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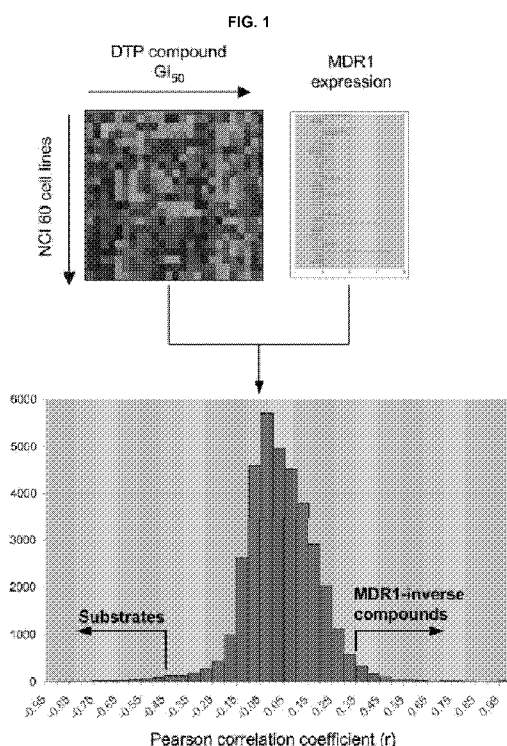
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(54) Title: **MDRI-INVERSE AGENTS**

(57) **Abstract:** A method for inhibiting the growth of drug resistant cells in a subject, comprising identifying a subject having drug resistant cells; and administering to the subject a compound or a pharmaceutically acceptable salt or ester thereof, that is a MDR1 -inverse agent. Also disclosed is a method of inhibiting cancer in a subject, comprising administering to the subject an antiproliferative agent, wherein the antiproliferative effect of the agent is potentiated by P-glycoprotein and the agent is a compound, or a pharmaceutically acceptable salt or ester thereof, that is a MDR1 -inverse agent.



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MDR1-INVERSE AGENTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No.
5 61/182,511, filed on May 29, 2009, which is herein incorporated by reference in its entirety.

FIELD

Disclosed herein are compounds useful for the treatment of drug resistant
10 cells.

BACKGROUND

Multidrug resistance (MDR) conferred by the ABC transporter family that includes MDR1 (ABCB1, P-glycoprotein, P-gp), presents a significant clinical
15 challenge for drug design and development. MDR1, for example, exhibits wide substrate specificity for structurally different drugs. This wide specificity mediates drug resistance to a variety of drugs, including Vinca alkaloids, anthracyclines, epipodophyllotoxins, taxols, actinomycin D, cardiac glycosides, immunosuppressive agents, glucocorticoids, and anti-HIV protease inhibitors. Since many drugs are
20 substrates of MDR1, its degree of expression and functionality directly affects the therapeutic effectiveness of these agents. In particular, the multidrug resistant phenotype of malignant cells is the main obstacle in the chemotherapeutic treatment of subjects having hyperproliferative disorders. MDR1 expression is well characterized in hematological malignancies, sarcomas, and other solid cancers, and
25 is frequently correlated with poor clinical response to chemotherapy for those tumors. Strategies employed to circumvent the reduced drug accumulation conferred by these poly-specific efflux transporters have relied heavily on the development of clinical inhibitors of MDR1 for concurrent administration with chemotherapeutics. Although a number of these inhibitors have shown promise *in*
30 *vitro*, translation to the clinic has taken longer than may have been expected,

possibly due to side effects caused by inhibition of endogenous function, and alternative strategies are required.

SUMMARY

5 According to one embodiment, disclosed herein is a method for inhibiting the growth of drug resistant cells in a subject, comprising identifying a subject having drug resistant cells; and

 administering to the subject a compound or a pharmaceutically acceptable salt or ester thereof, as described below in more detail.

10 According to another embodiment, disclosed herein is a method of inhibiting cancer in a subject, comprising administering to the subject an antiproliferative agent, wherein the antiproliferative effect of the agent is potentiated by P-glycoprotein and the agent is a compound, or a pharmaceutically acceptable salt or ester thereof, as described in more detail below.

15 In one aspect the compounds are particularly effective against cells that exhibit multidrug resistance. Accordingly treatment regimens employing the disclosed compounds typically involve first identifying a subject having a multidrug resistant disorder, such as a multidrug resistant tumor or infection. Certain examples of the compounds described above are not particularly cytotoxic, particularly to cells
20 that are not multidrug resistant. Moreover, in one embodiment the disclosed compounds effectively re-sensitize multidrug resistant cells to anti-proliferative agents that are substrates for an MDR transporter. Thus, in one aspect, the disclosed compounds are co-administered with another chemotherapeutic agent, such as an antibiotic or antineoplastic agent. In another embodiment the disclosed compounds
25 are both cytotoxic and render multidrug resistant cells susceptible to one or more additional chemotherapeutic agents by inhibiting an MDR transporter. Accordingly, also disclosed herein are treatment regimens and compositions formulated for combination therapy.

The foregoing and other objects, features, and advantages will become more apparent from the following detailed description, which proceeds with reference to the accompanying figures.

5

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Identification of candidate MDR-inverse compounds. DTP's public dataset, consisting of publicly available cytotoxicity (GI_{50}) profiles of candidate anticancer agents was screened using the mRNA expression pattern of Pgp (MDR1) (Szakacs et al., 2004). Merging of the two datasets (top panel) resulted in drug-gene pairs, giving a Pearson correlation coefficient (r) for each compound, and a distribution histogram for ~36,000 curated compounds (bottom panel). Negative correlation coefficients indicate that a given cytotoxic compound is less effective in the presence of Pgp (putative Pgp-substrates). Conversely, a small number of compounds that elicit positive Pearson values ($r \geq 0.3$) suggest that their toxicity is potentiated (rather than antagonized) by the presence of Pgp (putative MDR-inverse agents).

Figure 2. Dendrogram showing the average-linkage hierarchical clustering of 64 putative MDR-inverse compounds ($r \geq 0.4$). The distance matrix is derived from Tanimoto similarity indices (<http://pubchem.ncbi.nlm.nih.gov>). Numbers represent NSC codes. Black: compound not available for testing; green: confirmed MDR-inverse activity; red: lack of MDR-inverse activity; asterix (*): metal complex. Clusters of structurally related compounds where one or more analogs are highlighted by their core common.

25

Figure 3. Dendrogram showing the average-linkage hierarchical clustering of the 37 confirmed MDR1-inverse compounds. The distance matrix is derived from Tanimoto similarity indices. Numbers represent NSC codes. The two major clusters are colored green ("TSC-cluster") and yellow ("10580-cluster"). Pharmacophore models derived from the two sets are shown.

30

Figure 4. QSAR analysis of the thiosemicarbazone MDR-inverse compounds identified in the NCI DTP drug library. Scatter plot and comparison of the calculated and measured MDR-inverse ratios.

5 Figure 5. Self-organizing map-based (SOM) cluster analysis of the activity of the 22 DTP compounds verified to demonstrate MDR-inverse activity. SOM clustering of the DTP drug response data defines six major response categories: mitosis (M), membrane function (N), nucleic acid metabolism (S), metabolic stress and cell survival (Q), and two unexplored regions P and R. Each of these regions is
10 further divided into a total of 51 sub-regions. Larger hexagons (yellow) represent a greater number of compounds. Clusters represent the following compounds (1) NSC695331, NSC695333, (2) NSC697125, (3) NSC672036, (4) NSC673999, NSC713048, (5) NSC716765, (6) NSC641208, (7) NSC716766, NSC716768, (8) NSC43320, NSC73306, NSC693871, NSC693872, NSC697124, (9) NSC2924508,
15 (10) NSC168468, (11) NSC1580, (12) NSC356777, (13) NSC649816, 716772, (14) NSC710857. Red hexagon is the SOM cluster overlay of NSC4265, 1,10-phenanthroline.

Figure 6. Chelation alone is not sufficient to confer MDR-inverse activity **A**.
20 A number of coordination modes are possible for the thiosemicarbazone NSC73306 (left), the most likely being bidentate (middle) or tridentate (right). **B**. Solution color changes of NSC73306 indicating complexation with metal sulfate salts, L to R: NSC73306, NSC73306 + Fe²⁺, NSC73306 + Cu²⁺ and NSC73306 + Zn²⁺. **C**. ESI-MS (ES+) of NSC73306 (L, mw = 326.1 g mol⁻¹), and mixtures with metal ions (+II
25 oxidation state) in 1:1 MeOH:H₂O. The highest mass peak observed is shown, in each case corresponding to a 2:1 ligand:metal complex **D**. Compounds such as NSC632738 and NSC292408 that possess 1,10-phenanthroline ligands can dissociate to yield free 1,10-phenanthroline, capable of exerting its own MDR-inverse activity. KP772, a tris(1,10-phenanthroline)lanthanum(III) complex reported
30 to display MDR-inverse activity, that may also release phen. In contrast, the highly

[Ru(phen)₃] complex that does not release phen does not display MDR-inverse activity.

Figure 7. Table 1 lists examples of compounds identified as having MDR1-selective activity.

DETAILED DESCRIPTION

The following explanations of terms and methods are provided to better describe the present compounds, compositions and methods, and to guide those of ordinary skill in the art in the practice of the present disclosure. It is also to be understood that the terminology used in the disclosure is for the purpose of describing particular embodiments and examples only and is not intended to be limiting.

As used herein, the singular terms "a," "an," and "the" include plural referents unless context clearly indicates otherwise. Similarly, the word "or" is intended to include "and" unless the context clearly indicates otherwise. Also, as used herein, the term "comprises" means "includes." Hence "comprising A or B" means including A, B, or A and B.

Variables such as R, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, X, Y and Z, used throughout the disclosure are the same variables as previously defined unless stated to the contrary.

"Optional" or "optionally" means that the subsequently described event or circumstance can but need not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

The term "derivative" refers to a compound or portion of a compound that is derived from or is theoretically derivable from a parent compound.

"ABC transporters" are transporter proteins belonging to the ABC protein superfamily and are capable of, in their native, active, wild type form, extruding drugs from the cells expressing them. Herein, the term "ABC transporter" also covers mutant variants of the wild type proteins retaining at least one function of the wild type, even if lacking another.

The term "acyl" refers group of the formula $RC(O)-$ wherein R is an organic group.

The term "alkoxy" refers to a group of the formula $-OR$, wherein R is an organic group.

5 The term "alkyl" refers to a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, pentyl, hexyl, heptyl, octyl, decyl, tetradecyl, hexadecyl, eicosyl, tetracosyl and the like. A "lower alkyl" group is a saturated branched or unbranched hydrocarbon having from 1 to 10 carbon atoms.

10 The term "alkenyl" refers to a hydrocarbon group of 2 to 24 carbon atoms and structural formula containing at least one carbon-carbon double bond.

The term "alkynyl" refers to a hydrocarbon group of 2 to 24 carbon atoms and a structural formula containing at least one carbon-carbon triple bond.

15 The term "aliphatic" is defined as including alkyl, alkenyl, alkynyl, halogenated alkyl and cycloalkyl groups as described above. A "lower aliphatic" group is a branched or unbranched aliphatic group having from 1 to 10 carbon atoms.

20 The term "amine" or "amino" refers to a group of the formula $-NRR'$, where R and R' can be, independently, hydrogen or an alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, halogenated alkyl, or heterocycloalkyl group described herein.

The term "amide group" is represented by the formula $-C(O)NRR'$, where R and R' independently can be a hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, halogenated alkyl, or heterocycloalkyl group described herein.

25 "Carboxyl" refers to a $-COOH$ radical. Substituted carboxyl refers to $-COOR$ where R is aliphatic, heteroaliphatic, alkyl, heteroalkyl, or a carboxylic acid or ester.

30 The term "aryl" refers to any carbon-based aromatic group including, but not limited to, benzene, naphthalene, etc. The term "aromatic" also includes "heteroaryl group," which is defined as an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorous. The aryl

group can be substituted with one or more groups including, but not limited to, alkyl, alkynyl, alkenyl, aryl, halide, nitro, amino, ester, ketone, aldehyde, hydroxy, carboxylic acid, or alkoxy, or the aryl group can be unsubstituted.

5 The term "alkyl amino" refers to alkyl groups as defined above where at least one hydrogen atom is replaced with an amino group.

The term "co-administration" or "co-administering" refers to administration of the compound disclosed herein with at least one other therapeutic agent within the same general time period, and does not require administration at the same exact moment in time (although co-administration is inclusive of administering at the same exact moment in time). Thus, co-administration may be on the same day or on
10 different days, or in the same week or in different weeks.

The term "hydroxyl" is represented by the formula -OH . The term "alkoxy group" is represented by the formula -OR , where R can be an alkyl group, optionally substituted with an alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, halogenated
15 alkyl, or heterocycloalkyl group as described above.

The terms "halogenated alkyl" or "haloalkyl group" refer to an alkyl group as defined above with one or more hydrogen atoms present on these groups substituted with a halogen (F, Cl, Br, I).

The term "cycloalkyl" refers to a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not
20 limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. The term "heterocycloalkyl group" is a cycloalkyl group as defined above where at least one of the carbon atoms of the ring is substituted with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorous.

25 "Carbonyl" refers to a radical of the formula -C(O)- . Carbonyl-containing groups include any substituent containing a carbon-oxygen double bond (C=O), including acyl groups, amides, carboxy groups, esters, ureas, carbamates, carbonates and ketones and aldehydes, such as substituents based on -COR or -RCHO where R is an aliphatic, heteroaliphatic, alkyl, heteroalkyl, hydroxyl, or a secondary, tertiary,
30 or quaternary amine.

"Carboxyl" refers to a -COOH radical. Substituted carboxyl refers to -COOR where R is aliphatic, heteroaliphatic, alkyl, heteroalkyl, or a carboxylic acid or ester.

5 Multidrug resistance (MDR) refers to the ability of target cells and microorganisms, particularly cancer cells and mycobacterial cells, to resist the effects of different –often structurally and functionally unrelated– cytotoxic compounds. MDR can develop after sequential or simultaneous exposure to various drugs. MDR also can develop before exposure to many compounds to which a cell or microorganism may be found to be resistant.

10 Although MDR may be caused by a variety of factors, most commonly MDR is associated with overexpression of P-glycoprotein (P-gp). P-gp is a member of a superfamily of membrane proteins, termed adenosine triphosphate (ATP)-binding cassette (ABC) proteins, which behave as ATP-dependent transporters and/or ion channels for a wide variety of substrates. P-gp is a multiple transmembrane-
15 spanning glycoprotein. Transfection experiments with the P-gp gene (MDR1, or ABCB1) have demonstrated that P-gp confers MDR upon drug-sensitive tumor cells by providing an energy-dependent efflux pump that lowers the intracellular concentration of the cytotoxic agent, thereby allowing survival of the cell.

The term "neoplasm" refers to an abnormal cellular proliferation, which
20 includes benign and malignant tumors, as well as other proliferative disorders.

The term "pharmaceutically acceptable salt or ester" refers to salts or esters prepared by conventional means that include basic salts of inorganic and organic acids, including but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, malic acid, acetic
25 acid, oxalic acid, tartaric acid, citric acid, lactic acid, fumaric acid, succinic acid, maleic acid, salicylic acid, benzoic acid, phenylacetic acid, mandelic acid and the like. "Pharmaceutically acceptable salts" of the presently disclosed compounds also include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and from bases such as ammonia, ethylenediamine, N-methyl-glutamine, lysine, arginine, ornithine, choline, N,N'-
30 dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-

benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethylammonium hydroxide. These salts may be prepared by standard procedures, for example by reacting the free acid with a suitable organic or inorganic base. Any chemical compound recited in this specification may alternatively be administered as a pharmaceutically acceptable salt thereof. "Pharmaceutically acceptable salts" are also inclusive of the free acid, base, and zwitterionic forms. Descriptions of suitable pharmaceutically acceptable salts can be found in *Handbook of Pharmaceutical Salts, Properties, Selection and Use*, Wiley VCH (2002). When compounds disclosed herein include an acidic function such as a carboxy group, then suitable pharmaceutically acceptable cation pairs for the carboxy group are well known to those skilled in the art and include alkaline, alkaline earth, ammonium, quaternary ammonium cations and the like. Such salts are known to those of skill in the art. For additional examples of "pharmacologically acceptable salts," see Berge et al., *J. Pharm. Sci.* 66:1 (1977).

"Pharmaceutically acceptable esters" includes those derived from compounds described herein that are modified to include a hydroxy or a carboxyl group. An in vivo hydrolysable ester is an ester, which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C₁₋₆ alkoxymethyl esters for example methoxy-methyl, C₁₋₆ alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃₋₈ cycloalkoxycarbonyloxyC₁₋₆ alkyl esters for example 1-cyclohexylcarbonyl-oxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆ alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyl-oxyethyl which may be formed at any carboxy group in the compounds.

An in vivo hydrolysable ester containing a hydroxy group includes inorganic esters such as phosphate esters and α -acyloxyalkyl ethers and related compounds which as a result of the in vivo hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted

benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters),
dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give
carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on
benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a
5 methylene group to the 3- or 4-position of the benzoyl ring.

For therapeutic use, salts of the compounds are those wherein the counter-ion
is pharmaceutically acceptable. However, salts of acids and bases which are non-
pharmaceutically acceptable may also find use, for example, in the preparation or
purification of a pharmaceutically acceptable compound.

10 The pharmaceutically acceptable acid and base addition salts as mentioned
hereinabove are meant to comprise the therapeutically active non-toxic acid and base
addition salt forms which the compounds are able to form. The pharmaceutically
acceptable acid addition salts can conveniently be obtained by treating the base form
with such appropriate acid. Appropriate acids comprise, for example, inorganic acids
15 such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric,
phosphoric and the like acids; or organic acids such as, for example, acetic,
propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic
(i.e. butanedioic acid), maleic, fumaric, malic (i.e. hydroxybutanedioic acid),
tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic,
20 cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids. Conversely said
salt forms can be converted by treatment with an appropriate base into the free base
form.

The compounds containing an acidic proton may also be converted into their
non-toxic metal or amine addition salt forms by treatment with appropriate organic
25 and inorganic bases. Appropriate base salt forms comprise, for example, the
ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium,
potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the
benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids
such as, for example, arginine, lysine and the like.

The term "addition salt" as used hereinabove also comprises the solvates which the compounds described herein are able to form. Such solvates are for example hydrates, alcoholates and the like.

The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds are able to form by reaction between a basic nitrogen of a compound and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyl iodide or benzyl iodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

It will be appreciated that the compounds described herein may have metal binding, chelating, complex forming properties and therefore may exist as metal complexes or metal chelates.

Some of the compounds described herein may also exist in their tautomeric form.

The term "subject" includes both human and veterinary subjects.

"Transport protein" refers to a protein that acts to remove chemotherapeutic substances from cells. Examples of transport proteins include, without limitation, P-glycoprotein, the protein product of the MDR1 gene. Expression of such transport proteins confers resistance to numerous chemotherapeutic agents and sometimes entire classes of chemotherapeutics, including Vinca alkaloids, anthracyclines, epipodophyllotoxins, actinomycin D and taxanes. P-glycoprotein is over-expressed in certain chemotherapy resistant tumors and is upregulated during disease progression following chemotherapy in other malignancies. MRPs, also belonging to the ABC family, confer a multidrug resistance phenotype that includes many natural product drugs, but is distinct from the resistance phenotype associated with P-gp. In addition to P-gp and the MRPs there may be other transporters that are involved in cytotoxic drug resistance. In the case of natural product drugs, resistant

cell lines have been described that display a multidrug resistant phenotype associated with a drug accumulation deficit, but do not overexpress P-gp or any of the MRPs.

"Treatment" refers to a therapeutic intervention that ameliorates a sign or symptom of a disease or pathological condition after it has begun to develop. As used herein, the term "ameliorating," with reference to a disease or pathological condition, refers to any observable beneficial effect of the treatment. The beneficial effect can be evidenced, for example, by a delayed onset of clinical symptoms of the disease in a susceptible subject, a reduction in severity of some or all clinical symptoms of the disease, a slower progression of the disease, an improvement in the overall health or well-being of the subject, or by other parameters well known in the art that are specific to the particular disease. The phrase "treating a disease" refers to inhibiting the full development of a disease or condition, for example, in a subject who is at risk for a disease such as cancer, particularly a metastatic cancer. By the term "coadminister" is meant that each of at least two compounds be administered during a time frame wherein the respective periods of biological activity overlap. Thus, the term includes sequential as well as coextensive administration of two or more drug compounds. "Treating multidrug resistance" means increasing or restoring sensitivity of multidrug resistant cells to therapeutic agents. Treating multidrug resistance also may include inhibiting the development of multidrug resistance in nonresistant cells.

The term "prodrug" also is intended to include any covalently bonded carriers that release a disclosed compound or a parent thereof *in vivo* when the prodrug is administered to a subject. Since prodrugs often have enhanced properties relative to the active agent pharmaceutical, such as, solubility and bioavailability, the compounds disclosed herein can be delivered in prodrug form. Thus, also contemplated are prodrugs of the presently claimed compounds, methods of delivering prodrugs and compositions containing such prodrugs. Prodrugs of the disclosed compounds typically are prepared by modifying one or more functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to yield the parent compound. In

particular, ester prodrugs are specifically contemplated herein. Similarly, prodrugs include compounds having an amino or sulfhydryl group functionalized with any group that is cleaved to yield the corresponding free amino or free sulfhydryl group. Examples of prodrugs include, without limitation, compounds having a hydroxy,
5 amino and/or sulfhydryl group acylated with an acetate, formate, or benzoate group.

