Cyanooxime Inhibitors of Carbonyl Reductase and Methods of Using Said Inhibitors in Treatments Involving Anthracyclines

Henry A. Charlier  
Boise State University

Nikolay Gerasimchuk
Cyanooxime inhibitors of carbonyl reductase and methods of using said inhibitors in treatments involving anthracyclines

Inventors: Henry A. Charlter, Jr., Boise, ID (US); Nikolay Gerasimchuk, Springfield, MO (US)

Assignee: Boise State University, Boise, ID (US)

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U.S. Cl. ............................. 514/34; 514/640

Field of Classification Search ................. 514/34, 514/640

See application file for complete search history.

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Abstract
Compositions of matter for treating cancer patients are used to prevent or limit cardiotoxicity during or after treatment with anthracycline drugs, and to prevent or lower resistance to anthracycline drugs, both of which are believed to be caused by the human enzyme carbonyl reductase. Preferred embodiments comprise a pharmaceutical composition comprising compounds having halogenated (or pseudo-halogenated) ary1 groups, preferably halogenated (or pseudo-halogenated) arylcyanooximes or phenylcyanooximes and derivatives or analog thereof, including those comprising —Cl or —F, or other substituents on an aryl/phenyl ring. The preferred composition of arylcyanooxime(s) may be administered in a pharmaceutical composition also comprising at least one anthracycline compound, or may be administered separately from the at least one anthracycline compound.

2 Claims, 8 Drawing Sheets

OTHER PUBLICATIONS
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"2,2'-Sulfinyl-bis (4,6-dichlorophenol) Product Information," 222. sigmaldrich.com; May 24, 2005.
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Primary Examiner—Shaojia Anna Jiang
Assistant Examiner—Scarlett Goon
Attorney, Agent, or Firm—Pedersen & Company, PLLC; Ken J. Pedersen; Barbara S. Pedersen
**Arrow designates the carbon at position 13**

**Fig. 1**
Fig. 2

NADPH + H⁺ → CARBONYL REDUCTASE → DAUNORUBICIN

NADP⁺ → DAUNORUBICINOL
<table>
<thead>
<tr>
<th>Structure</th>
<th>Compound name</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>oximino(2,4-difluorophenyl)acetonitrile</td>
</tr>
<tr>
<td>C2</td>
<td>oximino(2,6-difluorophenyl)acetonitrile</td>
</tr>
<tr>
<td>C3</td>
<td>oximino(2,5-difluorophenyl)acetonitrile</td>
</tr>
<tr>
<td>C4</td>
<td>oximino(2-chloro-6-fluorophenyl)acetonitrile</td>
</tr>
<tr>
<td>C5</td>
<td>oximino(2,4-dichlorophenyl)acetonitrile</td>
</tr>
<tr>
<td>C6</td>
<td>oximino(2,6-dichlorophenyl)acetonitrile</td>
</tr>
</tbody>
</table>

Fig. 3
colorless liquid or solid

\[
\begin{align*}
Y & X \\
\text{NC} & \\
\end{align*}
\]

+ Na + CH₃-ONO \rightarrow

\[
\begin{align*}
Y & X \\
\text{NC} & \text{N} \\
\text{O}^\text{Na}^+ & \\
\end{align*}
\]

yellow solid + H₂O + CH₃OH

1) + dilute HCl to pH ~ 4
2) extraction with ether

\[
\begin{align*}
Y & X \\
\text{NC} & \text{N} \\
\text{OH} & \\
\end{align*}
\]

+ NaCl

colorless needle-type crystals

X and Y are: F and Cl atoms at the 2,4-; 2,5-; and 2,6-positions (refer to Figures 3A – 3F)

**Fig. 4**
Fig. 5A
Fig. 5B
<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>$K_I$ (µM)</th>
<th>Inhibition Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>29 ± 2</td>
<td>uncompetitive</td>
</tr>
<tr>
<td>C2</td>
<td>51 ± 2</td>
<td>uncompetitive</td>
</tr>
<tr>
<td>C3</td>
<td>42 ± 1</td>
<td>uncompetitive</td>
</tr>
<tr>
<td>C4</td>
<td>72 ± 4</td>
<td>uncompetitive</td>
</tr>
<tr>
<td>C5</td>
<td>11.8 ± 0.7</td>
<td>uncompetitive</td>
</tr>
<tr>
<td>C5*</td>
<td>10.6 ± 0.6</td>
<td>uncompetitive</td>
</tr>
<tr>
<td>C6</td>
<td>62 ± 4</td>
<td>uncompetitive</td>
</tr>
</tbody>
</table>

*This study was performed with a fixed menadione concentration of 250 µM and varied NADPH concentrations ranging from 2 – 50 µM.

