Selected copper(I) complexes as potential anticancer agent

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Introduction

Cancer is the second most frequent cause of death in the world [1]. The discovery of antitumor activity of cisplatin began a search for other metal complexes with cytotoxic properties against cancer cells. One of the transition metal, whose complexes are extensively tested for antitumor application is copper. Copper is a trace element essential for human life. It is a building element of several important enzymes (e.g. superoxide dismutase, cytochrome oxidase, tyrosinase) and it regulates the intracellular redox potential, while its complexes possess antibacterial, antifungal, antiviral, anti-inflammatory and anticancer properties. As potential anticancer drugs, there are currently extensively studied mainly complexes of copper(II). There are only few complexes of copper(I) in the literature, whereas they also show a very strong cytotoxic activity against tumor cells *in vitro* [2].

Anticancer activity of copper

Over 95% of copper (both Cu(II) and Cu(I)) that is present in serum is bound to ceruloplasmin (ferroxidase). However, it is not responsible for transporting copper inside the cell. Before they enter the cell, copper(II) ions are reduced to copper(I) by metalo-reducatases located on the cell's surface. Cu^+ ions are transported into the cell mainly by a specific copper transporter (hCtr). The independent system of entering the cell, enables biologically active copper compounds to penetrate the cell surface without binding to other agents as opposite to coordination compounds of other metals [2÷4].

Anticancer activity of copper(I) compounds may be a result of different mechanisms. They are described in the following paragraphs of this review.

Anticancer activity of copper complex compounds is related to their ability to produce reactive oxygen species (ROS). Copper(I) ions can reduce hydrogen peroxide to hydroxyl radical. Copper(II) ions may in turn be reduced to Cu(I) by superoxide anion($O_2^{\bullet -}$), or glutathione. Therefore, it can be concluded that the production of reactive oxygen species such as $OH^\bullet$ are driven by the copper, regardless of the form in which it is initially introduced into the body – Cu^+, or Cu^{2+} [2, 5].

$$Cu^{2+} + O_2^{\bullet -} \rightarrow Cu^+ + O_2$$
$$Cu^+ + H_2O_2 \rightarrow Cu^{2+} + OH^\bullet + OH^-$$

Superoxide anion ($O_2^{\bullet -}$) is the product of reduction of the molecular oxygen that occurs in many biological processes. It is converted into hydrogen peroxide through dismutation. Both of these forms of ROS lead to the formation of another type of reactive oxygen species – the hydroxyl radical ($OH^\bullet$). It occurs in a reaction catalysed by copper (or iron) ions. This radical is believed to be the main factor causing DNA damage in cells under oxidative stress [6].

Copper compounds are also thought to have nuclease activity. The ability of copper to cut a DNA helix has been proved in studies conducted with the use of Cu(I) complexes with two molecules of 1,10-phenanthroline (phen). $[Cu(phen)_2]^+$ was initially non-covalently bound to DNA. In this form, it was oxidized to a copper(II) compound in the presence of hydrogen peroxide. The final result of those processes was cutting DNA or RNA strands into fragments. The postulated factor directly responsible for cutting the DNA was an adduct in which $[Cu(phen)_2]^{2+}$ was coordinated with the hydroxyl radical $OH^\bullet$ and linked by non-covalent interactions with DNA [7, 8].

Copper compounds coordinated to phenanthroline skeleton ligands (see Fig. 1), such as $[Cu(dmp)_2]^+$, are thought to have the ability of intercalation. Furthermore, it was indicated that the $[Cu(dmp)_2]^+$ (dmp=2,9-dimethyl-1,10-phenanthroline) can be an inhibitor of the process of DNA transcription [9]. The $[Cu(bcp)_2]^+$ (bcp=2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline) is in turn believed to possess the ability of forming bridges between double-stranded fragment of DNA and another fragment of such a type [10].