Protected derivatives of the disclosed compounds also are contemplated. The term "protecting group" or "blocking group" refers to any group that when bound to a functional group prevents or diminishes the group's susceptibility to reaction. "Protecting group" generally refers to groups well known in the art which
10 are used to prevent selected reactive groups, such as carboxy, amino, hydroxy, mercapto and the like, from undergoing undesired reactions, such as nucleophilic, electrophilic, oxidation, reduction and the like. The terms "deprotecting," "deprotected," or "deprotect," as used herein, are meant to refer to the process of removing a protecting group from a compound.

15 It is understood that substituents and substitution patterns of the compounds described herein can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art and further by the methods set forth in this disclosure. Reference will now be made in detail to the present preferred embodiments.

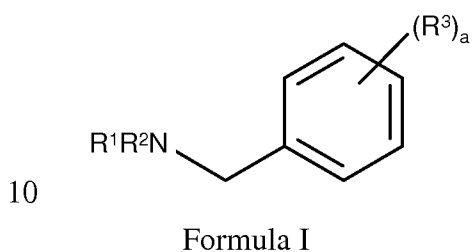
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I. Compounds having MDR-inverse activity

The compounds disclosed herein exploit, rather than suppress, Pgp function to induce cytotoxicity. Such "MDR-inverse compounds" target multidrug resistant cycling cells, avoiding side effects associated with the damage of resting cells that
25 constitutively express Pgp. It has been determined that a positive correlation between a compound's cytotoxicity profile and the expression of Pgp in the NCI-60 cell panel may be the result of a causal interaction, where the activity of Pgp sensitizes the cell to the cytotoxicity of the compound. In one embodiment, possible MDR-inverse compounds are those whose cytotoxicity profile shows positive
30 correlation (Pearson correlation coefficient $r \geq 0.3$) to the mRNA expression of MDR1 in the NCI60 panel.

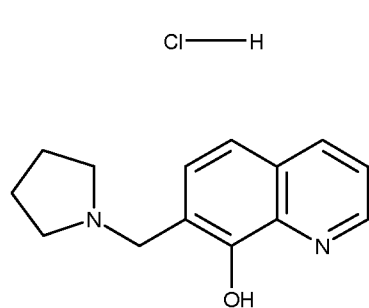
Disclosed herein are drug compounds that have MDR-inverse activity and thus are effective against multidrug-resistant cells. Examples of the disclosed compounds have been found to have, *inter alia*, efficacy in directly treating multidrug resistant cells, rendering multidrug resistant cells susceptible to other
 5 chemotherapeutics and in some instances reversing multidrug resistance.

One group of MDR1-inverse compounds, or a pharmaceutically acceptable salt or ester thereof, are represented by the formula:

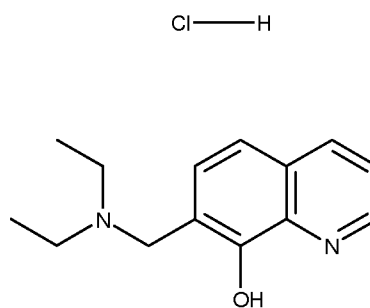


wherein R¹ and R² are each independently H, alkyl (particularly lower alkyl), cycloalkyl, aryl, or substituted alkyl, or R¹ and R² together with the N form a
 15 heterocyclic ring such as a pyrrolidinyl, pyrrolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperziny, indolinyl, morpholinyl, pyrrolyl, pyrazolyl, or pyrazinyl;
 R³ is alkyl (particularly lower alkyl), substituted alkyl, alkyl amino, hydroxyl, amino, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl; and
 a is 0 to 5, with the proviso that the following compounds are not included

20

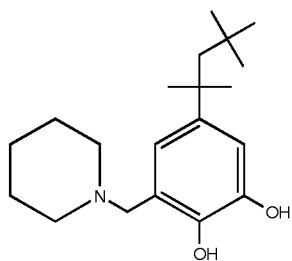


NSC693871,



NSC693872,

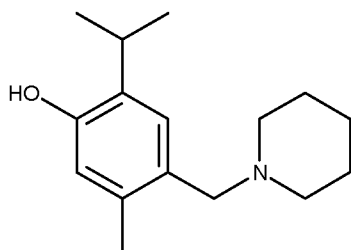
or



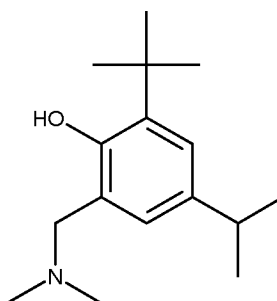
NSC10580.

Particular examples of compounds of formula I are listed below:

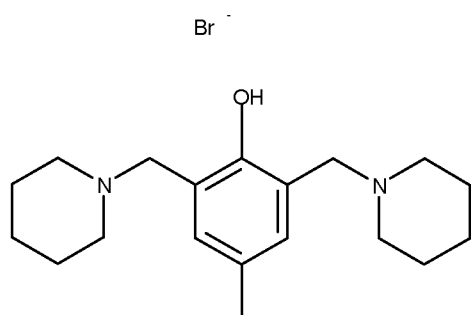
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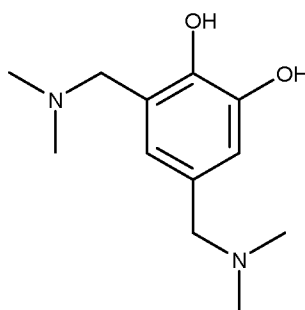
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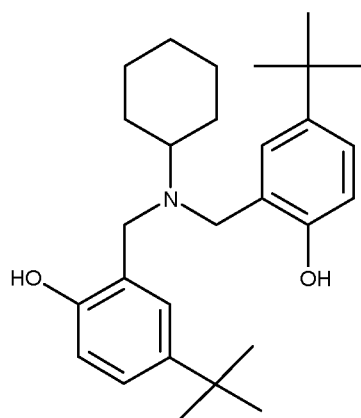
NSC21518



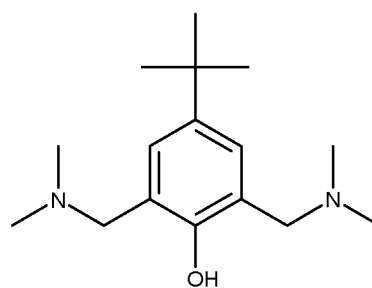
10 NSC37881



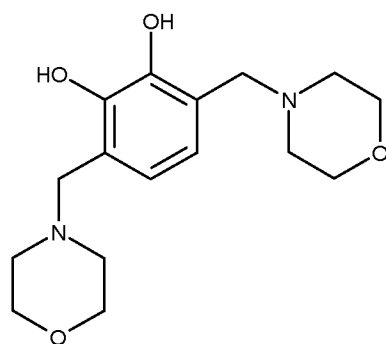
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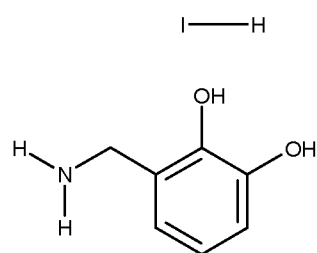
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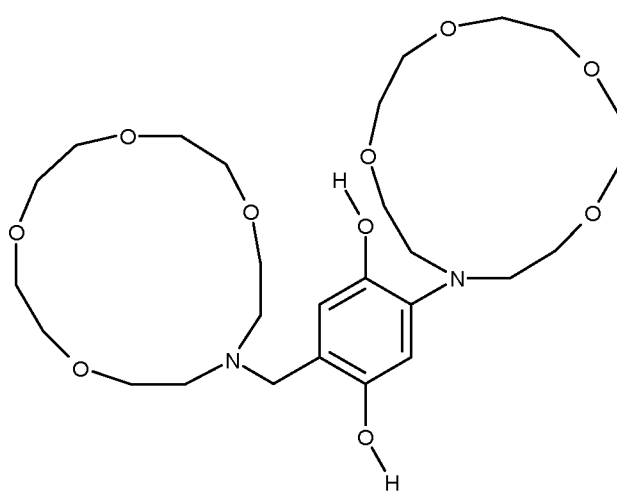
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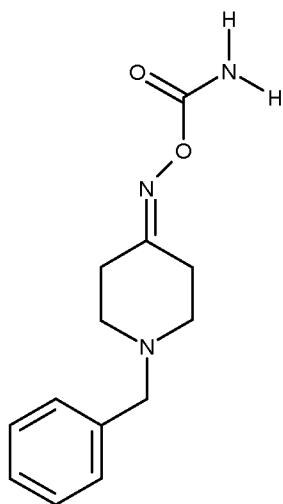
5 NSC85459



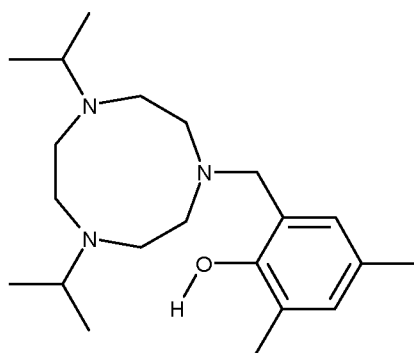
NSC329100



NSC653043



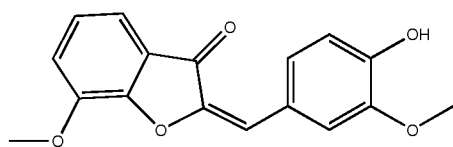
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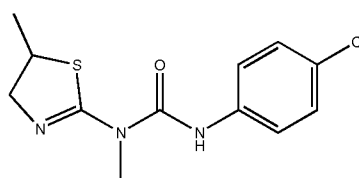
5 NSC696893

Lanthanoid metal(s) complexed to bidentate 1,10-phenanthroline or 2,2'-bipyridyl ligands are further examples of MDR1-inverse agents.

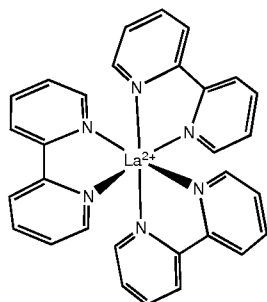
10 Additional MDR1-inverse agents are shown below:



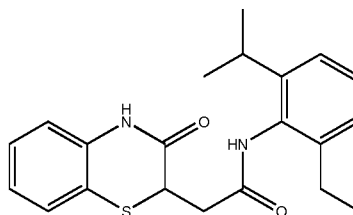
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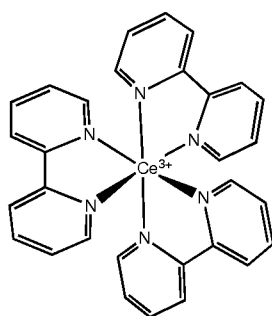
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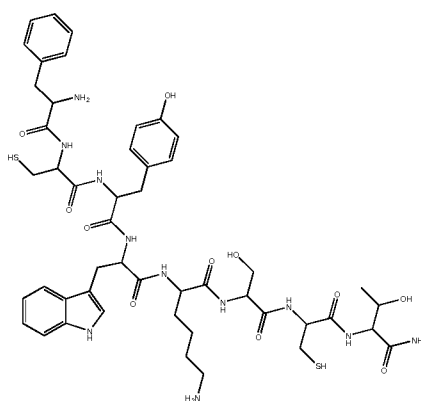
NSC632736



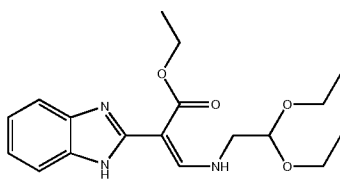
NSC632955



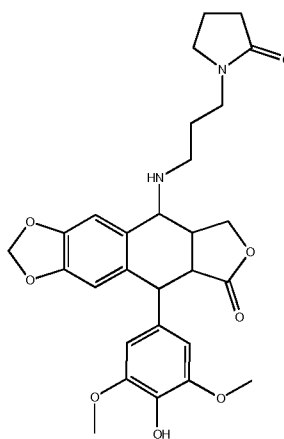
5 NSC632733



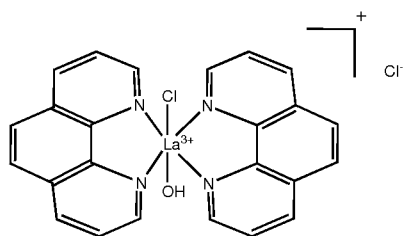
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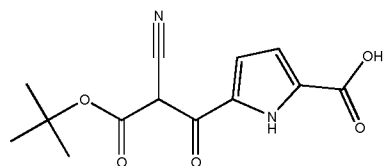
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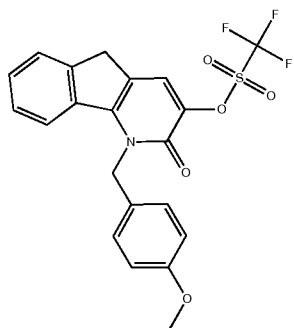
NSC651859



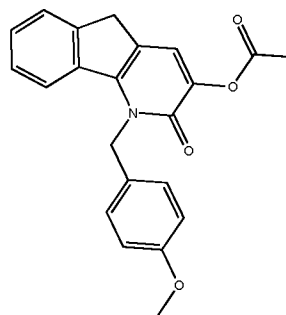
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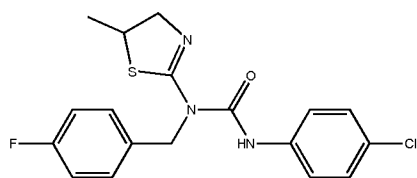
NSC693046



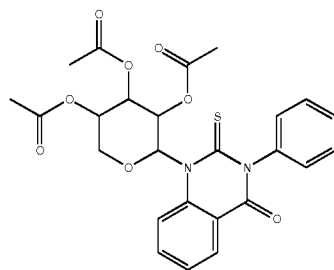
5 NSC705305



NSC705301

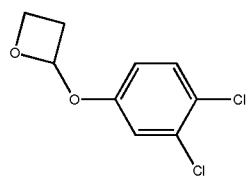


NSC672036

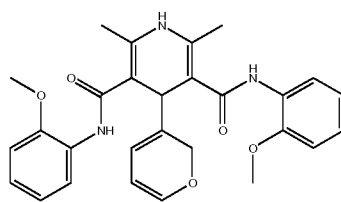


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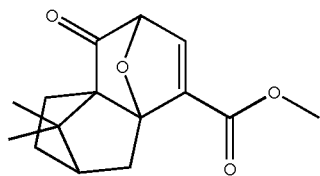
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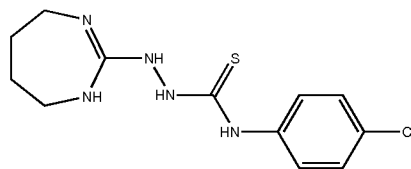
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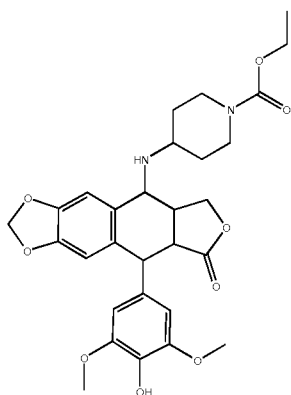
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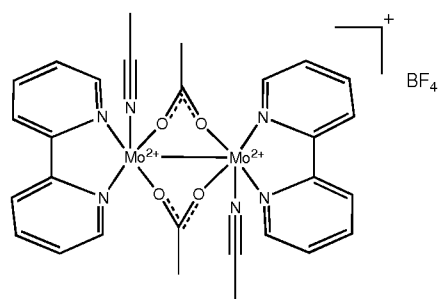
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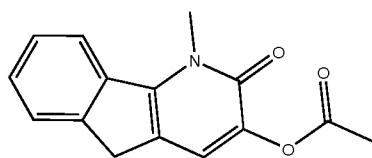
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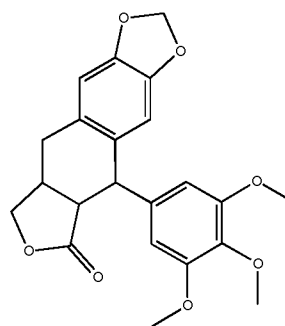
5 NSC653864



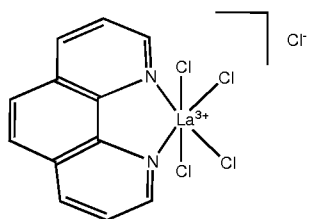
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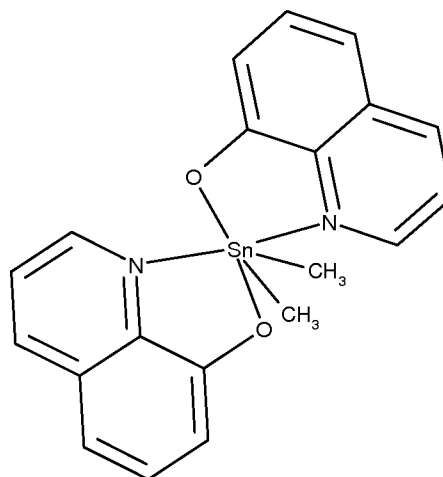
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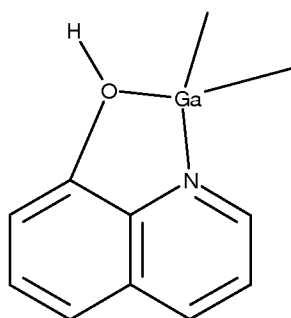
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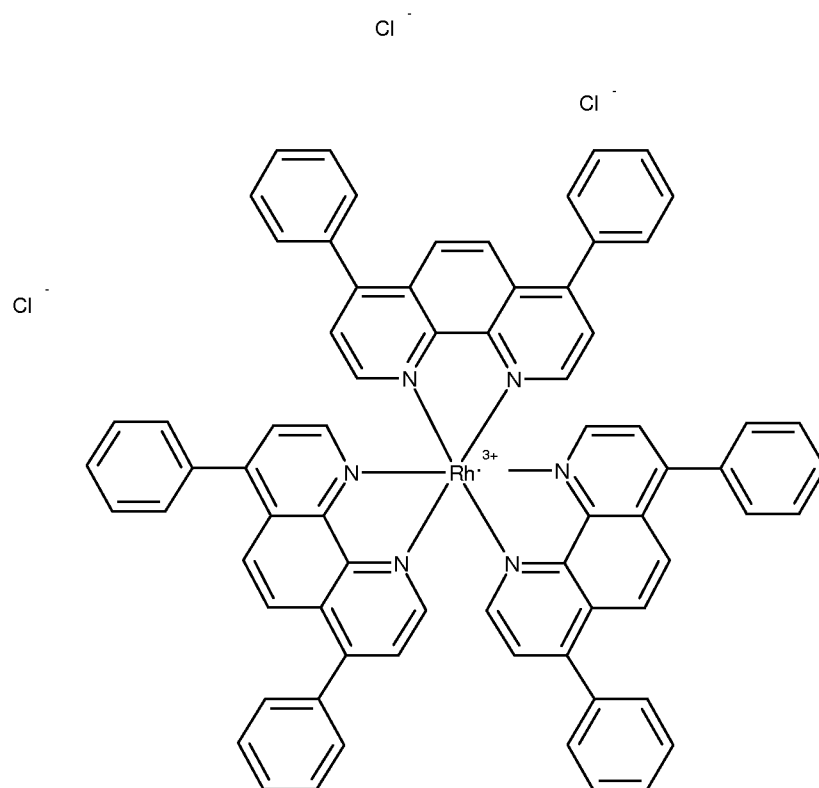


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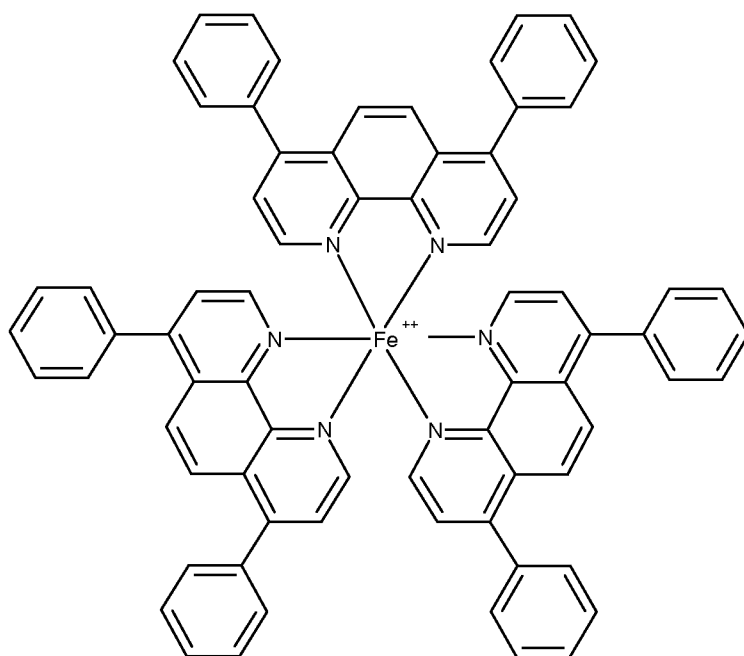


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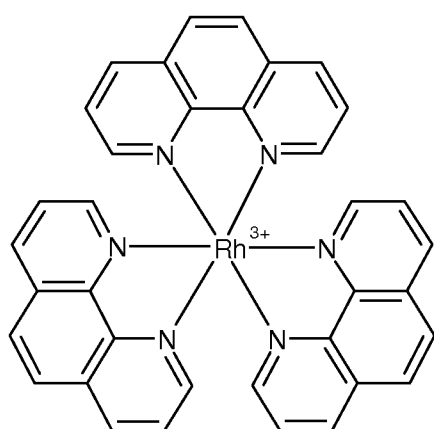
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NSC619179

