavailability, and other factors that affect plasma levels of a compound following administration within the unit dose ranges disclosed further herein for different routes of administration.
- [38] "Treatment" or "treating" refers to any manner in which the symptoms of a condition, disorder or disease are ameliorated or otherwise beneficially altered. In the context of treating the cancers disclosed herein, the cancer can be onset, relapsed or refractory. Full eradication of the condition, disorder or disease is not required. Amelioration of symptoms of a particular disorder refers to any lessening of symptoms, whether permanent or temporary, that can be attributed to or associated

with administration of a therapeutic composition of the present invention or the corresponding methods and combination therapies. Treatment also encompasses pharmaceutical use of the compositions in accordance with the methods disclosed herein.

- [39] “Hematological cancer” as used herein refers to a cancer of the blood or bone marrow. Examples of hematological cancer include acute lymphoblastic leukemia, adult; acute lymphoblastic leukemia, childhood; acute myeloid leukemia, adult; acute myeloid leukemia, childhood; AIDS-related lymphoma; Burkitt lymphoma; central nervous system lymphoma, primary; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloproliferative disorders; cutaneous T-cell lymphoma; hairy cell leukemia; Hodgkin lymphoma, adult; Hodgkin lymphoma, childhood; leukemia, acute lymphoblastic, adult; leukemia, acute lymphoblastic, childhood; leukemia, acute myeloid, adult; leukemia, acute myeloid, childhood; leukemia, chronic lymphocytic; leukemia, chronic myelogenous; leukemia, hairy cell; lymphoma, AIDS-related; lymphoma, Burkitt; lymphoma, Hodgkin, adult; lymphoma, Hodgkin, childhood; lymphoma, Non-Hodgkin, adult; lymphoma, Non-Hodgkin, childhood; lymphoma, primary central nervous system; multiple myeloma/plasma cell neoplasm; mycosis fungoides; myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; myelogenous leukemia, chronic; myeloid leukemia, adult acute; myeloid leukemia, childhood acute; myeloma, multiple; myeloproliferative disorders, chronic; Non-Hodgkin lymphoma, adult; Non-Hodgkin lymphoma, childhood; plasma cell neoplasm/multiple myeloma; primary central nervous system lymphoma; Sézary syndrome; and Waldenström macroglobulinemia. Certain hematological malignancies, such as cancers include monocytic leukemia, acute erythroleukemia, acute monocytic leukemia, B myelomonocytic leukemia, non-Hodgkin’s lymphoma, acute promyelocytic leukemia, Burkitt’s lymphoma, B cell lymphoma, and B lymphoblastoid.

- [40] “Mammal” as used herein includes humans.

- [41] "Prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, *i.e.* active ingredient of formula I or a salt thereof, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a modified analog or latent form of a therapeutically-active compound.
- [42] "Metabolite" as used herein refers to any compound formed as a result of the drug substance, *i.e.* the active ingredient of formula 1 or a salt thereof, being administered to a biological system, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s).
- [43] "Solubilizing group(s) R_z " is a substituent that increases the water solubility of the compound of formula I compared to the corresponding compound lacking the R_z substituent. Examples of solubilizing groups include substituents independently selected from substituted (C_1 - C_6)alkyl, (C_1 - C_6)alkoxycarbonyl (e.g. $-\text{CO}_2\text{Me}$), cyano, halo, hydroxy, oxo ($=\text{O}$), carboxy (COOH), aryloxy, heteroaryloxy, heterocyclooxy, nitro, and $-\text{NR}_a\text{R}_b$, wherein R_a and R_b may be the same or different and are chosen from hydrogen, alkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic.
- [44] Specific R_1 groups are exemplified by, for example, groups such as hydroxymethyl, hydroxyethyl, hydroxypropyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-dimethylaminopropyl, 2-carboxyethyl, hydroxylated alkyl amines, such as 2-hydroxyaminoethyl, and like groups. Other specific R_1 groups are (C_1 - C_6)alkyl groups substituted with one or more substituents of the formula $-\text{NR}_a\text{R}_b$ where R_a and R_b together with the nitrogen to which they are attached form a nitrogen containing heterocyclic ring, or (C_1 - C_6)alkyl groups substituted with one or more oxygen containing heterocyclic rings. Specific examples of such heterocyclic rings include piperazino, pyrrolidino, piperidino, morpholino, or thiomorpholino. Still other specific R_1 groups are (C_1 - C_6)alkyl groups substituted with one or more carbon-linked oxygen containing heterocyclic rings. Specific examples of such oxygenated

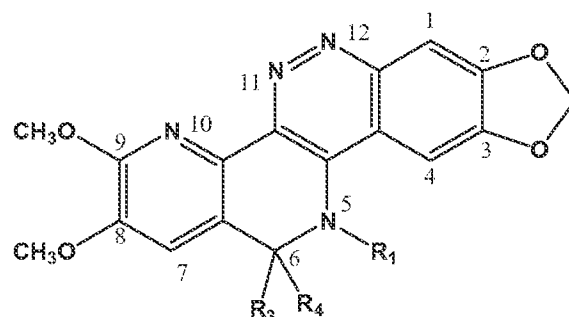
heterocyclic rings are, for example, tetrahydrofuranyl, tetrahydropyranyl, 1,4-dioxanyl, and like groups.

- [45] Specific and specific values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.
- [46] A specific value for A is CH.
- [47] Another specific value for A is N.
- [48] A specific value for B is N.
- [49] Another specific value for B is CH.
- [50] A specific value for W is N.
- [51] Another specific value for W is CH.
- [52] A specific value for Y is OH.
- [53] Another specific value for Y is (C₁-C₆)alkoxy.
- [54] Another specific value for Y is -OCH₃.
- [55] Another specific value for Y is substituted (C₁-C₆)alkoxy.
- [56] Another specific value for Y is -OCH₂CH₂OH.
- [57] Another specific value for Y is -OCH₂CH₂OCH₂CH₃.
- [58] Another specific value for Y is -O-CH₂-CHOH-CH₂-OH.
- [59] Another specific value for Y is -O-CH₂CH₂-NR_aR_b wherein R_a and R_b are hydrogen or (C₁-C₆)alkyl.

- [60] Another specific value for Y is $-O-CH_2CH_2-NR_aR_b$ wherein R_a and R_b together with the nitrogen to which they are attached form a piperazino, pyrrolidino, piperidino, morpholino, or thiomorpholino ring.
- [61] Another specific value for Y is $-O-C(=O)CH_2-NR_aR_b$.
- [62] Another specific value for Y is $-O-C(=O)-CHOH-CH_2-OH$.
- [63] Another specific value for Y is (C_1-C_6) alkyl substituted with one or more tetrahydrofuranyl, tetrahydropyranyl, or 1,4-dioxanyl rings.
- [64] Another specific value for Y is $-O-C(=O)CH_2-NR_aR_b$.
- [65] A specific value for Z is OH.
- [66] Another specific value for Z is (C_1-C_6) alkoxy.
- [67] Another specific value for Z is OCH_3 .
- [68] Another specific value for Z is substituted (C_1-C_6) alkoxy.
- [69] Another specific value for Z is $-OCH_2CH_2OH$.
- [70] Another specific value for Z is $-OCH_2CH_2OCH_2CH_3$.
- [71] Another specific value for Z is $-O-CH_2-CHOH-CH_2-OH$.
- [72] Another specific value for Z is $-O-CH_2CH_2-NR_aR_b$ wherein R_a and R_b are hydrogen or (C_1-C_6) alkyl.
- [73] Another specific value for Z is $-O-CH_2CH_2-NR_aR_b$ wherein R_a and R_b together with the nitrogen to which they are attached form a piperazino, pyrrolidino, piperidino, morpholino, or thiomorpholino ring.
- [74] Another specific value for Z is $-O-C(=O)-CHOH-CH_2-OH$.

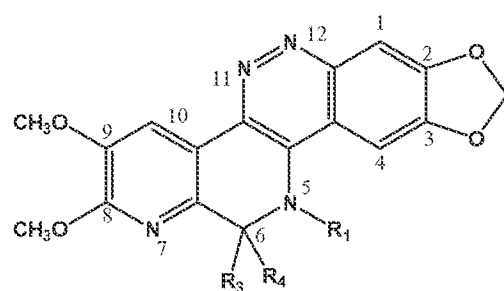
- [75] Another specific value for Z is (C₁-C₆)alkyl substituted with one or more tetrahydrofuranyl, tetrahydropyranyl, or 1,4-dioxanyl rings.
- [76] Another specific value for Z is -O-C(=O)CH₂-NR_aR_b.
- [77] A specific value for R₃ and R₄ is H.
- [78] Another specific value for R₃ and R₄ together is =O.
- [79] Another specific value for R₃ and R₄ together is =S.
- [80] Another specific value for R₃ and R₄ together is =NH.
- [81] Another specific value for R₃ and R₄ together is =N-R₂.
- [82] Another specific value for R₃ and R₄ together is =N-R₂ where R₂ is (C₁-C₆)alkyl.
- [83] Another specific value for R₃ and R₄ together is =N-R₂ where R₂ is substituted (C₁-C₆)alkyl.
- [84] Another specific value for R₃ is H and R₄ is (C₁-C₆)alkyl.
- [85] Another specific value for R₃ is H and R₄ is substituted (C₁-C₆)alkyl.
- [86] Another specific value for R₃ is (C₁-C₆)alkyl and R₄ is substituted (C₁-C₆)alkyl.
- [87] Another specific value for R₃ and R₄ is substituted (C₁-C₆)alkyl.
- [88] A specific value for R₁ is 2-hydroxyethyl.
- [89] Another specific value for R₁ is 2-aminoethyl.
- [90] Another specific value for R₁ is 2-(N,N'-dimethylamino)ethyl.
- [91] Another specific value for R₁ is 2-(N,N'-diethylamino)ethyl.
- [92] Another specific value for R₁ is 2-(N,N'-diethanolamino)ethyl of the formula -CH₂-CH₂-N(-CH₂-CH₂-OH)₂.

- [93] Another specific value for R_1 or R_2 is a (C_1-C_6) alkyl substituted with one or more hydroxy, mercapto, carboxy, amino, piperazinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, tetrahydropyranyl, or 1,4-dioxanyl groups.
- [94] Another specific value for R_1 or R_2 is a (C_1-C_6) alkyl with from 2 to 4 carbon atoms and substituted with one to two groups selected from hydroxy, mercapto, carboxy, amino, piperazinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, tetrahydropyranyl, or 1,4-dioxanyl.
- [95] Another specific value for R_1 or R_2 is $-CH_2CH_2-NR_aR_b$ wherein R_a and R_b are hydrogen or (C_1-C_6) alkyl.
- [96] Another specific value for R_1 or R_2 is $-CH_2CH_2-NR_aR_b$ wherein R_a and R_b together with the nitrogen to which they are attached form a piperazino, pyrrolidino, piperidino, morpholino, or thiomorpholino ring.
- [97] A specific compound of formula (I) is the compound 11,12-dihydro-2,3-dimethoxy-8,9-methylenedioxy-11-[2-(dimethylamino)ethyl]-5,6,11-triazachrysen-12-one, or a pharmaceutically acceptable salt, prodrug or metabolite thereof.
- [98] A specific compound of formula I is a compound of formula II:



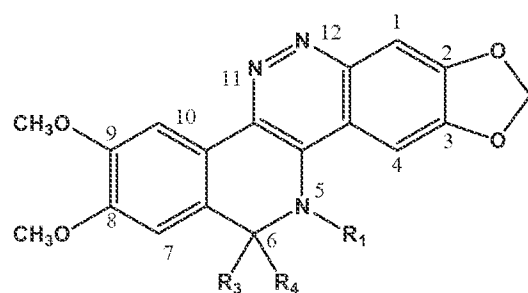
Formula II

- [99] Another specific compound of formula I is a compound of formula III:



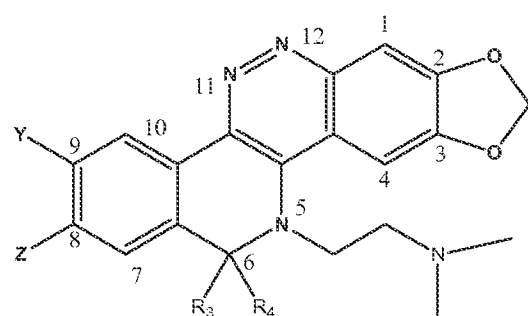
Formula III

[100] Another specific compound of formula I is a compound of formula IV:



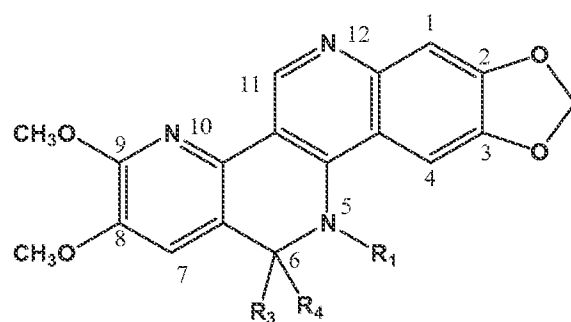
Formula IV

[101] Another specific compound of formula I is a compound of formula V:



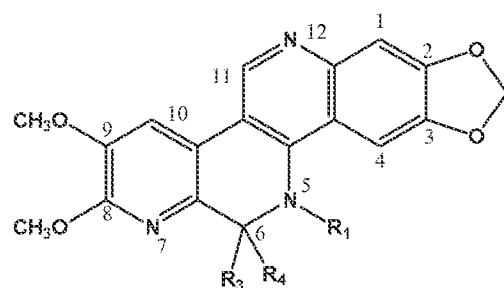
Formula V

[102] Another specific compound of formula I is a compound of formula VI:



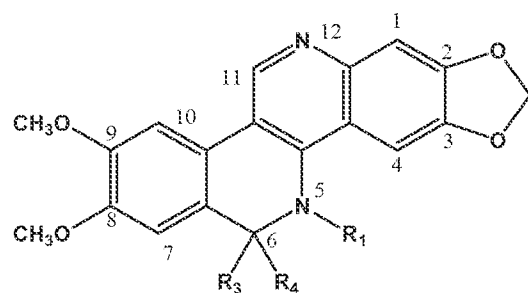
Formula VI

[103] Another specific compound of formula I is a compound of formula VII:



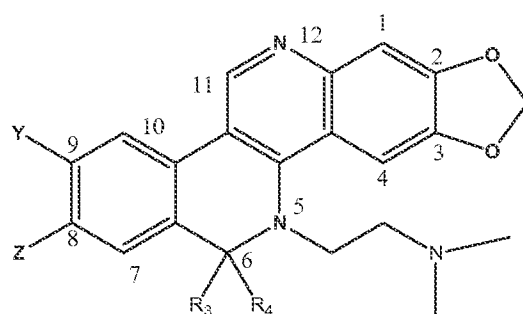
Formula VII

[104] Another specific compound of formula I is a compound of formula VIII:



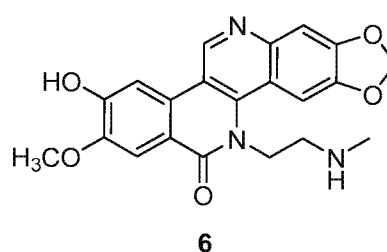
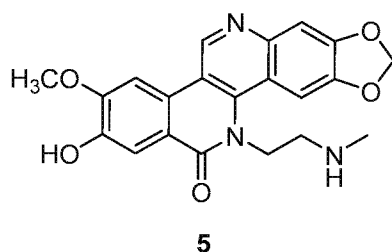
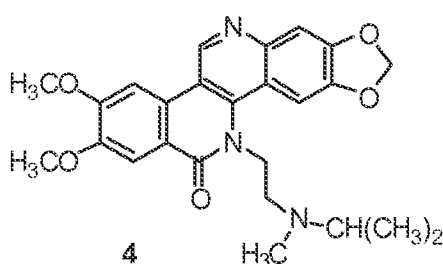
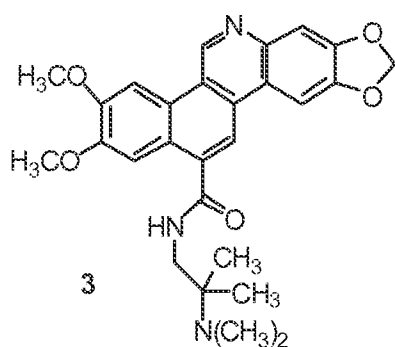
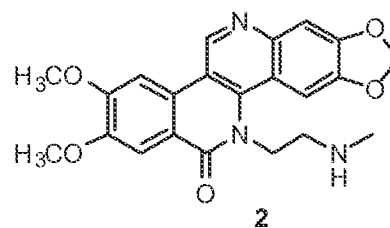
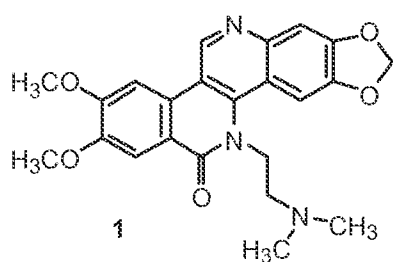
Formula VIII

[105] Another specific compound of formula I is a compound of formula IX:



Formula IX

- [106] Another specific compound of formula I is any of the above compounds of formulas I-IX as a pharmaceutically acceptable salt.
- [107] Specific compounds useful for the methods of treating hematological cancers and corresponding pharmaceutical compositions of the present disclosure include 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N,N-diethylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; and 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N-methylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; and pharmaceutically acceptable salts, prodrugs and or metabolites thereof. A specific compound of formula I that has been found to be particularly active against hematological cancers is 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N-methylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one referred to herein as Compound 2.
- [108] Structures of certain compounds within the scope of the present disclosure include Compound 1, Compound 2, Compound 3, Compound 4, Compound 5, and Compound 6 below.



[109] The compounds described herein including those of formulae I-IX and structures 1-6 above can be prepared as described in international patent application number PCT/US02/36901, the entire content of which is hereby incorporated herein by reference.

[110] Certain examples are described herein of compounds with reference to various chemical formulae or IUPAC names. The compounds referred to herein may exhibit

the phenomena of tautomerism, conformational isomerism, stereo isomerism or geometric isomerism. As the formulae drawings within this specification can represent only one of the possible tautomeric, conformational isomeric, enantiomeric or geometric isomeric forms, it should be understood that the invention encompasses any tautomeric, conformational isomeric, enantiomeric or geometric isomeric forms which exhibit biological or pharmacological activity as described herein.

- [111] The structure of some of the compounds of the invention may include asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from such asymmetry (*e.g.*, all enantiomers and diastereomers) are included within the scope of the invention, unless indicated otherwise. Such isomers may be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis. Furthermore, the structures and other compounds and moieties discussed in this application also include all tautomers thereof. Alkenes and imines can include either the E- or Z-geometry, where appropriate.
- [112] Embodiments of the present invention include salts of the compounds of Formula 1 and those otherwise described herein and are likewise referred to as compounds of the present disclosure. Solutions of active compounds as free base or pharmacologically acceptable salts are prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.
- [113] Examples of acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of basic residues such as carboxylic acids; and the like. The acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts from non-toxic inorganic acids. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

- [114] For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, mandelic tartaric, citric, ascorbic, palmoic, maleic, hydroxymaleic, phenylacetic, glutamine, benzoic, salicylic, sulfanilic, 2-acteoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like. Specifically, the acceptable salts can include those salts that naturally occur in vivo in a mammal.
- [115] In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate as described above. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α -ketoglutarate, and α -glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.
- [116] Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal, for example, sodium, potassium or lithium, or alkaline earth metal, for example calcium, salts of carboxylic acids can also be made.
- [117] The compositions of the present disclosure may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients. The pharmaceutically acceptable carrier can be any such carrier known in the art including those described in, for example, Remington's Pharmaceutical Sciences, Mack Publishing Co., (A. R. Gennaro edit. 1985). Pharmaceutical compositions of the compounds presently disclosed may be prepared by conventional means known in the art including, for example, mixing at least one presently disclosed compound with a pharmaceutically acceptable carrier.

- [118] The compounds presently disclosed may also be formulated for sustained delivery according to methods well known to those of ordinary skill in the art. Examples of such formulations can be found in United States Patents 3,119,742, 3,492,397, 3,538,214, 4,060,598, and 4,173,626.
- [119] Thus, the active compounds of the disclosure may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous), rectal administration, in a form suitable for administration by inhalation or insufflation, or the active compounds may be formulated for topical administration.
- [120] Thus, the present compounds may be systemically administered, for example, orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.
- [121] The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the

solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

- [122] The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.
- [123] The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the

compositions of agents delaying absorption, for example, aluminum monostearate and gelatin. In certain embodiments where the pharmaceutical composition is formulated for parenteral administration, a compound of formula 1 or a pharmaceutically acceptable salt thereof is prepared in a 2 mg/mL solution of predominantly USP water for injection.

- [124] Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the specific methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.
- [125] For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.
- [126] Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.
- [127] Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

- [128] Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).
- [129] Useful dosages of the compounds described herein can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.
- [130] Generally, the concentration of the compound(s) described herein in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.
- [131] The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.
- [132] In general, however, a suitable dose will be in the range of from about 0.5 to about 100 mg/kg, e.g., from about 10 to about 75 mg/kg of body weight per day, such as 3 to about 50 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day.
- [133] The compound may conveniently be administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form.
- [134] Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.5 to about 75 μ M, preferably, about 1 to 50 μ M, most preferably, about 2 to about 30 μ M. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active

ingredient, optionally in saline, or orally administered as a bolus containing about 1-100 mg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the active ingredient(s).