Selected cuprous complexes

Selected complexes of copper(I), which were extensively investigated for anticancer activity, are presented in the subsequent paragraphs. Diversity of ligands used to synthesize those complexes causes that each one could possess other mechanism of action.

Mononuclear compounds

In 1987 Berners-Price and co-workers [11] presented copper(I) complexes with molecular formula $[Cu(P\text{-}P)_2]Cl$, where central Cu^+ ion was coordinated with two molecules of bidentate phosphine. The structures of these complexes are presented in Figure 1.

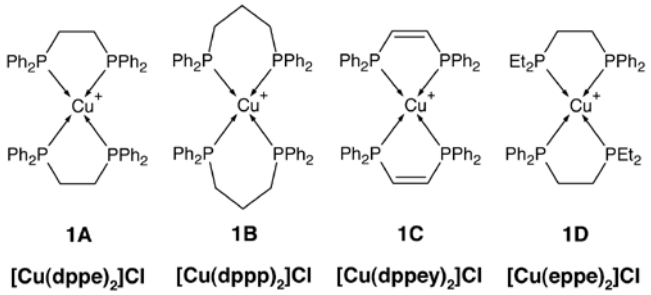

Fig. 1. The structures of copper(I) complexes with bidentate phosphine

Cytotoxicity of compounds **1B** and **1C** are several times higher than the one presented by uncoordinated ligands tested in the same cell line. Compound **1D** possesses anticancer activity (only *in vitro*), however it is lower than in **1B** and **1C**. Moreover, **1C** also possesses *in vivo* anticancer activity. Additionally, the equilibrium between mononuclear $[Cu(dppe)_2]Cl$ and binuclear form $(CuCl)_2(dppe)_3$ is observed in **1A** solution. For this reason cytotoxicity cannot be unambiguously assigned to mononuclear $[Cu(dppe)_2]Cl$ [11].

In order to increase solubility of copper(I) complexes in water, Marzano et al. introduced the hydroxyl groups to analysed phosphines. It is worth to mention that introduction of OH does not destabilize cuprous complexes. Structure of copper(I) complex ion of compound $[Cu(thp)_4][PF_6]$ (**2**), synthesized by the same research group, is shown in Figure 2. In this compound central ion Cu^+ is coordinated with four molecules of tris(hydroxymethyl)phosphine.

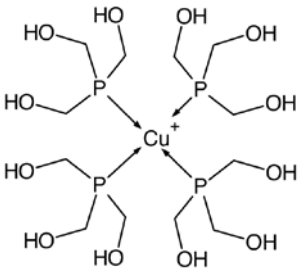

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Fig. 2. Complex ion of the compound $[Cu(thp)_4][PF_6]$

$[Cu(thp)_4][PF_6]$ exhibits even 40-fold higher cytotoxicity than cisplatin (*e.g.* for colorectal adenocarcinoma cell line CaCo-2: IC_{50} = 1.08 ± 0.12 μM for **2**, IC_{50} = 35.42 ± 1.40 μM for cisplatin; 48-hours test) [12]. Moreover, in survey performed on cancer cells of a colon **2** reacts selectively with cancer cells, but at the same time it is not harmful for healthy cells. The selectivity is higher than the one observed at cisplatin or oxaliplatin – the drug applied in colorectal cancer treatment (*e.g.* for non-tumour human fibroblasts cell line MRC-5: IC_{50} = 32.67 ± 1.34 μM for **2**, IC_{50} = 19.66 ± 1.31 μM for cisplatin and IC_{50} = 23.93 ± 1.35 μM for oxaliplatin; 72-hours test) [13]. What is more, this compound is effective in case of those types of cancer which are resistant to platin complexes (*e.g.* for colon carcinoma cell line LoVo IC_{50} = 2.05 ± 0.43 μM for oxaliplatin, 1.37 ± 0.35 μM for compound **2**, whereas for resistant to oxaliplatin cell line LoVo-OxPt IC_{50} = 10.89 ± 1.34 μM for oxaliplatin and IC_{50} = 1.46 ± 0.27 μM for **2**; 48-hours assay) [13]. The described complex of copper leads to cell death via nonapoptotic way (so-called type III cell death). Cell death is not caused by DNA fragmentation. What is more, activation of caspases does not take place. On the contrary, **2** may even inhibit caspases 3 and 7. Characteristic of this type of cell death are: massive cytoplasmic vacuolization, endoplasmic reticulum stress and inhibition of proteasome 26S functions. Furthermore, an increased production of reactive oxygen species (ROS) was observed, which caused an oxidative stress and led cells to death. It was unexpected that the complex $[Cu(bhpe)_2][PF_6]$ synthesized by the same research group (Fig. 3), where monodentate phosphines were replaced by bidentate phosphines, would show only an inconsiderable anticancer activity. It was much lower not only than **2**, but also than cisplatin (*e.g.* for colorectal adenocarcinoma cell line CaCo-2: IC_{50} = 52.50 ± 0.81 μM for **3**, IC_{50} = 1.08 ± 0.12 μM for **2**, IC_{50} = 35.42 ± 1.40 μM for cisplatin; 48-hours test) [12].