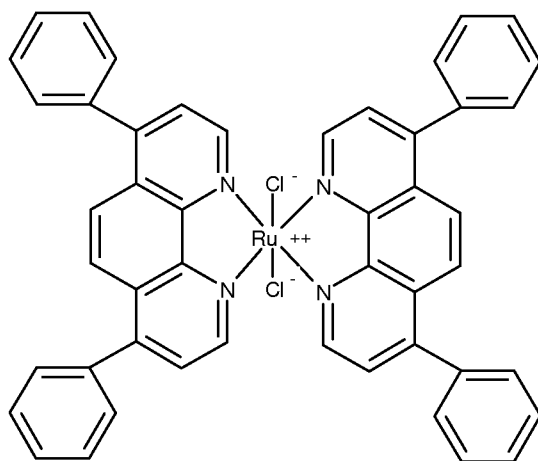
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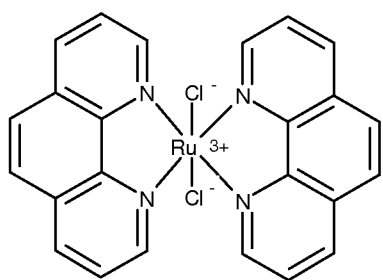
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5

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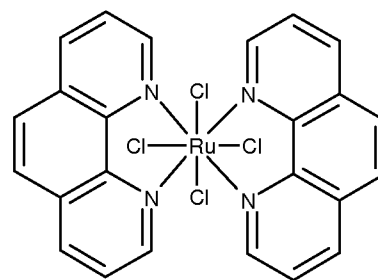


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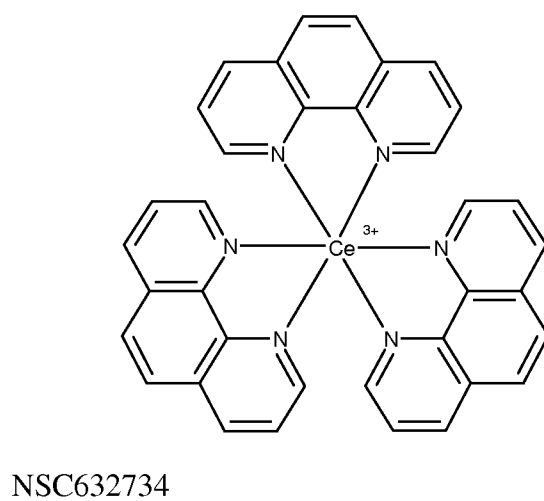
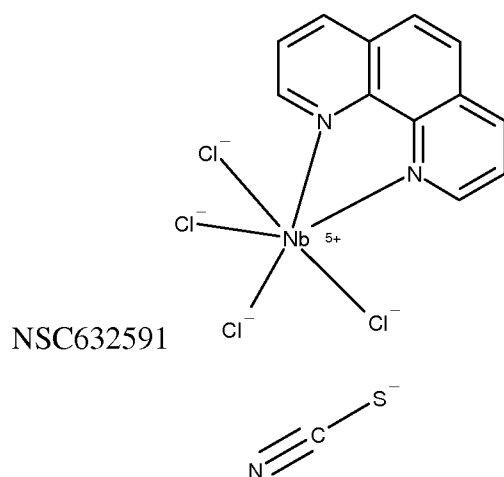
Cl⁻

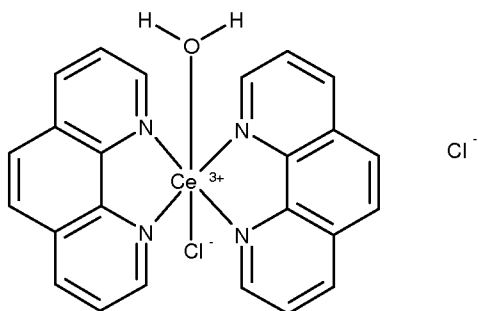
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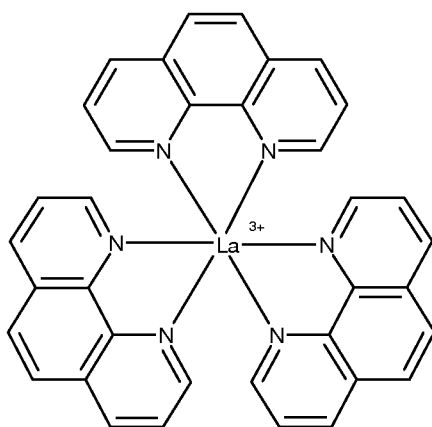
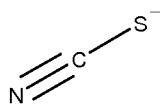


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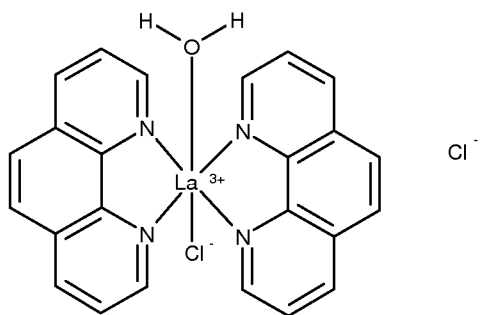




NSC632735



NSC632737



5

NSC632738

Among the metal complex compounds listed above, the chelating ligands alone may possess response profiles similar to their metal chelates indicating that the active metal complexes may serve as carriers for chelators, which themselves are the active drug molecules. While chelation is probably key to the cytotoxicity of at least a subset of the MDR-inverse compounds disclosed herein, data presented in Figure 6 indicate that metal chelation alone is not sufficient for Pgp potentiated activity. Since metal complexes were as active as the ligands alone (Figure 6), chelates may serve as chaperones facilitating free diffusion of the ligands into the cells. It appears that evasion of Pgp mediated efflux as well as the ability to chelate metals are necessary, if not sufficient requirements for the MDR-inverse activity of the chelator compounds. Dissociation of the complexes within the cells leading to the release of the free ligand and MDR-inverse activity may be related to reactive oxygen species generated by redox cycling. Taken together, it appears that the target of the MDR-inverse compounds may not be Pgp *per se*. Multidrug resistant cells become hypersensitive to MDR-inverse agents in proportion to the increased Pgp function, which probably reveals a downstream target in the cells. The paradoxical vulnerability uncovered by the MDR-inverse compounds may be linked to the efflux of an endogenous substrate providing e.g. redox-resistance, to the influence of Pgp on membrane lipid composition, or to other, Pgp-related metabolic changes that characterize MDR cells.

Additional potential MDR-inverse compounds are listed below in Table A.

Table A

Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation
688241	0.99997	654275	0.772805	665338	0.603408
165528	0.999511	660031	0.76579	654948	0.599645
176656	0.998687	688249	0.760533	658236	0.599381
655253	0.990908	601904	0.754405	627173	0.592019
668557	0.985748	659221	0.745624	673999	0.591147
661908	0.983992	661900	0.74101	650975	0.590699
662142	0.981768	656071	0.731994	682721	0.590126
689202	0.979283	662382	0.730935	695333	0.584867
664243	0.975636	664001	0.722093	672072	0.579556
663624	0.966291	689209	0.716768	320656	0.573866
662137	0.965593	683137	0.713949	697538	0.571486
698233	0.964855	694667	0.703766	652566	0.565951
640235	0.955947	655503	0.701704	631309	0.565519
660854	0.947623	715277	0.692264	631669	0.564553
675262	0.939671	695330	0.689883	43320	0.560712
661242	0.936973	661111	0.683793	652280	0.558234
684431	0.935528	693871	0.681029	720611	0.554275
663007	0.906376	648232	0.678319	650044	0.553916
663547	0.903811	669171	0.662893	681781	0.552688
699386	0.902281	668902	0.662752	691225	0.551109
101335	0.888607	663333	0.656593	672027	0.549446
648409	0.873171	688253	0.653379	640164	0.548647
718600	0.872361	254668	0.646183	646123	0.548424
159953	0.865468	720612	0.636104	617147	0.545763
85242	0.821712	617041	0.608211	631062	0.544992
168670	0.811966	160040	0.605381	39688	0.543808

Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation
78118	0.543465	657422	0.518181	662135	0.477129
662448	0.542791	716772	0.516341	660339	0.476207
658891	0.542541	685680	0.512669	679534	0.475093
28427	0.540374	73306	0.511215	709976	0.474818
635310	0.539624	696459	0.510565	679278	0.472991
665885	0.536232	631310	0.510021	643810	0.472159
697125	0.535806	681055	0.508745	632736	0.471322
656993	0.534734	662794	0.508509	649816	0.469699
661110	0.534672	645257	0.508297	632955	0.469645
637446	0.532755	676722	0.507127	629222	0.469186
86715	0.532288	665724	0.506564	631817	0.46858
665294	0.532283	676911	0.505435	672959	0.467438
617963	0.531712	716765	0.504093	673294	0.466984
649424	0.530937	646285	0.503142	697129	0.466266
688238	0.53018	675810	0.501244	636330	0.464807
698794	0.529344	665730	0.501205	691808	0.464435
632731	0.527683	651042	0.498062	698231	0.463848
698194	0.527114	702986	0.495557	697124	0.463633
665867	0.526788	657814	0.495541	103005	0.463283
665865	0.526562	702985	0.49402	624478	0.462112
688218	0.525085	645331	0.493574	632733	0.461092
696572	0.523701	635540	0.492388	697574	0.459087
716768	0.52295	661822	0.490417	623069	0.459056
670009	0.519692	662824	0.487363	653814	0.458277
649973	0.51946	698964	0.486692	683505	0.458206
644576	0.518771	13875	0.485815	665859	0.457985
669316	0.518753	168468	0.483849	674626	0.457358
695327	0.518416	716766	0.480799	659488	0.457238

Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation
685288	0.457082	697128	0.434971	617278	0.424132
674627	0.45645	662446	0.434656	667277	0.423922
693336	0.453791	671123	0.434223	617961	0.422953
654278	0.453631	648848	0.434173	672036	0.422256
626626	0.450856	662452	0.433942	692419	0.421785
292408	0.450681	694525	0.43186	637410	0.421366
662449	0.450597	697678	0.431396	639743	0.420494
662125	0.449886	672099	0.430846	629783	0.418101
620678	0.448955	617259	0.43072	647774	0.41783
642581	0.44883	651700	0.430024	626670	0.417813
681602	0.448816	651859	0.4299	629779	0.417666
633657	0.448069	697137	0.429661	634739	0.417402
693872	0.447442	641208	0.429287	617161	0.417353
621481	0.447005	113112	0.428717	640643	0.417184
627450	0.445442	652255	0.428248	641613	0.417105
697120	0.44337	632738	0.428139	635977	0.416942
644868	0.443098	662132	0.427953	620677	0.416938
641814	0.442007	646208	0.427549	667276	0.41575
681125	0.44042	652771	0.426804	636097	0.415475
632849	0.439524	693046	0.426325	647656	0.415469
710857	0.438493	650296	0.426213	636111	0.415295
695331	0.438282	705301	0.425571	662579	0.414077
694563	0.43797	699123	0.425224	677374	0.412507
603443	0.437258	651816	0.42515	624967	0.41184
682716	0.437125	697135	0.425061	713048	0.411138
646796	0.436532	647574	0.424391	347512	0.41094
663653	0.43633	658339	0.424239	669341	0.4109
646367	0.435702	625216	0.424227	10580	0.410583

Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation
629580	0.408559	716771	0.399927	622427	0.388046
654724	0.408326	658237	0.3999	641199	0.388024
653864	0.408324	141586	0.397652	681114	0.38728
165839	0.406611	674210	0.396701	407286	0.386841
672071	0.406525	641074	0.396501	639912	0.385457
647050	0.406127	669446	0.396437	641617	0.385294
115549	0.405965	695066	0.396073	657181	0.38489
716193	0.405937	681112	0.395378	677238	0.38473
697920	0.405823	688248	0.394631	634740	0.384714
640887	0.405311	625349	0.39365	605762	0.384402
650031	0.404751	665892	0.393588	654636	0.383716
632953	0.404268	647124	0.393453	635533	0.383649
619877	0.404166	688940	0.393414	648638	0.383467
252841	0.403819	675881	0.393074	615425	0.381879
293556	0.403601	637672	0.392924	641604	0.381135
639900	0.403555	686335	0.392631	658857	0.380652
639906	0.403541	697130	0.392559	691100	0.380238
356777	0.402181	645542	0.392509	651653	0.380137
632591	0.402145	645669	0.392097	653454	0.379919
675863	0.401632	697881	0.391757	677207	0.379109
693630	0.401422	665691	0.391031	647110	0.378943
688942	0.401233	716097	0.3904	719214	0.378271
627542	0.40103	650977	0.390057	636672	0.37808
672068	0.400682	663618	0.389885	692027	0.378059
622927	0.400316	685826	0.389825	654726	0.37794
666998	0.400246	627451	0.389488	666659	0.377862
666715	0.400018	693326	0.389182	687141	0.377548
682718	0.40001	639619	0.389117	653840	0.376466

Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation
689626	0.376249	651667	0.36448	648072	0.357859
673117	0.37621	641288	0.364271	663627	0.357844
642037	0.375937	371168	0.364254	648264	0.357631
319951	0.375035	687585	0.364158	675974	0.357518
715186	0.373227	356903	0.364125	683238	0.357009
706806	0.372928	675877	0.363946	688114	0.356966
698129	0.372507	686397	0.363717	668878	0.356888
692760	0.372289	358873	0.363581	657004	0.356865
657576	0.371906	645796	0.363311	711994	0.356755
638744	0.371646	634373	0.36301	20514	0.356204
617966	0.371478	709973	0.362209	697132	0.355846
693931	0.370866	687109	0.361934	658217	0.355556
661168	0.370486	677228	0.361864	629374	0.354769
310618	0.369851	638436	0.361701	2053	0.354767
632038	0.369397	684733	0.361666	650826	0.354576
647115	0.368919	635558	0.360758	715729	0.354507
633925	0.36877	672035	0.360628	311432	0.35415
647575	0.368498	696564	0.360384	672880	0.353962
612238	0.368396	676569	0.360351	680475	0.353953
677074	0.368335	690229	0.360056	709979	0.353881
618312	0.368211	698252	0.359758	713288	0.353774
625019	0.367531	635148	0.359578	665860	0.353586
666764	0.367516	683497	0.35947	646339	0.353575
624795	0.366876	50922	0.359207	709974	0.35352
666293	0.36656	668495	0.358904	627452	0.353456
648854	0.366121	617959	0.358645	635563	0.35326
676920	0.365368	688948	0.358508	615537	0.352755
709975	0.36529	117028	0.357898	672102	0.35258

Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation
672094	0.35258	683594	0.347588	647127	0.343708
672110	0.35258	685005	0.347554	676321	0.343612
56845	0.35255	629915	0.347271	715711	0.343367
624434	0.352511	672881	0.346888	627577	0.343269
669812	0.35245	670115	0.346743	692754	0.342966
655280	0.35244	622938	0.346632	663304	0.342569
697131	0.352383	693329	0.346544	632735	0.34209
607301	0.352332	657924	0.346539	649238	0.342061
163133	0.351666	641139	0.346349	632803	0.341838
691980	0.351614	698459	0.346243	695304	0.341752
667536	0.35129	621343	0.346072	630964	0.341275
667000	0.351263	715072	0.346063	660151	0.341217
627025	0.351263	665362	0.346057	637719	0.341137
635543	0.351242	635534	0.345767	20138	0.340866
642576	0.351204	672070	0.345739	673100	0.340411
631674	0.351065	672074	0.345739	676737	0.340342
703011	0.35102	672077	0.345739	674199	0.340266
679285	0.350476	675885	0.345564	673148	0.340264
645888	0.350308	692756	0.345563	664245	0.339923
680791	0.350213	653035	0.345121	660337	0.339771
635128	0.35012	642632	0.344796	694981	0.339606
675879	0.349973	647100	0.34477	627321	0.339605
18894	0.349424	675263	0.34474	664723	0.339544
689218	0.349183	687558	0.344672	655455	0.339395
649556	0.348764	697933	0.34444	643486	0.339277
647759	0.348419	715753	0.343881	165697	0.339159
651246	0.348279	695318	0.343771	668499	0.339092
258317	0.347928	620232	0.34372	627775	0.339038

Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation
693984	0.33875	650973	0.334388	675575	0.329634
643474	0.338499	677241	0.334309	641846	0.3294
636093	0.338369	632002	0.33334	255917	0.329284
639526	0.338011	710359	0.333192	702651	0.329265
2066	0.337894	694682	0.333192	657753	0.329207
632734	0.337866	3094	0.332992	522958	0.328993
675869	0.337783	692758	0.332611	630509	0.328653
13413	0.337609	127713	0.332543	663774	0.328588
669339	0.337222	655058	0.332369	650956	0.328429
674209	0.336853	692764	0.332258	648062	0.328377
633915	0.336582	643914	0.33193	95848	0.328211
674007	0.336396	624439	0.3319	654898	0.328117
647958	0.336179	681629	0.331788	650836	0.328016
672087	0.336057	638631	0.33159	690737	0.327587
623078	0.335965	625220	0.331474	692026	0.327438
356200	0.335895	649905	0.331387	681864	0.327145
622372	0.335739	631441	0.331214	617938	0.327071
654634	0.335708	664947	0.330946	705079	0.326991
639746	0.335611	628934	0.330884	329696	0.326913
625038	0.335093	638368	0.330803	697138	0.326729
679284	0.335082	650758	0.330565	691081	0.326612
707140	0.33496	633390	0.330503	623834	0.326508
672090	0.334882	666999	0.33033	632729	0.326486
697133	0.334773	702670	0.330033	670093	0.326163
674211	0.334645	634605	0.330017	670111	0.326142
688034	0.33455	165765	0.329995	643477	0.326135
715735	0.334499	673836	0.329854	675274	0.325942
659925	0.334417	692759	0.329665	649775	0.325552

Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation
667914	0.325154	383336	0.32022	268907	0.316479
356778	0.325142	625142	0.320004	645253	0.316425
658577	0.325035	615802	0.319558	196524	0.316379
638048	0.324598	254667	0.319358	643003	0.316343
703107	0.324501	639529	0.319299	339585	0.31602
661184	0.324219	39225	0.319037	715737	0.315747
641601	0.324151	668292	0.318994	631836	0.315596
636101	0.324101	703105	0.318514	641110	0.315404
631949	0.324027	181491	0.318504	339145	0.315402
669667	0.323952	667929	0.318342	678372	0.315078
701020	0.323848	697506	0.318338	639540	0.314888
668496	0.323616	677626	0.318219	617934	0.314879
721126	0.323603	676720	0.318209	651924	0.314865
636085	0.323128	693335	0.31815	682719	0.314638
677376	0.32303	630310	0.318135	676305	0.31456
640077	0.322691	657341	0.317984	660368	0.314526
697127	0.322639	83085	0.317946	114381	0.314409
715742	0.322474	690556	0.317686	695041	0.31378
659924	0.322473	673102	0.317589	658228	0.313735
671476	0.322117	643727	0.317414	628878	0.313695
636674	0.322011	721124	0.31735	33052	0.313687
106995	0.321751	36437	0.3169	627402	0.313571
626645	0.321598	656260	0.316888	621945	0.31342
636105	0.3215	699709	0.31687	627741	0.312998
608624	0.321408	705293	0.316761	696125	0.312918
682714	0.320627	654630	0.316667	633923	0.312888
674198	0.32041	689530	0.316557	685977	0.312874
692755	0.320347	636137	0.316545	627455	0.31262

Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation
691794	0.312619	667057	0.308344	646211	0.304847
689868	0.312593	657441	0.308205	630374	0.304836
43321	0.312424	693986	0.307655	677610	0.304749
628877	0.312238	634634	0.307328	106486	0.304731
693864	0.312177	682826	0.306822	632574	0.304474
684910	0.312169	647583	0.306618	645818	0.304392
698407	0.312156	635002	0.306541	72861	0.304374
613056	0.311927	670101	0.306496	365081	0.304322
697161	0.311646	703064	0.306317	635583	0.304074
652568	0.311453	646209	0.306304	373854	0.304017
617956	0.311415	674213	0.306185	625588	0.303912
529861	0.310952	628527	0.306138	639985	0.303691
176392	0.310572	715599	0.306111	636086	0.303584
142055	0.310556	718583	0.30604	625574	0.30339
318728	0.31047	637010	0.305998	692761	0.303306
653148	0.310298	676966	0.305991	7833	0.303263
163443	0.310286	693248	0.305811	77036	0.303244
645680	0.310234	629914	0.30547	636502	0.303234
664873	0.310012	715267	0.30545	634506	0.30304
649903	0.309993	309741	0.305446	652202	0.302839
617972	0.309803	674914	0.305339	652920	0.302786
650014	0.309713	682813	0.305221	24817	0.302684
638269	0.309594	635967	0.305014	352741	0.302555
626767	0.309575	656083	0.305012	691113	0.302403
602130	0.309539	695585	0.305005	640345	0.302195
36586	0.309275	308787	0.304974	641405	0.301858
12825	0.309074	670668	0.304912	693325	0.301607
630300	0.308685	617965	0.30487	698601	0.301438

Compound (NSC)	Pearson's Correlation	Compound (NSC)	Pearson's Correlation
60417	0.301328	617260	0.300513
705315	0.301194	657726	0.300478
645757	0.300953	136722	0.30034
650785	0.300938	693327	0.300079
686513	0.30079	691215	0.300078

II. *Pharmaceutical Compositions and Methods for their Use*

Another aspect of the disclosure includes pharmaceutical compositions prepared for administration to a subject and which include a therapeutically effective amount of one or more of the currently disclosed compounds. The therapeutically effective amount of a disclosed compound will depend on the route of administration, the species of subject and the physical characteristics of the subject being treated. Specific factors that can be taken into account include disease severity and stage, weight, diet and concurrent medications. The relationship of these factors to determining a therapeutically effective amount of the disclosed compounds is understood by those of skill in the art.