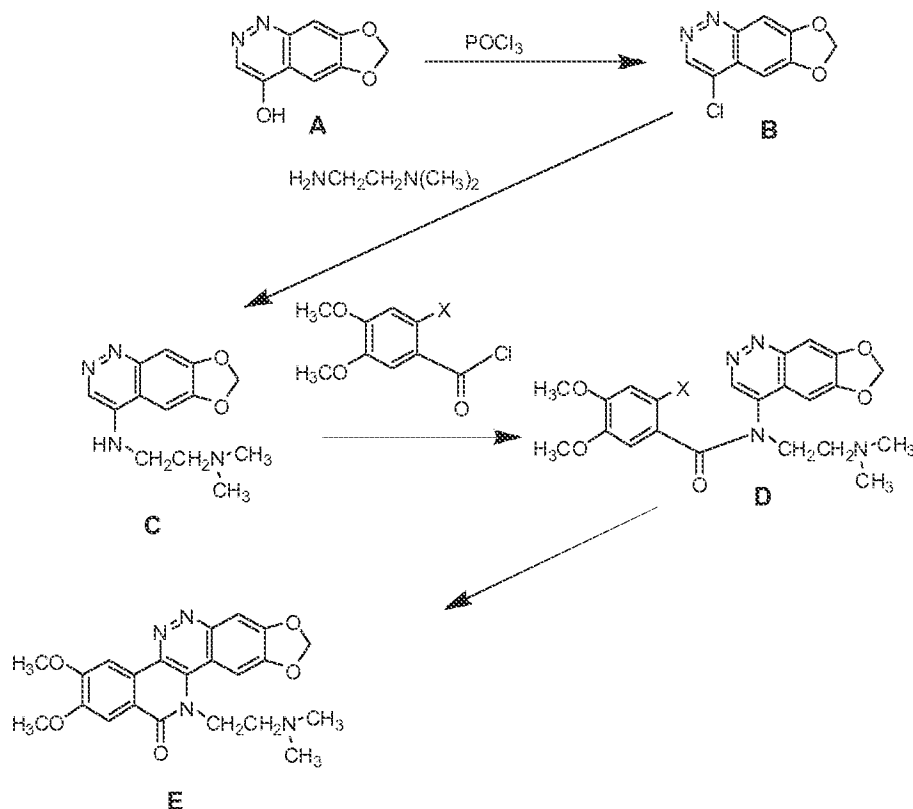
- [135] The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.
- [136] One or more compounds of the present disclosure alone or together with one or more pharmacologically active agents may be administered to a patient simultaneously, sequentially, or in combination. It will be appreciated that when using a combination of the invention, the compound(s) of the invention and the other pharmacologically active agent(s) may be in the same pharmaceutically acceptable carrier and therefore administered simultaneously. They may be in separate pharmaceutical carriers such as conventional oral dosage forms, which are taken simultaneously. The term "combination" further refers to the case where the compounds are provided in separate dosage forms and are administered sequentially.
- [137] "Combination therapy" (or "co-therapy") includes the administration of a compound of the invention and at least a second agent as part of a specific treatment regimen intended to provide the beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected). "Combination therapy" may, but generally is not, intended to encompass the administration of two or more of these therapeutic agents as part of separate monotherapy regimens that incidentally and arbitrarily result in the combinations of the present invention. "Combination therapy"

is intended to embrace administration of these therapeutic agents in a sequential manner, that is, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, inhalation, oral routes, intravenous routes, intramuscular routes, subcutaneous, rectal, intraperitoneal, parenteral, transdermal, gastrointestinal, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, therapeutic agents may be administered orally or by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical. "Combination therapy" also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies (*e.g.*, surgery or radiation treatment). Where the combination therapy further comprises a non-drug treatment, the non-drug treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and non-drug treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the non-drug treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

EXAMPLE I

Synthesizing Compounds

- [138] Representative compounds of formula I can be prepared as described in the Examples of international patent application number PCT/US02/36901, which are reproduced below.



[139] **Example 1.** **11,12-dihydro-2,3-dimethoxy-8,9-methylenedioxy-11-[2-(dimethylamino)ethyl]-5,6,11-triazachrysen-12-one (E).** A mixture of 4-N-(2-Dimethylaminoethyl)-N-(2-bromo-4,5-dimethoxybenzoyl)amine-6,7-methylenedioxycinnoline (**D**, 220 mg, 0.40 mmol), $\text{Pd}(\text{OAc})_2$ (18.0 mg, 0.08 mmol), $\text{P}(o\text{-tolyl})_3$ (48.8 mg, 0.16 mmol), and silver carbonate (225 mg, 0.80 mmol) were heated to reflux in DMF (12 mL) and stirred under nitrogen for 75 minutes. The reaction mixture was cooled to room temperature, diluted with chloroform and filtered through a bed of celite. The solvent was removed under reduced pressure and the resulting residue was chromatographed on silica gel using 95:5 chloroform:methanol to give the title compound (60 mg) in 36 % yield; ^1H NMR (CDCl_3) δ 2.42(s, 6H), 3.04(t, 2H, $J=7.2$ Hz), 4.08(s, 3H), 4.17(s, 3H), 4.64(t, 2H, $J=7.2$ Hz), 6.25(s, 2H), 7.81(s, 1H), 7.84(s, 1H), 8.07(s, 1H), 8.65(s, 1H); ^{13}C NMR (CDCl_3) δ 45.9, 47.4, 56.4, 56.7, 57.7, 99.4, 102.8, 104.3, 106.6, 107.9, 113.7, 119.6,

129.1, 131.0, 134.4, 149.4, 150.2, 151.5, 154.4, 163.1; HRMS calcd. for $C_{22}H_{22}O_5N_4H$: 423.1668; found 423.1653.

[140] The intermediate 4-N-(2-Dimethylaminoethyl)-N-(2-bromo-4,5-dimethoxybenzoyl)amine-6,7-methylenedioxcinnoline (**D**) was prepared as follows:

[141] a. **4-N-(2-Dimethylaminoethyl)-N-(2-bromo-4,5-dimethoxybenzoyl)amine-6,7-methylenedioxcinnoline (D)**. A 2.0M solution of oxalyl chloride in methylene chloride (5 mL, 10.0 mmol) was added to a solution of 2-iodo-4,5-dimethoxybenzoic acid (1.50g, 4.8mmol) in anhydrous methylene chloride (45 mL) and the stirred mixture was refluxed for 2 hours. The mixture was then concentrated to dryness under reduced pressure. To this residue was added a solution of N-(2-Dimethylaminoethyl)-4-amino-6,7-methylenedioxcinnoline (**3**, 1.0 g, 3.84 mmol), and triethylamine (760 mg 7.52 mmol) in methylene chloride (60 mL) and the resulting mixture was stirred at reflux under nitrogen for 4 hours, then cooled to room temperature; stirring was continued overnight. The reaction mix was washed with a saturated solution of sodium bicarbonate (3 x 40 mL), dried (anhydrous $MgSO_4$), and concentrated *in vacuo*. The crude material was chromatographed over silica using 90:10 chloroform:methanol to give compound **D** (1.59 g), in 75 % yield; ^1H NMR ($CDCl_3$) δ 2.27(s, 6H), 2.53(m, 2H), 3.43(s, 3H), 3.75(s, 3H), 3.97(m, 1H), 4.44(m, 1H), 6.24(s, 1H), 6.25(s, 1H), 6.43(s, 1H), 7.02(s, 1H), 7.43(s, 1H), 7.68(s, 1H), 9.18(s, 1H); ^{13}C NMR ($CDCl_3$) δ 45.5, 47.1, 55.7, 56.1, 56.7, 82.8, 96.7, 102.9, 105.4, 110.6, 121.9, 123.2, 133.1, 136.0, 144.8, 148.2, 149.9, 150.9, 151.7, 152.4, 169.8; HRMS calcd for $C_{22}H_{23}O_5N_4H$: 551.0791; found 551.0795.

[142] b. **N-(2-Dimethylaminoethyl)-4-amino-6,7-methylenedioxcinnoline (C)**. 4-Chloro-6,7-methylenedioxcinnoline (350 mg, 1.7 mmol) and copper powder (100 mg, 1.6 mmol) in *N,N*-dimethylethylenediamine (3.75 g, 42.6 mmol) were stirred at 105 °C under nitrogen for 3 hours. Excess *N,N*-dimethylethylenediamine was removed by rotoevaporation, and the residue was dissolved in chloroform (50 mL), and washed with water (3x 30 mL), dried (anhydrous $MgSO_4$), and concentrated *in vacuo* to give compound **C** (324 mg) in 74% yield; ^1H NMR ($CDCl_3$) δ 2.33 (s, 6H),

2.70 (t, 2H), 3.38 (dt, 2H), 6.15 (s, 2H), 7.03 (s, 1H), 7.56 (s, 1H), 8.53 (s, 1H); ^{13}C NMR (CDCl_3) δ 39.5, 45.1, 57.0, 94.7, 102.1, 105.3, 112.7, 128.8, 139.8, 147.8, 149.5, 150.7; HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2\text{N}_4$: 260.1273; found 260.1267.

[143] c. **4-Chloro-6,7-methylenedioxcinnoline (B).** 4-Hydroxy-6,7-methylenedioxcinnoline (**A**, 1.0 g, 5.3 mmol) was added in small portions to a stirred mixture of phosphorus pentachloride (1.4 g, 6.7 mmol) and phosphorus oxychloride (4 mL, 6.6 mmol) at room temperature. The reaction flask was heated to 80 °C for 1 hour, then cooled to room temperature and poured onto 50 g of crushed ice. After neutralization of the solution with solid sodium acetate the precipitate was removed by filtration and recrystallized from ethanol to give 800 mg of 4-chloro-6,7-methylenedioxcinnoline, compound **B**, in 73 % yield; ^1H NMR (CDCl_3) δ 6.25 (s, 2H), 7.39 (s, 1H), 7.73 (s, 1H), 9.14 (s, 1H); ^{13}C NMR (CDCl_3) δ 97.8, 102.9, 105.1, 124.2, 133.4, 144.0, 150.0, 152.3, 152.7; HRMS calcd for $\text{C}_9\text{H}_5\text{O}_2\text{N}_2\text{Cl}$: 208.0040; found 208.0042.

[144] d. **4-Hydroxy-6,7-methylenedioxcinnoline (A).** 6'-Amino-3',4'-(methylenedioxy)acetophenone (2.4 g, 13.4 mmol) in concentrated hydrochloric acid (92 mL) and water (13 mL) was cooled to -5 °C and diazotized by the dropwise addition of a solution of sodium nitrite (0.925 g, 13.4 mmol) in water (4 mL). After stirring for an additional hour at -5 °C the mixture was transferred to a bath preheated at 75 °C and left to stir at this temperature overnight. The reaction mixture was cooled to 5 °C to complete crystallization of the product in the form of its hydrochloride salt. This material was filtered and then added to 10% aqueous NaOH (100 mL) to generate the free base, which was again filtered and dried under vacuum to yield 2.37 g of the hydroxycinnoline, compound **1**, in 93% yield; ^1H NMR (d_6 -DMSO) δ 6.21(s, 2H), 6.97 (s, 1H), 7.30 (s, 1H), 7.63 (s, 1H); ^{13}C NMR (d_6 -DMSO) δ 94.9, 100.29, 103.3, 120.1, 139.7, 139.9, 147.4, 153.5, 169.4; HRMS calcd for $\text{C}_9\text{H}_6\text{O}_3\text{N}_2$: 190.0378; found 190.0372.

Examples 2-6

- [145] The representative compounds of the invention at Examples 2-6 were prepared using the following general procedure from the intermediates prepared in the correspondingly numbered sub-parts a below.
- [146] A mixture of the requisite 4-amino-6,7-methylenedioxcinnoline *o*-iodobenzamide derivative (1.0 mmol equiv.), Pd(OAc)₂ (0.2 mmol equiv.), P(*o*-tolyl)₃ (0.4 mmol equiv.), and Ag₂CO₃ (2.0 mmol equiv) was heated to reflux in DMF (30 mL per mmol equiv.) with stirring. The reaction mixture was allowed to cool to room temperature, diluted with CHCl₃, and filtered through Celite. The siccate was extensively washed with 10% CH₃OH in CHCl₃. The filtrate was concentrated *in vacuo* and the residue chromatographed on silica gel using chloroform:methanol to provide the title compound.
- [147] **Example 2. 2,3-Dimethoxy-8,9-methylenedioxy-11-[(2-diethylamino)ethyl]-11H-5,6,11-triaza-chrysen-12-one:** Prepared from N-(6,7-Methylenedioxcinnolin-4-yl)-N-(N,N-diethylaminoethyl)-2-iodo-4,5-dimethoxybenzamide (578 mg, 1.0 mmol); (18% yield); reaction time 25 min; mp 245-247 °C (dec.); IR (CHCl₃) 1652; ¹H NMR (CDCl₃) δ 1.08 (t, 6H, *J*=7.0), 2.67 (q, 4H, *J*=7.0), 3.14 (t, 2H, *J*=7.1), 4.08 (s, 3H), 4.17 (s, 3H), 4.64 (t, 2H, *J*=7.1), 6.25 (s, 2H), 7.80 (s, 1H), 7.84 (s, 1H), 8.18 (s, 1H), 8.63 (s, 1H); ¹³C NMR (CDCl₃) δ 11.8, 47.7, 48.0, 51.5, 56.4, 56.6, 99.7, 102.7, 104.3, 106.4, 108.0, 113.7, 119.7, 129.1, 131.1, 134.4, 149.4, 150.3, 151.2, 151.5, 154.4, 163.2; HRMS calcd for C₂₄H₂₆O₅N₄H: 451.1952; found: 451.1960.
- [148] **Example 3. 2,3-Dimethoxy-8,9-methylenedioxy-11-[(2-dimethylamino)-1-methylethyl]-11H-5,6,11-triaza-chrysen-12-one:** Prepared from N-(6,7-Methylenedioxcinnolin-4-yl)-N-[2-(N,N-dimethylamino)-1-methylethyl]-2-iodo-4,5-dimethoxybenzamide (100 mg, 0.18 mmol); (28% yield); reaction time 2 h; mp 235-36 °C; IR(KBr) 1659; ¹H NMR (CDCl₃) δ 1.93 (d, 3H, *J*=8.2), 1.97 (s, 3H), 2.74 (dd, 1H, *J*=5.8,13.6), 3.27 (dd, 1H, *J*=7.4,12.8), 4.07 (s, 3H), 4.15 (s, 3H), 4.80 (m, 1H), 6.24 (s,2H), 7.74 (s,1H), 7.81 (s,1H), 8.57 (s,1H); ¹³C (CDCl₃) δ 19.4, 45.6, 56.3, 58.6, 63.0, 99.0, 102.6, 104.1, 106.2, 107.9, 114.2, 120.8, 125.6, 128.6, 131.0,

132.5, 132.8, 135.1, 149.2, 150.3, 150.6, 151.3, 154.2, 164.0; HRMS calcd for $C_{23}H_{24}N_4O_5H$ 436.1747; found 436.1832.

- [149] **Example 4. 2,3-Dimethoxy-8,9-methylenedioxy-11-(2-tetrahydrofuranyl)methyl-11H-5,6,11-triazachrysen-12-one:** Prepared from N-(6,7-Methylenedioxy-4-cinnolin-4-yl)-N-[2-(tetrahydrofuran-2-yl)methyl]-2-iodo-4,5-dimethoxybenzamide (140 mg, 0.25 mmol); (22% yield); reaction time 45 min; mp 300-303 °C (dec.) ; IR ($CHCl_3$) 1653; ^1H NMR ($CDCl_3$) δ 1.79 (m, 1H), 2.00 (m, 2H), 2.25 (m, 1H), 3.87 (m, 2H), 4.09 (s, 3H), 4.18 (s, 3H), 4.65 (m, 3H), 6.25 (s, 2H), 7.80 (s, 1H), 7.84 (s, 1H), 8.32 (s, 1H), 8.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.7, 30.8, 53.0, 56.4, 56.7, 68.4, 77.8, 100.0, 102.7, 104.3, 106.3, 108.0, 114.1, 119.7, 129.1, 131.4, 134.5, 149.5, 150.2, 150.8, 151.4, 154.4, 163.7; HRMS calcd for $C_{23}H_{21}O_6N_3$: 435.1430; found: 435.1427.
- [150] **Example 5. 2,3-Dimethoxy-8,9-methylenedioxy-11-[2-(pyrrolidin-1-yl)ethyl]-11H-5,6,11-triaza-chrysen-12-one:** Prepared from N-(6,7-Methylenedioxy-4-cinnolin-4-yl)-N-[(2-pyrrolidin-1-yl)ethyl]-2-iodo-4,5-dimethoxybenzamide (150 mg, 0.2 mmol) in 24% yield with a reaction time 30 min; mp 229 °C; IR (KBr) 1644; ^1H NMR ($CDCl_3$) δ 1.83 (m, 4H), 2.71 (m, 4H), 3.23 (t, 2H, $J=7$), 4.06 (s, 3H), 4.61 (s, 3H), 4.63 (t, 2H, $J=7$), 6.23 (s, 2H), 7.74 (s, 1H), 7.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.7, 54.0, 54.2, 56.3, 56.6, 99.4, 102.7, 104.2, 106.3, 107.7, 113.5, 119.4, 129.0, 134.1, 140.2, 150.2, 151.4, 154.3, 154.3, 163.0; HRMS calcd for $C_{24}H_{24}N_4O_5H$: 449.1825; found 449.1822.
- [151] **Example 6. 2,3-Dimethoxy-8,9-methylenedioxy-11-[2-(piperidin-1-yl)ethyl]-11H-5,6,11-triaza-chrysen-12-one:** Prepared from N-(6,7-Methylenedioxy-4-cinnolin-4-yl)-N-[2-(piperidin-1-yl)ethyl]-2-iodo-4,5-dimethoxybenzamide (295 mg, 0.5 mmol); (32.4% yield); reaction time 30 min; mp 294-95 °C; IR (KBr) 1662; ^1H NMR ($CDCl_3$) δ 1.59 (s, 6H), 2.51 (s, 4H), 3.02 (t, 2H, $J=6.6$), 4.08 (s, 3H), 4.17 (s, 3H), 4.64 (t, 2H, $J=6.6$), 6.26 (s, 2H), 7.81 (s, 1H), 7.85 (s, 1H), 8.36 (s, 1H), 8.65 (s, 1H); ^{13}C ($CDCl_3$) δ 24.3, 26.0, 47.5, 55.0, 56.3, 56.6, 57.4, 99.9, 102.7, 104.2, 106.3, 107.9, 113.7, 119.6, 129.0, 131.1, 134.3, 149.3, 150.2, 151.1, 151.4, 154.3, 163.1; HRMS calcd for $C_{25}H_{26}N_4O_5H$ 463.1981 ; found 463.1986.

Examples 2.a-6.a

- [152] The intermediate 4-amino-6,7-methylenedioxcinnoline *o*-iodobenzamide derivatives used in Examples 2-6 were prepared using the following general procedure.
- [153] A 2.0M solution of oxalyl chloride in CH₂Cl₂ (1.3 equiv.) was added to a solution of 2-iodo-4,5-dimethoxybenzoic acid (1.0 equiv.) in anhydrous CH₂Cl₂ (≈ 60 mL per 10 mmol benzoic acid) and the solution stirred at reflux for 3 h. The mixture was allowed to cool and was then concentrated to dryness in vacuo. To the residues was added a solution of requisite 4-amino-6,7-dimethoxyquinoline (1.0 equiv), triethylamine (2 equiv.) in CH₂Cl₂ (≈ 60 mL per 4 mmol aminoquinoline). The reaction mixture was then stirred at reflux under N₂. The reaction mixture was cooled and washed with sat. NaHCO₃ and extracted with 3% HCl. The aqueous layer was neutralized with 20% NaOH and extracted with CHCl₃, dried (MgSO₄) and evaporated.
- [154] **Example 2.a. N-(6,7-Methylenedioxcinnolin-4-yl)-N-(N,N-diethylaminoethyl)-2-iodo-4,5-dimethoxybenzamide:** Prepared from N'-(6,7-Methylenedioxcinnolin-4-yl)-N,N-diethylethane-1,2-diamine (640 mg, 2.2 mmol); (87% yield); reaction time 16 h; IR (CHCl₃) 1656; ¹H NMR (CDCl₃) δ 0.92 (t, 6H, *J*=7.0), 2.50 (q, 4H, *J*=7.0), 2.80 (t, 2H, *J*=6.8), 3.39 (s, 3H), 3.71 (s, 3H), 3.94 (m, 1H), 4.41 (m, 1H), 6.21 (d, 2H, *J*=1.4), 6.39 (s, 1H), 7.01 (s, 1H), 7.39 (s, 1H), 7.64 (s, 1H), 9.11 (s, 1H); ¹³C NMR (CDCl₃) δ 11.6, 46.9, 47.8, 51.1, 55.7, 56.1, 82.9, 96.9, 102.9, 105.5, 110.9, 122.1, 122.9, 133.0, 136.5, 144.9, 148.3, 150.1, 150.9, 151.7, 152.3, 169.8; HRMS calcd for C₂₄H₂₇O₅N₄IH: 579.1105; found: 579.1105.
- [155] **Example 3.a. N-(6,7-Methylenedioxcinnolin-4-yl)-N-[2-(N,N-dimethylamino)-1-methylethyl]-2-iodo-4,5-dimethoxybenzamide:** Prepared from N-(6,7-difluorocinnolin-4-yl)-N¹,N¹-dimethylpropane-1,2-diamine (240 mg, 0.87 mmol); (83% yield); reaction time 16 h, mp 110-111 °C; ¹H NMR (CDCl₃) was a mixture of atropisomers δ isomer #1 1.03-1.36 (m, 3H), 2.21-2.37 (m, 6H), 2.74-3.07 (m, 1H), 3.43-3.65 (m, 6H), 3.84-3.91 (m, 1H), 5.15 (m, 1H), 6.18 (s, 2H), 6.59 (s, 1H), 6.91 (s, 1H), 7.56 (s, 1H), 8.04 (s, 1H), 9.34 (s, 1H) isomer #2 1.03-1.36 (m, 3H), 2.31-

2.37 (m, 6H), 2.74-3.07 (m, 1H), 3.43-3.65 (m, 6H), 3.84-3.91 (m, 1H), 5.15 (m, 1H), 6.18 (s, 2H), 6.59 (s, 1H), 6.91 (s, 1H), 7.56 (s, 1H), 8.04 (s, 1H), 9.34 (s, 1H); HRMS calcd for C₂₃H₂₅O₅N₄IH: 565.0870; found: 565.0926.

[156] **Example 4.a. N-(6,7-Methylenedioxcinnolin-4-yl)-N-[2-(tetrahydrofuran-2-yl)methyl]-2-iodo-4,5-dimethoxybenzamide:** Prepared from 2-[[[N-(6,7-Methylenedioxcinnolin-4-yl)]amino]methyl]tetrahydrofuran (400 mg, 1.5 mmol); (34% yield); reaction time 16 h;; IR (CHCl₃) 1654; ¹H NMR, a mixture of atropisomers, (CDCl₃) δ isomer #1 1.94 (m, 4H), 3.70 (m, 4H), 3.73 (s, 3H), 3.94 (s, 3H), 4.34 (m, 1H) 6.23 (s, 2H), 7.00 (s, 1H), 7.40 (s, 1H), 7.70 (s, 1H), 9.31 (s, 1H), isomer #2 1.94 (m, 4H), 3.70 (m, 4H), 3.73 (s, 3H), 3.94 (s, 3H), 4.34 (m, 1H) 6.46 (s, 2H), 7.36 (s, H), 7.49 (s, 1H), 7.65 (s, 1H), 9.17 (s, 1H); HRMS calcd for C₂₃H₂₂O₆N₃IH: 564.0632; found: 564.0650.