The reason for an insignificant cytotoxicity of compound **3** could be its high stability and inertness in process of ligands exchange. It could be confirmed by results obtained from a mass spectrometry. For complex **3** no fragmentation was observed, as opposed to **2**, in whose spectrum not only $[Cu(thp)_4]^+$ ion peak was observed, but also peaks ascribed to $[Cu(thp)_3]^+$ and $[Cu(thp)_2]^+$. It can be concluded that ability to exchange ligands has crucial influence for cytotoxicity of the described complexes [12,13].

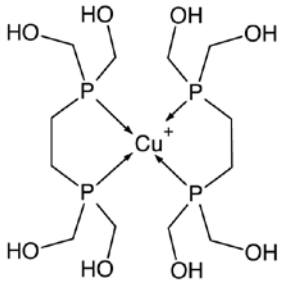

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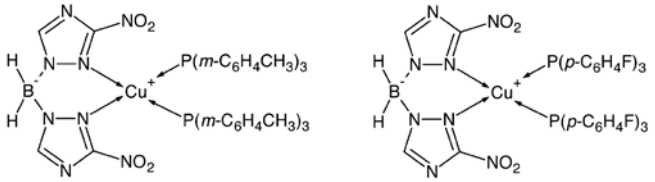
Fig. 3. Complex ion of compound $[Cu(bhpe)_2][PF_6]$

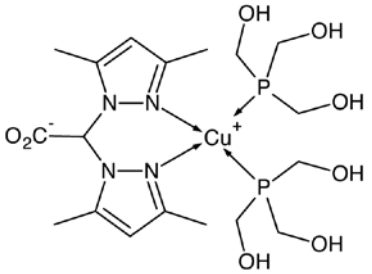
Anticancer activity is exhibited by copper(I) complexes possessing pyridine-type ligands (pyridine, bipyridine, phenanthroline ect.), or such where copper(I) ion is coordinated to phosphine ligands. Presumably, introduction of both types of ligands mentioned to one molecule would make it possible to create a compound with an increased activity against cancer cells. Marzano research group, mentioned before, synthesized complexes depicted in Figure 4, which contained triazolylborate ligands.



4A **4B**

Fig. 4. Complexes of Cu^+ with triazolylborate ligands

These compounds present activity higher than the one observed at cisplatin for all cell lines tested (Tab. 1), especially for lung adenocarcinoma cells (A549 cell line), where the IC_{50} value was approximately 17-fold lower for compound **4B** (IC_{50} = 2.35 ± 0.9 μM) and 26-fold lower for complex **4A** (IC_{50} = 1.52 ± 0.7 μM), than for tested in the same condition cisplatin (IC_{50} = 39.27 ± 1.9 μM; 48-hours test) [14]. The mechanism of the action has been unknown so far. However, it is posited that it could be similar to that exhibited by copper(I) complex showed in Figure 5.