Pharmaceutical compositions for administration to a subject can include carriers, thickeners, diluents, buffers, preservatives, surface active agents and the like in addition to the molecule of choice. Pharmaceutical compositions can also include one or more additional active ingredients such as antimicrobial agents, anti-inflammatory agents, anesthetics, and the like. Pharmaceutical formulations can include additional components, such as carriers. The pharmaceutically acceptable carriers useful for these formulations are conventional. *Remington's Pharmaceutical Sciences*, by E. W. Martin, Mack Publishing Co., Easton, PA, 19th Edition (1995), describes compositions and formulations suitable for pharmaceutical delivery of the compounds herein disclosed.

In general, the nature of the carrier will depend on the particular mode of administration being employed. For instance, parenteral formulations usually contain injectable fluids that include pharmaceutically and physiologically acceptable fluids such as water, physiological saline, balanced salt solutions, aqueous dextrose, glycerol or the like as a vehicle. For solid compositions (for example, powder, pill, tablet, or capsule forms), conventional non-toxic solid carriers can include, for example, pharmaceutical grades of mannitol, lactose, starch, or magnesium stearate. In addition to biologically-neutral carriers, pharmaceutical compositions to be administered can contain minor amounts of non-toxic auxiliary substances, such as wetting or emulsifying agents, preservatives, and pH buffering agents and the like, for example sodium acetate or sorbitan monolaurate.

Pharmaceutical compositions disclosed herein include those formed from pharmaceutically acceptable salts and/or solvates of the disclosed compounds. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids. Particular disclosed compounds possess at least one basic group that can form acid-base salts with acids. Examples of basic groups include, but are not limited to, amino and imino groups. Examples of inorganic acids that can form salts with such basic groups include, but are not limited to, mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid. Basic groups also can form salts with organic carboxylic acids, sulfonic acids, sulfo acids or phospho acids or N-substituted sulfamic acid, for example acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid, gluconic acid, glucaric acid, glucuronic acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid or isonicotinic acid, and, in addition, with amino acids, for example with α -amino acids, and also with methanesulfonic acid, ethanesulfonic acid, 2-hydroxymethanesulfonic acid, ethane-1,2-disulfonic acid, benzenedisulfonic acid, 4-methylbenzenesulfonic acid, naphthalene-2-sulfonic acid, 2- or 3-phosphoglycerate, glucose-6-phosphate or N-cyclohexylsulfamic acid (with formation of the cyclamates) or with other acidic

organic compounds, such as ascorbic acid. In particular, suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium and magnesium, among numerous other acids well known in the pharmaceutical art.

5 Certain compounds include at least one acidic group that can form an acid–base salts with an inorganic or organic base. Examples of salts formed from inorganic bases include salts of the presently disclosed compounds with alkali metals such as potassium and sodium, alkaline earth metals, including calcium and magnesium and the like. Similarly, salts of acidic compounds with an organic base,
10 such as an amine (as used herein terms that refer to amines should be understood to include their conjugate acids unless the context clearly indicates that the free amine is intended) are contemplated, including salts formed with basic amino acids, aliphatic amines, heterocyclic amines, aromatic amines, pyridines, guanidines and amidines. Of the aliphatic amines, the acyclic aliphatic amines, and cyclic and
15 acyclic di- and tri- alkyl amines are particularly suitable for use in the disclosed compounds. In addition, quaternary ammonium counterions also can be used.

 Particular examples of suitable amine bases (and their corresponding ammonium ions) for use in the present compounds include, without limitation, pyridine, *N,N*-dimethylaminopyridine, diazabicyclononane, diazabicycloundecene,
20 *N*-methyl-*N*-ethylamine, diethylamine, triethylamine, diisopropylethylamine, mono-, bis- or tris- (2-hydroxyethyl)amine, 2-hydroxy-*tert*-butylamine, tris(hydroxymethyl)methylamine, *N,N*-dimethyl-*N*-(2- hydroxyethyl)amine, tri-(2-hydroxyethyl)amine and *N*-methyl-D-glucamine. For additional examples of "pharmacologically acceptable salts," see Berge et al., *J. Pharm. Sci.* 66:1 (1977).

25 Compounds disclosed herein can be crystallized and can be provided in a single crystalline form or as a combination of different crystal polymorphs. As such, the compounds can be provided in one or more physical form, such as different crystal forms, crystalline, liquid crystalline or non-crystalline (amorphous) forms. Such different physical forms of the compounds can be prepared using, for example
30 different solvents or different mixtures of solvents for recrystallization. Alternatively or additionally, different polymorphs can be prepared, for example, by

performing recrystallizations at different temperatures and/or by altering cooling rates during recrystallization. The presence of polymorphs can be determined by X-ray crystallography, or in some cases by another spectroscopic technique, such as solid phase NMR spectroscopy, IR spectroscopy, or by differential scanning calorimetry.

In one embodiment, the presently disclosed compounds are useful for the treatment of hyperproliferative disorders wherein the hyperproliferative cells exhibit MDR or are likely to develop MDR. In general, MDR is likely to develop in proliferative disorders being treated with an MDR-inducing chemotherapeutic agent. Chemotherapeutics that tend to induce MDR are known to those of skill in the arts of pharmacology and oncology and include, for example Vinca alkaloids, anthracyclines, epipodophyllotoxins, taxols, actinomycin D, cardiac glycosides, immunosuppressive agents, glucocorticoids, and anti-HIV protease inhibitors.

One aspect of the present disclosure includes methods for treating a hyperproliferative disorder by administering a therapeutically effective amount of the disclosed compounds to a subject in need thereof. For example, particular proliferative disorders that can be so treated include solid tumors, such as sarcomas and carcinomas, include fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, and other sarcomas, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, lymphoid malignancy, pancreatic cancer, breast cancer, lung cancers, ovarian cancer, prostate cancer, hepatocellular carcinoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, Wilms' tumor, cervical cancer, testicular tumor, bladder carcinoma, and CNS tumors (such as a glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma and retinoblastoma).

The present disclosure also provides methods to treat hyperproliferative disorders that are characterized by multidrug resistance. By way of example, the presently disclosed compounds and compositions can be used to inhibit multidrug resistant prostate, breast, colon, bladder, cervical, skin, testicular, kidney, ovarian, stomach, brain, liver, pancreatic or esophageal cancer, or lymphoma, leukemia or multiple myeloma. In certain embodiments the disclosed compounds and compositions are used to treat a subject is at risk of developing a metastatic proliferative disorder.

Examples of hematological tumors that can be treated as disclosed herein include leukemias, including acute leukemias (such as acute lymphocytic leukemia, acute myelocytic leukemia, acute myelogenous leukemia and myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia), chronic leukemias (such as chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia), polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma (indolent and high grade forms), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia and myelodysplasia.

The therapeutically effective amount of the compound or compounds administered can vary depending upon the desired effects and the factors noted above. Typically, dosages will be between about 0.01 mg/kg and 250 mg/kg of the subject's body weight, and more typically between about 0.05 mg/kg and 100 mg/kg, such as from about 0.2 to about 80 mg/kg, from about 5 to about 40 mg/kg or from about 10 to about 30 mg/kg of the subject's body weight. Thus, unit dosage forms can be formulated based upon the suitable ranges recited above and a subject's body weight. The term "unit dosage form" as used herein refers to a physically discrete unit of therapeutic agent appropriate for the subject to be treated.

Alternatively, dosages are calculated based on body surface area and from about 1 mg/m² to about 200 mg/m², such as from about 5 mg/m² to about 100 mg/m² will be administered to the subject per day. In particular embodiments, administration of the therapeutically effective amount of the compound or compounds involves administering to the subject from about 5 mg/m² to about 50

mg/m², such as from about 10 mg/m² to about 40 mg/m² per day. It is currently believed that a single dosage of the compound or compounds is suitable, however a therapeutically effective dosage can be supplied over an extended period of time or in multiple doses per day. Thus, unit dosage forms also can be calculated using a
5 subject's body surface area based on the suitable ranges recited above and the desired dosing schedule.

It is contemplated that in some embodiments the disclosed compounds are used in combination with other types of treatments, such as cancer treatments. For example the disclosed inhibitors may be used with other chemotherapies, including
10 those employing an anti-proliferative agent, such as, without limitation, microtubule binding agent, a toxin, a DNA intercalator or cross-linker, a DNA synthesis inhibitor, a DNA and/or RNA transcription inhibitor, an enzyme inhibitor, a gene regulator, enediyne antibiotics and/or an angiogenesis inhibitor. In one embodiment the presently disclosed compounds are used to render a neoplasm susceptible to one
15 or more anti-proliferative compounds to which it is resistant. Additionally, the disclosed compounds can be used in combination with radiation therapy, surgery, or other modalities of cancer therapy.

"Microtubule binding agent" refers to an agent that interacts with tubulin to stabilize or destabilize microtubule formation thereby inhibiting cell division.
20 Examples of microtubule binding agents that can be used in conjunction with the presently disclosed compounds include, without limitation, paclitaxel, docetaxel, vinblastine, vindesine, vinorelbine (navelbine), the epothilones, colchicine, dolastatin 15, nocodazole, podophyllotoxin and rhizoxin. Analogs and derivatives of such compounds also can be used and will be known to those of ordinary skill in
25 the art. For example, suitable epothilones and epothilone analogs for incorporation into the present compounds are described in International Publication No. WO 2004/018478, which is incorporated herein by reference. Taxoids, such as paclitaxel and docetaxel are currently believed to be particularly useful as therapeutic agents in combination with the presently disclosed compounds. Examples of additional useful
30 taxoids, including analogs of paclitaxel are taught by U.S. Patent Nos. 6,610,860 to

Holton, 5,530,020 to Gurram et al. and 5,912,264 to Wittman et al. Each of these patents is incorporated herein by reference.

Suitable DNA and/or RNA transcription regulators for use with the disclosed compounds include, without limitation, actinomycin D, daunorubicin, doxorubicin
5 and derivatives and analogs thereof also are suitable for use in combination with the presently disclosed compounds.

DNA intercalators, cross-linking agents and alkylating agents that can be used in combination therapy with the disclosed compounds include, without limitation, cisplatin, carboplatin, oxaliplatin, mitomycins, such as mitomycin C,
10 bleomycin, chlorambucil, cyclophosphamide, isophosphoramide mustard and derivatives and analogs thereof.

DNA synthesis inhibitors suitable for use as therapeutic agents include, without limitation, methotrexate, 5-fluoro-5'-deoxyuridine, 5-fluorouracil and analogs thereof.

15 Examples of suitable enzyme inhibitors for use in combination with the presently disclosed compounds include, without limitation, camptothecin, etoposide, formestane, trichostatin and derivatives and analogs thereof.

Suitable therapeutics for use with the presently disclosed compounds that affect gene regulation include agents that result in increased or decreased expression
20 of one or more genes, such as, without limitation, raloxifene, 5-azacytidine, 5-aza-2'-deoxycytidine, tamoxifen, 4-hydroxytamoxifen, mifepristone and derivatives and analogs thereof.

The term "angiogenesis inhibitor" is used herein, to mean a molecule including, but not limited to, biomolecules, such as peptides, proteins, enzymes,
25 polysaccharides, oligonucleotides, DNA, RNA, recombinant vectors, and small molecules that function to inhibit blood vessel growth. Angiogenesis inhibitors are known in the art and examples of suitable angiogenesis inhibitors include, without limitation, angiostatin K1-3, staurosporine, genistein, fumagillin, medroxyprogesterone, SFTI-1, suramin, interferon-alpha, metalloproteinase
30 inhibitors, platelet factor 4, somatostatin, thrombospondin, endostatin, thalidomide, and derivatives and analogs thereof.

Other therapeutic agents, particularly anti-tumor agents, that may or may not fall under one or more of the classifications above, also are suitable for administration in combination with the presently disclosed compounds. By way of example, such agents include adriamycin, apigenin, erlotinib, gefitinib, 5 temozolomide, rapamycin, topotecan, carmustine, melphalan, mitoxantrone, irinotecanetoposide, tenoposide, zebularine, cimetidine, and derivatives and analogs thereof.

Suitable dosages and treatment regimes for administering the above-identified therapeutic agents are known to those of ordinary skill in the art of 10 oncology and also are described, for example, in Physicians' Cancer Chemotherapy Drug Manual **2005** By Edward Chu and Vincent T. DeVita (ISBN 0763734616), which is incorporated herein by reference. Such dosages and treatment regimens can be used in combination with a presently disclosed MDR-inverse compound.

The compounds disclosed herein may be administered orally, topically, 15 transdermally, parenterally, via inhalation or spray and may be administered in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles.

Typically, oral administration or administration via implantation or intravenously, such as via injection is preferred. However the particular mode of 20 administration employed may be dependent upon the particular disease, condition of patient, toxicity of compound and other factors as will be recognized by a person of ordinary skill in the art.

III. Identification of Subjects having MDR Disorders

25 There are a variety of techniques to detect expression of MDR1. The detection and/or quantitation of MDR1 protein typically is accomplished using immunological techniques. For hematopoietic cells such as those from leukemia or lymphoma patients, the techniques include flow cytometry and fixed cells on microscope slides. The cells are treated with antibodies specific for the MDR1 30 protein, such as the mouse ARK-16 monoclonal antibody. Such antibodies can be directly labeled with fluorescent probe, or detected using subsequent reagents such

as goat anti-mouse IgG-FITC. Flow cytometry allows for direct quantitative determinations of the full spectrum of MDR1 expression using channel number or fluorescence intensity. Microscopic examination of the slide preparations can give qualitative results (-, +, ++, and the like) or, in conjunction with an image analyzer,
5 quantitative evaluations typically expressed in pixels.

For solid tumors, such as breast cancer, typically immunocytochemistry (ICC) or immunohistochemistry (IHC) techniques are employed. Using, for example, frozen sections or paraffin blocks, the detection techniques are the same as described for fixed leukemia cells on microscope slides. Expression of MDR1 can
10 also be monitored by the measurement of specific mRNA levels. Cell slides can be processed, and levels of mRNA discerned using basic molecular biology techniques such as quantitative fluorescent PCR. Alternatively, the cells of interest can be lysed, processed, and following PCR of the mRNA, the product can be detected and quantitated following gel electrophoresis. Anti-sense targeting of MDR1 mRNA is
15 also possible, followed by standard techniques for quantitative determinations. Radio-labeled probes followed by autoradiography or other radiodetection techniques can also be used to obtain a relative estimate of MDR1 protein or mRNA expression. Thus, there exists a broad range of methods for the detection and quantitation of the spectrum of MDR1 expression exhibited by a subject.

20 Monitoring of the relative expression of MDR1 is possible *in vivo*. MDR1-specific antibodies labeled with any number of detectable markers, such as radioactive compounds detectable with positron emission tomography (PET), single-photon emission computed tomography (SPECT) or compounds detectable with magnetic resonance imaging (MRI) can be used to assess MDR1 expression in a
25 subject having cancer or an MDR1-expressing infection, such as multidrug resistant tuberculosis.

MDR1 function, *i.e.*, functional expression of MDR1 also can be evaluated. MDR1 functions as a cytoplasmic membrane pump, effluxing compounds such as drugs and toxins from the cytoplasm to the exterior of the cell. Compounds acted on
30 by MDR1 are termed MDR1 substrates. Detection of MDR1 function therefore involves detection of substrate efflux, such as the efflux of a particular drug, or

alternatively, detection of efflux of surrogate fluorescent dye markers that also are MDR1 substrates, such as DiOC2 (3,3'-diethyloxacarbocyanine iodide) or Rhodamine 123 (Rh123, or 2-(6-amino-3-imino-3H-xanthen-9-yl)benzoic acid, methyl ester). For single cell suspensions, such as blood or bone marrow from leukemia patients, the cells are exposed in tissue culture to a substrate for MDR1, such as the aforementioned dye markers, radiolabeled drugs, or drugs that can be detected and/or quantitated by other means such as fluorescence. At physiological temperature (37° C) the net accumulation of the substrate over time, in the presence or absence of specific MDR1 inhibitors, gives an indication of the MDR1 functional activity exhibited by the cells. Alternatively, the single cell suspension can be exposed to the substrate and subsequent efflux of the substrate over time monitored at physiological temperature in the presence or absence of specific MDR1 inhibitors.

PET, SPECT, and MRI techniques also can be used to assess MDR1 function in cancer patients. Thus, small organic molecules as well as metal complexes that serve as MDR1 substrates can be labeled with radionuclides or other detectable markers. Additionally, functional expression in solid tumors can be more efficiently ascertained by ICC/IHC techniques with prior labeling of the tumor cells in the patient.

Diagnostic testing methods for MDR1 expression and efflux pump activity can be used to prospectively stratify patients for treatment optimization in treating malignancies exhibiting MDR1 expression or function, such as acute myelogenous leukemia, most solid tumors, lymphomas, bladder cancer, pancreatic cancer, ovarian cancer, liver cancer, myeloma, lymphocytic leukemia, and sarcoma.

The disclosed techniques for identifying subjects having MDR-resistant cells are applicable to any therapeutic drug that is a substrate for P-gp-mediated efflux. Such drugs include, but are not limited to, P-glycoprotein substrates; anticancer drugs as described above and including, by way of example Vinca alkaloids such as vinblastine and vincristine; anthracyclines such as doxorubicin, daunorubicin, epirubicin; anthracenes such as bisantrene and mitoxantrone; epipodophyllo-toxins such as etoposide and teniposide; and other anticancer drugs such as actinomycin D, mithomycin C, mitamycin, methotrexate, docetaxel, etoposide (VP-16),

paclitaxel, docetaxel, and adriamycin; immunosuppressants, including cyclosporine A and tacrolimus; steroids, by way of example, dexamethasone, hydrocortisone, corticosterone, triamcinolone, aldosterone and methylprednisolone; antiepileptics, such as phenytoin; antidepressants, including without limitation, citalopram, 5 thioperidone, trazodone, trimipramine, amitriptyline and phenothiazines; antipsychotics, such as fluphenazine, haloperidol, thioridazine and trimipramine; HIV protease inhibitors, for example, amprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir; calcium blockers, for example, bepridil, diltiazem, flunarizine, lomerizine, secoverine, tamolarizine, verapamil, nicardipine, 10 prenylamine and fendiline.

Monotherapy using MDR-Inverse Compounds

This example describes the treatment of a subject having a multidrug resistant disorder, such as a multidrug resistant tumor. Subjects having such 15 disorders can be identified, for example, as set forth above.. In one embodiment, a subject having a multidrug resistant disorder is administered an MDR-inverse compound disclosed herein, in an amount sufficient to elevate the target tissue concentration of the MDR-inverse compound in the subject to at least about 10 nM, such as from about 0.1 μ M to about 100 μ M, and typically from about 1 μ M to 20 about 10 μ M. In one embodiment, the MDR-inverse compound is administered intravenously in an amount of 400 mg/day or less to about 1,600 mg/day or more, preferably from about 500, 600, or 700 mg/day to about 900, 1000, 1100, 1200, 1300, 1400, or 1500 mg/day, and most preferably about 700 mg/day. In the course of a treatment regimen, the MDR-inverse compound preferably is administered on 25 two, three, or four separate days. The dosage typically is administered in intravenously continuously over the course of about 3 to about 90 hours, more preferably over the course of about 4, 6, 12, 18, 24 or 30, 36, or 42 hours to about 54, 60, 66, 72, 78, or 84 hours, most preferably over about 24 hours, 48 hours, or 72 hours, depending upon the treatment regimen. Preferably the MDR-inverse 30 compound is administered on multiple days of the treatment regimen.

Combination Therapy using MDR-Inverse Compounds

The drugs which are substrates of P-gp are quite varied as are the associated disease states. Chemotherapeutic agents that are P-gp substrates include, without limitation, anthracyclines (for example, doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone), Vinca alkaloids (for example, vincristine, vinblastine, vinorelbine, vindesine), Topoisomerase-II inhibitors (for example, etoposide, teniposide), taxanes (e.g., paclitaxel, docetaxel), and others (for example, Gleevec and dactinomycin). The MDR1-inverse compounds disclosed herein can be administered in combination with any of these chemotherapeutic agents.

Examples

Materials and Methods

Chemicals. Unless otherwise stated, compounds were obtained from the NCI DTP drug repository. The octapeptide NSC633657 (D-Phe-Cys-Tyr-D-Trp-Lys-Ser-Cys-Thr-NH₂) was prepared by John Stonik, NCI and purified by HPLC at the US FDA Center for Biologics Evaluation and Research.

Drug database. The DTP Human Tumor Cell Line Screen has screened tens of thousands of compounds for growth inhibition of human cancer cell lines. Screening results for ~43,000 compounds were downloaded from <http://discover.nci.nih.gov> (July 2007 Release). Scrutiny of the dataset indicated that it was not immediately amenable to stringent statistical analysis due to missing dose-response values or lack of activity in the dose window tested. Since uninformative drug profiles are not expected to yield useful leads, we selected only those drugs that were measured inside the range of cytotoxicity with no more than 50% missing values, resulting in a higher quality activity dataset. Putative MDR-inverse compounds were identified based on correlation of their cytotoxicity patterns to ABCB1 expression, as described in (Szakacs et al., 2004).

- Evaluation of structural similarity.** Structural analogs within the DTP dataset were identified based on Tanimoto coefficients defined by the Leadscape software (LeadScope, Inc, Columbus, OH, USA) (Mutch et al., 2004). Clustering of the Discovery-set was performed using the PubChem Structure Clustering algorithm (<http://pubchem.ncbi.nlm.nih.gov/>). For additional analysis shown (Figure 3), chemical fingerprints were generated using the Chemaxon GenerateMD software. Structural clustering was performed using the average linkage method with a threshold distance of 0.6 (R package, www.r-project.org).
- 10 **Pharmacophore generation and QSAR.** The 3D structure of the molecules serving as templates (NSC693871 and NSC337743 for the “TSC” and “10580” cluster, respectively) was calculated using the MOPAC2007 program (Stewart Computational Chemistry, USA). The molecules were aligned using the FieldAlign software (Cresset BDL, USA), which aligns molecules based on electrostatic, surface and topological properties. The simplified pharmacophore model is visualized using LigandScout software (InteLigand). For each compound of the two major clusters shown in Figure 2, 3368 molecular descriptors were calculated by the PCLIENT algorithm (Tetko et al., 2005). The initial descriptor set was preprocessed in order to eliminate ineffective descriptors (those with too many zero values or with very small standard deviations). The QSAR study was carried out with the enhanced replacement method (Mercader et al., 2008) using the Matlab software (The MathWorks, Inc.).