[157] **Example 5.a. N-(6,7-Methylenedioxcinnolin-4-yl)-N-[(2-pyrrolidin-1-yl)ethyl]-2-iodo-4,5-dimethoxybenzamide:** Prepared from 1-[2-[N-(6,7-Methylenedioxcinnolin-4-yl)]amino]ethylpyrrolidine (400 mg, 0.4 mmol) in 42% yield with a reaction time 4 h at 50 °C from the acid chloride prepared using 4.1 mmol of oxalyl chloride and 1.6 mmol of 2-iodo-4,5-dimethoxybenzoic acid. Compound **8f** had: IR (KBr) 1655; ¹H NMR (CDCl₃) δ 1.60 (m, 4H), 2.40 (m, 4H), 2.67 (m, 2H), 3.28 (s, 3H), 3.60 (s, 3H), 4.32 (m, 1H), 6.11 (d, 2H, *J* = 2.2), 6.32 (s, 1H), 6.91 (s, 1H), 7.37 (s, 1H), 7.50 (s, 1H), 9.04 (s, 1H); ¹³C NMR (CDCl₃) δ 23.6, 29.7, 47.6, 52.9, 53.9, 55.7, 56.0, 56.4, 82.8, 96.7, 102.9, 105.4, 110.6, 121.9, 123.1, 132.8, 135.9, 144.7, 148.2, 149.9, 150.9, 151.7, 152.4, 169.9.

[158] **Example 6.a. N-(6,7-Methylenedioxy-4-cinnolin-4-yl)-N-[2-(piperidin-1-yl)ethyl]-2-iodo-4,5-dimethoxybenzamide:** Prepared from 1-[2-[N-(6,7-Methylenedioxcinnolin-4-yl)]amino]ethylpiperidine (500 mg, 1.66 mmol); (85.4% yield); reaction time overnight at 50 °C. mp 93-94 °C; IR (KBr) 1655; ¹H NMR (CDCl₃) δ 1.43 (m, 6H), 2.35 (m, 4H), 2.50-2.71 (m, 2H), 3.43 (s, 3H), 3.73 (s, 3H), 3.78-3.93 (m, 1H), 4.32-4.42 (m, 1H), 6.22 (d, 2H, *J* = 1.6), 6.42 (s, 1H), 7.02 (s, 1H), 7.47 (s, 1H), 7.66 (s, 1H), 9.19 (s, 1H); ¹³C (CDCl₃) δ 24.3, 25.9, 46.0, 46.4, 54.5,

55.6, 56.0, 56.4, 82.9, 97.0, 102.8, 105.3, 110.8, 122.0, 113.7, 123.2, 133.1, 136.3, 145.0, 148.2, 149.9, 150.8, 151.6, 152.1, 169.8 HRMS calcd for $C_{23}H_{25}IN_4O_3H$: 591.1105; found 591.1108.

Examples 2.b-6.b

- [159] The intermediate 4-amino-6,7-dimethoxyquinoline derivatives used in Examples 2.a-6.a. were prepared using the following general procedure.
- [160] The appropriate primary amine (1.0 mol equiv.) added with stirring to 4-Chloro-6,7-methylenedioxyquinoline (see Example 1 above). The reaction was then allowed to stir at 100 °C for several hours, and the phenol removed by Kugelrohr distillation under reduced pressure. The residue was partitioned between $CHCl_3$ and 10% NaOH. The aqueous layer was repeatedly separated with $CHCl_3$. All of the $CHCl_3$ solutions (initial partition and extracts) were combined and dried ($MgSO_4$).
- [161] **Example 2.b. N'-(6,7-Methylenedioxyquinolin-4-yl)-N,N-diethylethane-1,2-diamine:** Prepared from 4-Chloro-6,7-methylenedioxyquinoline (1.0 g, 4.8 mmol); (70% yield); reaction time 3 h; mp 230-232 °C; ^1H NMR ($CDCl_3$) δ 1.10 (t, 6H, $J=7.2$), 2.63 (q, 4H, $J=7.2$), 2.84 (t, 2H, $J=5.7$), 3.35 (q, 2H, $J=5.7$), 5.78 (br, 1H), 6.15 (s, 2H), 6.96 (s, 1H), 7.57 (s, 1H), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.2, 39.5, 46.6, 50.8, 94.4, 102.0, 105.4, 112.8, 129.0, 139.8, 147.8, 149.5, 150.7; HRMS calcd for $C_{15}H_{20}O_2N_4$: 288.1586; found: 288.1575.
- [162] **Example 3.b. N-(6,7-difluorocinnolin-4-yl)-N¹,N¹-dimethylpropane-1,2-diamine:** Prepared from 4-Chloro-6,7-methylenedioxyquinoline (0.52 g, 2.5 mmol); (42% yield), reaction time 4 h, mp 196-197 °C; ^1H NMR (CD_3OD) δ 1.31 (d, 3H, $J=6.6$), 2.33 (s, 6H), 2.45 (dd, 1H, $J=5.4, 12.8$), 2.74 (dd, 1H, $J=8.2, 12.6$), 4.12 (dd, 1H, $J=5.8, 13.8$), 6.19 (s, 2H), 7.32 (s, 1H), 7.56 (s, 1H), 8.51 (s, 1H); ^{13}C NMR (CD_3OD) δ 17.1, 44.0, 45.3, 63.5, 95.1, 101.6, 102.0, 112.6, 126.7, 140.8, 149.3, 151.2; HRMS calcd for $C_{14}H_{18}O_2N_4$: 274.1430; found: 274.1429.
- [163] **Example 4.b. 2-[[[N-(6,7-Methylenedioxyquinolin-4yl)]amino]methyl]tetrahydrofuran:** prepared from 4-Chloro-6,7-

methylenedioxcinnoline (500 mg, 2.4 mmol); (78% yield); reaction time 2 h; mp 196-198 °C; ¹H NMR (CDCl₃) δ 1.74 (m, 1H), 2.11 (m, 3H), 3.30 (m, 1H), 3.58 (m, 1H), 3.92 (m, 2H), 4.29 (m, 1H), 5.22 (br, 1H), 6.12 (s, 2H), 6.98 (s, 1H), 7.52 (s, 1H), 8.54 (s, 1H); ¹³C NMR (CDCl₃) δ 25.9, 29.2, 46.9, 68.4, 76.9, 94.4, 102.2, 105.2, 112.8, 128.7, 139.8, 147.9, 149.6, 150.8; HRMS calcd for C₁₄H₁₅O₃N₃: 273.1130; found: 273.1130.

[164] Example 5.b. 1-[2-[N-(6,7-Methylenedioxcinnolin-4-yl)]amino]ethylpyrrolidine:

Prepared from 4-Chloro-6,7-methylenedioxcinnoline (750 mg, 3.5 mmol), 1-(2-aminoethyl)pyrrolidine (3 ml) and copper powder (300 mg) in 75% yield; reaction time 18 h at 90 °C; mp 215 °C (dec); ¹H NMR (CDCl₃) δ 1.85 (m, 4H), 2.63 (m, 4H), 2.90 (t, 2H, *J* = 6), 3.42 (t, 2H, *J* = 6), 5.63 (s, 1H), 6.14 (s, 2H), 7.04 (s, 1H), 7.57 (s, 1H), 8.53 (s, 1H); ¹³C NMR (DMSO-d₆) δ 23.9, 42.0, 54.5, 54.7, 97.0, 102.9, 104.4, 112.7, 126.8, 140.8, 149.3, 151.0; HRMS calcd for C₁₅H₁₈N₄O₂: 293.1590; found 293.1579.

[165] Example 6.b. 1-[2-[N-(6,7-Methylenedioxcinnolin-4-yl)]amino]ethylpiperidine:

Prepared from 4-Chloro-6,7-methylenedioxcinnoline (1.04 g, 5.0 mmol); (37% yield); reaction time 2h; mp 238-239 °C; ¹H NMR (CD₃OD) δ 1.56 (d, 2H, *J*=5.2), 1.70 (d, 2H, *J*=4.6), 2.87 (t, 2H, *J*=7), 3.65 (t, 2H, *J*=6.6), 6.20 (s, 2H), 7.32 (s, 1H), 7.43 (s, 1H), 8.46 (s, 1H); ¹³C (CD₃OD) δ 23.1, 24.7, 38.5, 53.6, 56.1, 94.7, 101.7, 102.1, 112.4, 126.6, 141.1, 14.7, 149.4, 151.2 (CDCl₃); HRMS calcd for C₁₆H₂₀N₄O₂H: 300.1586; found 300.1586.

Examples 7-12

[166] The representative compounds of the invention at Examples 7-12 were prepared using the following general procedure from the intermediates prepared in the correspondingly numbered sub-parts a below.

[167] A mixture of the requisite 4-amino-6,7-methylenedioxyquinoline *o*-iodobenzamide derivative (1.0 mmol equiv.), Pd(OAc)₂ (0.2 mmol equiv.), P(*o*-tolyl)₃ (0.4 mmol equiv.), and Ag₂CO₃ (2.0 mmol equiv) was heated to reflux in DMF (30 mL per

mmol equiv.) with stirring. The reaction mixture was allowed to cool to room temperature, diluted with CHCl_3 , and filtered through Celite. The siccate was extensively washed with 10% CH_3OH in CHCl_3 . The filtrate was concentrated *in vacuo* and the residue chromatographed on silica gel using chloroform:methanol.

- [168] **Example 7. 8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5H-dibenzo[*c,h*]1,6-naphthyridin-6-one.** Prepared from N-(6,7-Methylenedioxyquinolin-4-yl)-N-(N,N-dimethylaminoethyl)-2-iodo-4,5-dimethoxybenzamide; (41% yield); reaction time 25 min; mp 283-285 °C (dec.); IR (CHCl_3) 1653; ^1H NMR (CDCl_3) δ 2.33 (s, 6H), 3.04 (t, 2H, $J = 7.2$), 4.07 (s, 3H), 4.14 (s, 3H), 4.64 (t, 2H, $J = 7.2$), 6.18 (s, 2H), 7.47 (s, 1H), 7.68 (s, 1H), 7.89 (s, 2H), 9.37 (s, 1H); ^{13}C NMR (CDCl_3) δ 45.9, 49.2, 56.3, 56.3, 57.9, 101.2, 102.0, 102.3, 107.1, 108.8, 111.7, 114.8, 119.3, 127.6, 140.9, 143.5, 147.3, 147.7, 149.9, 150.3, 154.2, 164.1; HRMS calcd for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_5\text{H}$: 422.1716; found 422.1710.
- [169] **Example 8. 8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)-1-methylethyl]-5H-dibenzo[*c,h*]1,6-naphthyridin-6-one:** Prepared from N-(6,7-Methylenedioxyquinolin-4-yl)-N-[2-(N,N-dimethylamino)-1-methylethyl]-2-iodo-4,5-dimethoxybenzamide; (30.4% yield); reaction time 30 min; mp 186-187 °C; IR (KBr) 1649; ^1H NMR (CDCl_3) δ 1.95-1.98 (m, 9H), 2.77 (dd, 1H, $J = 12.0, 8.0$), 3.21 (dd, 1H, $J = 12.0, 8.0$), 4.06 (s, 3H), 4.13 (s, 3H), 4.84-4.92 (m, 1H), 6.17 (s, 2H), 7.46 (s, 1H), 7.66 (s, 1H), 7.77 (s, 1H), 7.87 (s, 1H), 9.35 (s, 1H); ^{13}C NMR (CDCl_3) δ 19.7, 45.5, 56.2, 56.3, 59.5, 63.1, 100.9, 101.9, 102.1, 107.0, 108.7, 112.4, 115.2, 120.5, 127.3, 142.6, 143.3, 147.0, 147.3, 149.9, 150.1, 154.0, 164.9; HRMS calcd for $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_5\text{H}$: 436.1794; found 436.1863.
- [170] **Example 9. 8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(pyrrolidin-1-yl)ethyl]-5H-dibenzo[*c,h*]1,6-naphthyridin-6-one:** Prepared from N-(6,7-Methylenedioxyquinolin-4-yl)-N-[(2-pyrrolidin-1-yl)ethyl]-2-iodo-4,5-dimethoxybenzamide; (36% yield); reaction time 30 min; mp 255-257 °C (dec.); IR (CHCl_3) 1653; ^1H NMR (CDCl_3) δ 1.79 (m, 4H), 2.64 (m, 4H), 3.20 (t, 2H, $J = 7.1$), 4.07 (s, 3H), 4.14 (s, 3H), 4.69 (t, 2H, $J = 7.1$), 6.18 (s, 2H), 7.46 (s, 1H), 7.68 (s,

1H), 7.89 (s, 1H), 7.95 (s, 1H), 9.37 (s, 1H); ¹³C NMR (CDCl₃) δ 23.7, 49.6, 54.3, 56.3, 56.4, 56.4, 101.3, 102.0, 102.3, 107.0, 108.7, 111.7, 114.8, 119.3, 127.7, 140.9, 143.4, 147.3, 147.8, 150.0, 150.3, 154.2, 164.2; HRMS calcd for C₂₅H₂₅N₃O₅H: 448.1872; found 448.1872.

[171] **Example 10. 8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(4-methylpiperazin-1-yl)ethyl]-5H-dibenzo[*c,h*]1,6-naphthyridin-6-one:** Prepared from N-(6,7-Methylenedioxyquinolin-4-yl)-N-[2-(4-methyl-1-piperazinyl)ethyl]-2-iodo-4,5-dimethoxybenzamide; (18% yield); reaction time 25 min; mp 244-246 °C; IR (CHCl₃) 1651; ¹H NMR (CDCl₃) δ 2.27 (s, 3H), 2.51 (m, 8H), 2.95 (t, 2H, *J* = 6.2), 4.07 (s, 3H), 4.15 (s, 3H), 4.69 (t, 2H, *J* = 6.2), 6.19 (s, 2H), 7.48 (s, 1H), 7.70 (s, 1H), 7.91 (s, 2H), 7.92 (s, 1H), 9.39 (s, 1H); ¹³C NMR (CDCl₃) δ 29.8, 45.9, 48.6, 53.0, 55.0, 56.4, 56.4, 101.2, 102.0, 102.2, 107.1, 108.9, 112.0, 115.0, 119.5, 127.6, 141.2, 143.4, 147.4, 147.2, 150.0, 150.3, 154.1, 164.4; HRMS calcd for C₂₆H₂₈N₄O₅H: 477.2138; found 477.2139.

[172] **Example 11. 8,9-Dimethoxy-2,3-methylenedioxy-5-[3-(N,N-dimethylamino)propyl]-5H-dibenzo[*c,h*]1,6-naphthyridin-6-one:** Prepared from N-(6,7-Methylenedioxyquinolin-4-yl)-N-[3-(N,N-dimethylamino)propyl]-2-iodo-4,5-dimethoxybenzamide; (45% yield); reaction time 30 min; mp 262-264 °C (dec.); IR (CHCl₃) 1648; ¹H NMR (CDCl₃) δ 2.29 (m, 8H), 2.45 (m, 2H), 4.07 (s, 3H), 4.14 (s, 3H), 4.53 (t, 2H, *J* = 7.4), 6.19 (s, 2H), 7.48 (s, 1H), 7.65 (s, 1H), 7.69 (s, 1H), 7.90 (s, 1H), 9.40 (s, 1H); ¹³C NMR (CDCl₃) δ 26.9, 45.3, 49.2, 56.3, 56.4, 56.9, 100.8, 101.9, 102.3, 107.1, 108.7, 111.6, 114.9, 119.4, 127.5, 141.0, 143.6, 147.2, 147.7, 149.9, 150.3, 154.1, 164.1; HRMS calcd for C₂₄H₂₅N₃O₅H: 436.1872; found 436.1878.

[173] **Example 12. 8,9-Dimethoxy-2,3-methylenedioxy-5-(2-tetrahydrofuranyl)methyl-5H-dibenzo[*c,h*]1,6-naphthyridin-6-one:** Prepared from N-(6,7-Methylenedioxyquinolin-4-yl)-N-[2-(tetrahydrofuran-2-yl)methyl]-2-iodo-4,5-dimethoxybenzamide; (22% yield); reaction time 30 min; mp 270-273 °C; IR (CHCl₃) 1648; ¹H NMR (CDCl₃) δ 1.87 (m, 4H), 3.72 (m, 2H), 4.07 (s, 3H), 4.14 (s,

3H), 4.68 (m, 3H), 6.18 (s, 2H), 7.48 (s, 1H), 7.69 (s, 1H), 7.90 (s, 1H), 8.04 (s, 1H), 9.39 (s, 1H); ^{13}C NMR (CDCl_3) δ 25.6, 30.3, 54.7, 56.3, 56.4, 68.1, 77.3, 101.7, 102.2, 102.3, 107.0, 109.0, 112.1, 115.2, 119.5, 127.7, 141.2, 143.5, 147.2, 147.4, 149.9, 150.3, 154.2, 164.6; HRMS calcd for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_6\text{H}$ 435.1556; found 435.1566.

Examples 7.a-12.a

- [174] The intermediate 4-amino-6,7-methylenedioxyquinoline *o*-iodobenzamide derivatives used in Examples 7-12 were prepared using the following general procedure.
- [175] A 2.0M solution of oxalyl chloride in CH_2Cl_2 (1.3 equiv.) was added to a solution of 2-iodo-5,6-dimethoxybenzoic acid (1.0 equiv.) in anhydrous CH_2Cl_2 ($\approx$ 60 mL per 10 mmol benzoic acid) and the solution stirred at reflux for 3 h. The mixture was allowed to cool and was then concentrated to dryness *in vacuo*. To the residue was added a solution of appropriate 4-amino-6,7-dimethoxyquinoline (1.0 equiv), triethylamine (2 equiv.) in CH_2Cl_2 ($\approx$ 60 mL per 4 mmol aminoquinoline). The reaction mixture was then stirred at reflux under N_2 . In the case of those derivatives that have an alkylamine incorporated in their structure, the residue was partitioned between CHCl_3 and 10% NaOH. The aqueous layer was repeatedly separated with CHCl_3 . All of the CHCl_3 solutions (initial partition and extracts) were combined and dried (MgSO_4). The aqueous layer was neutralized with 20% NaOH and extracted with CHCl_3 , dried (MgSO_4) and evaporated.
- [176] **Example 7.a. N-(6,7-Methylenedioxyquinolin-4-yl)-N-(N,N-dimethylaminoethyl)-2-iodo-4,5-dimethoxybenzamide.** Prepared from N'-(6,7-Methylenedioxyquinolin-4-yl)-N,N-dimethylethane-1,2-diamine (1.0 g, 3.84 mmol) in 71% yield with a reaction time of 3 h, from the acid chloride prepared using 10 mmol of oxalyl chloride and 4.8 mmol of 2-iodo-5,6-dimethoxybenzoic acid. Compound **7a** had: IR (CHCl_3) 1652; ^1H NMR (CDCl_3) δ 2.74 (s, 6H), 2.66 (t, 2H, $J = 7.0$), 3.33 (s, 3H), 3.74 (s, 3H), 3.96 (m, 1H), 4.49, (m, 1H), 6.15 (s, 2H), 6.41 (s, 1H), 7.03 (s, 1H), 7.34 (d, 1H, $J = 4.8$), 7.37 (s, 1H), 7.44 (s, 1H), 8.56 (d, 1H, $J = 4.8$); ^{13}C NMR (CDCl_3) δ 45.7, 46.9, 55.5, 56.1, 56.6, 82.7, 98.5, 102.2, 106.7, 110.2,

120.2, 121.5, 122.9, 121.5, 122.9, 133.8, 145.9, 148.0, 148.3, 148.5, 149.0, 149.6, 151.0, 170.0; HRMS calcd for $C_{23}H_{24}IN_3O_5H$: 550.0839; found 550.0823.

[177] **Example 8.a.** **N-(6,7-Methylenedioxyquinolin-4-yl)-N-[2-(N,N-dimethylamino)-1-methylethyl]-2-iodo-4,5-dimethoxybenzamide.** Prepared from N'-(6,7-Methylenedioxyquinolin-4-yl)-N,N-dimethylpropane-1,2-diamine (273 mg, 1.0 mol) in 60.4% yield with a reaction time of 12 h, from the acid chloride prepared using 4.8 mmol of oxalyl chloride and 1.2 mmol of 2-iodo-5,6-dimethoxybenzoic acid. Compound **7b** had: mp 82-84 °C; IR (KBr) 1648, 3415; HRMS calcd for $C_{24}H_{26}IN_3O_5H$ 564.0917; found 564.0997

[178] **Example 9.a.** **N-(6,7-Methylenedioxyquinolin-4-yl)-N-[(2-pyrrolidin-1-yl)ethyl]-2-iodo-4,5-dimethoxybenzamide.** Prepared from 1-[2-[N-(6,7-Methylenedioxyquinolin-4-yl)]amino]ethylpyrrolidine (285 mg, 1.0 mmol), in 87% yield with a reaction time of 12 h, from the acid chloride prepared using 4 mmol of oxalyl chloride and 1.36 mmol of 2-iodo-5,6-dimethoxybenzoic acid. Compound **7c** had: IR ($CHCl_3$) 1650; ^1H NMR ($CDCl_3$) δ 1.78 (m, 4H), 2.22 (m, 1H), 2.59 (m, 3H), 2.83 (t, 2H, $J = 6.6$), 3.33 (s, 3H), 3.74 (s, 3H), 3.96 (d, 1H, $J = 4$), 4.54 (m, 1H), 6.15 (s, 1H), 6.42 (s, 1H), 7.03 (s, 1H), 7.34 (d, 1H, $J = 4.8$), 7.36 (s, 1H), 7.44 (s, 1H), 8.55 (d, 1H, $J = 4.8$); ^{13}C NMR ($CDCl_3$) δ 23.7, 47.7, 52.9, 54.1, 55.5, 56.1, 82.7, 98.4, 102.2, 106.7, 106.7, 120.1, 121.5, 122.9, 133.7, 145.9, 148.0, 148.3, 148.4, 149.0, 149.6, 151.0, 170.0; HRMS calcd for $C_{25}H_{26}IN_3O_5H$: 576.0995; found 576.1003.