**Fig. 6**
ALL INHIBITORS (C1-C6) BIND TO TERNARY AND/OR THE ENZYME-NADP+ BINARY COMPLEX

NADP+ (Q)

Menadione (P)

Menadione (B)

NADPH (A)

EAB⇌EPQ

E

EQ

EQ

or

EPQ1

Fig. 7
CR is a key factor in anthracycline-induced cardiotoxicity. Studies have shown that CR expression is increased in the myocardium of patients with anthracycline-induced heart failure. The exact mechanisms by which CR contributes to cardiotoxicity are not fully understood, but it is thought to play a role in the regulation of intracellular calcium homeostasis and mitochondrial function.

The present invention comprises inhibiting carbonyl reductase enzyme(s) and/or other enzyme(s) that catalyze anthracycline conversion to anthracycline metabolites. This has the direct effect of maintaining concentrations of anthracyclines, which are desirable for their cell-killing abilities, and, therefore, for their cancer-cell-killing abilities. Inhibition also has the indirect effect of lowering formation of metabolites that build up during or after treatment with anthracycline drugs, said metabolites being ones that are believed to disrupt heart muscle processes and therefore to interfere with heart function. Therefore, by using embodiments of the invented compositions and/or methods, much less anthracycline drug is expected to be needed to achieve the desired therapeutic effect.
desired killing of cells, and much less cardiotoxic metabolite will be produced over the duration of the cancer treatment. The invented compositions comprise compounds having at least one aryl group (preferably at least one phenyl group), wherein at least one of said at least one aryl/phenyl group comprises halogen or pseudo-halogen. In the preferred embodiments disclosed herein, these halogenated (or pseudo-halogenated) aryl/phenyl compounds further comprise at least one cyanooxime group. Especially-preferred embodiments of the invention comprise one or more substituted arylcyanooximes (or use thereof), and preferably at least one of the following compounds: oximino(2,4-difluorophenyl)acetonitrile (herein referred to as “C1”) and/or oximino(2,6-difluorophenyl)acetonitrile (herein referred to as “C2”) and/or oximino(2,5-difluorophenyl)acetonitrile (herein referred to as “C3”) and/or oximino(2-chloro-6-fluorophenyl)acetonitrile (herein referred to as “C4”) and/or oximino(2,4-dichlorophenyl)acetonitrile (herein referred to as “C5”) and/or oximino(2,6-dichlorophenyl)acetonitrile (herein referred to as “C6”) and/or derivatives or analogs thereof. The preferred composition of C1, C2, C3, C4, C5, and C6, and/or derivatives or analogs thereof, may be administered to a human (or other mammal) in a pharmaceutical composition comprising at least one antracycline compound, or may be administered separately from the at least one antracycline compound either at the same time as the antracycline(s), or any different time found to be effective for inhibiting formation of the antracycline metabolites.

Therefore, an object of the present invention is to inhibit one or more of the members of the aldo-keto reductase and/or short chain dehydrogenase/reductase protein superfamilies, which catalyze the conversion of antracyclines to anthracycline metabolites. The preferred compositions and methods are adapted to inhibit member(s) of these superfamilies, currently associated with cardiotoxicity from anthracycline chemotherapy, that is, human carbonyl reductase. A synergistic effect of inhibiting said reductase enzyme is expected to be that lower dosages of the anthracycline drug will be effective for cancer-cell-killing.

A method for synthesizing disubstituted arylcyanooximes, including C1, C2, C3, C4, C5, and C6 is also disclosed. Such compounds can be synthesized by nitrating the appropriate disubstituted phenylacetonitriles by treatment with neat organic nitrates.

