New metal [Cu(II), Co(II), Zn(II)/Ag(I), Zn(II)/Au(I)] complexes with Schiff bases decrease viability and 2D/3D growth of cultured human cancer cells

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Introduction and Aim

The need for effective new anticancer agents is one of the main challenges in modern biomedicine. Successful application of cisplatin in clinical oncology has encouraged the search for other metals and metal compounds with antineoplastic properties.

The aim of this study was to evaluate the influence of newly synthesized metal [Cu(II), Co(II), Zn(II)/Ag(I), Zn(II)/Au(I)] complexes with Schiff bases on viability and 2D/3D growth of cultured tumor cells.

Results and Conclusion

The examined metal complexes express cytotoxic activity in 2D and 3D cell cultures that is time- and concentration-dependent. Zn(II)/Au(I) and Zn(II)/Ag(I) complexes with Schiff bases Salen, Salampy and Saldmen are found to be the most promising cytotoxic agents. Their cytotoxic activity is higher than those of cisplatin, oxaliplatin and epirubicin. Cu(II) complexes revealed higher cytotoxic activity than Co(II) complexes with the same ligands.

Materials and methods

Cell lines established from human breast cancer and cervical carcinoma as well as osteosarcoma. Short-term (3 – 96h, with monolayer cell cultures) and long-term (> 2 weeks, with 3D cell colonies) experiments were carried out using cytotoxicity assays, cytological / immunocytochemical, biochemical and molecular-biological methods to assess the influence of the compounds on cell viability and proliferation and their ability to induce apoptosis/necrosis (in monolayer cell cultures) as well as colony-forming method (with 3D cell colonies) to examine their capacity to prevent 3D cell growth

Cytotoxic concentration 50 (CC50, μM) that reduces viability and 2D growth of the treated cells by 50% as compared to the control and inhibitory concentration (IC, μM) that completely suppresses the formation of 3D cell colonies in a semi-solid medium were determined.

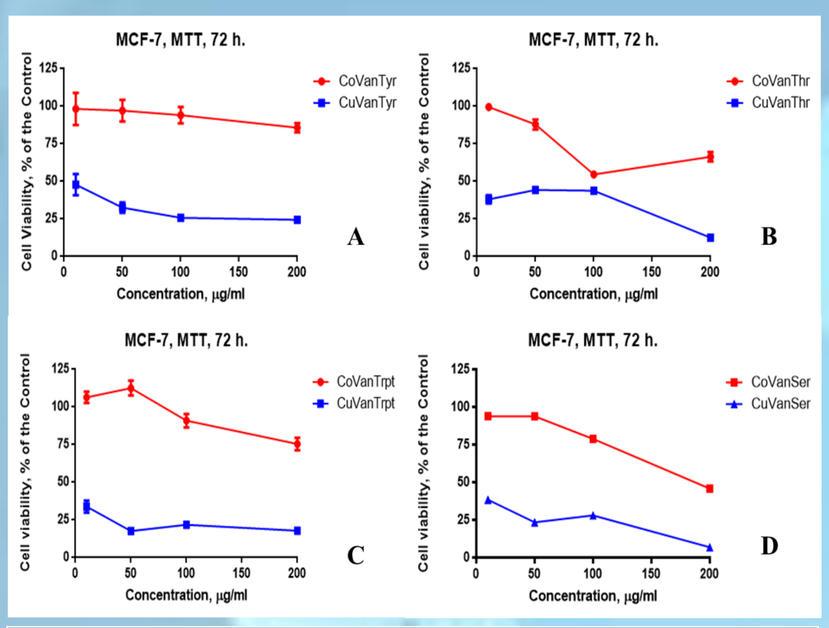
Permanent cell lines in human used as model

	Cell line	Origin / Brief description
1	HeLa	Cervical carcinoma; the cells contain human papilloma virus type 18 (HPV – 18); the first human cell line established in culture, one of the most widely used cell culture models to carry out a wide range of investigations
2	MCF-7	breast cancer - (ER+, PR+, HER2/Neu-, luminal type A);
3	MDA-MB-231	Triple negative breast cancer, (ER-, PR-, HER2-, triple negative)
4	SAOS-2	Osteosarcoma