- Cell lines and culture conditions.** KB-3-1 is the parental human (HeLa) epidermoid carcinoma cell line of KB-V1 cells that overexpress Pgp (MDR1) as a result of long-term selection in vinblastine (Shen et al., 1986). NIH-MDR-G185 is a clone of NIH3T3 cells transfected with wild type pHaMDR1/A (Cardarelli et al., 1995). MES-SA Dx5, a drug resistant cell line expressing high levels of Pgp, was derived from a human uterine sarcoma line (MES-SA) by doxorubicin selection (Wang et al., 2000). KB-3-1, KB-V1, NIH3T3 and NIH-MDR-G185 cells were grown in DMEM cell culture medium at 37 °C in 5% CO₂. MES-SA and MES-SA

Dx5 cells were grown in McCoy's medium. NIH-MDR-G185, KB-V-1 and Dx5 cells were maintained in 60 ng/mL colchicine, 1 µg/mL vinblastine and 500 nM doxorubicin (adriamycin) respectively to maintain Pgp expression. All cell culture media (GIBCO) was supplemented with 10% fetal bovine serum (FBS, GIBCO), 5 mM glutamine (GIBCO) and 50 unit/ml penicillin and streptomycin (GIBCO). Retroviral expression of ABCB1 in A431 cells was achieved by a method described previously (Ujhelly et al., 2003). The human skin-derived, epidermoid carcinoma cells, A431, were maintained in alpha-MEM (Life Technologies, Grand Island, NY) supplemented with 10% FBS, 50 units/mL penicillin, 50 units/mL streptomycin, and 5 mM glutamine at 37°C in 5% CO₂.

Cell viability assay. Cells were trypsinized, counted and seeded in 100 µL medium supplemented with 10% FBS at a density of 3,000 per well in 96-well plates and incubated for 24 hours at 37 °C in a humidified atmosphere with 5% CO₂ and 95% air to allow exponential growth. After 24 h, 100 uL medium containing serially diluted compounds were added to give the indicated final concentrations in three replicated wells. Cells were then incubated for a further 72 hours. Antiproliferative activity of drugs was evaluated using the MTT ([3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay (Szakacs et al., 2004). Cytotoxicity assays were performed in triplicate, and curves were fitted by Prism software (GraphPad Software, Inc., San Diego, CA) using nonlinear least-squares regression in a sigmoidal dose-response model with variable slope, also known as the four-parameter logistic equation. Curves were normalized at 100 and 0, the expected upper and lower boundaries of normalized percentage inhibition data, respectively. Curve fit statistics were used to determine the concentration of test compound that resulted in 50% toxicity (IC₅₀) (in µM). Differences between the GI50 values were analyzed by two-sided paired Student's t test and results were considered statistically significant at p < 0.05.

Results

The results are shown in Figures 1-7, and in Table B below. In particular, compounds identified as having MDR1-selective activity, listed in descending order for their Pearson's correlation coefficients, the correlation between MDR1 expression and DTP determined efficacy of each compound across the NCI-60 cell line panel, are shown in Table 1 in Figure 7. The structure listed in the NCI DTP database is shown for each NSC compound, along with any relevant references to the compound found in the literature, and the average GI₅₀ value for each compound against the NCI-60 panel to give an indication of overall potency of each compound (not its MDR1 inverse activity). Compounds were sourced by a variety of methods, predominately through the NCI DTP drug library, but also via other investigators and synthesis in our laboratories. For compounds that were available, IC₅₀ values were determined using the MTT cytotoxicity against the parental KB-3-1 cell line, and the P-glycoprotein expressing cell line KB-V1. The MDR1 selectivity is calculated as the ratio of a compound's IC₅₀ against KB-3-1 cells divided by its IC₅₀ against KB-V1 cells. A value > 1 indicates that the compound kills P-gp-expressing cells more effectively than parental cells, so-called MDR1-inverse activity. A value < 1 indicates that the P-gp expressing cells are resistant to the compound, relative to parental cells, as is normally observed for P-gp substrates. Compounds with an IC₅₀ > 50 μ M were considered to be not toxic (NT), and as such their MDR1 selectivity could not be determined.

Table B

Compound (NSC)	Pearson's Correlation	MDR1 Selectivity Ratio
10776	NA	<=1
21518	0.00	<=1
37881	0.01	<=1
39225	0.32	3.06
48151	-0.23	<=1
48477	0.29	<=1

85459	0.07	2.32
329100	0.04	<=1
653043	0.05	<=1
665711	-0.07	NA
696893	-0.23	NA
162800	0.11	<=1
165697	0.34	<=1
619179	-0.22	NA
619181	-0.10	NA
619183	-0.08	NA
619184	-0.41	NA
619188	NA	NA
630123	0.25	NA
632591	0.40	NA
632734	0.34	NA
632735	0.34	NA
632737	0.28	NA
632738	0.43	NA

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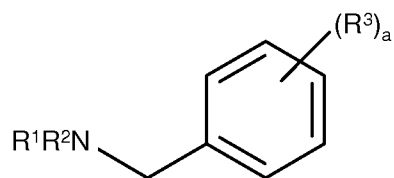
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In view of the many possible embodiments to which the principles of the disclosed compounds, compositions and methods may be applied, it should be recognized that the illustrated embodiments are only preferred examples and should not be taken as limiting the scope of the invention.

What is claimed is:

1. A method for inhibiting the growth of drug resistant cells in a subject, comprising identifying a subject having drug resistant cells; and
- 5 administering to the subject a compound or a pharmaceutically acceptable salt or ester thereof, of the formula



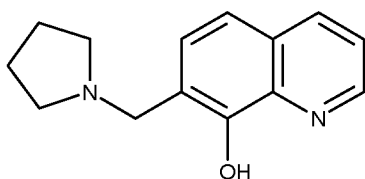
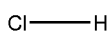
Formula I

10

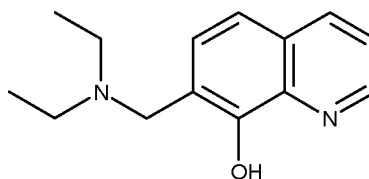
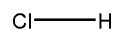
wherein R^1 and R^2 are each independently H, alkyl, cycloalkyl, aryl, or substituted alkyl, or R^1 and R^2 together with the N form a heterocyclic ring selected from a pyrrolidinyl, pyrrolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperziny, indolinyl, morpholinyl, pyrrolyl, pyrazolyl, or pyrazinyl;

- 15 R^3 is alkyl, substituted alkyl, alkyl amino, hydroxyl, amino, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl; and

a is 0 to 5, with the proviso that the following compounds are not included

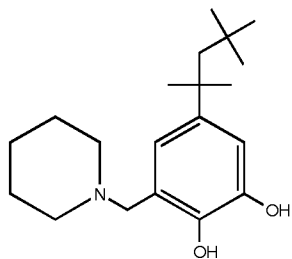


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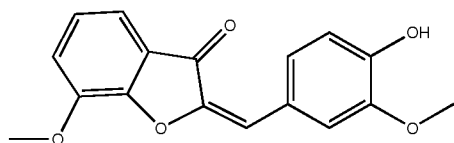
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or

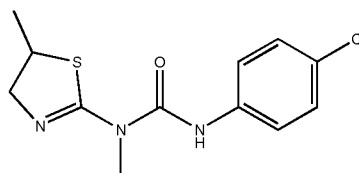


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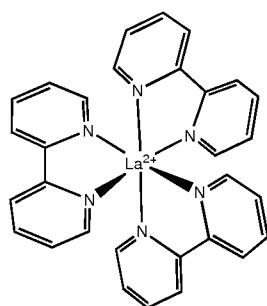
2. A method for inhibiting the growth of drug resistant cells in a subject,
 5 comprising identifying a subject having drug resistant cells; and
 administering to the subject at least one compound, or a pharmaceutically
 acceptable salt or ester thereof, selected from



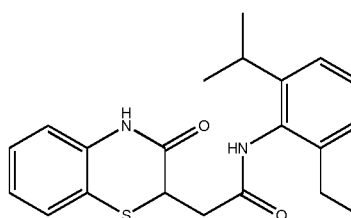
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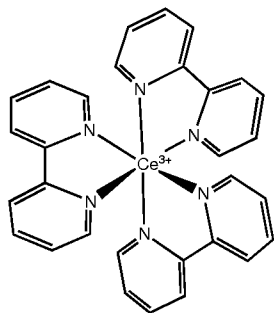
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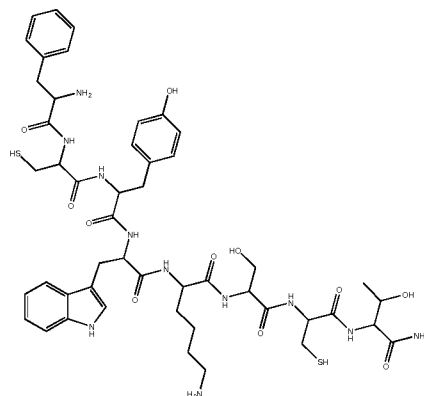
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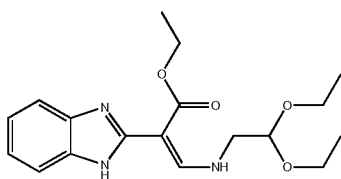
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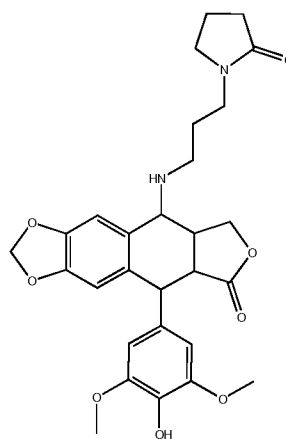
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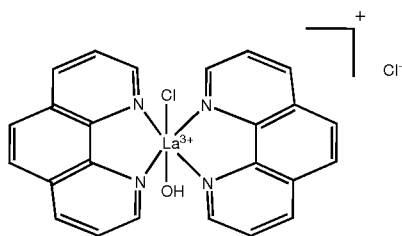
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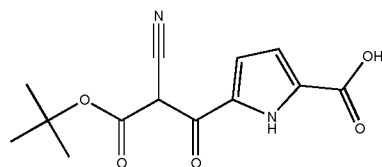
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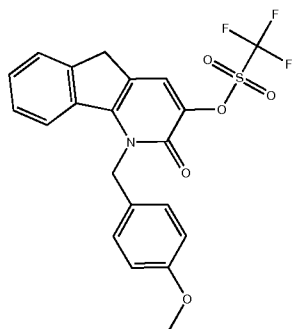
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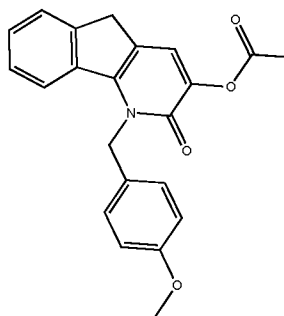
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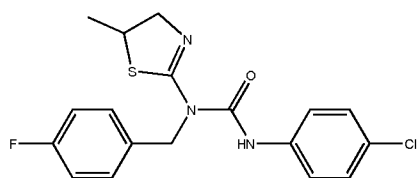
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NSC705305

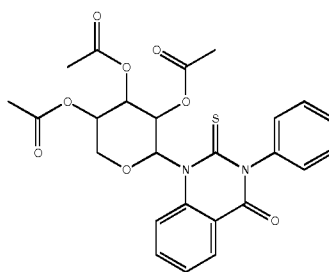


NSC705301

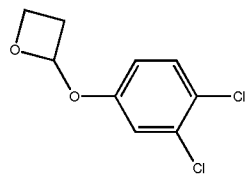


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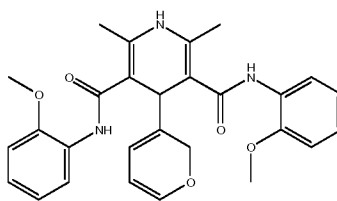
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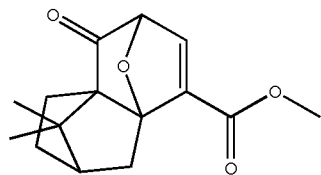
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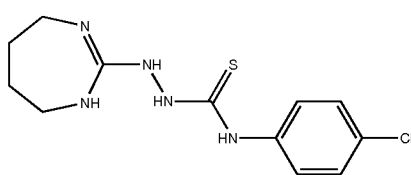
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NSC636097

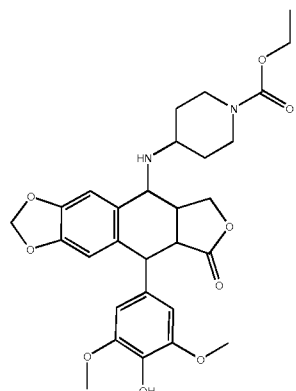


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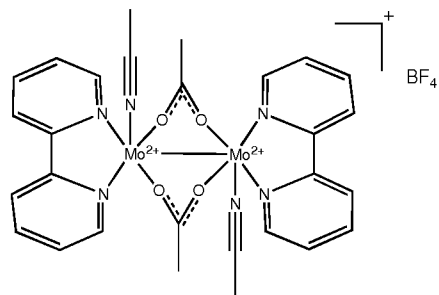


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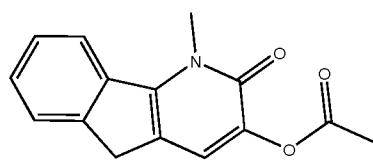
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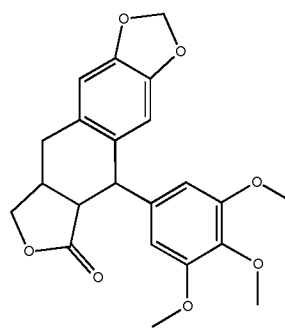
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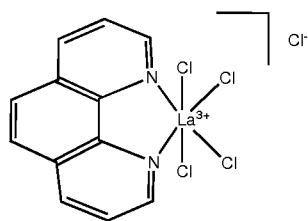
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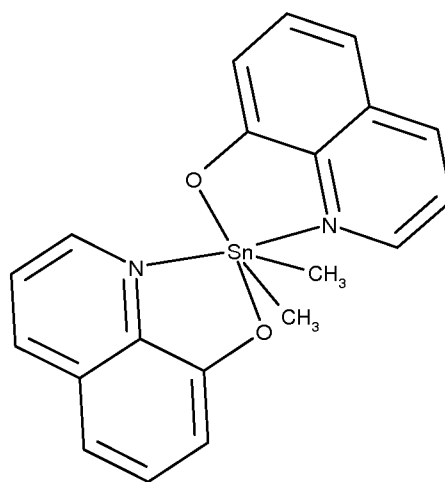
5 NSC697920



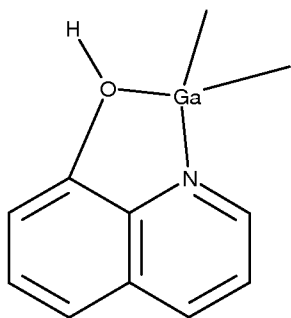
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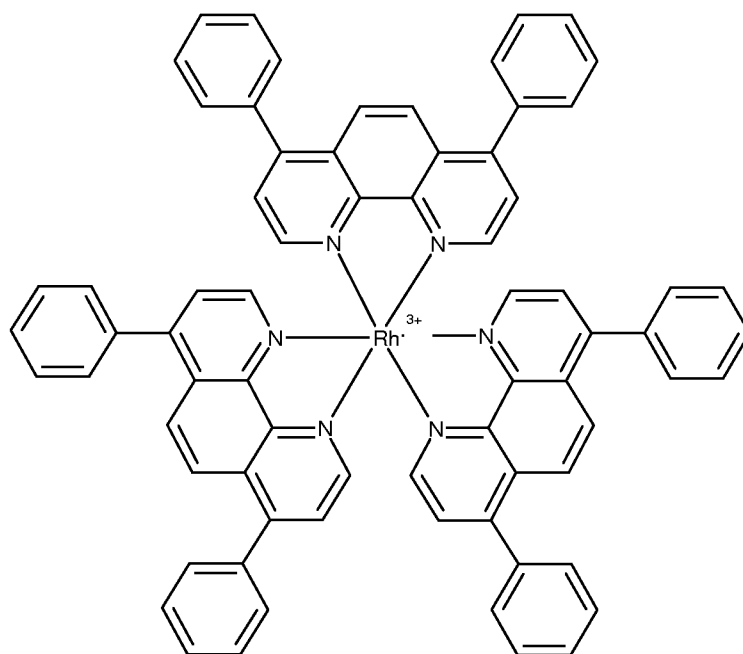
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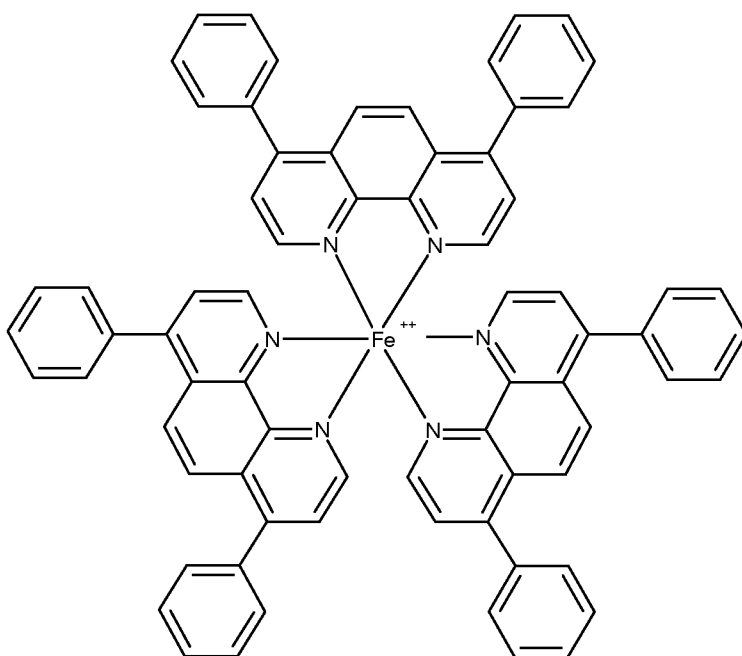


NSC165697

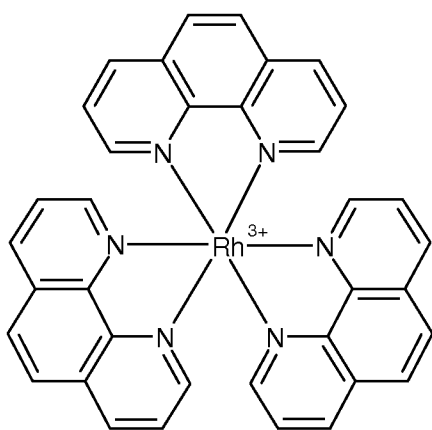
 Cl^- Cl^- Cl^- 

5

NSC619179

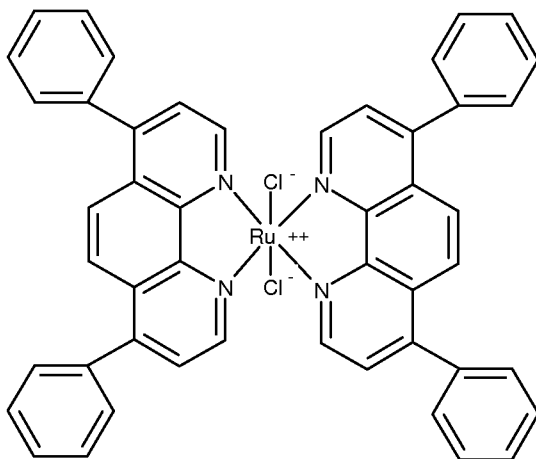
Cl^- 

NSC619181

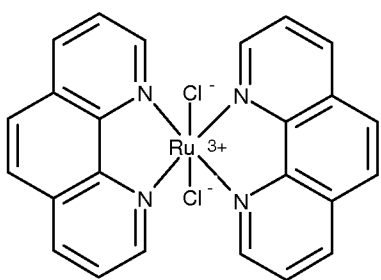
 Cl^- 

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NSC619183

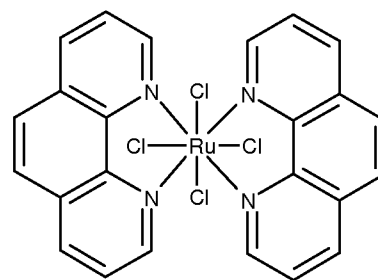


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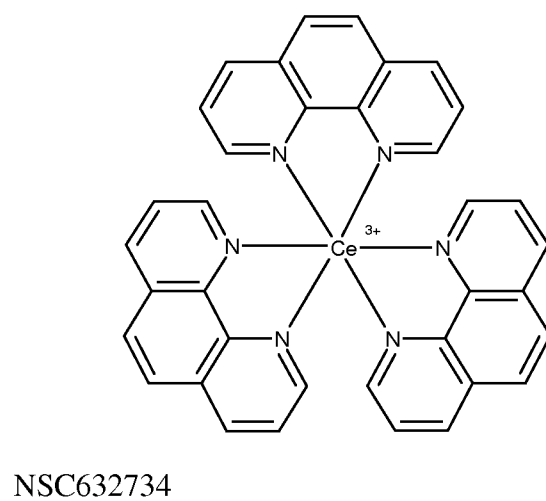
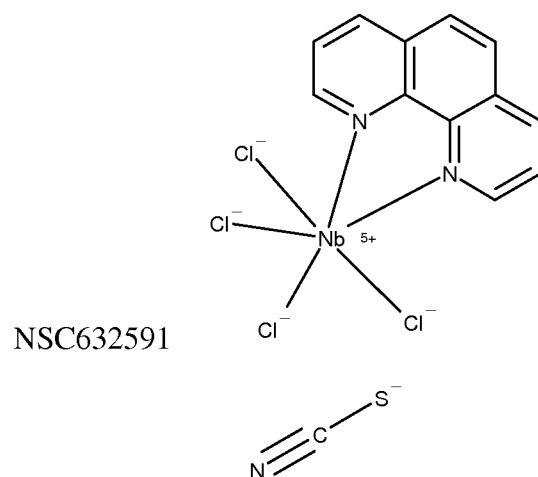
Cl⁻