**BRIEF DESCRIPTION OF THE DRAWINGS**

FIG. 1 is a representation of an anthracycline compound, which may be doxorubicin (R—OH) or daunorubicin (R=H), wherein the arrow designates the carbon at position 13.

FIG. 2 is a representation of a carbonyl reductase-NADPH mechanism for reducing the antracyline daunorubicin to the antracyline alcohol metabolite daunorubicinol.

FIGS. 3A-F show the chemical structures of oximino(2,4-difluorophenyl)acetonitrile (C1, in FIG. 3A); oximino(2,6-difluorophenyl)acetonitrile (C2, in FIG. 3B); oximino(2,5-difluorophenyl)acetonitrile (C3, in FIG. 3C); oximino(2-chloro-6-fluorophenyl)acetonitrile (C4, in FIG. 3D); oximino(2,4-dichlorophenyl)acetonitrile (C5, in FIG. 3E); oximino(2,6-dichlorophenyl)acetonitrile (C6, in FIG. 3F).

FIG. 4 shows a scheme describing the general synthetic strategy used to create C1, C2, C3, C4, C5, and C6, wherein X and Y may be F and C1 atoms at the 2,4-; the 2,5-; and the 2,6-positions (as will be understood by viewing FIGS. 3A-F), and wherein R—ONO refers to alkyl nitrites.

**FIGS. 5A and B are graphs showing oximino(2,4-dichlorophenyl)acetonitrile (C5) as an uncompetitive inhibitor against both menadione (FIG. 5A) and NADPH (FIG. 5B).**

**FIG. 6 describes inhibition patterns seen with inhibitors C1, C2, C3, C4, C5, and C6 wherein K_i stands for the intercept inhibition constant.**

**FIG. 7 summarizes data showing that all of the inhibitors bind to enzyme forms distinct from those to which NADPH and menadione bind, as determined from inhibition studies such as those represented in FIGS. 5A, 5B, and 6. All of the inhibitors C1, C2, C3, C4, C5, and C6 (represented by "") bind to ternary and/or the enzyme-NADP+ binary complex. Enzyme (CR) is represented by “E". Menadione could be replaced by anthracyclines or other carbonyl-containing substrates.**

**DESCRIPTION OF THE PREFERRED EMBODIMENTS**

Referring to the figures, there are shown several, but not the only, embodiments of the invented composition of matter and methods for enhancing the efficacy of anthracycline drug cancer treatment and/or limiting side-effects thereof. The preferred methods and compositions of matter may maintain effective concentrations of anthracycline(s) during cancer treatment, by preventing or lowering conversion of the anthracycline(s) to metabolites that are less effective or ineffective as cancer-cell-killing species. The preferred methods and compositions may also prevent or lower the potentially life-threatening cardiotoxicity associated with anthracycline chemotherapy for cancer patients.

The preferred compounds, for use in the above-described prevention or lowering of anthracycline conversion, have at least one aryl (preferably phenyl) group, wherein at least one aryl/phenyl group comprises halogen or pseudo-halogen. Pseudo-halogen may include binary inorganic compounds of the general form X:Y, wherein X is a cyanide, cyanate, or thiocyanate and where Y is any of X or a true halogen, including but not limited to cyanogen ((CN)2) and iodine cyanide (ICN). Preferably, these halogenated (or pseudo-halogenated) aryl/phenyl compounds further comprise at least one cyanooxime group. The especially-preferred embodiments comprise one or more disubstituted arylcyanooximes, and preferably one or more of the following compounds: oximino(2,4-difluorophenyl)acetonitrile (herein referred to as “C1”), oximino(2,6-difluorophenyl)acetonitrile (herein referred to as “C2”), oximino(2,5-difluorophenyl)acetonitrile (herein referred to as “C3”), oximino(2-chloro-6-fluorophenyl)acetonitrile (herein referred to as “C4”), oximino(2,4-dichlorophenyl)acetonitrile (herein referred to as “C5”), or oximino(2,6-dichlorophenyl)acetonitrile (herein referred to as “C6”).