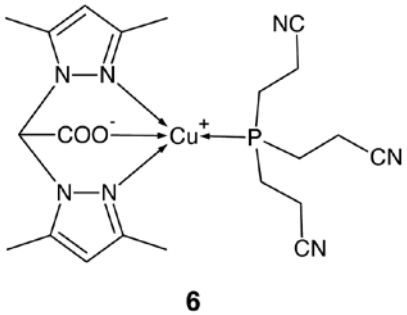


5

Fig. 5. Complex of Cu(I) leading to cell death in a nonapoptotic way

Compound **5** exhibits activity from 2 to 19 times higher than cisplatin for investigated cell lines (*e.g.* for breast cancer cell line MCF-7 IC_{50} = 1.55 ± 0.19 μM for **5** and IC_{50} = 30.18 ± 1.5 μM for cisplatin; 48-hours test) [15]. *In vitro* tests suggest that the complex mentioned leads to cell death in a nonapoptotic pathway, as it was observed at $[Cu(thp)_4][PF_6]$ (**2**). Lack of caspase 3 activity, an increase in a cell size and a cytoplasmic vacuolization confirm this hypothesis [15].

Other interesting compound revealing much higher cytotoxicity than cisplatin is a coordination compound of copper(I) displayed in Figure 6 (*e.g.* for colon carcinoma cell line HCT-15 IC_{50} = 1.05 ± 0.31 μM for **6** and IC_{50} = 16.65 ± 2.63 μM for cisplatin) [16].



6

Fig. 6. Electrically neutral copper(I) complex

Due to the fact that the applied tridentate ligand simultaneously neutralizes positive charge of Cu^+ ion, the received compound **6** is electrically neutral. A mechanism of cellular internalization has not been explained so far. It is assumed that penetration of a cell membrane is not supported by human copper transporters (hCtr), which can transfer positively charged molecules. As the authors postulate, a dentate ligand could be the factor, which supports complexes' transfer. It acts as ionophore, as it was the case with copper(II) complexes [16, 17].

Coordination number 4 is not the only one possible coordination number for copper(I) complexes. In Figure 7 a two-coordinated compound of Cu^+ is depicted. *In vitro* cytotoxic activity of the presented compound was approximately 2,5-fold higher than the one measured for cisplatin. What is remarkable, this effect was also observed for cell lines resistant to cisplatin (*e.g.* for sensitive to cisplatin human ovarian cancer cell line 2008 IC_{50} = 1.84 ± 0.32 μM for **7** and 3.12 ± 1.03 μM for cisplatin; in case of resistant to cisplatin human ovarian cancer cell line C13* IC_{50} is 2.08 ± 0.72 for **7** and 22.18 ± 2.01 for cisplatin; 72-hours assay) [18]. Presumably, mechanism of activity of compound **8** is connected with its confirmed ability to disturb respiration by altering mitochondrial membrane potential and producing reactive oxygen species [18].

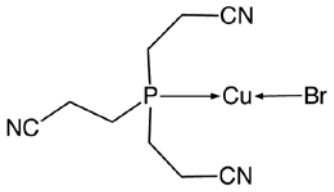


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Fig. 7. Two-coordinated complex of Cu(I)

Starosta et al. [19÷24] synthesized copper(I) complexes, whose general structure is displayed in Figure 8.