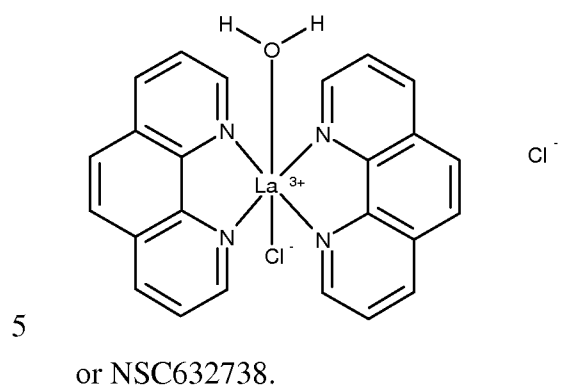
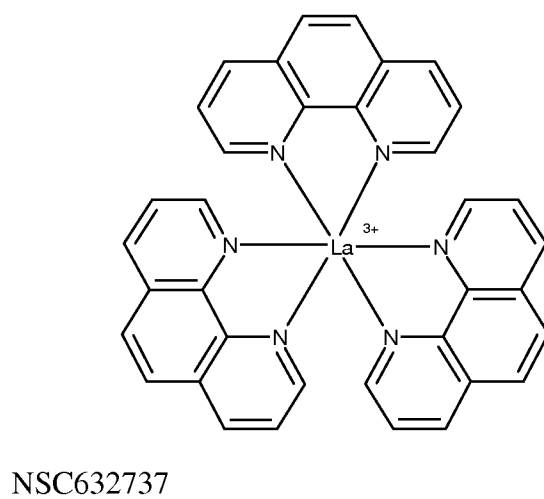
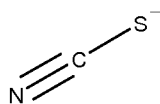
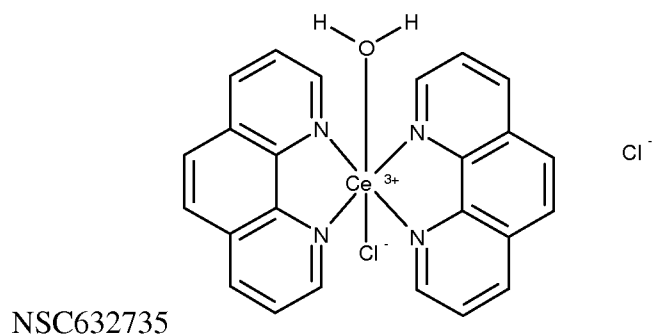
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NSC619188



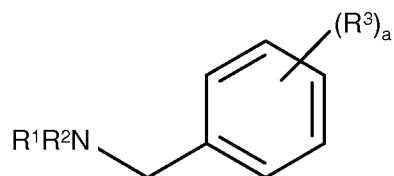
NSC630123





3. A method of inhibiting cancer in a subject, comprising administering to the subject an antiproliferative agent, wherein the antiproliferative effect of the agent is potentiated by P-glycoprotein and the agent is a compound, or a pharmaceutically acceptable salt or ester thereof, of the formula

5

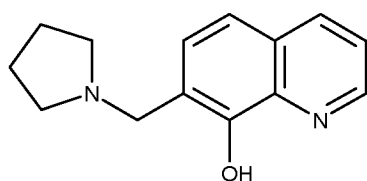


Formula I

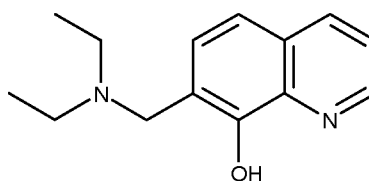
wherein R^1 and R^2 are each independently H, alkyl, cycloalkyl, aryl, or substituted alkyl, or R^1 and R^2 together with the N form a heterocyclic ring selected from a pyrrolidinyl, pyrrolinyl, pyrazolidinyl, pyrazolinyl, piperidinyl, piperzinyl, indolinyl, morpholinyl, pyrrolyl, pyrazolyl, or pyrazinyl;

R^3 is alkyl, substituted alkyl, alkyl amino, hydroxyl, amino, aryl, cycloalkyl, heterocycloalkyl, or heteroaryl; and

15 a is 0 to 5, with the proviso that the following compounds are not included

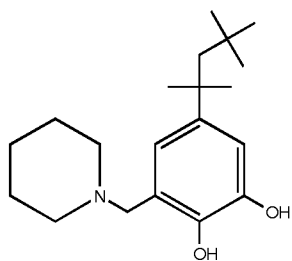


NSC693871,



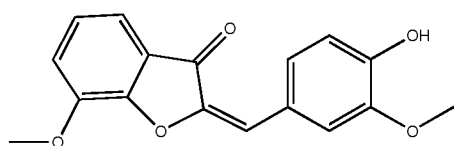
NSC693872,

or

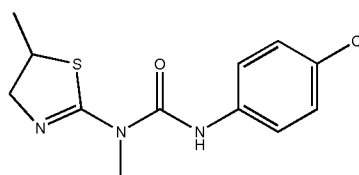


NSC10580.

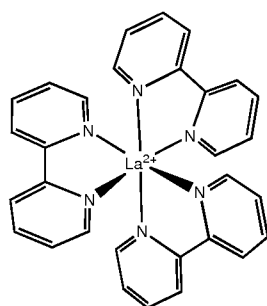
4. A method of inhibiting cancer in a subject, comprising administering to
 5 the subject an antiproliferative agent, wherein the antiproliferative effect of the agent is potentiated by P-glycoprotein and the agent is a compound, or a pharmaceutically acceptable salt or ester thereof, selected from



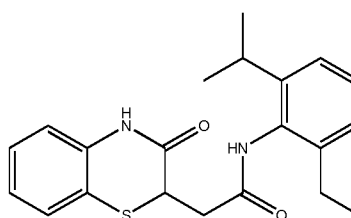
10 NSC43320



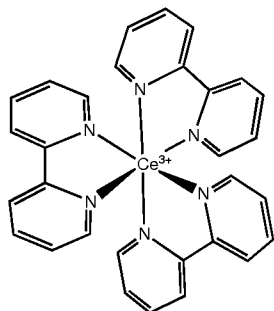
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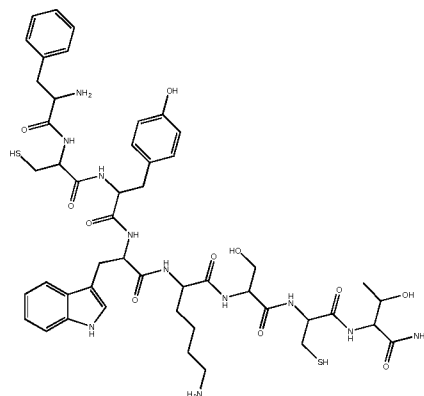
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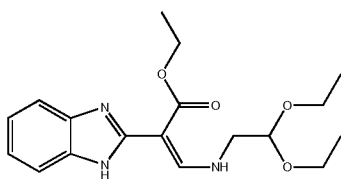
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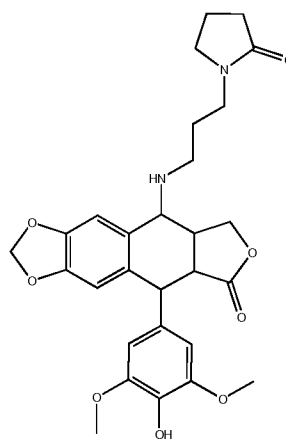
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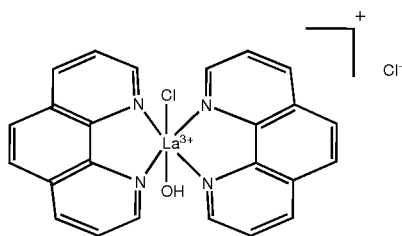
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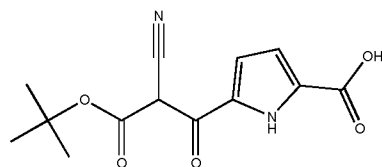
5 NSC710857



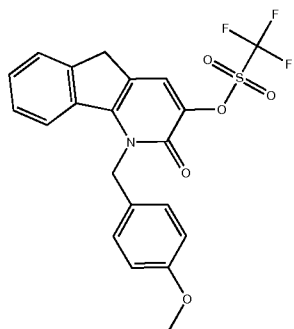
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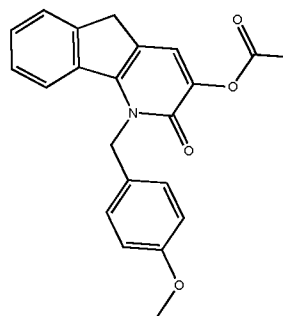
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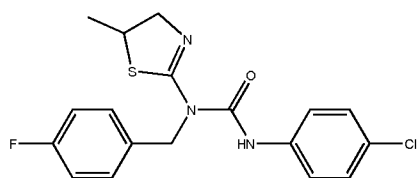
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NSC705305

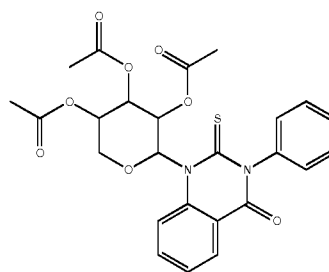


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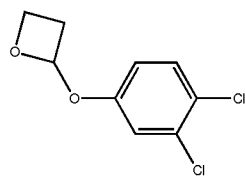


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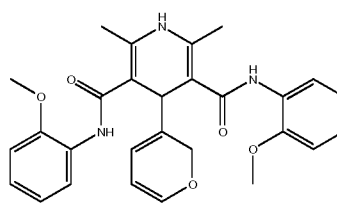
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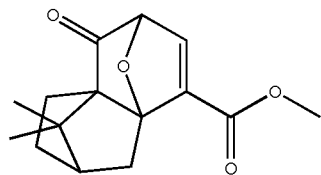
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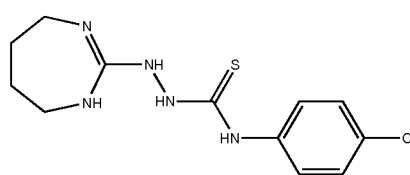
NSC635977



NSC636097

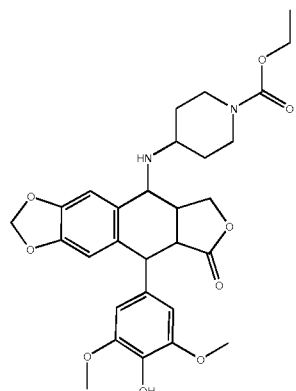


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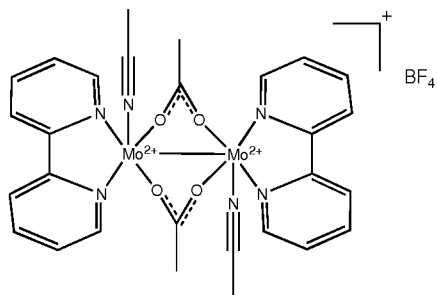


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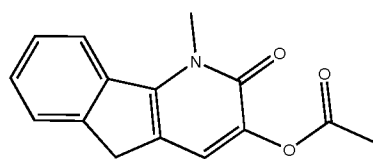
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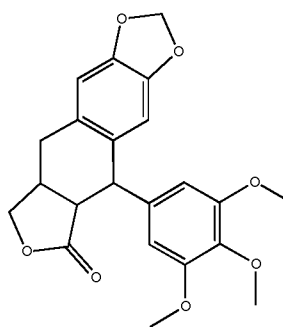
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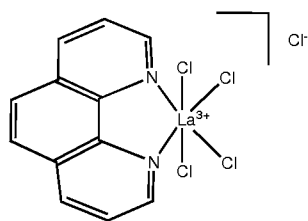
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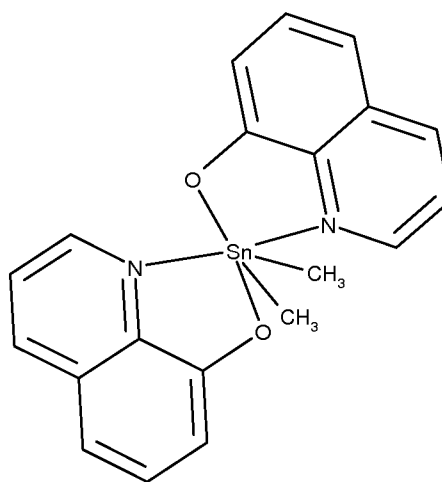
5 NSC697920



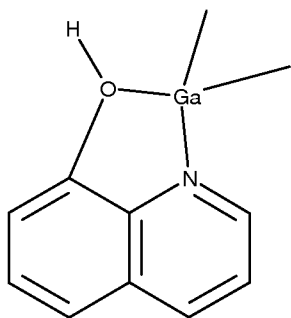
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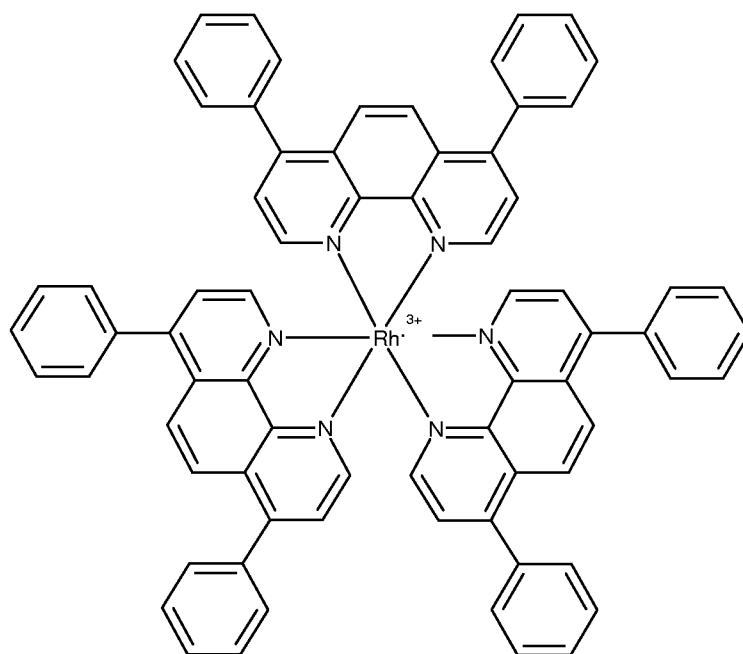
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NSC162800

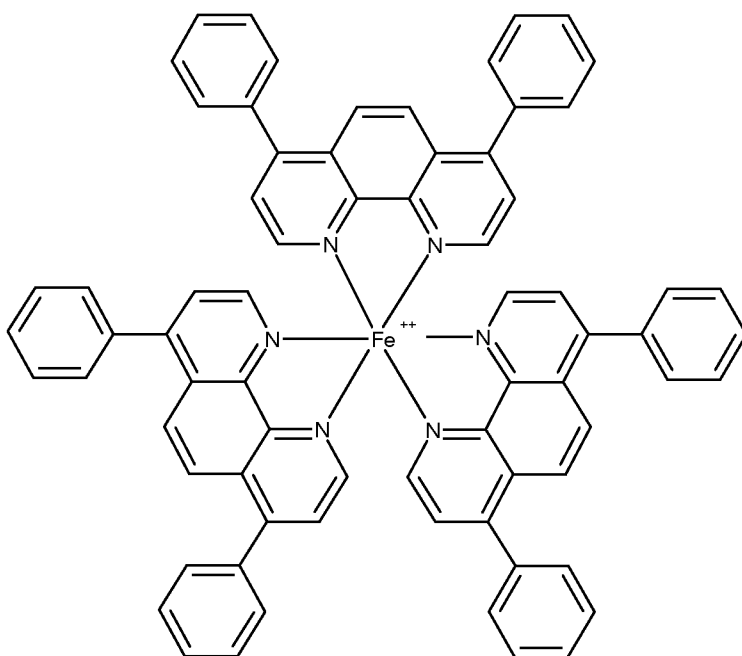


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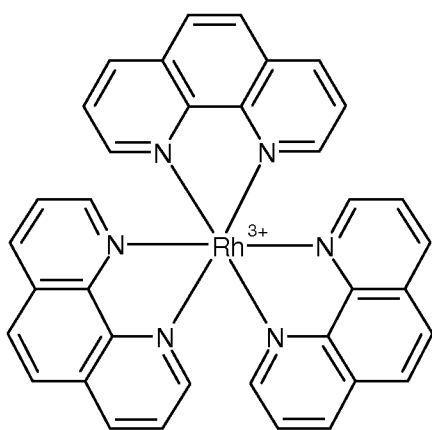
Cl⁻Cl⁻Cl⁻

5

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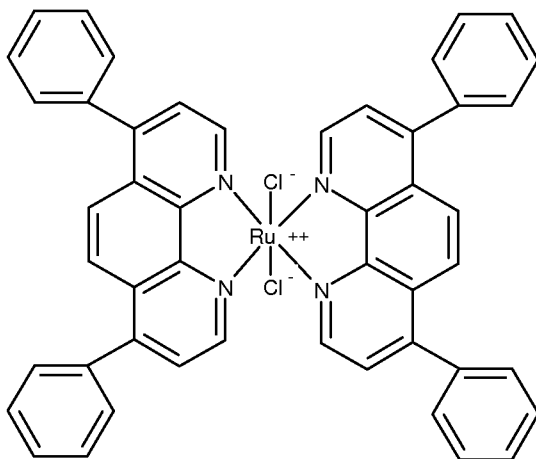
Cl^- 

NSC619181

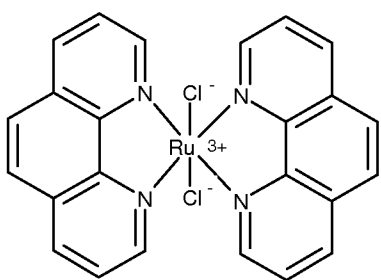
 Cl^- 

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NSC619183

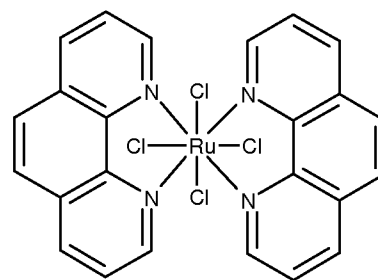


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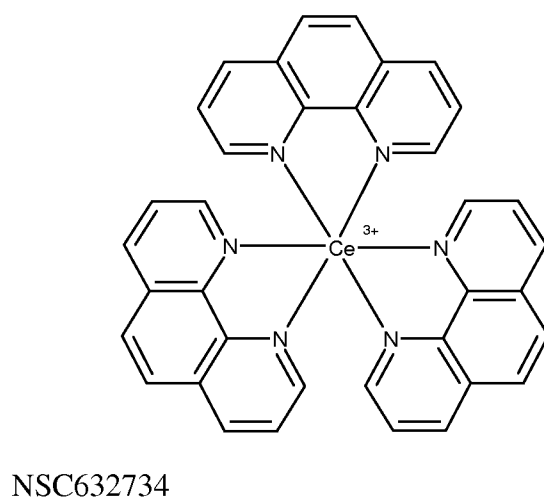
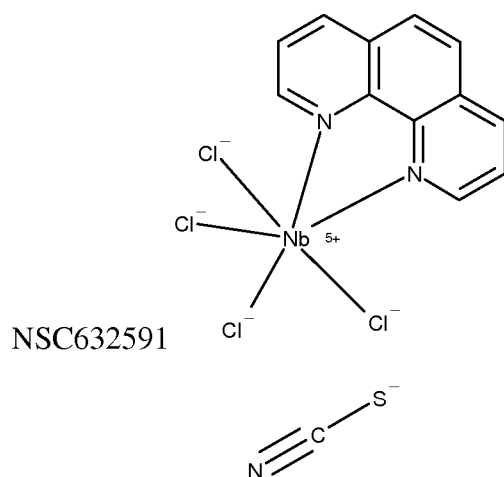
Cl⁻

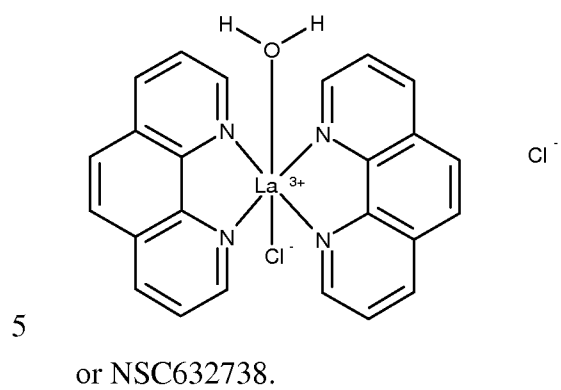
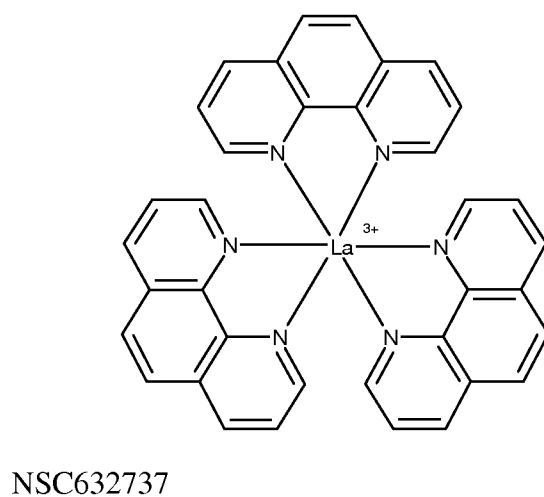
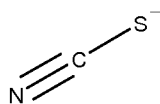
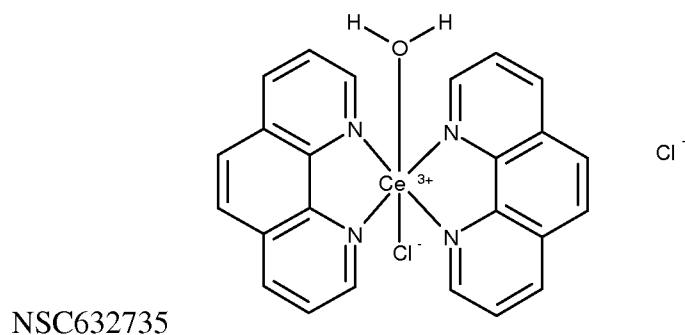
5

NSC619188



NSC630123





5. The method of any one of claims 1-4, wherein the cells exhibit a
 10 multidrug resistance phenotype.

6. The method of any one of claims 1-5, wherein administering the at least one compound re-sensitizes the cells to a MDR1 substrate.