[179] **Example 10.a.** **N-(6,7-Methylenedioxyquinolin-4-yl)-N-[2-(4-methyl-1-piperazinyl)ethyl]-2-iodo-4,5-dimethoxybenzamide.** Prepared from 1-[2-[N-(6,7-Methylenedioxyquinolin-4-yl)]amino]ethyl-4-methylpiperazine (290 mg, 0.9 mmol) in 50% yield with a reaction time of 12 h, from the acid chloride prepared using 4.0 mmol of oxalyl chloride and 1.8 mmol of 2-iodo-5,6-dimethoxybenzoic acid. Compound **7d** had: IR ($CHCl_3$) 1649; ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H), 2.51 (m, 10H), 3.35 (s, 3H), 3.75 (s, 3H), 3.95 (m, 1H), 4.46 (m, 1H), 6.15 (s, 1H), 6.42 (s, 1H), 7.03 (s, 1H), 7.35 (d, 1H, $J = 4.6$), 7.36 (s, 1H), 7.48 (s, 1H), 8.57 (d, 1H, $J =$

4.6); ^{13}C NMR (CDCl_3) δ 46.0, 46.2, 53.1, 55.2, 55.5, 55.5, 56.0, 82.7, 98.7, 102.2, 106.7, 110.4, 120.3, 121.6, 123.0, 133.7, 146.0, 148.0, 148.4, 148.4, 148.9, 149.6, 151.0, 170.0; HRMS calcd for $\text{C}_{26}\text{H}_{29}\text{IN}_4\text{O}_5\text{H}$: 605.1261; found 605.1261.

[180] **Example 11.a.** **N-(6,7-Methylenedioxyquinolin-4-yl)-N-[3-(N,N-dimethylamino)propyl]-2-iodo-4,5-dimethoxybenzamide.** Prepared from N'-(6,7-Methylenedioxyquinolin-4-yl)-N,N-dimethylpropane-1,3-diamine (273 mg, 1.0 mmol), in 79% yield with a reaction time of 12 h, from the acid chloride prepared using 4.0 mmol of oxalyl chloride and 1.36 mmol of 2-iodo-5,6-dimethoxybenzoic acid. Compound **7e** had: IR (CHCl_3) 1650; ^1H NMR (CDCl_3) δ 1.93 (m, 1H), 2.16 (m, 1H), 2.34 (s, 6H), 2.58 (m, 1H), 3.31 (s, 3H), 3.47 (m, 1H), 3.75 (s, 3H), 3.95 (m, 1H), 4.55 (m, 1H), 6.16 (s, 1H), 6.39 (s, 1H), 7.04 (s, 1H), 7.28 (d, 1H, $J = 5.0$), 7.31 (s, 1H), 7.38 (s, 1H), 8.56 (d, 1H, $J = 5.0$); ^{13}C NMR (CDCl_3) δ 25.8, 45.1, 47.2, 55.5, 56.1, 26.9, 82.7, 98.1, 102.3, 107.0, 110.1, 120.1, 121.5, 122.5, 133.5, 145.5, 148.1, 148.4, 148.6, 149.2, 149.7, 151.1, 170.1; HRMS calcd for $\text{C}_{24}\text{H}_{26}\text{IN}_3\text{O}_5\text{H}$: 564.0995; found 564.0990.

[181] **Example 12.a.** **N-(6,7-Methylenedioxyquinolin-4-yl)-N-[2-(tetrahydrofuran-2-yl)methyl]-2-iodo-4,5-dimethoxybenzamide.** Prepared from 2-[[[N-(6,7-Methylenedioxyquinolin-4-yl)]amino]methyl]tetrahydrofuran (272 mg, 1.0 mol) in 36% yield with a reaction time of 16 h, from the acid chloride prepared using 4.0 mmol of oxalyl chloride and 1.36 mmol of 2-iodo-5,6-dimethoxybenzoic acid. Compound **7g** had: IR (CHCl_3) 1652; HRMS calcd for $\text{C}_{24}\text{H}_{23}\text{N}_2\text{O}_6\text{IH}$: 563.0679; found 563.0703.

Examples 7.b-12.b

[182] The intermediate 4-amino-6,7-dimethoxyquinoline derivatives used in Examples 7.a-12.a. were prepared using the following general procedure.

[183] 4-Chloro-6,7-methylenedioxyquinoline was stirred in refluxing phenol (5.5 mol equiv.) for 2.5 h. The temperature was lowered to 100 °C and the primary amine (1.0 mol equiv.) added with stirring. The reaction was then allowed to stir at 100 °C for

several hours, and the phenol removed by Kugelrohr distillation under reduced pressure. In the case of those derivatives that have an alkylamine incorporated in their structure, the residue was partitioned between CHCl_3 and 10% NaOH. The aqueous layer was repeatedly separated with CHCl_3 . All of the CHCl_3 solutions (initial partition and extracts) were combined and dried (MgSO_4). Other 4-amino-6,7-methylenedioxyquinoline derivatives were purified by column chromatography.

- [184] **Example 7.b.** **N'-(6,7-Methylenedioxyquinolin-4-yl)-N,N-dimethylethane-1,2-diamine** was prepared from N,N-dimethylethylenediamine (2.55 g, 29 mmol) in 54% yield with a reaction time of 24h. Compound **6a** had: mp 193-194 °C; ^1H NMR (CDCl_3) δ 2.32 (s, 6H), 2.70 (t, 2H, $J = 6.6$), 3.29 (m, 2H), 5.62 (br, 1H), 6.10 (s, 2H), 6.36 (d, 1H, $J = 5.3$), 7.10 (s, 1H), 7.34 (s, 1H), 8.40 (d, 1H, $J = 5.3$); ^{13}C NMR (CDCl_3) δ 40.1, 45.2, 57.2, 96.3, 98.9, 101.6, 106.5, 114.4, 145.2, 146.8, 148.9, 149.7, 150.1; HRMS calcd for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_2$: 260.1399; found 260.1377.
- [185] **Example 8.b.** **N'-(6,7-Methylenedioxyquinolin-4-yl)-N,N-dimethylpropane-1,2-diamine** was prepared from 2-methyl-2-(N,N-dimethylamino)ethylamine (2.55 g, 29 mmol) from in 30.7% yield with a reaction time of 24 h. Compound **6b** had: mp 71-72 °C; ^1H NMR (CD_3OD); δ 1.26 (d, 3H, $J = 5.6$), 3.22 (s, 6H), 2.41 (dd, 1H, $J = 6.2$, 12), 2.65 (dd, 1H, $J = 5.8$, 12.2), 3.82-3.86 (m, 1H), 6.16 (s, 2H), 6.46 (d, 1H, $J = 5.8$), 7.16 (s, 1H), 7.45 s, 1H), 8.20 (d, 1H, $J = 6.0$); ^{13}C NMR δ 17.1, 44.0, 45.4, 63.6, 96.6, 97.3, 101.3, 101.8, 113.9, 144.8, 146.3, 146.8, 149.7, 150.0; HRMS calcd for $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_2\text{H}$: 273.1484; found 273.1477.
- [186] **Example 9.b.** **1-[2-[N-(6,7-Methylenedioxyquinolin-4-yl)]amino]ethylpyrrolidine** was prepared from 1-(2-aminoethyl)pyrrolidine (1.14 g, 10.0 mmol) in 31% yield with a reaction time of 20 h. Compound **6c** had: mp 179-182 °C; ^1H NMR (CDCl_3) δ 1.83 (m, 4H), 2.60 (m, 4H), 2.87 (t, 2H, $J = 5.9$), 3.33 (m, 2H), 5.58 (br, 1H), 6.08 (s, 2H), 6.34 (d, 1H, $J = 5.1$), 7.08 (s, 1H), 7.31 (s, 1H), 8.40 (d, 1H, $J = 5.1$); ^{13}C NMR (CDCl_3) δ 23.7, 41.4, 53.9, 54.0, 96.3, 98.9, 101.6, 106.6, 114.4, 146.4, 146.7, 149.1, 149.6, 150.0; HRMS calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_2$: 285.1477; found 285.1468.

- [187] **Example 10.b.** **1-[2-[N-(6,7-Methylenedioxyquinolin-4-yl)]amino]ethyl-4-methylpiperazine** was prepared from 2-(4-methylpiperidin-1-yl)ethylamine (1.43 g, 10.0 mmol) in 20% yield with a reaction time of 24 h. Compound **6d** had: mp 159-161 °C; ¹H NMR (CDCl₃) δ 2.34 (s, 3H), 2.54 (m, 10H), 2.80 (t, 2H, *J* = 5.9), 5.62 (br, 1H), 6.11 (s, 2H), 6.38 (d, 1H, *J* = 5.2), 7.05 (s, 1H), 7.33 (s, 1H), 8.41 (d, 1H, *J* = 5.2); ¹³C NMR (CDCl₃) δ 39.1, 46.2, 52.7, 55.4, 55.7, 96.0, 99.0, 101.6, 106.6, 114.3, 146.8, 146.8, 149.0, 149.5, 150.0; HRMS calcd for C₁₇H₂₂N₄O₂: 314.1743; found 314.1738.
- [188] **Example 11.b.** **N'-(6,7-Methylenedioxyquinolin-4-yl)-N,N-dimethylpropane-1,3-diamine** was prepared from N,N-dimethyl-1,3-diaminopropane (1.0 g, 10.0 mmol) in 25% yield with a reaction time of 20 h. Compound **6e** had: mp 178-181 °C; ¹H NMR (CDCl₃) δ 1.92 (m, 2H), 2.39 (s, 6H), 2.58 (t, 2H, *J* = 5.5), 3.39 (m, 2H), 6.08 (s, 2H), 6.29 (d, 1H, *J* = 5.6), 6.95 (s, 1H), 7.31 (s, 1H), 7.52 (br s, 1H), 8.37 (d, 1H, *J* = 5.6); ¹³C NMR (CDCl₃) δ 24.6, 44.4, 45.7, 59.7, 96.6, 98.0, 101.5, 106.4, 114.5, 146.2, 146.6, 148.9, 149.9, 150.5.; HRMS calcd for C₁₅H₁₉N₃O₂: 273.1477; found 273.1473.
- [189] **Example 12.b.** **2-[[[N-(6,7-Methylenedioxyquinolin-4-yl)]amino]methyl]tetrahydrofuran** was prepared from tetrahydrofurfurylamine (1.01 g, 10.0 mmol) in 84% yield with a reaction time of 20 h. Compound **6g** had: mp 276-278 °C; ¹H NMR (CD₃OD) δ 1.77 (m, 1H), 2.07 (m, 3H), 3.61 (m, 2H), 3.86 (m, 2H), 4.26 (m, 1H), 6.28 (s, 2H), 6.90 (d, 1H, *J* = 7.1), 7.19 (s, 1H), 7.74 (s, 1H), 8.21 (d, 1H, *J* = 7.1); ¹³C NMR (CDCl₃) δ 24.7, 28.1, 46.6, 67.3, 76.7, 96.5, 97.6, 97.8, 103.1, 112.2, 135.8, 138.6, 148.3, 153.2, 155.1; HRMS calcd for C₁₅H₁₆N₂O₃: 272.1161; found 272.1172.
- [190] The intermediate 4-Chloro-6,7-methylenedioxyquinoline was prepared as follows.
- [191] **Diethyl 3,4-methylenedioxyanilinomethylene malonate.** 3,4-Methylenedioxyaniline (41.0 g, 0.3 mmol) and diethyl ethoxymethylenemalonate (64.8g, 0.3 mmol) were refluxed in benzene for 3.5 hours. The solvent was

evaporated *in vacuo* and the residue was washed with petroleum ether to give 88.3 g as a shiny grey- brown solid, in 96% yield; mp 99.5-101.0 °C (lit.²²¹ mp 102 °C); ¹H NMR (CDCl₃) δ 1.34 (t, 3H, *J*=7.0), 1.40 (t, 3H, *J*=7.0) 4.25 (q, 2H, *J*=7.0), 4.31 (q, 2H, *J*=7.0), 6.01 (s, 2H), 6.60 (dd, 1H, *J*=8.5, *J*=2.2), 6.71 (d, 1H, *J*=2.2), 6.81 (d, 1H, *J*=8.5), 8.41 (d, 1H, *J*=14.0); ¹³C NMR (CDCl₃) δ 14.4, 14.6, 60.1, 60.4, 92.9, 99.4, 101.8, 108.9, 110.9, 134.3, 145.3, 148.9, 152.6, 165.8, 169.3.

- [192] **4-Hydroxy-6,7-methylenedioxy-3-quinolinecarboxylic acid ethyl ester. Diethyl 3,4-methylenedioxyanilinomethylene malonate** (80.0 g, 0.261 mol) was stirred in polyphosphate ester (PPE) (250 g, 0.528 mol) at 120°C with a mechanical stirrer for 2 hours. The reaction mixture was poured into ice water (700mL) and stirred until homogenous. The mixture was then neutralized (pH 8) with ammonium hydroxide, and the precipitate was filtered, washed well with water, and dried to give 54.7 g as a brown solid, in 80% yield; mp 277-278 °C; ¹H NMR (DMSO-*d*₆) δ 1.26 (t, 3H, *J*=7.0), 4.16 (q, 2H, *J*=7.0), 6.09 (s, 2H), 7.02 (s, 1H), 7.38 (s, 1H), 8.48 (s, 1H).
- [193] **4-Hydroxy-6,7-methylenedioxy-3-quinolinecarboxylic acid. 4-Hydroxy-6,7-methylenedioxy-3-quinolinecarboxylic acid ethyl ester** (45.0 g, 0.172 mol) was added to a solution of KOH (16.8 g, 0.258 mol) in ethanol (500 mL) and the mixture was heated to reflux with stirring for 20 hours. The reaction flask was then cooled and ethanol was evaporated under reduced pressure. Then 800 mL of water were added with stirring to fully dissolve the potassium salt, and the solution was filtered to remove any impurities. Concentrated HCl was added to bring the mixture to pH 1, and the free acid was filtered off and dried under vacuum, to give 33.9 g as a beige solid, in 84%; mp >300 °C (lit.²²¹ mp >290 °C); ¹H NMR (DMSO-*d*₆) δ 6.27 (s, 2H), 7.30 (s, 1H), 7.55 (s, 1H), 8.72 (s, 1H); ¹³C NMR (DMSO-*d*₆) δ 98.5, 101.8, 103.8, 107.9, 120.8, 137.9, 143.5, 148.1, 153.7, 167.4, 177.4.
- [194] **6,7-Methylenedioxy-4-quinolone.** A suspension of 4-hydroxy-6,7-methylenedioxy-3-quinolinecarboxylic acid (30 g, 0.129 mol) in diphenyl ether (320 mL) was heated to reflux with vigorous stirring. The reaction was carefully monitored until it became clear, about 1.5 h, and then immediately removed from heat. By this time all of the

starting material had dissolved but a black tarry residue remained. The solution was decanted and cooled, allowing the product to precipitate. This material was filtered and washed with ethyl ether to remove all traces of phenyl ether. A second crop was obtained by vigorously washing the tarry residue with ethanol (16 x 250 mL), filtering and evaporating the ethanol, and rinsing the material with ethyl ether. The total yield was 14.9 g as a pale yellow solid, in 61%; mp 285-289 °C (lit.²²¹ mp 276 °C); ¹H NMR (DMSO-*d*₆) δ 5.95 (d, 1H, *J*=7.3), 6.13 (s, 2H), 6.97 (s, 1H), 7.38 (s, 1H), 7.77 (d, 1H, *J*=7.3); ¹³C NMR (DMSO-*d*₆) δ 97.5, 102.1, 102.6, 108.7, 119.4, 122.0, 130.8, 138.7, 145.8, 151.7.

- [195] **4-Chloro-6,7-methylenedioxyquinoline.** 6,7-Methylenedioxy-4-quinolone (5.0 g, 26.5 mmol) was boiled in POCl₃ (75 mL) for 45 min and then cooled. Excess phosphoryl chloride was removed under reduced pressure and ice water (100 mL) was added to hydrolyze any residual phosphoryl chloride. The mixture was basified (pH 9) with ammonium hydroxide, and the solid precipitate was filtered. This material was extracted into ethyl ether (8 x 100 mL), and the ether solution was dried (MgSO₄) and evaporated to provide 4.55 g as a white solid, in 83%; mp 127.5-128 °C (lit. mp 129 °C); ¹H NMR (CDCl₃) δ 6.15 (s, 2H), 7.35 (d, 1H, *J*=4.7), 7.39 (s, 1H), 7.49 (s, 1H), 8.56 (d, 1H, *J*=4.7); ¹³C NMR (CDCl₃) δ 99.8, 102.2, 106.1, 119.9, 123.7, 129.8, 141.2, 147.7, 149.1, 151.4.

Examples 13-16

- [196] The representative compounds of the invention at Examples 13-16 were prepared by deprotection of the corresponding *tert*-butyldimethylsilyl ethers (13-15) or the corresponding acetal as described below.
- [197] **Example 13. 8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(hydroxy)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one:** Prepared from the corresponding *tert*-butyldimethylsilyl ether (Example 13.a.) by treatment with AcOH, THF, H₂O (3:1:1) at room temperature; (84% yield); reaction time 48 h; mp 285-286 °C; IR (KBr); 1653, 3448; ¹H NMR (DMSO-*d*₆) δ 3.91 (s, 3H), 4.04 (s, 3H), 4.54 (t, 2H, *J* = 4.4), 4.96 (t, 2H, *J* = 4), 6.26 (s, 2H), 7.44 (s, 1H), 7.71 (s, 1H), 7.98 (s, 1H), 8.03 (s, 1H),

9.64 (s, 1H); ^{13}C NMR (DMSO- d_6); δ 52.6, 56.4, 57.0, 59.5, 101.9, 103.0, 104.0, 106.8, 108.8, 111.9, 114.8, 119.1, 128.0, 141.2, 144.9, 147.4, 147.7, 150.2, 150.5, 154.6, 163.7; HRMS calcd (M^+ -OH) for $\text{C}_{21}\text{H}_{17}\text{O}_5\text{N}_2$ 377.1137; Found 377.1121.

[198] **Example 14. 8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(2-hydroxyethoxy)ethyl]-5H-dibenzo[*c,h*]1,6-naphthyridin-6-one:** Prepared from the corresponding *tert*-butyldimethylsilyl ether (Example 14.a.) by treatment by treatment with AcOH, THF, H_2O (3:1:1) at room temperature; (76% yield); reaction time 18 h; mp 235 °C; IR (KBr) 1654; ^1H NMR (CDCl_3); δ 3.61 (t, 2H, $J = 5.2$), 3.73 (t, 2H, $J = 5.2$), 4.07 (s, 3H), 4.14 (s, 3H), 4.22 (t, 2H, $J = 5.6$), 4.71 (t, 2H, $J = 5.6$), 6.2 (s, 2H), 7.53 (s, 1H), 7.69 (s, 1H), 7.88 (s, 1H), 8.05 (s, 1H), 9.39 (s, 1H). HRMS calcd for $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_7\text{H}$: 439.1506; found 439.1499.

[199] **Example 15. 8,9-Dimethoxy-2,3-methylenedioxy-5-[2-N,N-dimethylamino-1-(hydroxymethyl)ethyl]-5H-dibenzo[*c,h*]1,6-naphthyridin-6-one:** Prepared from the corresponding *tert*-butyldimethylsilyl ether (Example 15.a.) by treatment with 5N HCl in isopropanol at room temperature for 30 min; (57% yield); reaction time 30 min; mp 132 °C; IR (KBr) 1647; ^1H NMR (CDCl_3); δ 2.00 (s, 6H), 2.72-2.81 (m, 1H), 3.16-3.26 (m, 1H), 4.05 (s, 3H), 4.12 (s, 3H), 4.20-4.28 (m, 1H), 4.65-4.73 (m, 1H), 4.98 (m, 1H), 6.17 (q, 2H, $J = 1.2$), 7.44 (s, 1H), 7.51 (s, 1H), 7.64 (s, 1H), 7.82 (s, 1H), 7.82 (s, 1H); 9.33 (s, 1H); ^{13}C NMR (CDCl_3) δ : 45.6, 56.2, 56.3, 60.0, 64.1, 65.2, 100.9, 101.8, 102.3, 106.6, 108.5, 112.5, 115.0, 119.6, 127.5, 141.1, 143.0, 147.1, 147.5, 149.9, 150.0, 154.1, 165.0.

[200] **Example 16. 8,9-Dimethoxy-2,3-methylenedioxy-5-[2,3-dihydroxy)propyl]-5H-dibenzo[*c,h*]1,6-naphthyridin-6-one:** Prepared from the corresponding acetal (Example 16.a.) by treatment 80% AcOH at reflux for 2 h. The reaction mixture was allowed to cool, and then concentrated *in vacuo*. The crude residue was triturated with chloroform (1.5 mL), filtered, and washed with additional chloroform (10 mL), to provide 16.5 mg of pure material, in 60% yield; mp 272-274 °C (dec.); IR (KBr) 1631, 3407; ^1H NMR (DMSO- d_6) δ 3.31 (d, 2H, $J = 8.0$), 3.95 (s, 3H), 4.07 (s, 3H), 4.63 (m, 3H), 6.33 (s, 2H), 7.55 (s, 1H), 7.72 (s, 1H), 8.06 (s, 2H), 8.21 (s, 1H), 9.79

(s, 1H); ^{13}C NMR (DMSO- d_6) δ 54.4, 56.5, 57.3, 64.9, 68.8, 103.2, 103.8, 104.6, 108.9, 109.0, 112.6, 115.5, 119.3, 127.3, 138.5, 140.6, 148.2, 151.0, 151.3, 151.8, 154.8, 163.9; HRMS calcd for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_7\text{H}$: 425.1350; found 425.1359.