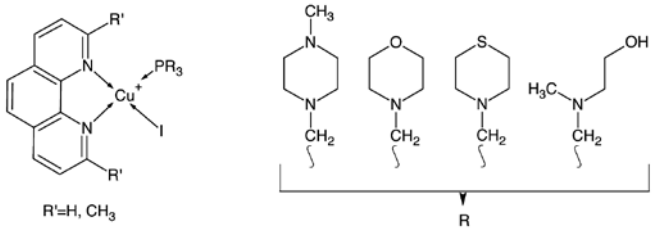

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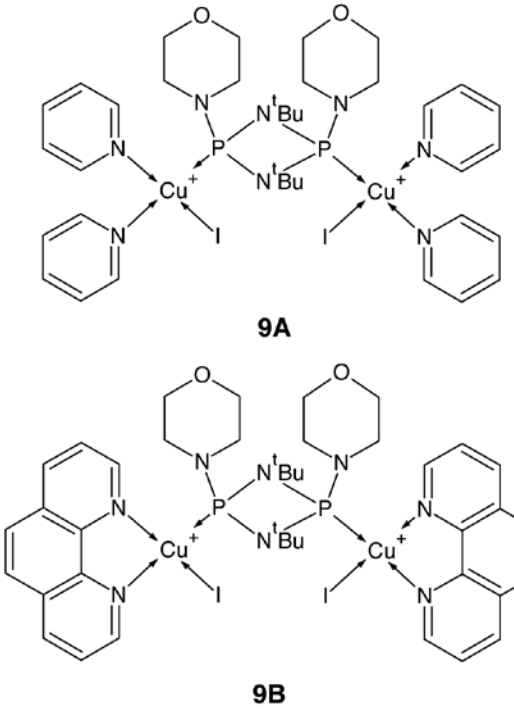
Fig. 8. General structure of copper(I) complexes containing phosphine, phenanthroline-type ligand and iodide ion

The obtained complexes show high cytotoxicity not only to human ovarian carcinoma cell lines sensitive to cisplatin, but also to those resistant to this drug (for resistant to cisplatin human ovarian carcinoma cell line SKOV 3 IC_{50} is approximately 2–3 μM depending on examined copper(I) compounds, whereas for cisplatin IC_{50} = 180.5 ± 9.3 μM; for sensitive to cisplatin human ovarian carcinoma cell line MDAH 2774 IC_{50} is approximately 2–7 μM for analysed copper(I) complex and 77.2±7.6 μM for cisplatin; 24-hours test) [19]. As the authors proved, activity exhibited by investigated cuprous compound is many times higher than the one presented by uncoordinated diimine or phosphine ligands (IC_{50}:100–500 μM in case of both cell lines: SKOV 3 and MDAH 2774) [19÷24].

Polinuclear compounds

In 2010 Balakrishna and co-workers [25] exhibited group of polinuclear copper(I) complexes, which possessed in their coordination sphere both pyridine-type and phospine-type ligands. In Figures 9 and 10 examples of synthesized compounds are depicted.