5 7. The method of claim 1 or 2, wherein the cells are neoplastic cells.

8. The method of any one of claims 1-7, wherein the subject has previously been treated with at least one MDR1 substrate.

10 9. The method of claim 1 or 2, wherein the cells comprise cancer.

10. The method of any one of claims 3, 4 or 9, wherein the cancer comprises brain cancer, breast cancer, bladder cancer, bone cancer, cervical cancer, colon cancer, central nervous system cancer, esophageal cancer, gall bladder cancer,
15 gastrointestinal cancer, head and neck cancer, Hodgkin's Disease, non-Hodgkin's lymphomas, laryngeal cancer, leukemia, lung cancer, melanoma, neuroblastoma, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, renal cancer, retinoblastoma, stomach cancer, testicular cancer, Wilms' tumor or a combination thereof.

20

11. The method of any one of claims 1-10, wherein the compound is administered in combination with a cytotoxic agent.

12. The method of claim 11, wherein the cytotoxic agent is an anticancer
25 agent.

13. The method of claim 12, wherein the anticancer agent is selected from the microtubule binding agents, DNA intercalators, DNA alkylating agents, DNA cross-linkers, DNA synthesis inhibitors, DNA and/or RNA transcription inhibitors,
30 enzyme inhibitors, gene regulators, enzymes, antibodies or angiogenesis inhibitors.

14. The method of claim 6, further comprising administering, subsequent to the at least at least one compound, at least one MDR1 substrate.

5 15. The method of claim 6, further comprising administering, subsequent to the at least at least one compound, at least one anticancer agent.

16. The method of claim 12 or 15, wherein the anticancer agent is selected from erlotinib, gefitinib, temozolomide, paclitaxel, docetaxel, daunorubicin, cisplatin, carboplatin, oxaliplatin, colchicine, dolastatin 15, nocodazole
10 podophyllotoxin, rhizoxin, vinblastine, vindesine, vinorelbine (navelbine), the epothilones, the mitomycins, bleomycin, chlorambucil, carmustine, melphalan, mitoxantrone, 5-fluoro-5'-deoxyuridine, camptothecin, SFTI-1, topotecan, irinotecanetoposide, tenoposide, geldanamycin, methotrexate, adriamycin, actinomycin D, medroxyprogesterone, mifepristone, raloxifene, 5-azacytidine, 5-
15 aza-2'-deoxycytidine, zebularine, tamoxifen, 4-hydroxytamoxifen, apigenin, rapamycin, angiostatin K1-3, L-asparaginase, staurosporine, genistein, fumagillin, endostatin, isophosphoramidate mustard, thalidomide or analogs thereof.

20

FIG. 1

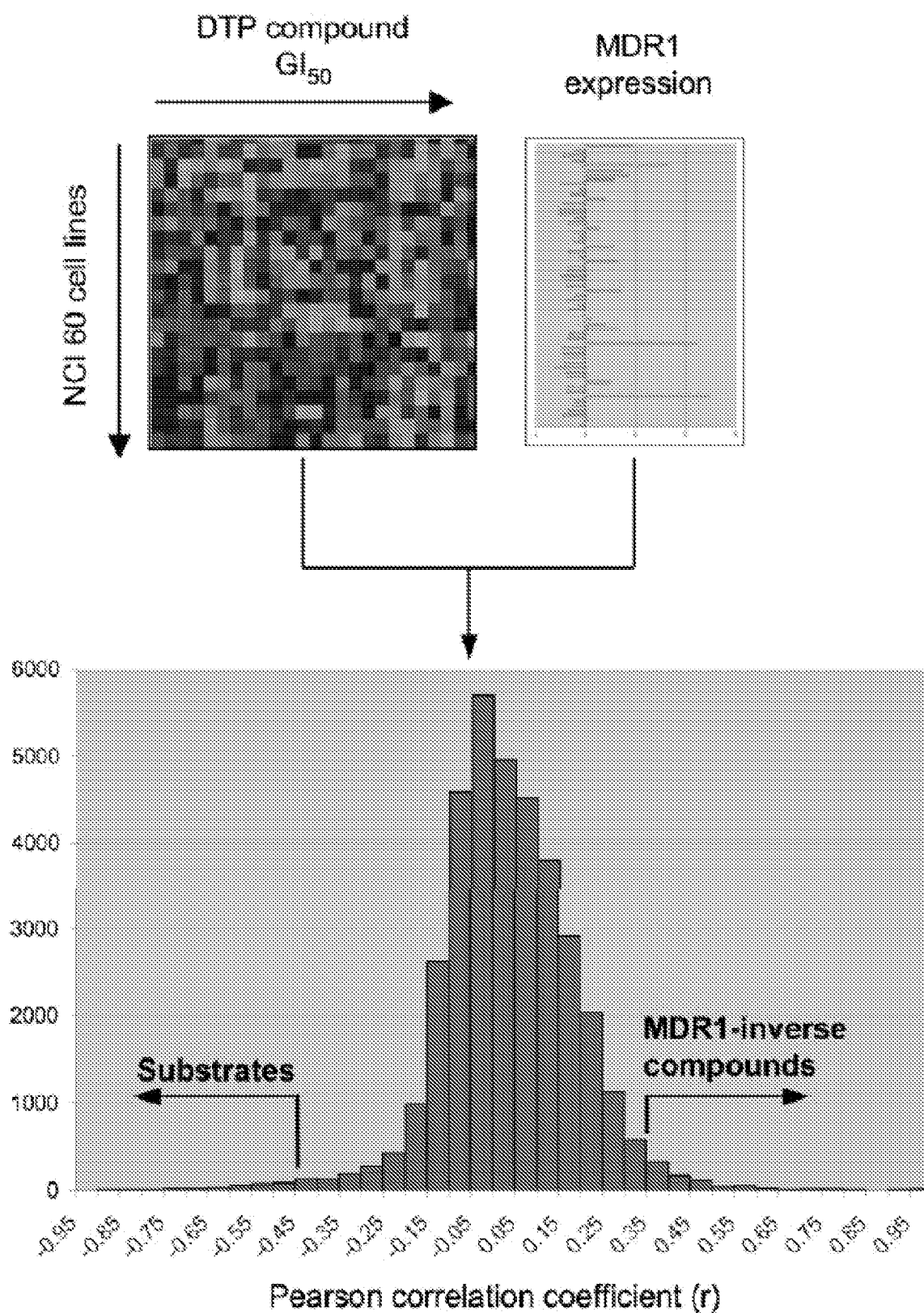


FIG. 2

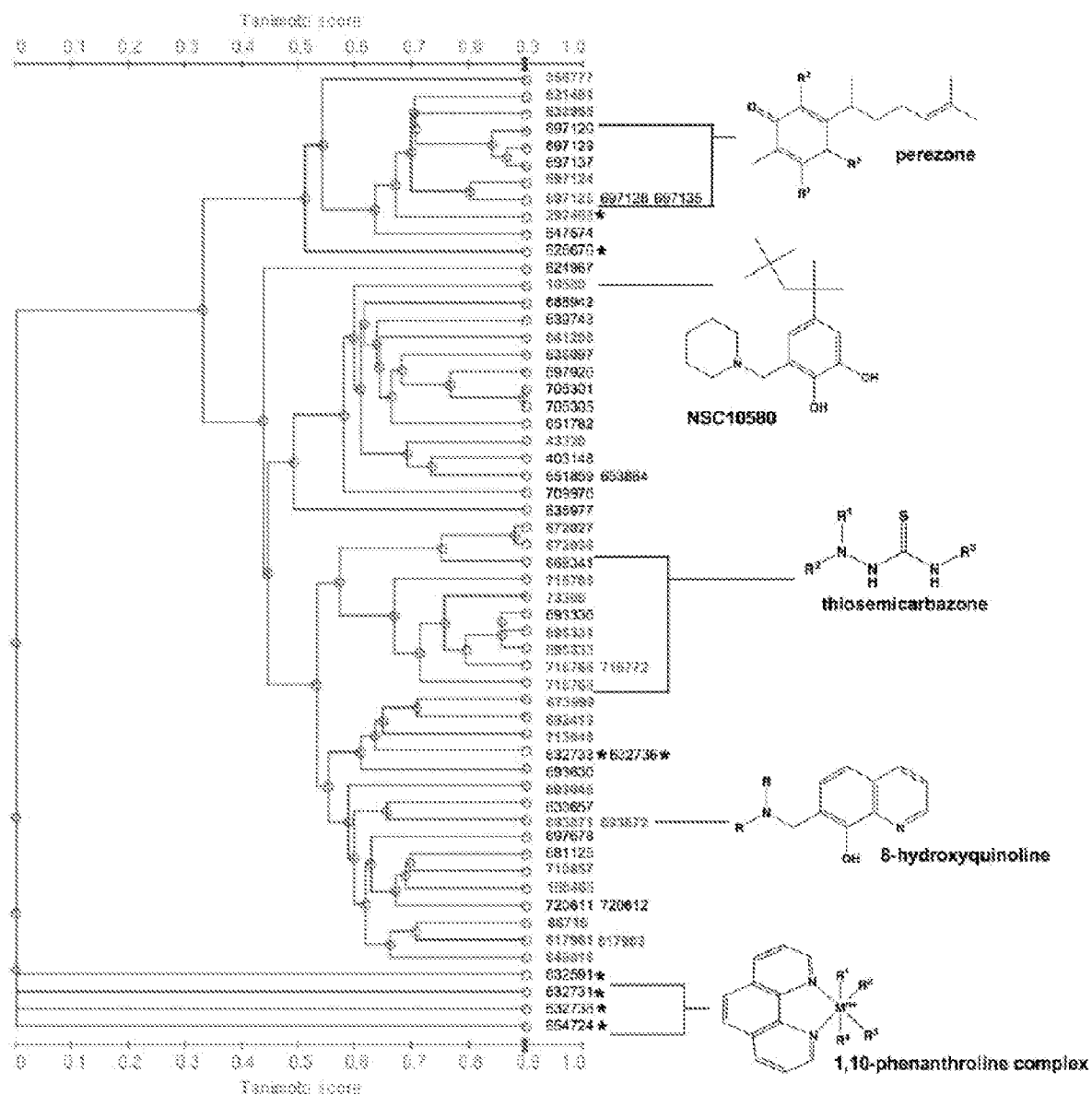


FIG. 3

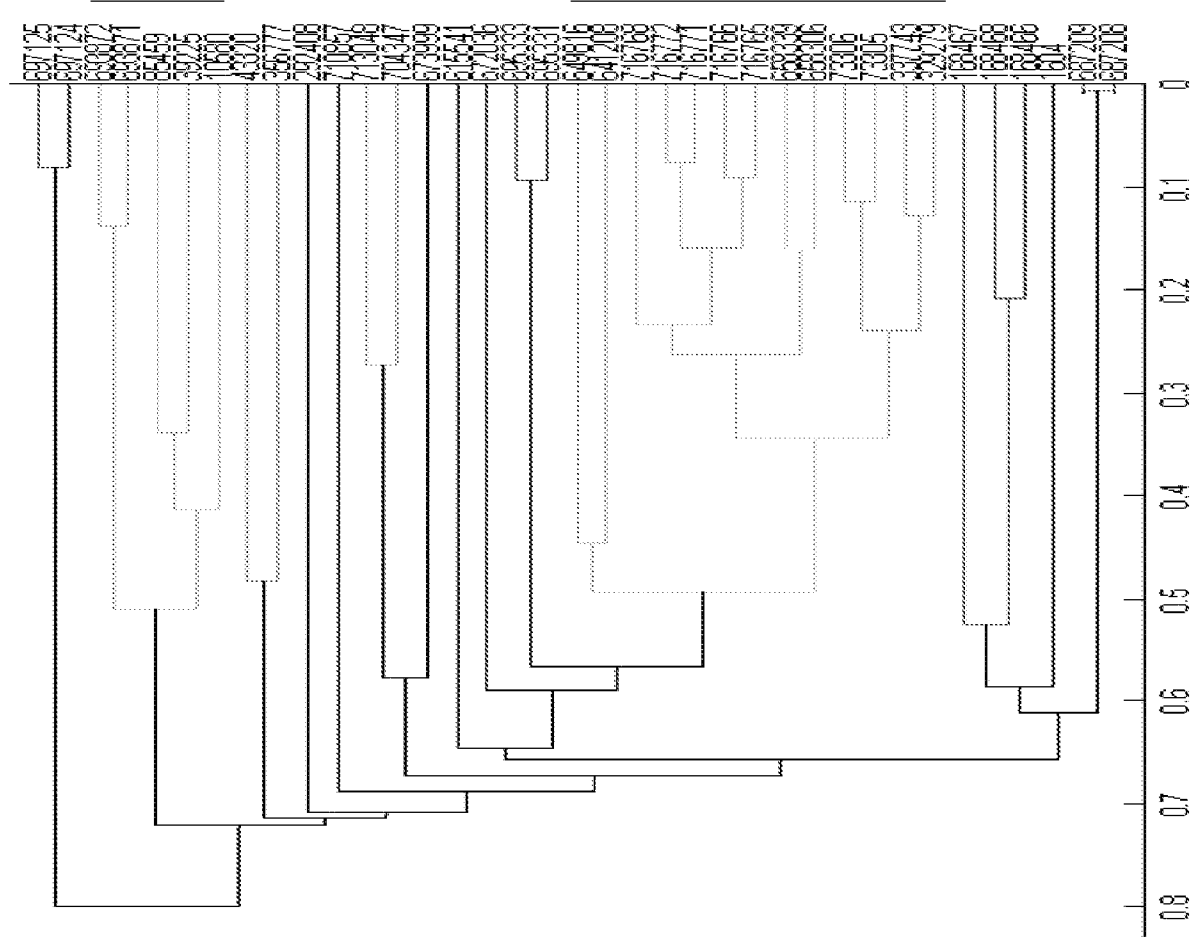
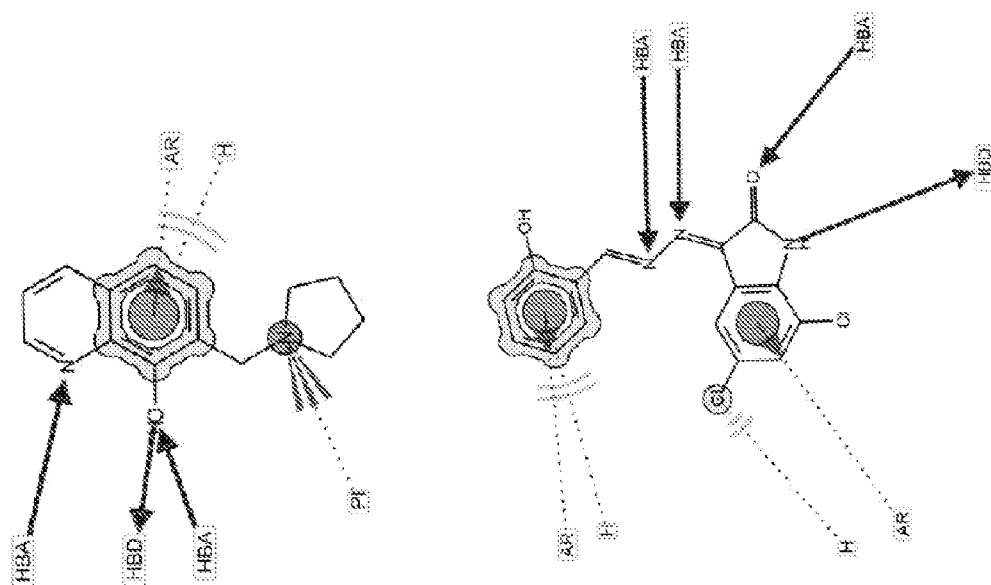