Examples 13.a-16.a

- [201] The intermediate iodo compounds of Examples 13.b.-16.b. were cyclized using the following general procedure.
- [202] A mixture of the requisite 4-amino-6,7-methylenedioxyquinoline *o*-iodobenzamide derivative (1.0 mmol equiv.), $\text{Pd}(\text{OAc})_2$ (0.2 mmol equiv.), $\text{P}(o\text{-tolyl})_3$ (0.4 mmol equiv.), and Ag_2CO_3 (2.0 mmol equiv) was heated to reflux in DMF (30 mL per mmol equiv.) with stirring. The reaction mixture was allowed to cool to room temperature, diluted with CHCl_3 , and filtered through Celite. The siccate was extensively washed with 10% CH_3OH in CHCl_3 . The filtrate was concentrated *in vacuo* and the residue chromatographed on silica gel using chloroform:methanol.
- [203] **Example 13.a.** Prepared from N-(6,7-Methylenedioxyquinolin-4-yl)-N-[(2-(*t*-butyldimethylsilyloxy)-ethyl]-2-iodo-4,5-dimethoxybenzamide (36.4% yield); reaction time 30 min; mp 271-273 °C; IR (KBr) 1658; ^1H NMR (CDCl_3) δ 0.00 (s, 6H), 0.68 (s, 9H), 4.04 (s, 3H), 4.12 (s, 3H), 4.24 (t, 2H, $J = 8$), 4.65 (t, 2H, $J = 8$), 6.18 (s, 2H), 7.44 (s, 1H), 7.64 (s, 1H), 7.85 (s, 1H), 8.01 (s, 1H), 9.29 (s, 1H); HRMS calcd for $\text{C}_{27}\text{H}_{33}\text{ISiN}_2\text{O}_6\text{H}$: 637.1153; found 637.1212
- [204] **Example 14.a.** Prepared from N-(6,7-Methylenedioxyquinolin-4-yl)-N-[2-(2-(*t*-butyldimethylsilyloxy)ethoxy)ethyl]-2-iodo-4,5-dimethoxybenzamide; (75% yield); reaction time 18 h; mp 238 °C (dec.); IR (KBr): 1639; ^1H NMR (CDCl_3) δ 0.00 (s, 6H), 0.85 (s, 9H), 3.54 (t, 2H, $J = 5.2$), 3.70 (t, 2H, $J = 5.2$), 4.07 (s, 3H), 4.14 (s, 3H), 4.16 (t, 2H, $J = 6.0$), 4.71 (t, 2H, $J = 6.0$), 6.17 (s, 2H), 7.48 (s, 1H) 7.70 (s, 1H), 7.94 (s, 1H), 9.39 (s, 1H); HRMS calcd for $\text{C}_{23}\text{H}_{23}\text{N}_2\text{O}_7\text{H}$: 439.1505; found 439.1506.
- [205] **Example 15.a.** Prepared from N-(6,7-Methylenedioxyquinolin-4-yl)-N-[1-[(*t*-butyldimethylsilyloxy)-methyl]-N-2-dimethylaminoethyl]]-2-iodo-4,5-

dimethoxybenzamide (95% yield); reaction time 45 min; ^1H NMR (CDCl_3); δ -0.13 (6H), 0.69 (s, 9H), 1.97(s, 6H), 1.92 (s, 6H), 2.52 (m, 1H), 2.80 (m, 1H) 3.20 (m, 1H), 4.01 (s, 3H), 4.09(s, 3H), 4.50 (m, 1H), 4.90 (m, 1H), 6.11 (m,2H), 7.30 (s, 1H), 7.61 (s, 1H) , 7.79 (s, 1H), 8.19 (s, 1H), 9.32 (s, 1H).

- [206] **Example 16.a. 8,9-Dimethoxy-2,3-methylenedioxy-5-[2,2-dimethyl[1,3]dioxolan-4-yl]methyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one** was prepared from N-(6,7-Methylenedioxyquinolin-4-yl)-N-[(2,3-dihydroxy)propyl]-2-iodo-5,6-dimethoxybenzamide (22 % yield); reaction time 45 min; mp 241-244 °C (dec.); IR (CHCl_3) 1652; ^1H NMR (CDCl_3) δ 1.34 (s, 3H), 1.36 (s, 3H), 3.95 (m, 2H), 4.08 (s, 3H), 4.14 (s, 3H), 4.35 (m, 1H), 4.55 (m, 1H), 4.77 (m, 1H), 6.19 (s, 2H), 7.48 (s, 1H), 7.70 (s, 1H), 7.87 (s, 2H), 8.05 (s, 1H), 9.40 (s, 1H); ^{13}C NMR (CDCl_3) δ 25.5, 26.5, 54.0, 56.3, 56.4, 69.4, 75.5, 101.6, 102.1, 102.3, 107.0, 108.7, 109.7, 111.8, 114.9, 119.1, 127.8, 141.1, 143.5, 147.4, 147.7, 150.1, 150.4, 154.4, 164.6; HRMS calcd for $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_7\text{H}$ 465.1662; found 465.1677. The compound 8,9-Dimethoxy-2,3-methylenedioxy-5-[2,2-dimethyl[1,3]dioxolan-4-yl]methyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one is also a compound of the invention.

Examples 13.b.-16.b.

- [207] The intermediate 4-amino-6,7-methylenedioxyquinoline *o*-iodobenzamide derivatives used in Examples 13.a.-16.a. were prepared using the following general procedure.
- [208] A 2.0M solution of oxalyl chloride in CH_2Cl_2 (1.3 equiv.) was added to a solution of 2-iodo-5,6-dimethoxybenzoic acid (1.0 equiv.) in anhydrous CH_2Cl_2 ($\approx$ 60 mL per 10 mmol benzoic acid) and the solution stirred at reflux for 3 h. The mixture was allowed to cool and was then concentrated to dryness *in vacuo*. To the residue was added a solution of appropriate 4-amino-6,7-dimethoxyquinoline (1.0 equiv), triethylamine (2 equiv.) in CH_2Cl_2 ($\approx$ 60 mL per 4 mmol aminoquinoline). The reaction mixture was then stirred at reflux under N_2 . . In the case of those derivatives that have an alkylamine incorporated in their structure, the residue was partitioned between CHCl_3 and 10% NaOH. The aqueous layer was repeatedly separated with CHCl_3 . All of the CHCl_3 solutions (initial partition and extracts) were combined and

dried (MgSO₄). The aqueous layer was neutralized with 20% NaOH and extracted with CHCl₃, dried (MgSO₄) and evaporated.

[209] **Example 13.b. N-(6,7-Methylenedioxyquinolin-4-yl)-N-[(2-(*t*-butyldimethylsilyloxy)-ethyl]-2-iodo-4,5-dimethoxybenzamide.** Prepared from 4-[N-[2-(*t*-Butyldimethylsilyloxy)]ethyl]amino-6,7-methylenedioxyquinoline (400 mg, 1.15 mmol) in 51.7% yield with a reaction time of 12 h, from the acid chloride prepared using 5.0 mmol of oxalyl chloride and 1.38 mmol of 2-iodo-5,6-dimethoxybenzoic acid. Compound **8h** had: mp 79-80 °C; IR (KBr); 1653 ¹H NMR (CDCl₃); δ 0.004 (d, 3H, *J* = 4.2Hz), 0.82 (s, 9H), 3.26 (s, 3H), 3.67 (s, 3H), 3.84-4.02 (m, 4H), 6.13 (d, 2H, *J* = 4Hz), 6.40 (s, 1H), 7.02 (s, 1H), 7.33 (d, 1H, *J* = 4.2Hz), 7.36 (s, 1H), 7.42 (s, 1H), 8.52 (d, 1H, *J* = 4Hz); HRMS calcd for C₂₇H₃₃ISiN₂O₆H 637.1232; observed 637.1212

[210] **Example 14.b. N-(6,7-Methylenedioxyquinolin-4-yl)-N-[2-(2-(*t*-butyldimethylsilyloxy)ethoxy)ethyl]-2-iodo-4,5-dimethoxybenzamide.** Prepared from 4-[N-[2-[2-(*t*-Butyldimethylsilyloxy)ethoxy]ethyl]ethyl]amino-6,7-methylenedioxyquinoline (354 mg, 9.0 mmol) in 60% yield with a reaction time of 24 h, from the acid chloride prepared using 4.5 mmol of oxalyl chloride and 1.8 mmol of 2-iodo-5,6-dimethoxybenzoic acid. Compound **8i** had: ¹H NMR (CDCl₃); δ 0.006 (s, 6H), 0.83 (s, 9H), 3.27 (s, 3H), 3.48 (t, 2H, *J* = 4.6), 3.67 (t, 2H, *J* = 5.6), 3.69 (s, 3H), 3.76-4.55 (m, 4H), 6.10 (s, 2H), 6.36 (s, 1H), 6.99 (s, 1H), 7.30-7.32 (three singlets, 3H), 8.52 (d, 1H, *J* = 4.8).

[211] **Example 15.b. N-(6,7-Methylenedioxyquinolin-4-yl)-N-[1-[(*t*-butyldimethylsilyloxy)-methyl]-N-2-dimethylaminoethyl]-2-iodo-4,5-dimethoxybenzamide.** Prepared from 4-[N-4-[2-(N,N-dimethylamino)-1-[(*t*-butyldimethylsilyloxy)methyl]-ethyl]amino-6,7-methylenedioxyquinoline (0.48 mg, 1.2 mol) in 55% yield with a reaction time of 18 h, from the acid chloride prepared using 5.9 mmol of oxalyl chloride and 2.4 mmol of 2-iodo-5,6-dimethoxybenzoic acid. Compound **8j** had: IR (CHCl₃) 1656; ¹H NMR (CDCl₃) [unresolved atropisomers in a an apparent 57:43 ratio at r.t.] major atropisomer δ 0.01

(s, 6H), 0.84 (s, 9H), 2.34 (s, 6H), 2.55 (m, 1H), 2.85 (m, 1H); 3.43 (s, 3H), 3.71(s, 3H) 3.86- 4.04 (m, 3H), 6.12 (s, 2H), 6.56 (s, 1H), 7.29-7.31 (s, 1H), 7.67 (d, 1H, $J = 5.0$), 8.00 (s, 1H), 8.59 (d, 1H, $J = 4.4$); minor atropisomer δ 0.17 (s, 6H), 0.96 (s, 9H), 2.15 (s, 6H), 2.55 (m, 1H), 2.85 (m, 1H), 3.36 (s, 3H), 3.72 (s, 3H) 3.86- 4.04 (m, 3H), 6.13 (s, 2H), 6.53(s, 1H), 7.00 (s, 1H), 7.31 (s, 1H), 7.51 (d, 1H, $J = 4.8$), 8.25 (s, 1H), 8.55 (d, 1H, $J = 5.2$).

- [212] **Example 16.b. N-(6,7-Methylenedioxyquinolin-4-yl)-N-[(2,3-dihydroxy)propyl]-2-iodo-5,6-dimethoxybenzamide.** Prepared from 4-[N-(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]amino-6,7-methylenedioxyquinoline (290 mg, 0.9 mmol) in 47% yield with a reaction time of 12 h, from the acid chloride prepared using 30 mmol of oxalyl chloride and 13 mmol of 2-iodo-5,6-dimethoxybenzoic acid. The acid chloride was added as a methylene chloride solution to a solution of **7k** in 125 mL of DME containing triethylamine (3.04 g 30.1 mmol). Compound **8k** had: IR (CHCl₃) 1653; ¹H NMR (CDCl₃) δ 1.21 (s, 3H), 1.33 (s, 3H), 3.33 (s, 3H), 3.76 (s, 3H), 3.94 (m, 3H), 4.61 (m, 2H), 6.18 (s, 1H), 6.39 (s, 1H), 7.05 (s, 1H), 7.31 (d, 1H, $J = 4.8$), 7.46 (s, 1H), 7.49 (s, 1H), 8.61 (d, 1H, $J = 4.8$); ¹³C NMR (CDCl₃) δ 25.6, 26.9, 55.6, 56.1, 56.4, 68.2, 73.2, 82.8, 98.2, 98.7, 102.4, 106.1, 110.3, 120.7, 121.7, 124.1, 133.3, 147.5, 148.0, 148.8, 149.5, 150.0, 151.5, 152.3, 167.8; HRMS calcd for C₂₅H₂₅N₂O₇IH: 593.0785; found 593.0802.

Examples 13.c.-15.c.

- [213] The intermediate alcohols from Examples 13.d. – 15.d. were converted to their corresponding silyl ethers using the following general procedure.
- [214] A mixture of the 4-amino-6,7-methylenedioxyquinoline derivative (1.0 mmol equiv.), imidazole (1.1 mmol equiv.) and *t*-butyldimethylsilyl chloride (1.2 mmol equiv.) in DMF (15 mL per mmol equiv) was stirred at room temperature for 6 h. DMF was removed *in vacuo*, water was added to residue, and solid was filtered and dried.
- [215] **Example 13.c. 4-[N-[2-(*t*-Butyldimethylsilyloxy)]ethyl]amino-6,7-methylenedioxyquinoline.** Prepared from N-(6,7-Methylenedioxyquinolin-4-

yl)ethanolamine in 48.7% yield; mp 215-216 °C; ¹H NMR (DMSO-*d*₆) δ 0.01 (s, 6H), 0.85 (s, 9H), 3.39 (dd, 2H, *J* = 6, 12), 3.80 (t, 2H, *J* = 6.2), 6.14 (s, 2H), 6.42 (d, 1H, *J* = 5.4), 7.12 (s, 1H), 7.60 (s, 1H), 8.18 (d, 1H, *J* = 4.8).

[216] **Example 14.c.** 4-[N-[2-[2-(*t*-Butyldimethylsilyloxy)ethoxy]ethyl]ethyl]amino-6,7-methylenedioxyquinoline. Prepared from 2-[2-[N-(6,7-Methylenedioxyquinolin-4-yl)]amino]ethoxyethanol in 39% yield (overall yield from **5**); ¹H NMR (CDCl₃) δ 0.1 (s, 6H), 0.92 (s, 9H), 3.64-3.69 (m, 4H), 3.84 (d, 2H, *J* = 5.2), 3.93 (d, 2H, *J* = 5.2), 6.15 (s, 2H), 6.56 (d, 1H, *J* = 6.4), 7.42 (s, 1H), 7.82 (s, 1H), 8.18 (d, 1H, *J* = 6.4).

[217] **Example 15.c.** 4-[N-4-[2-(N,N-dimethylamino)-1-(*t*-butyldimethylsilyloxy)methyl]-ethyl]amino-6,7-methylenedioxyquinoline. Prepared from 2-[[N-(6,7-Methylenedioxyquinolin-4-yl)]amino]-3-(N,N-dimethylamino)propanol in 25% yield (overall yield from **5**); ¹H NMR (CDCl₃) [unresolved atropisomers in a an apparent 57:43 ratio at r.t.] major atropisomer δ 0.07(s, 6H), 0.92-0.94 (s, 9H), 2.24 (s, 6H), 2.45-2.55 (m, 2H), 3.60- 4.05 (m, 3H), 5.40 (d, 1H), 6.09 (s, 2H), 6.45 (d, 1H, *J* = 6.4), 7.02 (s, 1H), 7.30 (s, 1H), 8.18 (d, 1H, *J* = 6.4); minor atropisomer δ 0.09 (s, 6H), 0.94 (s, 9H), 2.30 (s, 6H), 2.45-2.55 (m, 2H), 3.60- 4.05 (m, 3H), 5.40 (d, 1H), 6.0 (s, 2H), 6.45 (d, 1H, *J* = 6.4), 7.02 (s, 1H), 7.30 (s, 1H), 8.18 (d, 1H, *J* = 6.4)

[218] **Example 16.c.** 4-[N-(2,2-dimethyl-[1,3]dioxolan-4-yl)methyl]amino-6,7-methylenedioxyquinoline. A mixture of 3-[[N-(6,7-Methylenedioxyquinolin-4-yl)]amino]-1,2-propandiol (500 mg, 1.9 mmol), *p*-toluenesulfonic acid (5 mg, 0.02 mg) in DMF (20 mL) and 2,2-dimethoxypropane (5 mL), was heated to 80 °C and stirred at this temperature for 18 h. To the cooled solution was added 1 mL of pyridine and the solvent evaporated *in vacuo*. The crude material was chromatographed in 96:4 chloroform-methanol to give 466 mg of the acetone, in 81% yield; mp 219-221 °C; ¹H NMR (CD₃OD) δ 1.35 (s, 3H), 1.38 (s, 3H), 3.74 (m, 3H), 4.19 (m, 1H), 4.49 (m, 1H), 6.28 (s, 2H), 6.94 (d, 1H, *J* = 7.2), 7.20 (s, 1H), 7.74 (s, 1H), 8.24 (d, 1H, *J* = 7.2); ¹³C NMR (CD₃OD) δ 23.5, 25.1, 45.0, 66.0, 73.6, 96.5,

97.7, 97.8, 103.1, 109.1, 112.2, 135.8, 138.6, 148.4, 153.3, 155.3; HRMS calcd for $C_{16}H_{18}N_2O_4$: 302.1267; found 302.1267.

Examples 13.d-16.d.

- [219] The intermediate 4-amino-6,7-dimethoxyquinoline derivatives used in Examples 13.c-16.c. were prepared using the following general procedure.
- [220] 4-Chloro-6,7-methylenedioxyquinoline was stirred in refluxing phenol (5.5 mol equiv.) for 2.5 h. The temperature was lowered to 100 °C and the primary amine (1.0 mol equiv.) added with stirring. The reaction was then allowed to stir at 100 °C for several hours, and the phenol removed by Kugelrohr distillation under reduced pressure. In the case of those derivatives that have an alkylamine incorporated in their structure, the residue was partitioned between $CHCl_3$ and 10% NaOH. The aqueous layer was repeatedly separated with $CHCl_3$. All of the $CHCl_3$ solutions (initial partition and extracts) were combined and dried ($MgSO_4$). Other 4-amino-6,7-methylenedioxyquinoline derivatives were purified by column chromatography.
- [221] **Example 13.d. N-(6,7-Methylenedioxyquinolin-4-yl)ethanolamine** was prepared from ethanolamine (0.6 g, 10 mmol) from in 53.9% yield with a reaction time of 24 h: mp 233-234 °C; ^1H NMR ($DMSO-d_6$); δ 3.51 (dd, 2H, $J = 10.4, 6.$), 3.69 (t, 2H, $J = 6.0$), 6.27 (s, 2H), 6.72 (d, 1H, $J = 7.0$), 7.37 (s, 1H), 8.12 (s, 1H), 8.29 (d, 1H, $J = 7.0$); ^{13}C NMR ($DMSO-d_6$); 46.5, 59.5, 98.6, 98.8, 100.3, 103.8, 113.2, 137.6, 141.0, 148.2, 152.8, 155.0 ; HRMS calcd for $C_{12}H_{12}N_2O_3H$: 232.0848; found 232.0881.
- [222] **Example 14.d. 2-[2-[N-(6,7-Methylenedioxyquinolin-4-yl)]amino]ethoxyethanol** was prepared from 2-[2-(hydroxyethyl)ethoxy]ethylamine (0.76 g, 7.2 mmol) with a reaction time of 18 h. The compound was converted directly to its *t*-butyldimethylsilyloxy derivative in Example 14.c. above.
- [223] **Example 15.d. 2-[[N-(6,7-Methylenedioxyquinolin-4-yl)]amino]-3-(N,N-dimethylamino)propanol** was prepared from 1-(hydroxymethyl)-2-(N,N-dimethylethylenediamine (1.13 g, 9.6 mmol) with a reaction time of 48 h. The

compound was converted directly to its *t*-butyldimethylsilyloxy derivative in Example 15.c. above.

[224] **Example 16.d.** 3-[[N-(6,7-Methylenedioxyquinolin-4-yl)]amino]-1,2-propandiol was prepared from 3-amino-1,2-propanediol (1.32 g, 14.5 mmol) in 34% yield with a reaction time of 24 h: mp 213-217 °C (dec.); ¹H NMR (CD₃OD) δ 3.67 (m, 5H), 6.26 (s, 2H), 6.87 (d, 1H, *J* = 7.2), 7.19 (s, 1H), 7.71 (s, 1H), 8.21 (d, 1H, *J* = 7.2); ¹³C NMR (CD₃OD) δ 45.7, 63.1, 69.4, 96.8, 97.4, 97.8, 103.0, 112.3, 136.1, 138.9, 148.2, 153.0, 155.0; HRMS calcd for C₉H₇N₃O₂: 262.0954; found 262.0954.

[225] **Example 17.** **8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5,6-dihydro-dibenzo[*c,h*]1,6-naphthyridine (4a):**

[226] To a solution of 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one (160 mg, 0.38 mmol) in THF (650 mL) was added LiAlH₄ (75 mg, 2.0 mmol), and the mixture was stirred under nitrogen at reflux. After 2 h, an additional 2.0mmol of LiAlH₄ was again added. The reaction was refluxed for an additional 3h, then allowed to cool to room temperature. The reaction was quenched by the sequential addition of water (5 drops), 10% NaOH (5 drops), and water (5 drops). The mixture was filtered through Celite and evaporated, and the crude mixture was chromatographed on silica in 98:2 chloroform-methanol, to give 132 mg of the reduced product, in 85 % yield; mp 271-273 °C (dec.); ¹H NMR (CDCl₃) δ 2.24 (s, 6H), 2.58 (t, 2H, *J* = 6.8), 3.12 (t, 2H, *J* = 6.8), 3.97 (s, 3H), 4.02 (s, 3H), 4.27 (s, 2H), 6.13 (s, 2H), 6.79 (s, 1H), 7.38 (s, 2H), 7.61 (s, 1H), 9.05 (s, 1H); ¹³C NMR (CDCl₃) δ 46.0, 50.6, 51.2, 56.2, 26.3, 58.4, 99.6, 101.7, 105.7, 106.6, 110.0, 120.7, 123.1, 124.8, 131.1, 144.1, 146.9, 148.0, 149.0, 149.4, 149.8, 150.2; HRMS calcd for C₂₃H₂₅N₃O₄: 407.1845; found 407.1848.