9A

9B

Fig. 9. Binuclear copper(I) complexes synthesized by Balakrishna et al

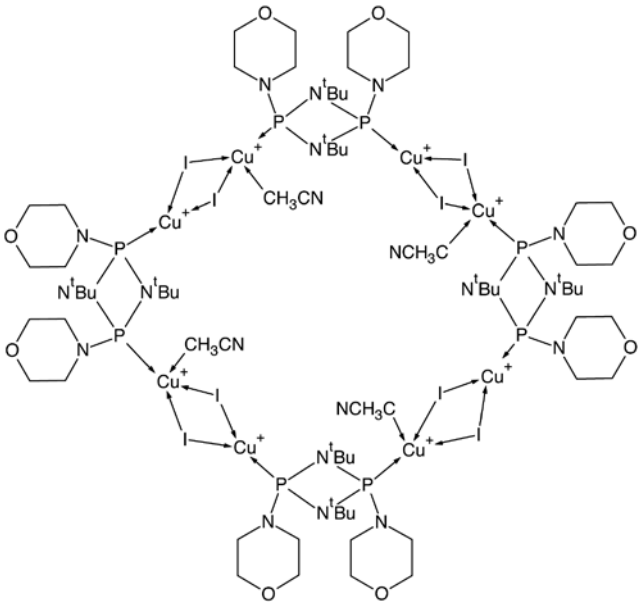


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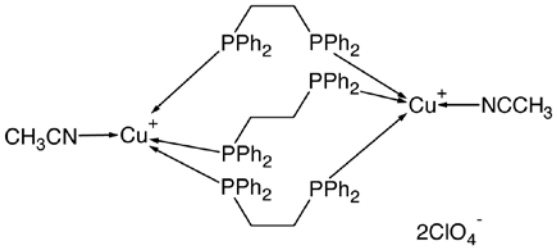
Fig. 10.Octanuclear Cu^+ compound synthesized by Balakrishna et al

Antiproliferative activity for cervical cancer cells was proved for all three copper complexes presented in Figures 10 and 11. Moreover, it was observed that inhibition of proliferation was more effective for the complexes discussed, than for cisplatin, especially for **9B** (antiproliferative ability was assessed as a percent of inhibition of cervical cancer HeLa cell line proliferation: 50 ± 4 % for **9A**, 62 ± 9 % for **10**, 100 % for **9B** and 49 ± 7 % for cisplatin; in 10 μM concentration) [25]. Biological tests carried out with the use of this complex show that **9B** inhibits proliferation not only of cervical cancer cells, but also of human breast cancer cells and Chinese hamster ovary cells. Moreover, it is several times more efficient than cisplatin. Furthermore **9B** has an ability to damage the DNA integration, block cell cycle in G1 phase and induce apoptosis [25].

Another interesting binuclear cuprous compound revealing anticancer activity, is depicted in Figure 12 complex with formula $[Cu_2(dppe)_3(CH_3CN)_4](ClO_4)$.



11

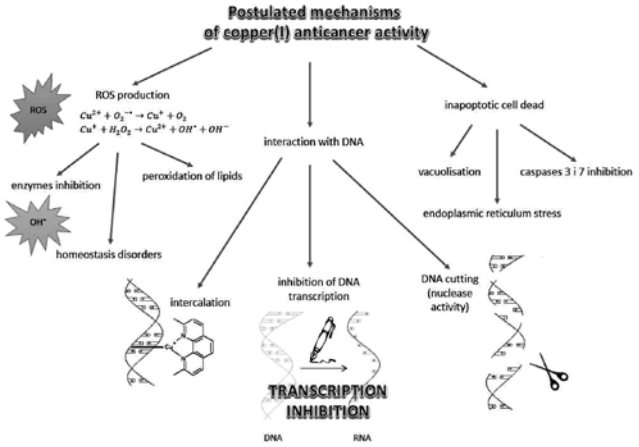
Fig. 11. $[Cu_2(dppe)_3(CH_3CN)_4](ClO_4)_2$

The anticancer activity of compound **11** was confirmed by tests carried out on several cell lines (Table 1) [26]. **11** managed to damage DNA helix, inhibit processes of its synthesis, stop cell cycle in G1 and G2 phases and induce apoptosis. If **11** and adriamycin (drug in cancer therapy) are used simultaneously in treatment, synergism of action is observed. **11** increases therapeutic effect of adriamycin and vice versa. It is believed that **11** binds to DNA by displacement of acetonitrile molecules. Simulations with a use of molecular modelling methods imply that the most profitable donor of a pair of electrons is the atom N7 of guanine. Since in one molecule of **11** two Cu^+ ions are present, the discussed copper(I) complex acts as chelate agent. It creates two bonds with DNA, as a result of replacement of two acetonitrile molecules for two guanine molecules of deoxyribonucleic acid. Mutual strengthening of anticancer activity between **11** and adriamycin suggests that both agents bind to other helix regions. Moreover each one causes changes in DNA in a way that facilitates binding of the second one [27].

Summary

Mechanisms of anticancer activity discussed in this article are presented on Scheme 1. Copper(I) coordination compounds described in this review are in turn collected in Table 1. It summarises their biological activity and types of cell line, in which complexes were tested *in vitro*.