FIG. 4

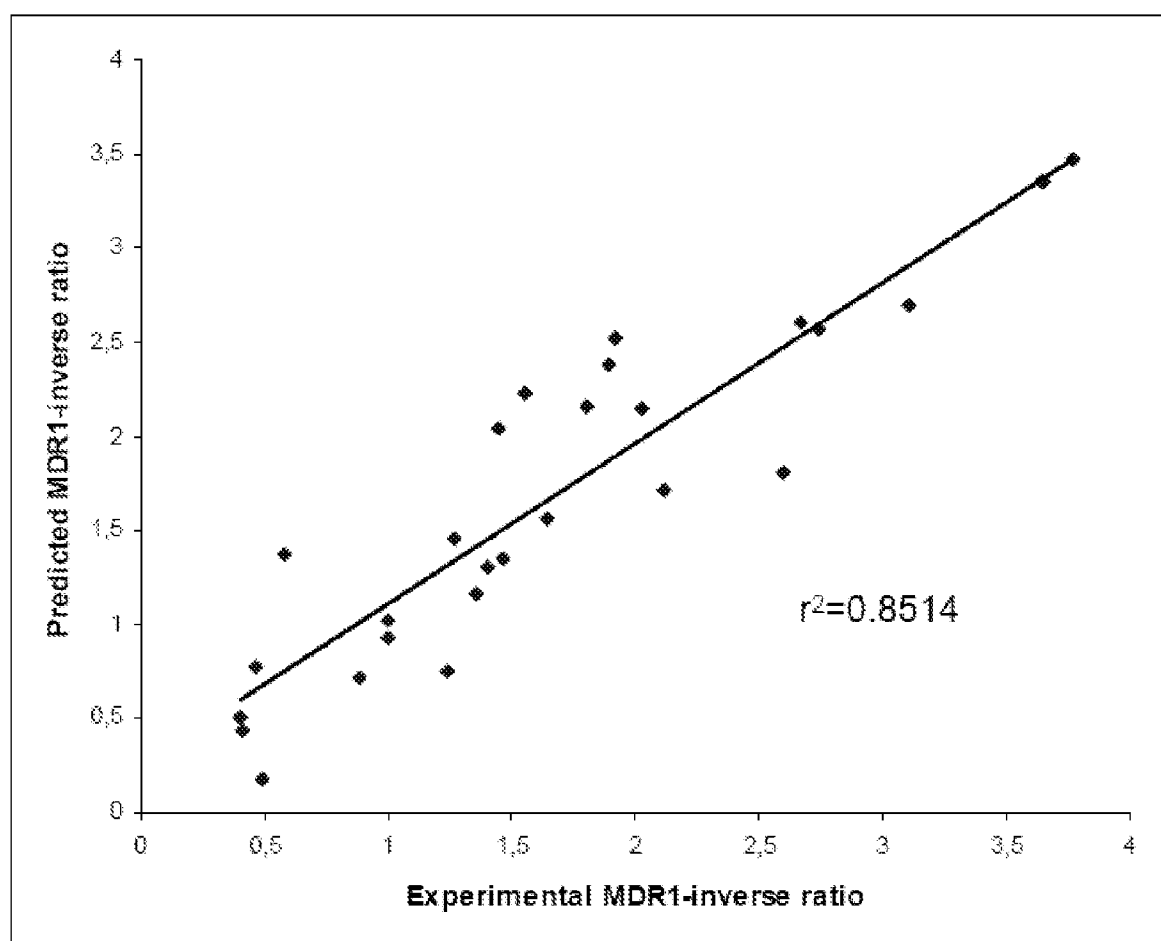


FIG. 5

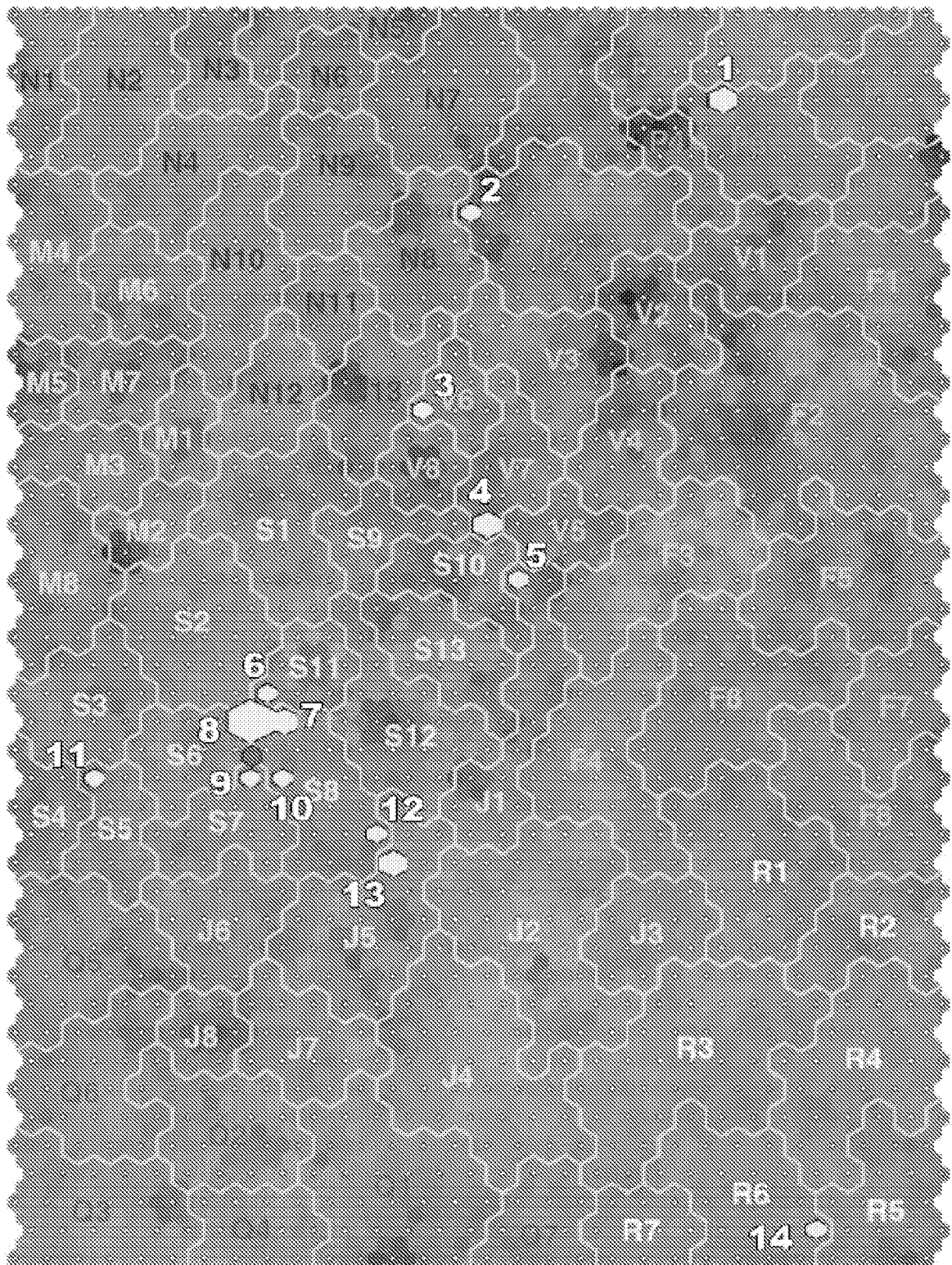


FIG. 6A



FIG. 6B

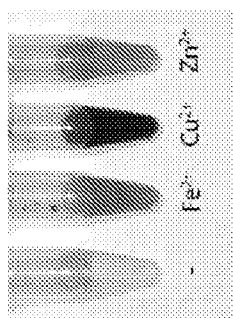


FIG. 6C

Mixture	Peak mass	Assignment
NSC77306	327.1	L+H
NSC77306 + Fe(II)	707.1	[Fe(L-H)] ₂ +H
NSC77306 + Cu(II)	714.1	[Cu(L-H)] ₂ +H
NSC77306 + Zn(II)	715.1	[Zn(L-H)] ₂ +H

FIG. 6D

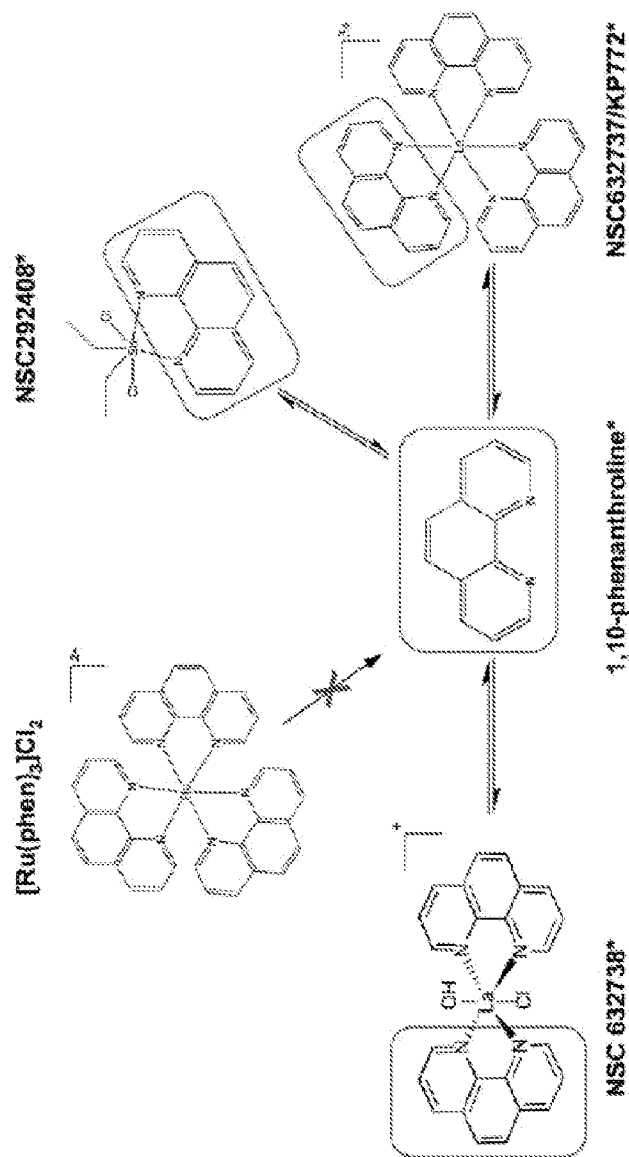


FIG. 7 (Page 1 of 8)

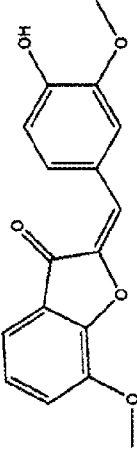
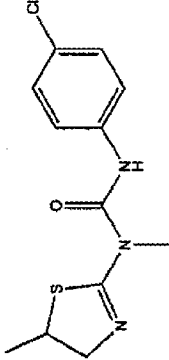
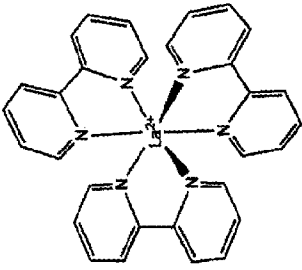
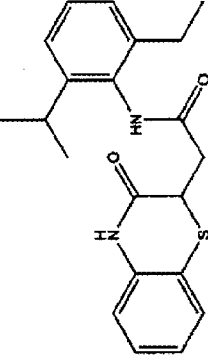
Molecule (NSC)	Pearson's Correlation	Structure	Reference	Av. GI ₅₀ (all cell lines)	MDR1 Selectivity (3-1/V1)
NSC43320	0.56		[3]	68.2 μ M	2.08
NSC672027	0.55		-	13.2 μ M	≤ 1
NSC632736	0.47		-	22.6 μ M	-
NSC632955	0.47		-	50.4 μ M	≤ 1

FIG. 7 (Page 2 of 8)

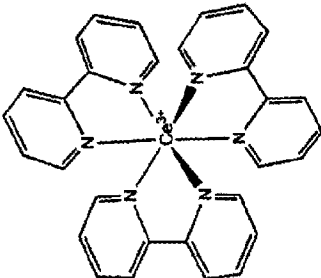
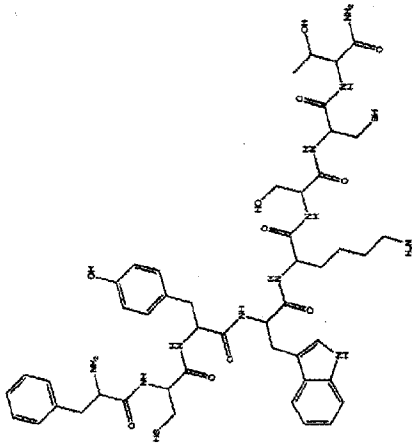
Molecule (NSC)	Pearson's Correlation	Structure	Reference	Av. GI ₅₀ (all cell lines)	MDR1 Selectivity (3-1V1)
NSC632733	0.46		-	15.4 μ M	-
NSC633657	0.45		-	22.5 μ M	NT

FIG. 7 (Page 3 of 8)

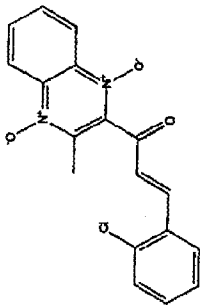
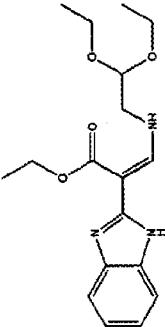
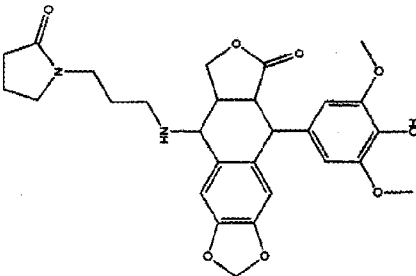
Molecule (NSC)	Pearson's Correlation	Structure	Reference	Av. GI ₅₀ (all cell lines)	MDR1 Selectivity (3-1/V1)
NSC621481	0.45		-	13.4 μ M	≤ 1
NSC710857	0.44		[24]	26.8 μ M	1.47
NSC651859	0.43		[26, 27]	0.9 μ M	-

FIG. 7 (Page 4 of 8)

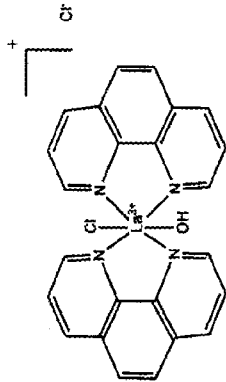
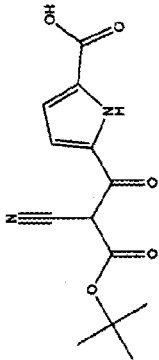
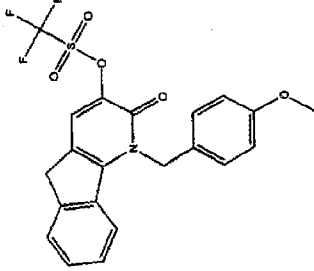
Molecule (NSC)	Pearson's Correlation	Structure	Reference	Av. GI ₅₀ (all cell lines)	MDR1 Selectivity (3-1/N1)
NSC632738	0.43		-	1.64 μ M	-
NSC693046	0.43		-	31.9 μ M	≤ 1
NSC705305	0.43		-	16.3 μ M	-

FIG. 7 (Page 5 of 8)

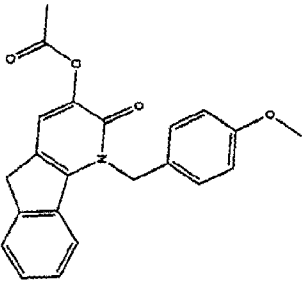
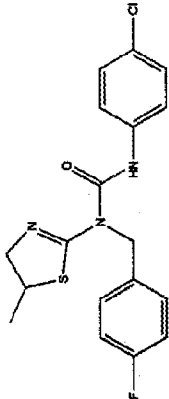
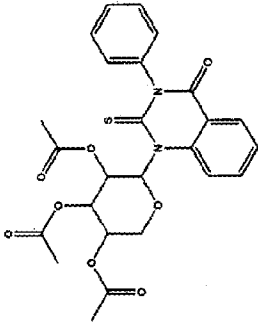
Molecule (NSC)	Pearson's Correlation	Structure	Reference	Av. GI ₅₀ (all cell lines)	MDR1 Selectivity (3-1/V1)
NSC705301	0.43		-	8.4 μ M	-
NSC672036	0.42		-	21.7 μ M	1.27
NSC639743	0.42		-	43.1 μ M	-

FIG. 7 (Page 6 of 8)

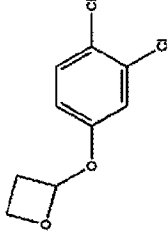
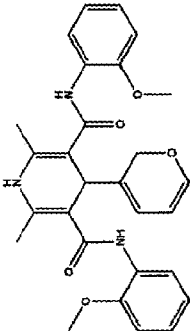
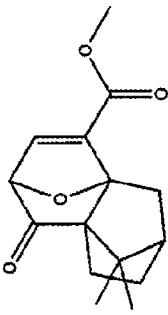
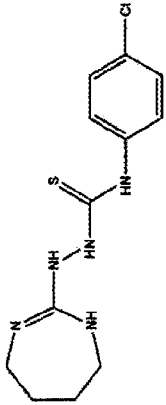
Molecule (NSC)	Pearson's Correlation	Structure	Reference	Av. GI ₅₀ (all cell lines)	MDR1 Selectivity (3-1/N/1)
NSC635977	0.42		-	65.1 μ M	-
NSC636097	0.42		-	11.3 μ M	≤ 1
NSC624967	0.41		[30, 31]	10.8 μ M	-
NSC669341	0.41		-	14.5 μ M	≤ 1

FIG. 7 (Page 7 of 8)

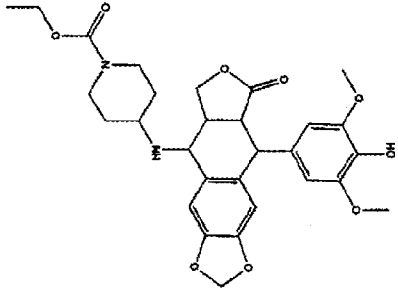
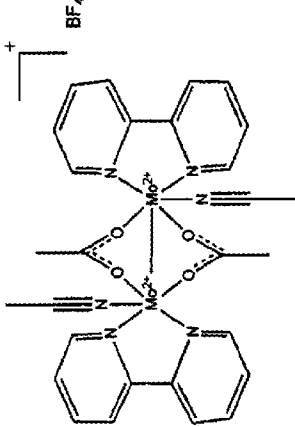
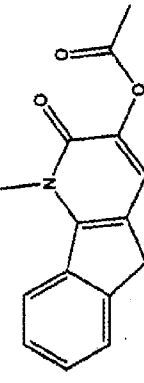
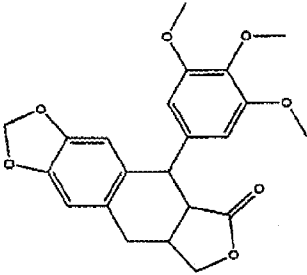
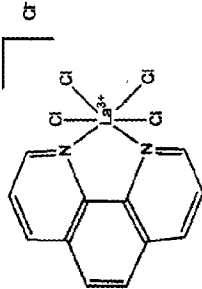
Molecule (NSC)	Pearson's Correlation	Structure	Reference	Av. GI ₅₀ (all cell lines)	MDR1 Selectivity (3-1/V1)
NSC653864	0.41		[33]	1.78 μ M	-
NSC654724	0.41		-	15.6 μ M	-
NSC697920	0.41		[34]	60.8 μ M	-

FIG. 7 (Page 8 of 8)

Molecule (NSC)	Pearson's Correlation	Structure	Reference	Av. GI ₅₀ (all cell lines)	MDR1 Selectivity (3-1/V1)
NSC403148	0.40		[27, 36, 37]	3.85 nM	NT
NSC632591	0.40		-	2.9 μM	-

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/036348

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/137 A61K31/337 A61K31/343 A61K31/395 A61K31/401
A61K31/4025 A61K31/4045 A61K31/4184 A61K31/427 A61K31/435
A61K31/4422 A61K31/4453 A61K31/4525 A61K31/517 A61K31/5375

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)

A61K

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

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

EPO-Internal, EMBASE, BIOSIS, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HEFFETER ET AL: "Multidrug-resistant cancer cells are preferential targets of the new antineoplastic lanthanum compound KP772 (FFC24)" BIOCHEMICAL PHARMACOLOGY, PERGAMON, OXFORD, GB LNKD- DOI:10.1016/J.BCP.2007.03.002, vol. 73, no. 12, 5 May 2007 (2007-05-05), pages 1873-1886, XP022062511 ISSN: 0006-2952	2,4-7,9, 11
Y	abstract; first of "results" ----- -/--	8,10, 12-16

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

☒ See patent family annex.

* Special categories of cited documents:

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

"E" earlier document 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

23 September 2010

Date of mailing of the international search report

05/10/2010

Name and mailing address of the ISA/

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Authorized officer

Dahse, Thomas

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2010/036348

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/009765 A2 (US HEALTH [US]; SZAKACS GERGELY [US]; ANNIREAU JEAN-PHILLIPE [FR]; LAB) 26 January 2006 (2006-01-26)	1,3,5-16
Y	p. 1, l. 11; p. 2, l. 9-16; claim 12; p. 11, l. 30 to p. 12, l. 6, in particular compound NSC10580	2,7-16
A	----- LIN A J ET AL: "Catecholamine analogs as potential antitumor agents. II" JOURNAL OF PHARMACEUTICAL SCIENCES 1981 US, vol. 70, no. 7, 1981, pages 806-808, XP002592579 ISSN: 0022-3549 abstract, compounds I, VI, X	1,3,5-16
A,P	----- ORINA J N ET AL: "Evaluation of current methods used to analyze the expression profiles of ATP-binding cassette transporters yields an improved drug-discovery database" MOLECULAR CANCER THERAPEUTICS 20090701 AMERICAN ASSOCIATION FOR CANCER RESEARCH INC. USA LNKD- DOI:10.1158/1535-7163.MCT-09-0256, vol. 8, no. 7, 1 July 2009 (2009-07-01), pages 2057-2066, XP002592580 ISSN: 1535-7163 Fig. 4B; p. 2065, col. 1, penultimate	1,3,5-16
X,P	----- TURK D ET AL: "Identification of compounds selectively killing multidrug-resistant cancer cells" CANCER RESEARCH 20091101 AMERICAN ASSOCIATION FOR CANCER RESEARCH INC. USA LNKD- DOI:10.1158/0008-5472.CAN-09-2422, vol. 69, no. 21, 1 November 2009 (2009-11-01), pages 8293-8301, XP002592581 ISSN: 0008-5472 abstract; table 4	1-16
Y	----- WO 02/102805 A1 (KAROLINSKA INNOVATIONS AB [SE]; LARSSON OLLE [SE]; AXELSON MAGNUS [SE]) 27 December 2002 (2002-12-27) table 5; fig. 2A/2B; claim 14	2,7, 9-13,16
	----- -/--	

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2010/036348

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/014128 A2 (FAUSTUS FORSCHUNGS CIE [DE]; KEPPLER BERNHARD [DE]) 20 February 2003 (2003-02-20) p. 12, example 2 -----	2,4-16
A	DE 101 38 538 A1 (FAUSTUS FORSCHUNGS CIE [DE]) 27 February 2003 (2003-02-27) example 2; claim 6 -----	2,4-16
A	US 4 699 978 A (BARTON JACQUELINE K [US]) 13 October 1987 (1987-10-13) col. 6, l. 19-20 and table 1; col. 2, l. 12-46 -----	2,4-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/036348

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.:
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:

see additional sheet

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 an 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.:
2(completely); 4-16(partially)
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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 3(completely); 5-16(partially)

directed to compounds of formula I for use as growth inhibitors of drug resistant cells.

2. claims: 2, 4-16(all partially)

directed to compound NSC43320 for use as growth inhibitors of drug resistant cells.

3. claims: 2, 4-16(all partially)

directed to compounds NSC672027, NSC672036 for use as growth inhibitors of drug resistant cells.

4. claims: 2, 4-16(all partially)

directed to compounds NSC632736, NSC632733, NSC632738, NSC654724, NSC632591, NSC162800, NSC165697, NSC619179, NSC619181, NSC619183, NSC619184, NSC619188, NSC630123, NSC632591, NSC632734, NSC632735, NSC632737, NSC632738 for use as growth inhibitors of drug resistant cells.

5. claims: 2, 4-16(all partially)

directed to compound NSC632955 for use as growth inhibitors of drug resistant cells.

6. claims: 2, 4-16(all partially)

directed to compound NSC633657 for use as growth inhibitors of drug resistant cells.

7. claims: 2, 4-16(all partially)

directed to compound NSC710857 for use as growth inhibitors of drug resistant cells.

8. claims: 2, 4-16(all partially)

directed to compounds NSC651859, NSC653864, NSC403148 for use as growth inhibitors of drug resistant cells.

9. claims: 2, 4-16(all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

directed to compound NSC693046 for use as growth inhibitors
of drug resistant cells.

10. claims: 2, 4-16(all partially)

directed to compounds NSC705305, NSC705301 for use as growth
inhibitors of drug resistant cells.

11. claims: 2, 4-16(all partially)

directed to compound NSC639743 for use as growth inhibitors
of drug resistant cells.

12. claims: 2, 4-16(all partially)

directed to compound NSC635977 for use as growth inhibitors
of drug resistant cells.

13. claims: 2, 4-16(all partially)

directed to compound NSC636097 for use as growth inhibitors
of drug resistant cells.

14. claims: 2, 4-16(all partially)

directed to compound NSC624967 for use as growth inhibitors
of drug resistant cells.

15. claims: 2, 4-16(all partially)

directed to compound NSC669341 for use as growth inhibitors
of drug resistant cells.

16. claims: 2, 4-16(all partially)

directed to compound NSC697920 for use as growth inhibitors
of drug resistant cells.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2010/036348

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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