See FIGS. 3A-F. Also, it is expected that derivatives or analogs of these compounds may be effective in the place of one or more of these six compounds, or as a supplement to one or more of these compounds.

The general synthetic strategy used to make compounds C1, C2, C3, C4, C5, and C6 is outlined in FIG. 4. Commercially-available alkyl nitrites were found to lack stability, and were less than optimal for the desired synthesis. Instead, an improved synthesis has been invented that comprises the use of gaseous methyl nitrite, CH₃—ONO, as a nitrating agent. Small quantities (2.5 L) of the gaseous methyl nitrite were made fresh before each use, from NaNO₂, CH₃OH, and H₂SO₄. This invention technique resulted in very high yields of the desired oxime. The typical procedure for the synthesis of the preferred dihalogenated arylcyanooximes is presented below:
Synthesis of oximinocarbonyl(2,4-difluorophenyl)acetanilide, ("C1")

Thinly sliced metallic sodium (0.754 g; 0.033 mol) was dissolved at room temperature under nitrogen protection in 300 mL of i-propanol. The starting 2,4-difluorophenylacetanilide, \( \text{C}_8\text{H}_5\text{C}=\text{C}(-\text{F})\text{C}_6\text{H}_4\text{F}_2 \) (5.00 g; 0.033 mol), was dissolved in 50.0 mL of i-propanol and then added to the sodium isopropanoxide solution. Freshly obtained, within about 10 minutes, from NaOH, 2,2-di-tert-butyl-4-methylphenol (1.00 mL; 0.050 mol), and H_2O, 2,4-difluorophenylacetanilide, \( \text{C}_8\text{H}_5\text{C}=\text{C}(-\text{F})\text{C}_6\text{H}_4\text{F}_2 \) (5.00 g; 0.033 mol), was dissolved in 50.0 mL of i-propanol and then added to the sodium isopropanoxide solution. After an overnight standing at 4°C, the solvent was removed using the rotovap and the remaining yellow solid residue of NaNal (L=2,6-difluorophenolate) was thoroughly dried at room temperature using an oil pump. The solid NaF was re-dissolved in 50.0 mL of water and the solution was slowly acidified with 1.0M HCl. After filtration, the precipitate of NaNal was collected and dried. Then, the precipitate of NaNal was dissolved in 50.0 mL of i-propanol and the solution was filtered. The filtrate was concentrated to dry. The resulting solid residue was dried in vacuo at 4°C. The yield was 91%, m.p.=64-66°C, Rf=0.28 (EtOAc:hexane=1:4).

1H NMR, ppm: 14.10 (1H, s, oxime group); 7.10 (1H, multiplet at 6-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)), 6.84 (1H, multiplet at 6-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)), 6.55 (1H, 2-proton at 5-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)), 3.87 (1H, multiplet at 6-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)).

25 NMR spectra evidenced the mixture of syn (60%) and anti (40%) isomers in DMSO-d_6. Data for syn-isomer: \(^1\)H NMR, ppm: 14.12 (1H, s, oxime group); 7.10 (1H, multiplet at 6-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)), 6.84 (1H, multiplet at 6-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)), 6.55 (1H, 2-proton at 5-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)), 3.87 (1H, multiplet at 6-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)).

25 NMR spectra evidenced the mixture of syn (60%) and anti (40%) isomers in DMSO-d_6. Data for anti-isomer: \(^1\)H NMR, ppm: 14.12 (1H, s, oxime group); 7.10 (1H, multiplet at 6-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)), 6.84 (1H, multiplet at 6-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)), 6.55 (1H, 2-proton at 5-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)), 3.87 (1H, multiplet at 6-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)).

Syntheses of the other cyanoximes followed similar procedures with the appropriate corresponding phenylacetonitrile. The characterization of the resulting products followed:

Oximinocarbonyl(2,6-difluorophenyl)acetanilide, ("C2")

Colorless needle-like crystals; yield=95%, m.p.=119-120°C, Rf=0.38 (EtOAc:hexane=1:4). Found: C, 48.33; H, 2.09; N, 14.11. NMR spectra indicate mixture of syn (73%) and anti (27%) isomers in DMSO-d_6. The following data for syn-isomer: \(^1\)H NMR, ppm: 14.51 (1H, s, oxime group); 7.66 (1H, multiplet at 5-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)), 6.84 (1H, multiplet at 5-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)), 6.55 (1H, 2-proton at 5-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)). 7.45 (1H, multiplet at 4-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)).