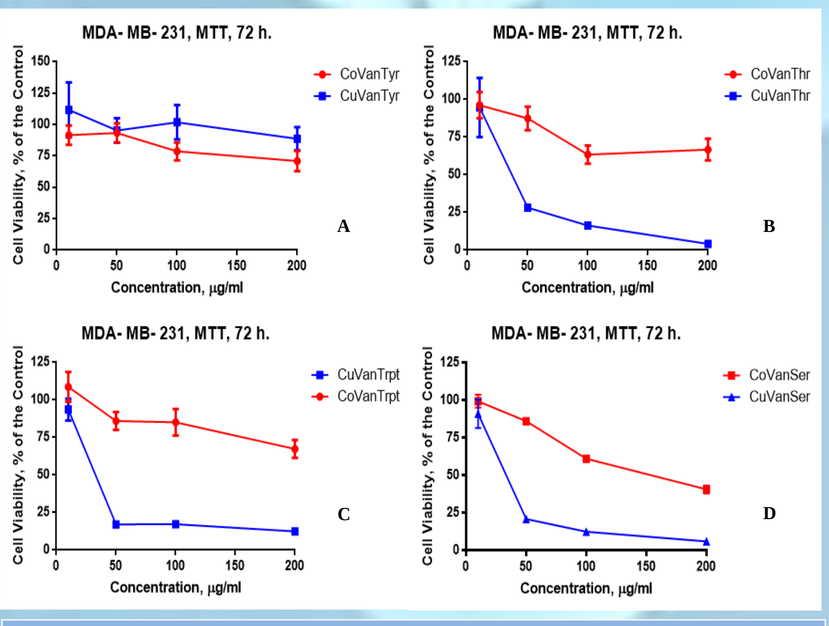
Cu(II) and Co(II) complexes with Schiff bases

Metal complex	Abbreviation	Molecular weight (g/mol)
[Cu(VanTyr)(bipy)]·MeOH	CuVanTyr	M_w = 565.53
[Cu(VanThr)(bipy)]·MeOH	CuVanThr	M_w = 503.46
[Cu(VanTrpt)(bipy)]·MeOH	CuVanTrpt	M_w = 588.57
[Cu(VanSer)(bipy)]·MeOH	CuVanSer	M_w = 489.43
[Co(VanTyr)(bipy)]·MeOH	CoVanTyr	M_w = 560.53
[Co(VanThr)(bipy)]·MeOH	CoVanThr	M_w = 498.46
[Co(VanTrpt)(bipy)]·MeOH	CoVanTrpt	M_w = 583.57
[Co(VanSer)(bipy)]·MeOH	CoVanSer	M_w = 487.43

Cu(II) and Co(II) complexes with Shciff bases

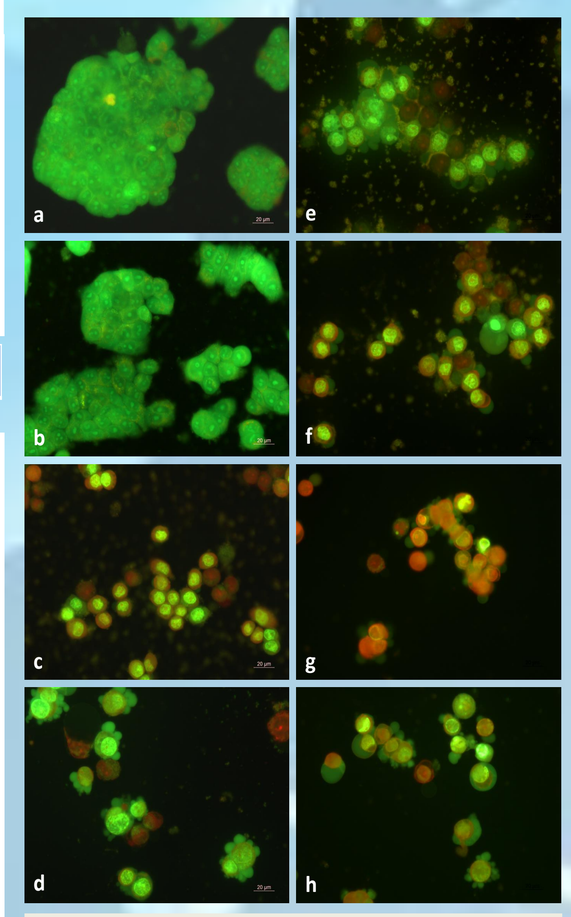


Effect of Cu(II) and Co(II) complexes with Schiff bases on viability and proliferation of cultured human human breast cancer (MCF-7 cell line). Cell viability was evaluated using MTT test after 72 hours of treatment.

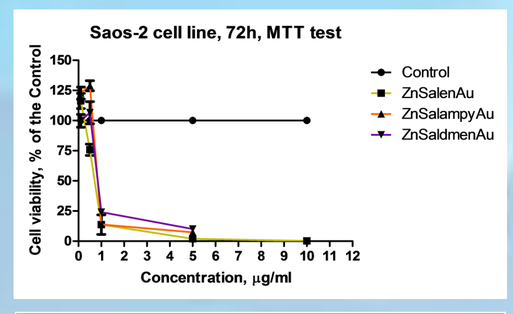


Effect of Cu(II) and Co(II) complexes with Schiff bases on viability and proliferation of cultured human human breast cancer (MDA-MB-231 cell line). Cell viability was evaluated using MTT test after 72 hours of treatment.