[227] **Example 18.** **8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)-1-methylethyl]-5,6-dihydro-dibenzo[*c,h*]1,6-naphthyridine.** The title compound was prepared as follows. 8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)-1-methylethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one (80 mg, 0.18 mmol; Example 7) in THF (150 mL) was added to LiAlH₄ (50 mg, 1.3 mmol), and

the mixture was stirred under nitrogen at reflux for 4h.. The reaction was quenched by the sequential addition of water (5 drops), 10% NaOH (5 drops), and water (5 drops). The mixture was filtered through Celite and evaporated, and the crude mixture was chromatographed on silica in 1.0 % methanol in chloroform to give 35 mg of the reduced product, in 45.4 % yield; mp 153-154 °C; ¹H NMR (CDCl₃) δ 1.16 (d, 3H, *J* = 8), 2.38 (dd, 2H, *J* = 12.2, 8.0), 3.68-3.80 (m, 1), 3.88 (s, 3H), 4.24 (s, 2H), 6.16 (s, 2H), 6.64 (s, 1H), 7.24 (s, 1H), 7.40 (s, 2H), 7.62 (s, 1H), 8.88 (s, 1H); ¹³C NMR (CDCl₃) δ : 17.7, 45.6, 46.0, 56.2, 56.4, 57.8, 64.2, 100.1, 101.7, 105.8, 106.4, 108.5, 120.5, 120.6, 123.6, 126.9, 143.4, 146.6, 147.7, 148.9, 149.5, 149.6, 150.0 ; HRMS calcd for C₂₄H₂₇N₃O₄H 422.2002; found 422.2081.

- [228] **Example 19. 8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(N,N-diethylamino)ethyl]-5H-dibenzo[*c,h*]1,6-naphthyridin-6-one.** A mixture of N-(6,7-Methylenedioxyquinolin-4-yl)-N-[2-(N,N-diethylamino)ethyl]-2-iodo-4,5-dimethoxybenzamide (577 mg, 1.0 mmol), Pd(OAc)₂ (45, 0.2 mmol), P(*o*-tolyl)₃ (122 mg, 0.4 mmol), and silver carbonate (550 mg, 2.0 mmol) was heated to reflux in DMF (30 mL) and stirred under nitrogen for 30 minutes. The reaction mixture was cooled to room temperature, diluted with chloroform and filtered though a bed of Celite. The filter was washed well with 90:10 chloroform-methanol. Then the solvent was removed under reduced pressure and the resulting residue was chromatographed on silica gel using 99:1 chloroform-methanol to give the cyclized compound (250 mg) as a white solid, in 56% yield; mp 221-223 °C (dec.); IR (CHCl₃) 3029, 3009, 2971, 2939, 2910, 1648, 1611, 1570, 1523, 1497, 1467, 1386, 1310, 1267, 1248, 1217, 1213, 1166, 1040; ¹H NMR (CDCl₃) δ 0.95 (t, 6H, *J*=7.0), 2.80 (1, 4H, *J*=7.0), 3.04 (t, 2H, *J*=6.7), 4.06 (s, 3H), 4.13 (s, 3H), 4.63 (t, 2H, *J*=6.7), 6.17 (s, 2H), 7.46 (s, 1H), 7.68 (s, 1H), 7.90 (s, 1H), 7.96 (s, 1H), 9.37 (s, 1H); ¹³C NMR (CDCl₃) δ 12.0, 47.6, 49.6, 51.7, 56.3, 101.4, 102.0, 102.2, 107.0, 108.9, 111.8, 115.0, 119.5, 127.7, 141.1, 143.5, 147.3, 147.7, 149.9, 150.3, 154.2, 164.2; HRMS calcd for C₂₅H₂₇O₅N₃H: 450.2030; found: 450.2032.

- [229] **a. 4-[[2-(Diethylamino)ethyl]amino]-6,7-methylenedioxyquinoline.** 4-Chloro-6,7-methylenedioxyquinoline. (1.0 g, 4.83 mmol) was stirred in boiling

phenol for 2.5 hours. Then the mixture was cooled to 140 °C and N,N-diethylethylenediamine (1.16 g, 10.0 mmol) was added. The reaction mixture was stirred at this temperature for 18 hours, and then phenol was removed on the Kugelrohr. The crude residue was partitioned between dilute HCl (100 mL) and chloroform (100 mL), and the organic phase was extracted with dilute HCl (100 mL). The combined aqueous phases were washed with chloroform (100 mL) and then basified with 30% NaOH, extracted into chloroform (3 x 100 mL), dried (MgSO₄) and evaporated to give 793 mg as a white solid, in 58% yield; mp 201-202 °C; IR (CHCl₃) 3364, 2967, 2936, 2907, 2875, 1620, 1546, 1466, 1295, 1222, 1218, 1210, 1152, 1041; ¹H NMR (CDCl₃) δ 1.09 (t, 6H, *J*=7.2), 2.61 (q, 4H, *J*=7.2), 2.82 (t, 2H, *J*=5.8), 3.26 (m, 2H), 5.71 (br, 1H), 6.08 (d, 2H), 6.35 (d, 1H, *J*=5.2), 7.03 (s, 1H), 7.31 (s, 1H), 8.40 (d, 1H, *J*=5.2); ¹³C NMR (CDCl₃) δ 12.2, 40.1, 46.7, 51.0, 96.1, 99.0, 101.5, 106.7, 114.5, 146.5, 146.7, 149.1, 149.6, 149.9; HRMS calcd for C₁₆H₂₁O₂N₃: 287.1634; found: 287.1631.

[230] b. **N-(6,7-Methylenedioxyquinolin-4-yl)-N-[2-(N,N-diethylamino)ethyl]-2-iodo-4,5-dimethoxybenzamide.** Oxalyl chloride (1.12 g, 8.8 mmol) was added to a solution of 2-Iodo-4,5-dimethoxybenzoic acid (820 mg, 2.6 mmol; see above) in anhydrous methylene chloride (40 mL) and the stirred mixture was refluxed for 4 hours. The mixture was then concentrated to dryness under reduced pressure. The acid chloride was dissolved in 40 mL of methylene chloride and added to a solution of 4-[[2-(Diethylamino)ethyl]amino]-6,7-methylenedioxyquinoline (640 mg, 2.2 mmol), and triethylamine (2.2g, 22 mmol) in methylene chloride (50 mL) and the resulting mixture was stirred at reflux under nitrogen for 2 hours. The reaction mix was cooled and washed with a saturated solution of sodium bicarbonate (3 x 75 mL), and extracted into dilute HCl (4 x 100 mL). The aqueous extract was then neutralized with 30% NaOH and extracted with CHCl₃ (4 x 100 mL), washed with brine (100mL), dried (MgSO₄) and evaporated, yielding 1.1 g as a sticky semisolid glue, in 86% yield; ¹H NMR (CDCl₃) δ 0.96 (t, 6H, *J*=7.2), 2.54 (q, 4H, *J*=7.2), 2.82 (m, 2H), 3.29 (s, 3H), 3.71 (s, 3H), 3.92 (m, 1H), 4.46 (m, 1H), 6.12 (s, 2H), 6.37 (s, 1H), 7.00 (s, 1H), 7.27 (d, 1H, *J*=4.8), 7.33 (s, 1H), 7.39 (s, 1H), 8.52 (d, 1H, *J*=4.8); ¹³C NMR (CDCl₃) δ 11.8, 47.1, 47.5, 50.7, 55.5, 56.1, 82.7, 98.5, 102.2, 106.7, 110.6, 120.1,

121.8, 122.7, 133.7, 146.3, 148.1, 148.3, 148.5, 149.0, 149.7, 151.0, 170.0; HRMS calcd for C₂₅H₂₈O₅N₃IH: 578.1153; found: 578.1153.

[231] The intermediate 4-Chloro-6,7-methylenedioxyquinoline was prepared as described above.

[232] The intermediate 2-Iodo-4,5-dimethoxybenzoic acid was prepared as follows.

[233] **c. 2-Iodo-4,5-dimethoxybenzoic acid.** A mixture of 2-amino-4,5-dimethoxybenzoic acid (10.0 g, 50mmol) in water (100 mL) and concentrated H₂SO₄ (14 mL) was cooled to 5 °C and a solution of NaNO₂ (3.5 g) in water (12.5 mL) was added in a dropwise fashion while maintaining the temperature between 0-5 °C. Following the addition the mixture was stirred at this temperature for an additional 30 minutes. Then a solution of KI (13.0 g, 78.3 mmol) in water (20.5 mL) and concentrated H₂SO₄ (4.4 mL) was rapidly added and the flask was transferred to an oil bath that had been preheated to 105 °C. The mixture was stirred for 30 minutes following the onset of reflux. The flask was then cooled and extracted into chloroform (3 x 300 mL), washed with water (3 x 200 mL), dilute HCl (200 mL), and brine (200 mL), then the solvent was dried (Na₂SO₄) and evaporated, and the residue was chromatographed in chloroform to give 13.1 g as a white solid, in 84% yield; mp 162.0-163.5 °C (lit. mp 159-160 °C); ¹H NMR (CDCl₃) δ 3.93 (s, 3H), 3.95 (s, 3H), 7.46 (s, 1H), 7.65 (s, 1H); ¹³C NMR (CDCl₃) δ 56.1, 56.4, 85.8, 114.8, 124.3, 124.5, 148.8, 152.7, 170.5.

[234] **Example 20.** Using procedures similar to those described above, the compound 2,3-dimethoxy-8,9-methylenedioxy-11-[2-(4-methylpiperazin-1-yl)ethyl]-11*H*-5,6,11-triazachrysen-12-one was also prepared.

[235] **Example 21.** Using procedures similar to those described above, the following compounds of the invention were also prepared: 8,9-dimethoxy-2,3-methylenedioxy-5-(2-piperidinoethyl)-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(4-benzylpiperazin-1-yl)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; 8,9-dimethoxy-2,3-methylenedioxy-5-formylmethyl-5*H*-

dibenzo[*c,h*]1,6-naphthyridin-6-one; and 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N-methylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one.

EXAMPLE II

Efficacy of Compounds

[236] Compound 2 was evaluated to determine the concentration response (i.e. growth inhibition) relationship in human tumor cell lines representing varied human hematologic malignancies in a 72-hr growth inhibition assay. Thirteen established human tumor cell lines were exposed to a concentration range of Compound 2 in two independent growth inhibition experiments. Human tumor cell lines representing varied hematologic tumor, leukemias, and lymphomas, were maintained frozen in liquid nitrogen until use. Cultures were passed several times prior to experiments. For experiments, tumor cells, 4×10^3 cells per well in 96-well plates, were plated in RPMI medium supplemented with 5% fetal bovine serum. Compound 2 was tested at concentrations covering a 4-log range (0.1 nM- 100 nM) with an exposure time of 72 hours and experimental endpoint of cell growth inhibition as determined by Cell Titer-Glo luminescence assay (Promega) for ATP content. The following established human tumor cell lines were tested:

<u>Cell Line</u>	<u>Tumor Type</u>	<u>Reference</u>
SKM-1	Monocytic leukemia	Leukemia 1992; 6: 1296-301
F-36P	Acute erythroleukemia	Blood 1991; 78: 2261-8
MOLM-13	Acute monocytic leukemia	Leukemia 1997; 11: 1469-77
MV-4-11	B myelomonocytic leukemia	Blood 1987; 70: 192-9 J Immunol 1987; 139: 3348-54
KARPAS 299	Non-Hodgkin's Lymphoma	Blood 1988; 72: 234-40
HL-60	Acute promyelocytic leukemia	Nature 1977; 270: 347-9; Blood 1979; 54: 713-33
Daudi	Burkitt's Lymphoma	Cancer Res 1968; 28:1300-10; Int J Cancer 1977;19: 337-44
B104	B cell lymphoma	J Immunol 1991; 146: 819-25
RAMOS	Burkitt's lymphoma	Intervirology 1975; 5: 319-34;

J Immunol 1982; 129: 1336-42

IM-9	B lymphoblastoid	Cytotechnology 1989; 3: 43-50
Pfeiffer	Non-Hodgkin's lymphoma	Eur J Immunol 1999; 63: 180-191
BL 31	Burkitt's lymphoma	Hematol Blood Transfusion 1985; 29: 261-5

EXAMPLE II

Procedures

Experiment Day 1

- [237] Cells (4×10^3) were plated in 96-well flat-bottomed tissue culture plates in 100 μ l RPMI medium supplemented with 5% FBS per well. Thirty-six wells (three rows of 12) were plated for each line to be tested, with 12 concentrations of Compound 2, each tested in triplicate. Six or seven cell lines were tested in each experiment, with two cell lines per plate. In addition, a separate 96-well plate was set up for an untreated time zero (T_0) measurement, with 6 wells of each cell line with 4×10^3 cells per well in 100 μ l RPMI medium supplemented with 5% FBS per well. Plates were incubated overnight at 37°C in humidified air with 5% CO₂.

Experiment Day 2

- [238] An aliquot of a stock solution of Compound 2 (100 μ M) in DMSO was removed from storage at -20°C. Two serial dilutions were made in RPMI medium supplemented with 5% FBS at twice the final concentrations in 15 ml tubes. The final Compound 2 concentrations that were tested are presented in Table 1 below.

Compound 2 Concentration in Well	Dilution Factor	Formula to Produce Compound 2 Concentrations
10 μ M	1:5	2 ml medium + 500 μ l 100 μ M stock solution
3 μ M	1:16.67	2.35 ml medium + 150 μ l 100 μ M stock solution
1 μ M	1:10	2.7 ml medium + 300 μ l 10 μ M
300 nM	1:10	2.7 ml medium + 300 μ l 3 μ M
100 nM	1:10	2.7 ml medium + 300 μ l 1 μ M
30 nM	1:10	2.7 ml medium + 300 μ l 300 nM
10 nM	1:10	2.7 ml medium + 300 μ l 100 nM
3 nM	1:10	2.7 ml medium + 300 μ l 30 nM
1 nM	1:10	2.7 ml medium + 300 μ l 10 nM
0.3 nM	1:10	2.7 ml medium + 300 μ l 3 nM
0.1 nM	1:10	2.7 ml medium + 300 μ l 1 nM
0		medium only

Experiments Day 2, 3, and 4

- [239] The 96-well plates were labeled and 100 μ l of each of the 12 compound solutions was added to the 100 μ l of RPMI medium supplemented with 5% FBS containing cells (4×10^3)/well in triplicate. Plates were placed into the incubator at 37°C with a humidified air/5% carbon dioxide atmosphere, and allowed to incubate for 72 hours. On Day 2, the T₀ plate was read utilizing Promega's Cell Titer-Glo Luminescent Cell Viability Assay (cat # G7571) according to the manufacturer's instructions. The T₀ plate was removed from the incubator and allowed to reach room temperature for 30 minutes. Cell Titer-Glo buffer was added to the Cell Titer-Glo substrate as described in the manufacturer's instructions (Promega). The complete Cell Titer-Glo solution

was added to the plate at room temperature. A BioTek Synergy HT plate reader was set for reading luminescence with a sensitivity setting of 100. The Cell Titer-Glo solution (100 μ l) was added to each well of the T₀ plate and timed for 3 minutes. After 3 minutes, the plate was read in the plate reader, and values obtained.

Experiment Day 5

- [240] After 72 hours incubation, the test plates were removed from the incubator and allowed to reach room temperature for 30 minutes. The complete Cell Titer-Glo solution was prepared from the Cell Titer-Glo buffer and Cell Titer-Glo substrate per the manufacturer's instructions for each plate to be read. The BioTek Synergy plate reader was set for reading luminescence with a sensitivity setting of 100. To read the test plates, half of the volume of medium (100 μ l of the 200 μ l) in each well was carefully removed and discarded, leaving 100 μ l medium remaining in each well. The complete Cell Titer-Glo solution (100 μ l) was added to each well in the first plate. After 3 minutes, the first plate was placed in the BioTek Synergy plate reader and luminescence of each well was determined. Luminescence value for each well was transferred to an Excel file. The second and third plates were similarly read and data recorded. The luminescence data were converted to growth fraction by comparison to the luminescence for the untreated control for each cell line. Concentration response curves over the concentration range from 0.1 nanomolar to 10 micromolar were plotted using the mean values for the triplicate determinations for each experiment. Each cell line was tested in at least two independent experiments. The results were plotted in Excel. IC₅₀ and IC₉₀ values were determined from the graphical data.

EXAMPLE III

Results

- [241] Compound 2 is a potent growth inhibitor of human tumor cells. Exposure to the compound produced exponential killing of cells in a manner consistent with potent inhibition of a critical molecular target.

Human Tumor Cell Lines and IC₅₀ Concentration Sensitivity

- [242] The IC₅₀ concentrations of the 13 human tumor cell lines were spread over a 100-fold concentration range from 0.046 nanomolar to 3.4 nanomolar. The steepness of the concentration response curves from the IC₅₀ to the IC₉₀ did not track with the sensitivity of the cells to Compound 2. Some cell lines had steep slopes between these values as reflected by IC₉₀/IC₅₀ ratios less than 10; while other lines had large differentials between IC₅₀ and IC₉₀ concentrations reaching 100-fold.
- [243] Human tumor cells IC₅₀ in nanomolar and IC₉₀ in micromolar values for Compound 2 are listed in the Table 2 below.

Disease	Cell Line	Concentration Values		Ratio IC ₉₀ / IC ₅₀
		IC ₅₀ , Nanomolar	IC ₉₀ , Nanomolar	
Monocytic leukemia	SKM-1	0.14	0.7	5
Acute erythroleukemia	F-36P	0.43	4.0	9.3
Acute monocytic leukemia	MOLM-13	0.06	0.43	7.2
B myelomonocytic leukemia	MV-4-11	0.046	0.3	6.5
Non-Hodgkin's Lymphoma	KARPAS 299	0.5	4.1	8.2
Acute promyelocytic leukemia	HL-60	0.08	8.1	101
Burkitt's Lymphoma	Daudi	0.15	15	100
B cell lymphoma	B104	0.6	9.1	15.2
Burkitt's lymphoma	RAMOS	0.22	2.1	9.5
B lymphoblastoid	IM-9	0.20	1.8	9
NHL	Pfeiffer	0.68	3.0	1.5
Burkitt's lymphoma	BL-31	0.3	11	36.7

- [244] Human tumor cell IC₅₀ values for Compound 2 in nanomolar concentrations are presented in Figure 1. As shown in Figure 1, four of the five leukemia lines tested were among the lines most sensitive to Compound 2 while most of the four Burkitt's lymphoma lines tended to be more sensitive to Compound 2 than the three non-Hodgkin's lymphoma lines.

Human Tumor Cell Lines and IC₉₀ Concentration Sensitivity

- [245] Human tumor cell IC₉₀ values for Compound 2 in nanomolar concentrations are presented in Figure 2. The IC₉₀ concentrations of the 13 human tumor cell lines were spread over about a 100-fold concentration range from 0.3 nanomolar to 30 nanomolar. The median IC₉₀ value for the 13 human tumor cell lines was 4 nanomolar and the median IC₅₀ value for the 13 cell lines was 0.22 nanomolar. There was reasonable agreement in the ranking of cell line sensitivity between the IC₅₀ sorting and the IC₉₀ sorting.
- [246] Figure 3 and Figure 4 are graphs of the surviving fraction versus concentration of Compound 2 over the full concentration range for human tumor cell lines representing hematologic malignancies.

EXAMPLE IV

In Vivo Studies

- [247] The *in vivo* anti-tumor activity of Compound 2 was evaluated in 2 pharmacodynamic studies in the human hematological malignancy models, the MOLM-13 acute monocytic leukemia and the KARPAS 299 non-Hodgkin's lymphoma. Vincristine was selected as the comparator compound on the basis of known clinical utility in the disease represented by the tumor line histogenesis. The tumor volume, body weight, abnormal clinical signs, tumor growth inhibition (TGI) and tumor growth delay (TGD) were determined. Tumor volumes were monitored twice weekly by measuring

the width (mm) and length (mm) of the tumor mass using digital calipers. Tumor measurements were converted to a tumor volume (mm^3) using the formula, $[\text{width (mm)}^2 \times \text{length (mm)}] \times 0.52$. Abnormal clinical signs were recorded for all mice before each dose, frequently after each dose, and at the time of body weight measurements on non-dose days. Mortality evaluations were performed on all mice daily. Mice were evaluated for two clinical endpoints: 1) percent tumor growth inhibition (T/C %), 2) tumor growth delay in days with corresponding increase-in-lifespan (ILS). Tumor growth delay (T-C) utilized the time required for the median mouse in each group to reach the tumor volume endpoint of 2000 mm^3 .

Compound 2 vs. MOLM-13 Human Acute Monocytic Leukemia Xenograft Model

[248] The efficacy of Compound 2 against the MOLM-13 human acute monocytic leukemia xenograft model was studied. Vincristine served as the positive control.

Materials and Methods:

[249] **Test and Control Article Formulation Preparation:** On each day of dosing, the test article, Compound 2, was weighed out and dissolved in the appropriate volume of M/6 lactate. The positive control article dosing solution was prepared on each day of dosing. A 10 mL/kg dose volume was administered to all animals.

[250] **Xenografts:** Male nude (nu/nu) mice were implanted subcutaneously in the axilla region by trocar with fragments of MOLM-13 human acute monocytic leukemia tumors harvested from subcutaneously growing tumors in nude mice hosts. The mice were approximately 4 weeks of age and weighed 18-20 g at the time of tumor implantation. When the tumors were $220\text{-}235 \text{ mm}^3$ in size, the animals were pair-matched into treatment and control groups.

[251] **Dose Administration and Schedule:** Beginning on Day 10, groups of 10 male nude (nu/nu) mice were IV administered Compound 2 at doses of 0 (untreated control), 0 (vehicle control), 1.00, 1.36, or 1.70 mg/kg/day ($4.1, 8.2, \text{ or } 16.3 \text{ mg/m}^2$) on a QOD x 3 weekly for 2 cycles dosing schedule. Another group of 10 male nude (nu/nu) mice

were IV administered vincristine, the positive control, at a dose of 1 mg/kg/day on a QD x 5 dosing schedule.

[252] Body Weight: All mice were individually weighed prior to each dose (for dose calculation purposes only) and twice weekly.

[253] Tumor Measurements and Study Endpoints: Tumor volumes were measured twice weekly. Mice were evaluated for two tumor growth endpoints, percent tumor growth inhibition (T/C%) and tumor growth delay (T-C days) with corresponding increase in life span.

[254] Results: Figure 5 shows the mean tumor volume of mice treated with Compound 2 versus vincristine in MOLM-13 human acute myeloid leukemia. Figure 6 shows the percent change in body weight of mice treated with Compound 2 versus vincristine in MOLM-13 human acute myeloid leukemia. As shown in Table 3 below, Compound 2 at 1.0 and 1.36 mg/kg/day resulted in low and moderate TGI activity. At the second evaluation point, Compound 2 at the low dose resulted in low TGD activity (T-C = 3 days) corresponding to a 1.1-fold ILS. The medium dose exhibited moderate TGD activity (TGD = 10 days) corresponding to a 1.4-fold ILS. The high dose exhibited high TGD activity (TGD = 14 days) corresponding to a 1.6-fold ILS. The high dose of Compound 2 (1.70 mg/kg/day) resulted in little weight loss (2.4%). Vincristine was highly effective against the MOLM-13 tumor such that endpoints could not be determined. However, this agent was toxic as determined by the body weight loss of 17% at the dose level tested. As evidenced by the tumor growth inhibition and delays in tumor growth, Compound 2 exhibited activity against the MOLM-13 human acute monocytic leukemia xenograft model.