Colorless needle-like crystals; yield=95%, m.p.=119-120°C, Rf=0.38 (EtOAc:hexane=1:4). Found: C, 48.33; H, 2.09; N, 14.11. NMR spectra indicate mixture of syn (73%) and anti (27%) isomers in DMSO-d_6. The following data for syn-isomer: \(^1\)H NMR, ppm: 14.51 (1H, s, oxime group); 7.66 (1H, multiplet at 5-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)), 6.84 (1H, multiplet at 5-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)), 6.55 (1H, 2-proton at 5-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)). 7.45 (1H, multiplet at 4-position; \( \delta_{\text{H}}=12.5 \text{Hz} \)).
chemotherapy by offsetting the negative side effects of this chemotherapy. Also, as discussed above, the preferred compositions and methods may decrease anthracycline drug resistance, further improving the results of anthracycline chemotherapy.

C1, C2, C3, C4, C5, and C6 have been shown by the inventor to be uncompetitive inhibitors against both coenzyme and carbonyl substrates, with $K_i$ values in the low to mid micromolar range (10.8-72 μM). These preferred compositions have been seen to exhibit inhibition patterns suggestive of binding to multiple enzyme forms, which may mean that increased anthracycline dosages may not overcome the inhibition.


To the inventors’ knowledge, however, the C1, C2, C3, C4, C5, and C6 arylecyanooximes reported herein have not been used in any process for improving efficacy of drugs used in cancer treatment or for treating or preventing side effects of cancer treatment or cardiotoxicity. Further, the synthetic methods for creation of C1, C2, C3, C4, C5, and C6 have not been previously reported. The inventors believe that said effective and safe doses may be found without undue experimentation by one of skill in the art after reading this disclosure.

In use, one or more of the preferred compounds (C1, C2, C3, C4, C5, and C6) may be used in a pharmaceutical composition, which may also comprise one or more of the anthracycline drugs and/or other chemotherapy drugs or other medicines that may be beneficial to the cancer patient. Preferably, the C1, C2, C3, C4, C5, and C6 and anthracycline compositions are given at levels that produce the desired anti-cancer effects without the cardiotoxicity side effects. Therefore, the relative compositions may be changed for different anthracyclines and/or for different patients and/or for different cancers. The methods include treatment of, or treatment of side effects, for all cancers for which anthracyclines are used. Embodiments of the invention therefore include a pharmaceutical composition comprising at least one anthracycline compound and C1, C2, C3, C4, C5, C6 or a mixture of some of all thereof. The inventor envisions that there may be analogs or derivatives of C1, C2, C3, C4, C5, and/or C6 that also may be effective in compositions and methods of the invention. For example, the compositions may include anthracycline compounds selected from the group consisting of adriamycin/doxorubicin, daunorubicin/daunomycin, epirubicin, idarubicin, and a mixture of two or more thereof.

While the preferred patients are humans, animals may also benefit from the compositions and methods. Embodiments of the invented method may be for preventing or treating cardiotoxicity associated with anthracycline cancer chemo...
therapy in a mammal in need thereof, wherein the method comprises administering to the mammal a composition comprising an effective amount of a pharmaceutical composition comprising at least one anthracycline compound and at least one compound or mixture selected from the group consisting of C1, C2, C3, C4, C5, C6, a mixture of some of all of C1, C2, C3, C4, C5, and/or C6, an analog and/or derivative of C1, C2, C3, C4, C5, C6, and mixtures of two or more thereof. Effective amounts will be determined by methods known to those of skill in the art. Examples of anthracycline compounds include adriamycin/doxorubicin, daunorubicin/daunomycin, epirubicin, idarubicin, and a mixture of two or more thereof.