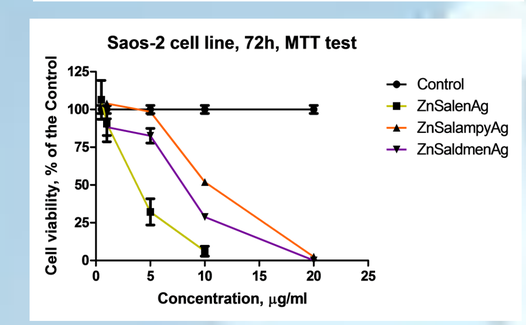
Zn(II)/Au(I) and Zn(II)/Ag(I) complexes with Shciff bases



Human osteosarcoma cells (Saos-2 cell line) - culture medium control (a) and treated 24 h with 10 μg/mL Salen (b); 1 μg/mL ZnSalenAu (c); 2.5 μg/mL ZnSalenAg (d); 1 μg/mL ZnSalampyAu(e); 1 ZnSaldmenAu(f); 10 ZnSalampyAgAu (g); 10 ZnSaldmenAg (h). Double staining with acridine orange and propidium iodide. Bar = 20 μm (Leica DM 5000B, Leica Microsystems, Germany, 40x)



Effect of ZnSalenAu , ZnSalampyAu , ZnSaldmenAu on viability and proliferation of cultured human osteosarcoma cells (Saos-2 cell line). Cell viability was evaluated using MTT test after 72 hours of treatment.



Effect of ZnSalenAg , ZnSalampyAg , ZnSaldmenAg on viability and proliferation of cultured human osteosarcoma cells (Saos-2 cell line). Cell viability was evaluated using MTT test after 72 hours of treatment.

Long-term experiments 3D

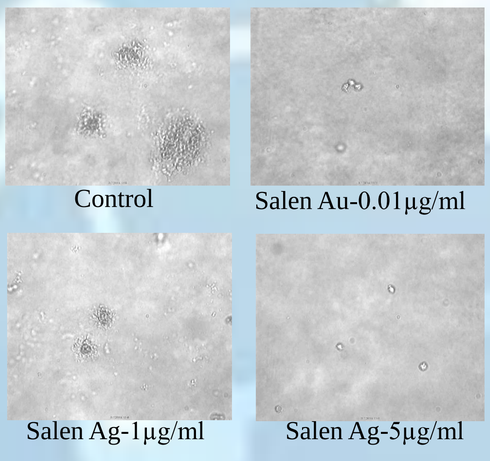
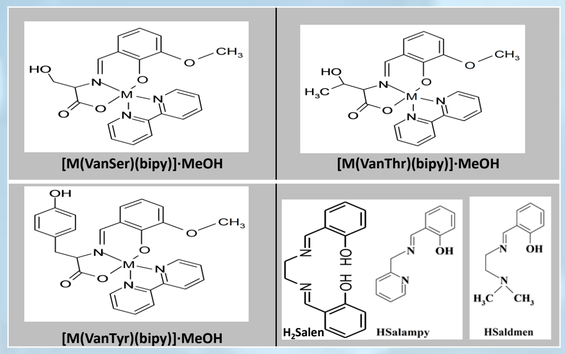


Table. Complexes of Zn(II)/Ag(I) and Zn(II)/Au(I) with Schiff base ligand (Salen, Salampy and Saldmen)

Abbreviation	Compound	Molecular weight (g/mol)
ZnSalenAu	$[Zn_3(Salen)_2\{(\mu\text{-}Au(CN)_2)_2\}]$	1226.71
ZnSalenAg	$[Zn_3(Salen)_2\{(\mu\text{-}Ag(CN)_2)_2\}]$	1048.51
ZnSalampyAu	$[ZnSalampy(\mu\text{-}Au(CN)_2)]$	525.61
ZnSaldmenAu	$[ZnSaldmen(\mu\text{-}Au(CN)_2)].H_2O$	541.66
ZnSalampyAg	$[ZnSalampy(\mu\text{-}Ag(CN)_2)]$	452.56
ZnSaldmenAg	$[ZnSaldmen(\mu\text{-}Ag(CN)_2)].H_2O$	452.56



Effect of Zn(II)/Au(I) and Zn(II)/Ag(I) with Salen, Salampy or Saldmen on 3D colony-forming ability of human osteosarcoma cells

Compound	Cell line
	Saos-2
Interval (days)	30-32
ZnSalenAg	≥ 1 μg/ml*
ZnSalampyAg	≥ 5 μg/ml
ZnSaldmenAg	≥ 5 μg/ml
ZnSalenAu	≥ 0.1 μg/ml
ZnSalampyAu	≥ 0.1 μg/ml
ZnSaldmenAu	≥ 0.1 μg/ml
Salen	No inhibition

Colony inhibitory concentration (CIC, μM) at which the compounds tested inhibited completely the 3D growth of cancer cells in a semi-solid medium.

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