Test Agent, Dose	Tumor Growth Delay, Days	Treated/Control, Days	Percent Max Body Weight Loss
Untreated Control MOLM-13	-	-	-
Vehicle Control	-	-	-

MOLM-13 M/6 Lactate, iv QODx3 for 2 cycles			
Compound 2 1 mg/kg/day, iv QODx3 for 2 cycles	3	1.1	0
Compound 2 1.36 mg/kg/day, iv QODx3 for 2 cycles	10	1.4	0
Compound 2 1.7 mg/kg/day, iv QODx3 for 2 cycles	14	1.6	2.4
Vincristine 1 mg/kg/day, iv QODx5	Not determined	-	16.8

Compound 2 v. Karpas 299 Human non-Hodgkin's Lymphoma Xenograft Model

[255] The efficacy of Compound 2 and an experimental compound against the Karpas 299 human non-Hodgkin's lymphoma xenograft model was studied. Vincristine served as the positive control.

Materials and Methods:

[256] **Test and Control Article Formulation Preparation:** On each day of dosing, the test article, Compound 2, was weighed out and dissolved in the appropriate volume of M/6 lactate. The positive control article dosing solution was prepared on each day of dosing. A 10 mL/kg dose volume was administered to all animals.

[257] **Xenografts:** Male nude (nu/nu) mice were implanted subcutaneously in the axilla region by trocar with fragments of Karpas 299 human non-Hodgkin's lymphoma tumors harvested from subcutaneously growing tumors in nude mice hosts. The mice were approximately 4 weeks of age and weighed 18-20 g at the time of tumor implantation. When the tumors were 220-235 mm³ in size, the animals were pair-matched into treatment and control groups.

- [258] **Dose Administration and Schedule:** Beginning on Day 10, groups of 10 male nude (nu/nu) mice were IV administered Compound 2 at doses of 0 (untreated control), 0 (vehicle control), 1.00, 1.36, or 1.70 mg/kg/day (4.1, 8.2, or 16.3 mg/m²) on a QOD x 3 weekly for 2 cycles dosing schedule. Another group of 10 male nude (nu/nu) mice were IV administered vincristine, the positive control, at a dose of 1 mg/kg/day on a QD x 5 dosing schedule.
- [259] **Body Weight:** All mice were individually weighed prior to each dose (for dose calculation purposes only) and twice weekly.
- [260] **Tumor Measurements and Study Endpoints:** Tumor volumes were measured twice weekly. Mice were evaluated for two tumor growth endpoints, percent tumor growth inhibition (T/C%) and tumor growth delay (T-C days) with corresponding increase in life span.
- [261] **Results:** Figure 7 shows the mean tumor volume of mice treated with Compound 2 versus vincristine in Karpas 299 human lymphoma tumor. Figure 8 shows the percent change in body weight of mice treated with Compound 2 versus vincristine in Karpas 299 human lymphoma tumor. As shown in Table 4 below, Compound 2 at 1.0 and 1.36 mg/kg/day resulted in low and moderate TGI activity. At the second evaluation point, Compound 2 at the low dose resulted in moderate tumor growth delay activity (T-C = 14 days) corresponding to a 1.6-fold ILS. The medium dose exhibited high tumor growth delay activity (TGD = 24 days) corresponding to a 2.1-fold ILS. The high dose exhibited high tumor growth delay activity (TGD = 24 days) corresponding to a 2.1-fold ILS. The medium and high doses of Compound 2 (1.36 and 1.7 mg/kg/day) resulted in little weight loss (0-0.8%). Vincristine was highly effective against the Karpas 299 tumor such that endpoints could not be determined. However, this agent was toxic as determined by the body weight loss of 18% at the dose level tested.
- [262] As evidenced by the tumor growth inhibition and delays in tumor growth, Compound 2 exhibited activity against the Karpas 299 human non-Hodgkin's lymphoma xenograft model.

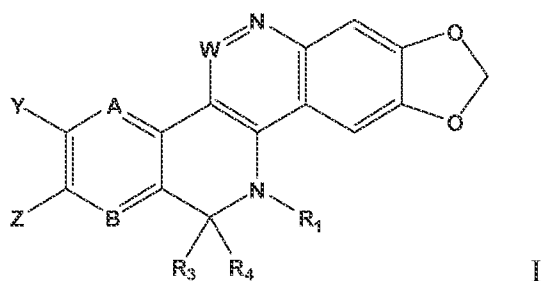
Karpas 299 Results

Test Agent, Dose	Tumor Growth Delay, Days	Treated/Control, Days	Percent Max Body Weight Loss
Untreated Control Karpas 299	-	-	-
Vehicle Control Karpas 299 M/6 Lactate, iv QODx3 for 2 cycles	-	-	-
Compound 2 1 mg/kg/day, iv QODx3 for 2 cycles	14	1.6	0
Compound 2 1.36 mg/kg/day, iv QODx3 for 2 cycles	24	2.1	0.8
Compound 2 1.7 mg/kg/day, iv QODx3 for 2 cycles	24	2.1	0
Vincristine 1 mg/kg/day, iv QODx5	Not determined	-	17.7

[263] All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

What is claimed is:

1. Use of a compound for the manufacture of a medicament for the treatment of a hematological cancer in a mammal, wherein the compound is a compound of formula I:



wherein:

A and B are independently N or CH;

W is N or CH;

R₃ and R₄ are each independently H, (C₁-C₆)alkyl, or substituted (C₁-C₆)alkyl, or R₃ and R₄ together are =O, =S, =NH or =N-R₂;

Y and Z are independently hydroxy, (C₁-C₆)alkoxy, substituted (C₁-C₆)alkoxy, (C₁-C₆)alkanoyloxy, substituted (C₁-C₆) alkanoyloxy, -O-P(=O)(OH)₂, or -O-C(=O)NR_cR_d; or Y and Z together with the ring carbon atoms to which they are attached form an alkylenedioxy ring with from 5 to 7 ring atoms;

R₁ is a -(C₁-C₆)alkyl substituted with one or more solubilizing groups R_z;

R₂ is (C₁-C₆)alkyl or substituted (C₁-C₆)alkyl; and

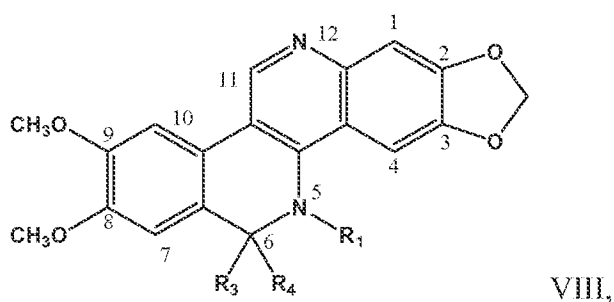
R_c and R_d are each independently (C₁-C₆) alkyl or substituted (C₁-C₆) alkyl; or R_c and R_d together with the nitrogen to which they are attached form a N'-{(C₁-C₆)alkyl}piperazino, pyrrolidino, or piperidino ring, which ring can optionally be substituted with one or more aryl, heteroaryl, or heterocycle;

or a pharmaceutically acceptable salt, prodrug or metabolite thereof.

2. The use of claim 1 wherein A is CH.

3. The use of any one of claims 1-2 wherein B is CH.

4. The use of any of claims 1-3 wherein Y is -OCH₃.
5. The use of any of claims 1-4 wherein Z is -OCH₃.
6. The use of any of claims 1-5 wherein R₁ is a (C1-C6)alkyl substituted with one or more NR_aR_b groups.
7. The use of any of claims 1-6 wherein R₃ and R₄ together are =O.
8. The use of any of claims 1-7 wherein W is CH.
9. The use of claim 1 wherein the compound is 11,12-dihydro-2,3-dimethoxy-8,9-methylenedioxy-11-{2-(dimethylamino)ethyl}-5,6,11-triazachrysen-12-one, or a pharmaceutically acceptable salt, prodrug or metabolite thereof.
10. The use of claim 1 wherein the compound of formula I is a compound of formula VIII:



or a pharmaceutically acceptable salt, prodrug or metabolite thereof.

11. The use of claim 1 wherein the compound of formula I is 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N,N-diethylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-

naphthyridin-6-one; or 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N-methylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; or a pharmaceutically salt, prodrug or metabolite thereof.

12. The use of claim 1 wherein the compound of formula I is

11,12-dihydro-2,3-dimethoxy-8,9-methylenedioxy-11-[2-(dimethylamino)ethyl]-5,6,11-triazachrysen-12-one (E);

2,3-Dimethoxy-8,9-methylenedioxy-11-[(2-diethylamino)ethyl]-11*H*-5,6,11-triazachrysen-12-one;

2,3-Dimethoxy-8,9-methylenedioxy-11-[(2-dimethylamino)-1-methylethyl]-11*H*-5,6,11-triaza-chrysen-12-one;

2,3-Dimethoxy-8,9-methylenedioxy-11-(2-tetrahydrofuryl)methyl-11*H*-5,6,11-triazachrysen-12-one;

2,3-Dimethoxy-8,9-methylenedioxy-11-[2-(pyrrolidin-1-yl)ethyl]-11*H*-5,6,11-triaza-chrysen-12-one;

2,3-Dimethoxy-8,9-methylenedioxy-11-[2-(piperidin-1-yl)ethyl]-11*H*-5,6,11-triaza-chrysen-12-one;

8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one;

8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)-1-methylethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one;

8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(pyrrolidin-1-yl)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one;

8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(4-methylpiperazin-1-yl)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one;

8,9-Dimethoxy-2,3-methylenedioxy-5-[3-(N,N-dimethylamino)propyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one;

8,9-Dimethoxy-2,3-methylenedioxy-5-(2-tetrahydrofuryl)methyl-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one;

8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(hydroxy)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one;

8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(2-hydroxyethoxy)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one;

8,9-Dimethoxy-2,3-methylenedioxy-5-[2-*N,N*-dimethylamino-1-(hydroxymethyl)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one;

8,9-Dimethoxy-2,3-methylenedioxy-5-[2,3-dihydroxy)propyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one;

8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(*N,N*-dimethylamino)ethyl]-5,6-dihydro-dibenzo[*c,h*]1,6-naphthyridine;

8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(*N,N*-dimethylamino)-1-methylethyl]-5,6-dihydro-dibenzo[*c,h*]1,6-naphthyridine;

8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(*N,N*-diethylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one;

2,3-dimethoxy-8,9-methylenedioxy-11-[2-(4-methylpiperazin-1-yl)ethyl]-11*H*-5,6,11-triazachrysen-12-one;

8,9-dimethoxy-2,3-methylenedioxy-5-(2-piperidinoethyl)-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one;

8,9-dimethoxy-2,3-methylenedioxy-5-[2-(4-benzylpiperazin-1-yl)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one;

8,9-dimethoxy-2,3-methylenedioxy-5-formylmethyl-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; or

8,9-dimethoxy-2,3-methylenedioxy-5-[2-(*N*-methylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one;

or a pharmaceutically acceptable salt, prodrug or metabolite thereof.

13. The use of any one of claims 1-12 wherein the hematological cancer is leukemia or lymphoma.

14. The use of any one of claims 1-12 wherein the cancer is acute lymphoblastic leukemia, adult; acute lymphoblastic leukemia, childhood; acute myeloid leukemia, adult; acute myeloid leukemia, childhood; AIDS-related lymphoma; Burkitt lymphoma; central nervous system lymphoma, primary; chronic lymphocytic leukemia; chronic myelogenous

leukemia; chronic myeloproliferative disorders; cutaneous T-cell lymphoma; hairy cell leukemia; Hodgkin lymphoma, adult; Hodgkin lymphoma, childhood; leukemia, acute lymphoblastic, adult; leukemia, acute lymphoblastic, childhood; leukemia, acute myeloid, adult; leukemia, acute myeloid, childhood; leukemia, chronic lymphocytic; leukemia, chronic myelogenous; leukemia, hairy cell; lymphoma, AIDS-related; lymphoma, Burkitt; lymphoma, Hodgkin, adult; lymphoma, Hodgkin, childhood; lymphoma, Non-Hodgkin, adult; lymphoma, Non-Hodgkin, childhood; lymphoma, primary central nervous system; mycosis fungoides; myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; myelogenous leukemia, chronic; myeloid leukemia, adult acute; myeloid leukemia, childhood acute; myeloproliferative disorders, chronic; Non-Hodgkin lymphoma, adult; Non-Hodgkin lymphoma, childhood; primary central nervous system lymphoma; Sézary syndrome; or Waldenström macroglobulinemia.

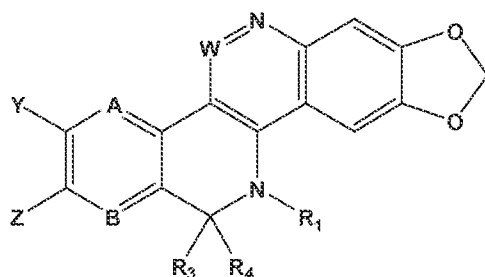
15. The use of claim 1, 13, or 14 wherein the compound is 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N-methylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; or a pharmaceutically acceptable salt, prodrug or metabolite thereof.

16. The use of claim 1, 13, or 14 wherein the compound is 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N-methylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one.

17. The use of claim 1, 13, or 14 wherein the compound is a citrate salt of 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N-methylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one.

18. A compound of formula I or a pharmaceutically acceptable salt, prodrug or metabolite thereof as described in any one of claims 1-12 and 15-17 for use in the prophylactic or therapeutic treatment of a hematological cancer.

19. A pharmaceutical composition for the treatment of a hematological cancer comprising a therapeutically effective amount of a compound of formula I:



I

wherein:

A and B are independently N or CH;

W is N or CH;

R₃ and R₄ are each independently H, (C₁-C₆)alkyl, or substituted (C₁-C₆)alkyl, or R₃ and R₄ together are =O, =S, =NH or =N-R₂;

Y and Z are independently hydroxy, (C₁-C₆)alkoxy, substituted (C₁-C₆)alkoxy, (C₁-C₆)alkanoyloxy, substituted (C₁-C₆) alkanoyloxy, -O-P(=O)(OH)₂, or -O-C(=O)NR_cR_d; or Y and Z together with the ring carbon atoms to which they are attached form an alkylenedioxy ring with from 5 to 7 ring atoms;

R₁ is a -(C₁-C₆)alkyl substituted with one or more solubilizing groups R₂;

R₂ is (C₁-C₆)alkyl or substituted (C₁-C₆)alkyl; and

R_c and R_d are each independently (C₁-C₆) alkyl or substituted (C₁-C₆) alkyl; or R_c and R_d together with the nitrogen to which they are attached form a N'-{(C₁-C₆)alkyl} piperazino, pyrrolidino, or piperidino ring, which ring can optionally be substituted with one or more aryl, heteroaryl, or heterocycle;

or a pharmaceutically acceptable salt, prodrug or metabolite thereof; and
a pharmaceutically acceptable excipient.

20. The pharmaceutical composition of claim 19 wherein the compound of formula I is 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N,N-dimethylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N,N-diethylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; or 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N-methylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; or a pharmaceutically acceptable salt, prodrug or metabolite thereof.

21. The pharmaceutical composition of any one of claims 19-20 wherein the cancer is leukemia.
22. The pharmaceutical composition of any one of claims 19-20 wherein the cancer is lymphoma.
23. The pharmaceutical composition of any one of claims 19-20 wherein the cancer is acute lymphoblastic leukemia, adult; acute lymphoblastic leukemia, childhood; acute myeloid leukemia, adult; acute myeloid leukemia, childhood; AIDS-related lymphoma; Burkitt lymphoma; central nervous system lymphoma, primary; chronic lymphocytic leukemia; chronic myelogenous leukemia; chronic myeloproliferative disorders; cutaneous T-cell lymphoma; hairy cell leukemia; Hodgkin lymphoma, adult; Hodgkin lymphoma, childhood; leukemia, acute lymphoblastic, adult; leukemia, acute lymphoblastic, childhood; leukemia, acute myeloid, adult; leukemia, acute myeloid, childhood; leukemia, chronic lymphocytic; leukemia, chronic myelogenous; leukemia, hairy cell; lymphoma, AIDS-related; lymphoma, Burkitt; lymphoma, Hodgkin, adult; lymphoma, Hodgkin, childhood; lymphoma, Non-Hodgkin, adult; lymphoma, Non-Hodgkin, childhood; lymphoma, primary central nervous system; mycosis fungoides; myelodysplastic syndromes; myelodysplastic/myeloproliferative diseases; myelogenous leukemia, chronic; myeloid leukemia, adult acute; myeloid leukemia, childhood acute; myeloproliferative disorders, chronic; Non-Hodgkin lymphoma, adult; Non-Hodgkin lymphoma, childhood; primary central nervous system lymphoma; Sézary syndrome; or Waldenström macroglobulinemia.
24. The pharmaceutical composition of any one of claims 19-23 wherein the compound is 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N-methylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one; or a pharmaceutically acceptable salt, prodrug or metabolite thereof.
25. The pharmaceutical composition of any one of claims 19-23 wherein the compound is 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N-methylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one.

26. The pharmaceutical composition any one of claims 19-23 wherein the compound is a citrate salt of 8,9-dimethoxy-2,3-methylenedioxy-5-[2-(N-methylamino)ethyl]-5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one.

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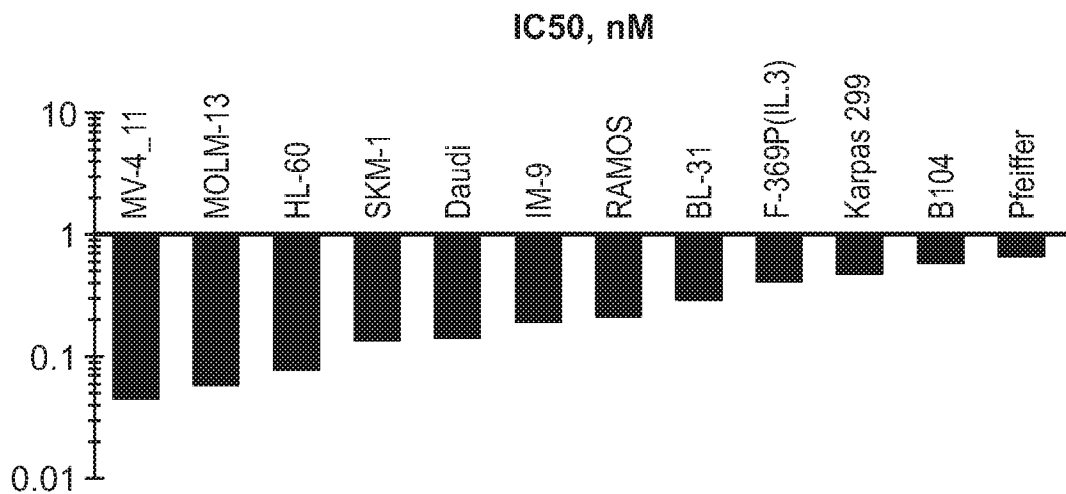