Instead of, or in addition to, administering a pharmaceutical composition including both anthracycline(s) and C1, C2, C3, C4, C5, and/or C6, separate pharmaceutical compositions may be used. For example, methods may include preventing or treating a disease or condition associated with carbonyl reductase in a mammal in need thereof by administering to the mammal a first pharmaceutical composition comprising at least one anthracycline compound; and also administering to the mammal a second pharmaceutical composition comprising C1, C2, C3, C4, C5, or C6, or a mixture of some or all thereof. The first and second pharmaceutical compositions may be administered at the same time, or may be administered at nearly the same time (for example, within 15 minutes or less), or preferably within a few hours of each other (for example, within 2 hours or less). It may be beneficial to treat the patient with C1, C2, C3, C4, C5, and/or C6 prior to anthracycline therapy (for example, two hours or less prior to anthracycline treatment), to block carbonyl reductase before administration of the anthracycline drug(s).

Inhibition Data
Six arylethanoximes (C1, C2, C3, C4, C5, and C6) were tested as possible inhibitors for carbonyl reductase. (See the syntheses described earlier in this disclosure.) All were found to be uncompetitive inhibitors against the carbonyl substrate, but only C5 (oximino(2,4-dichlorophenyl)acetonitrile) was found to be a potent inhibitor of carbonyl reductase. See FIGS. 3A-F for the structures of the arylethanoximes that were tested and found to be uncompetitive inhibitors. See FIGS. 5A and B, portraying the 1/rate vs. 1/substrate concentration taken with C5, with menadione and NADPH as the varied substrates, respectively. As will be understood by those of skill in the art, the FIGS. 5A and B data show changes in only y-intercept, indicating uncompetitive inhibition. As illustrated in FIG. 6, all of the inhibitors tested showed uncompetitive inhibition. Therefore, while compositions comprising C5 are preferred, compositions comprising C1, C2, C3, C4, and/or C6 are also included in embodiments of the invention and are also expected by the inventors to be beneficial in the methods of the invention.

From the above inhibition patterns, the inhibitors C1, C2, C3, C4, C5, and C6 more likely bind to the enzyme-NADP+ binary complex, or possibly the enzyme-menadione-NADPH ternary complex as illustrated in FIG. 7. It is expected that substrate carbonyls should not appreciably compete against the preferred inhibitors at these sites. Thus, said preferred inhibitors according to the invention are expected to remain available for, and will effectively carry out, inhibition of the mechanism that would otherwise result in lower efficacy of anthracycline(s) drugs and in cardiotropic compounds.

Although this invention has been described above with reference to particular means, materials and embodiments, it is to be understood that the invention is not limited to these disclosed particulars, but extends instead to all equivalents within the broad scope of the following claims.

The invention claimed is:
1. A pharmaceutical composition for reducing cardiotoxicity during anthracycline cancer treatment, the composition comprising at least one anthracycline compound selected from the group consisting of adriamycin, daunomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, and mixtures of two or more thereof, and at least one compound adapted to limit formation of anthracycline alcohol metabolite(s) and being a human carbonyl reductase enzyme inhibitor selected from the group consisting of: oximino(2,4-difluorophenyl)acetonitrile ("C1"), oximino(2,6-difluorophenyl)acetonitrile ("C2"), oximino(2,5-difluorophenyl)acetonitrile ("C3"), oximino(2-chloro-6-fluorophenyl)acetonitrile ("C4"), oximino(2,4-dichlorophenyl)acetonitrile ("C5"), oximino(2,6-dichlorophenyl)acetonitrile ("C6"), and mixtures of two or more thereof, wherein the pharmaceutical composition comprises an amount of said anthracycline compound effective for cancer cell cytotoxicity, and the pharmaceutical composition comprises an amount of human carbonyl reductase enzyme inhibitor such that the concentration gives a Kd value in the range of 10.8-72 µM.
2. A composition as in claim 1 wherein said human carbonyl reductase enzyme inhibitor is made by nitrosating a substituted phenylacetonitrile by treatment with gaseous methylnitrite, CH3ONO, at room temperature or below.

* * * * *
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page
Name of the Assignee Item (73) should read: Boise State University
Assignee of the interest of Henry A. Charlier, Jr.

Signed and Sealed this Tenth Day of April, 2012

[Signature]

David J. Kappos
Director of the United States Patent and Trademark Office