Copper(I) compounds may become an alternative for cisplatin, which possesses a few drawbacks but is still most popular. Copper, as an essential element for human life is supposed to be less toxic than other metals, like platinum or ruthenium, analysed for medical application. Both copper ions, Cu^+ and Cu^{2+} can induce oxidation stress via catalysis and production of reactive oxygen species. Superiority of copper(I) compounds over copper(II) compounds results from nuclease activity of Cu^+ complexes and selectivity exhibited by human copper transporters (hCtr) in introduction of Cu^+ ions to cells. Copper as an antibacterial agent is used in hospitals, health centres and public buildings for various sanitary applications (for instance handles, holders, handrails ect.) [28]. As it was presented in this article, copper(I) coordination compounds have remarkable application potential. Intensive research may enable to finally apply them as anticancer drugs.



Scheme 1. Selected examples of anticancer activity and mode of action of Cu(I) complexes

Table 1

Biological activity of described cuprous complexes

Cu(I) compound	Cancer cell line, in which investigations were performed	Biological activity	Lit.
1C	• P388 (mouse leukemia) • B16 (melanoma) • M5076 (reticulum cell sarcoma)	• probably DNA damages, single-strand breaks in supercoiled plasmid-DNA *in vitro*	11
2	• A549 (lung carcinoma) • MCF-7 (breast carcinoma) • HepG2 (liver carcinoma) • CaCo-2, HCT-15, LoVo , DLD1, SW480 (colon cancer) • HeLa (cervix carcinoma) • A375 (melanoma) • Daudi (Brukitt lymphoma) • HL60 (promyelocytic leukemia)	• strong antiproliferative activity • reactive oxygen species production • nonapoptotic cell death (inhibitionof caspases 3 and 7) - cytoplasmic vacuolization, endoplasmic reticulum stress, proteasome 26S inhibition)	12 13
4A, 4B	• A549 (lung adenocarcinoma) • A375 (melanoma) • HL60 (promyelocytic leukemia) • A431 (cervix cancer) • 2008 (ovarian cancer)	• changes in redox potential of cell membrane which is the result of disruption in oxidative phosphorylation process	14
5	• A549 (lung carcinoma) • HL60 (promyelocytic leukemia) • MCF-7 (breast carcinoma) • A375 (melanoma) • LoVo (colon carcinoma)	• nonapoptotic cell death (caspase-3 activity was not observed, cytoplasmic vacuolisation and increase in cell size)	15
6	• MCF-7 (breast carcinoma) • A549 (lung carcinoma) • A375 (melanoma) • HL60 (promyelocytic leukemia) • HCT-15, LoVo (colon carcinoma) • A431 (cervix cancer) • 2008, C13* (ovarian cancer)	• mechanism still unknown • ligand acts as ionophore	16
7	• HL60 (promyelocytic leukemia) • MCF-7 (breast cancer) • HCT-15 (colon carcinoma) • HeLa (cervix carcinoma) • A549 (lung carcinoma) • 2008, C13* (ovarian cancer)	• ability to disturb respiration by altering mitochondrial membrane potential and producing reactive oxygen species	18
8	• SKOV 3, MDAH 2774 (human ovarian carcinoma)	• mechanism unknown	19÷24
9A, 10	• HeLa (cervical cancer)	antiproliferative activity	25
9B	• HeLa (cervical cancer) • MCF-7 and MDA-MB 231 (breast cancer) • CHO (Chinese hamster ovarian cancer)	• antiproliferative activity • ability to damage DNA integrity • inhibition of cell cycle in G1 phase • induction of apoptosis	25
11	• H460 (lung cancer)	• DNA damages • DNA synthesis inhibition • inhibition of cell cycle in G1 phase • induction of apoptosis • synergetic enhancement of activity when it is used simultaneously with adriamycin	26 27

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