FIG. 1

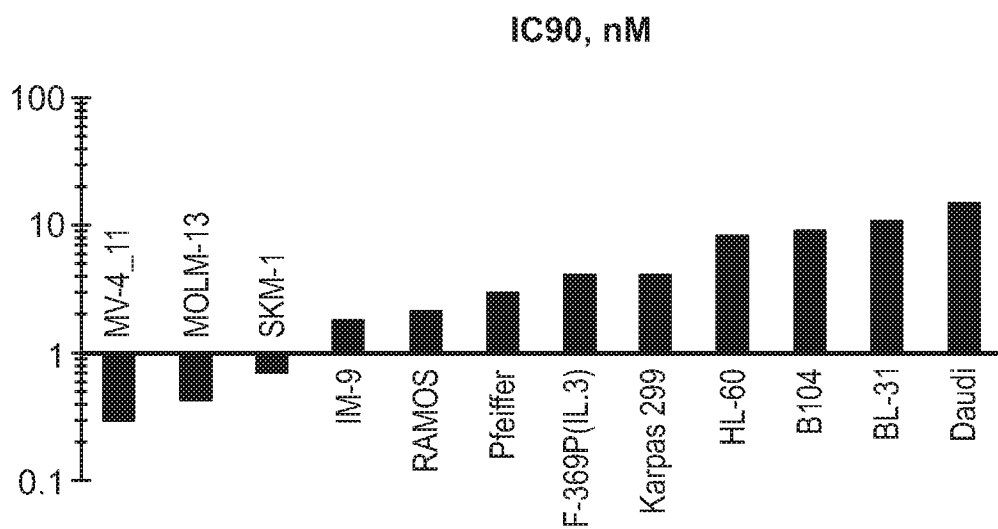


FIG. 2

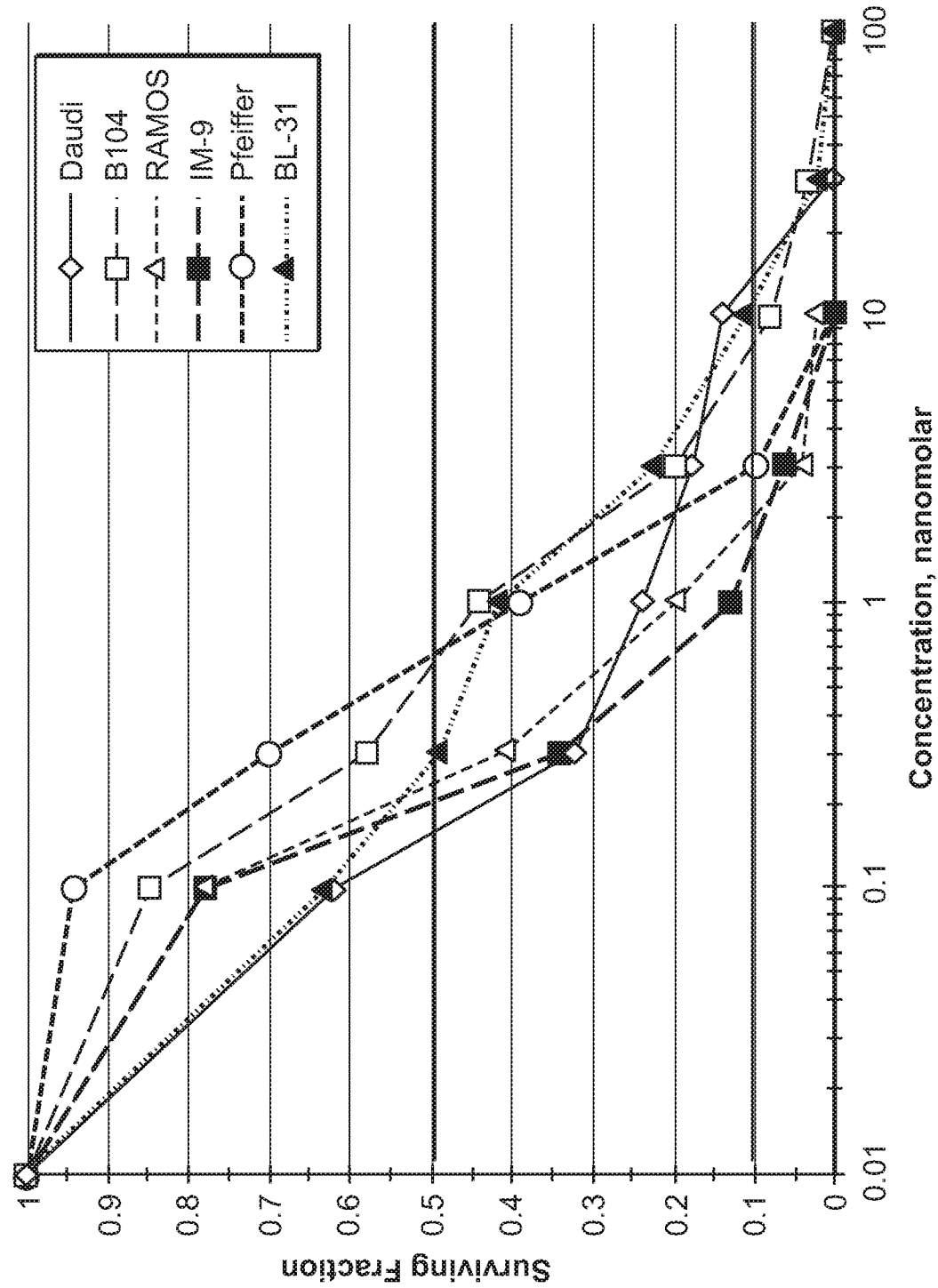


FIG. 3

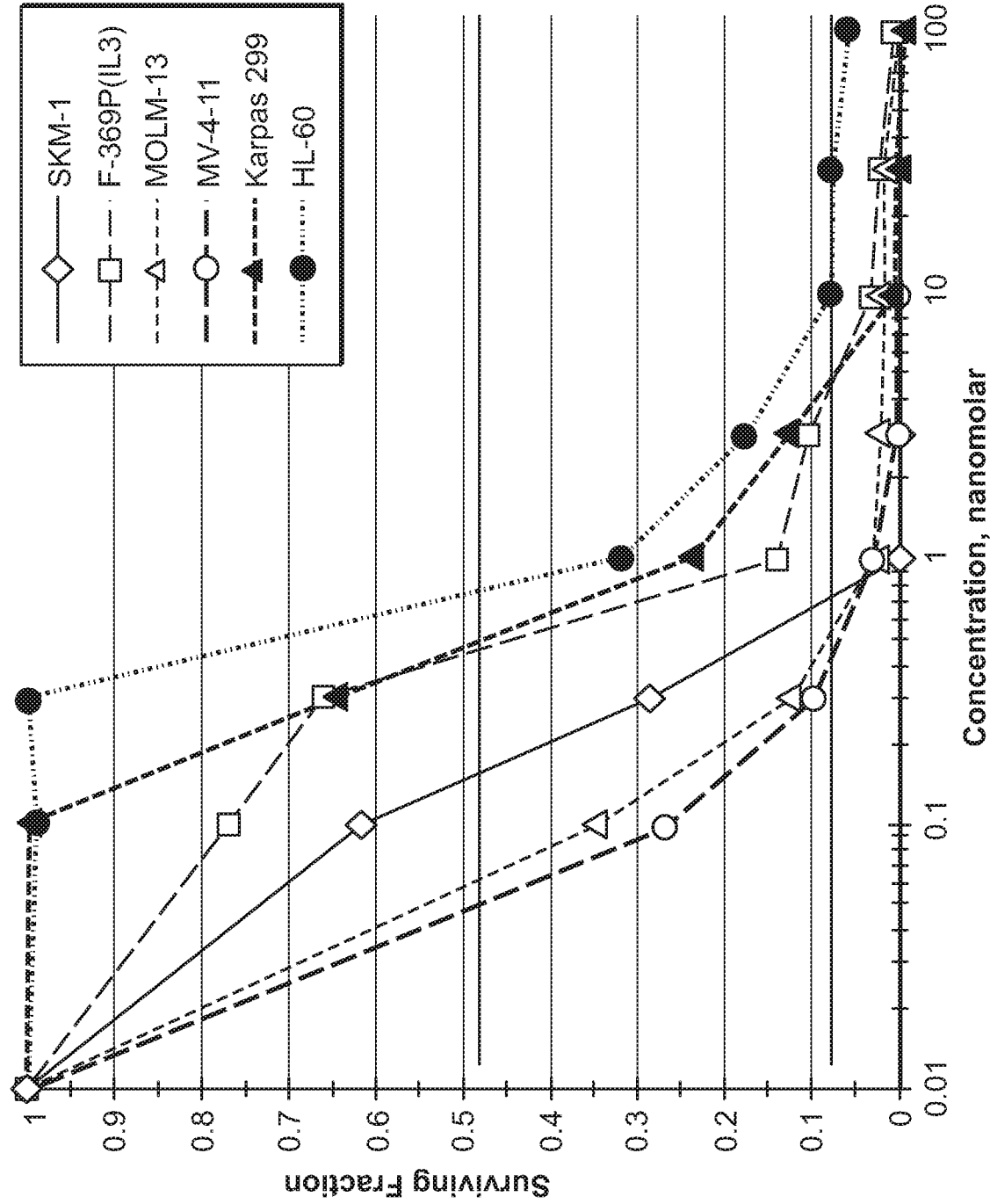


FIG. 4

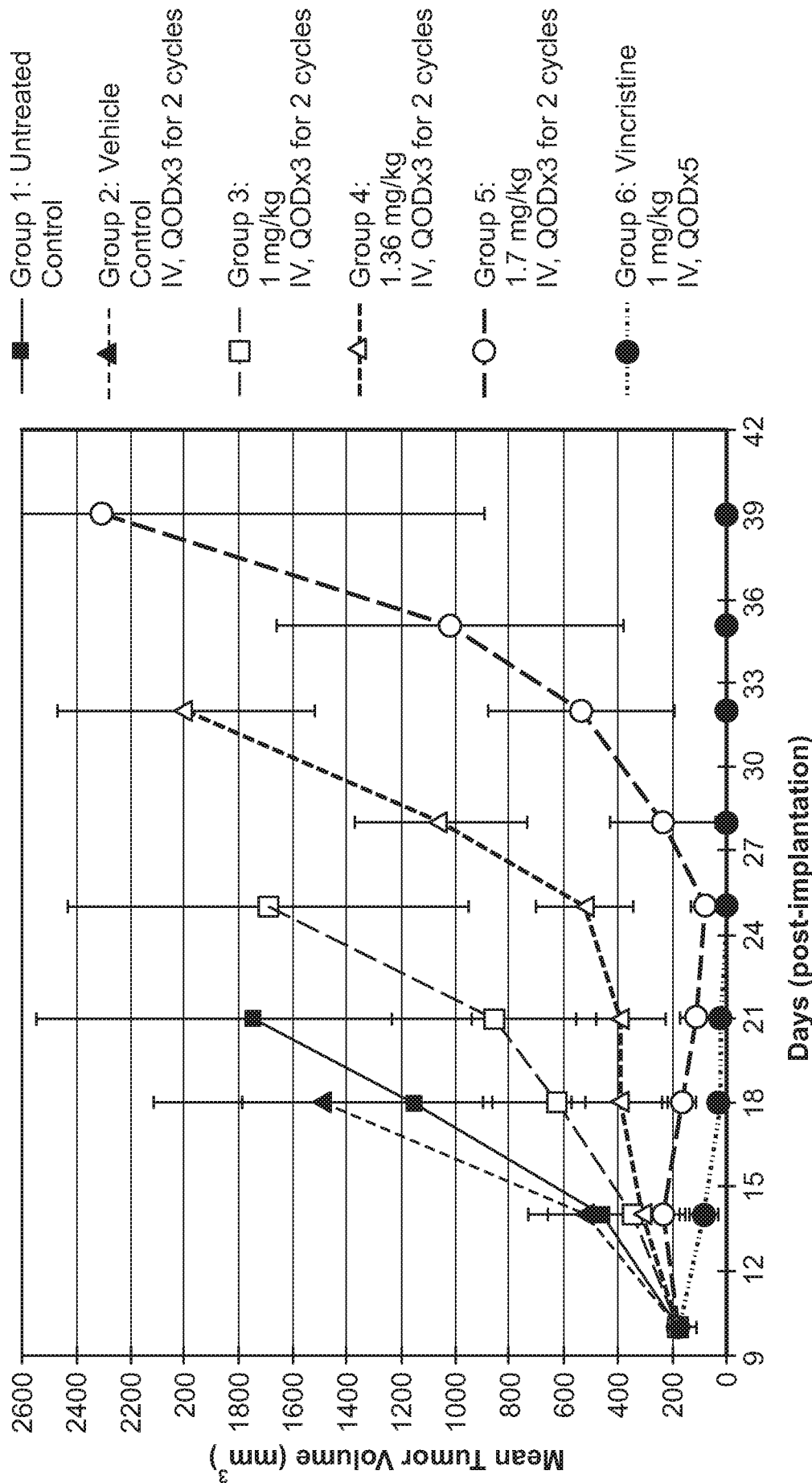


FIG. 5

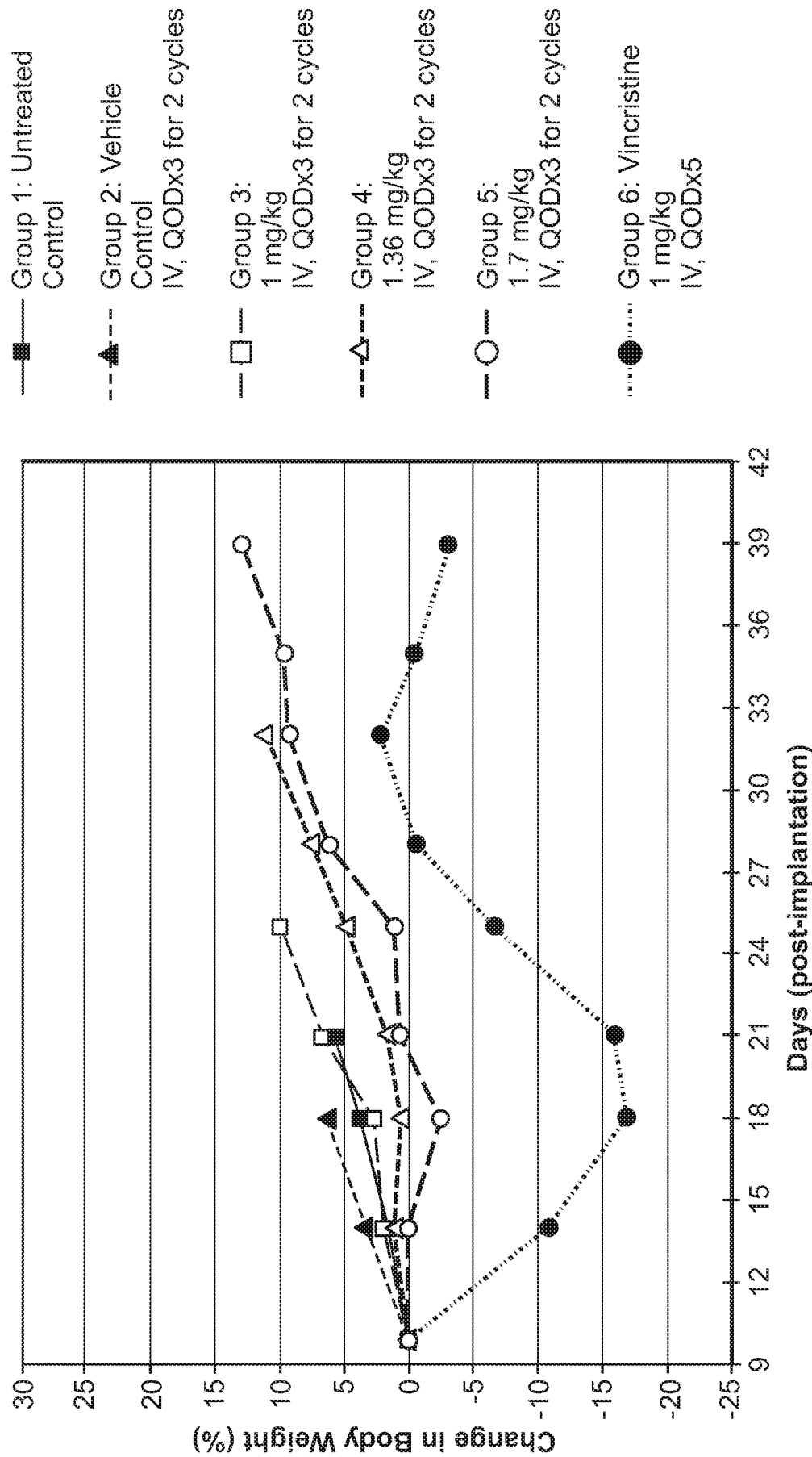


FIG. 6

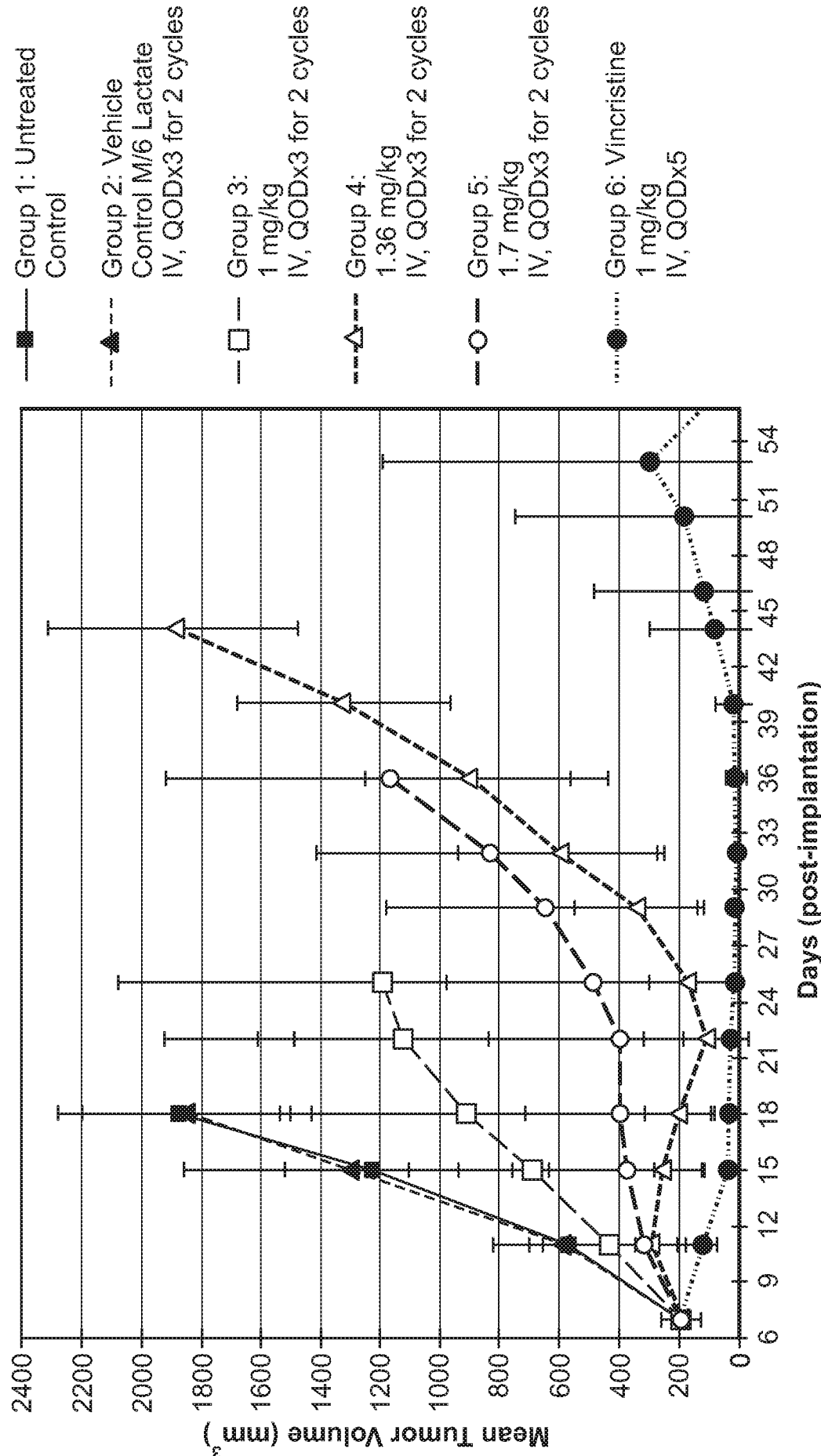


FIG. 7

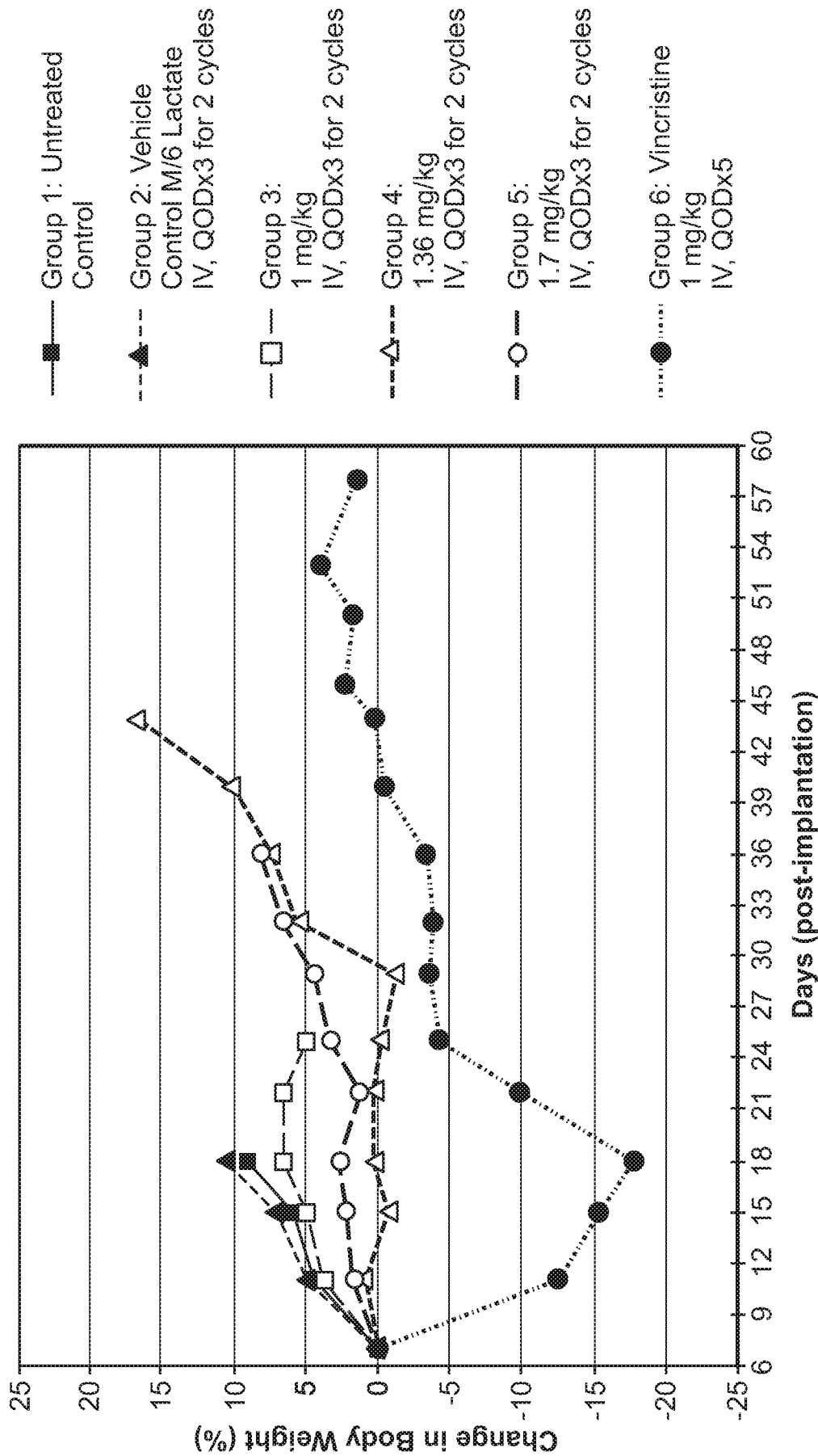


FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/45471

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 45/00; A61K 31/56 (2011.01)

USPC - 514/169

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC - 514/169

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/26; 514/182; 514/530; 514/573 (see search terms below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: topoisoemrase poisons, topoisoemrase I, pharmaceutical composition, administering, mammal, treatment, cancer, manufacture, medicament, dibenzo[c,h]1,6-naphthyridin-6-one, 2,3-methylenedioxy, hematological malignancies, leukemia, chronic lymphocytic leukemia, lymphoma. INTERNET se

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 196 205 A1 (LAVOIE et al.) 16 June 2010 (16.06.2010) para [0003]-[0005], [0008], [0012], [0026], [0130]	1-3, 9-12 and 19-23

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

21 November 2011 (21.11.2011)

Date of mailing of the international search report

12 DEC 2011

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/45471

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 4-8, 13-18 and 24-26
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on Protest

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