# Monolacunary Wells-Dawson polyoxotungstate as a potential anti-tumor agent

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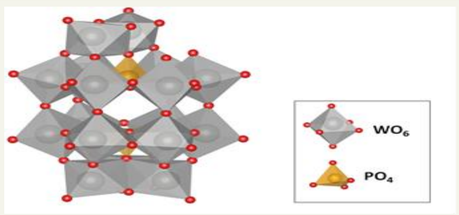
## INTRODUCTION

Polyoxometalates (POMs) are polyanions containing early transition metals (such as V, W, Pd, and Mo) in their high oxidation states surrounded by oxygen. These metal-based inorganic nanoclusters have been studied as promising biomedical agents due to their approved biological actions such as anti-microbial, -cancer, and -diabetic activities as well as promising contrast properties for clinical imaging [1, 2]. Numerous *in vitro* and *in vivo* studies recently reported remarkable POM-induced cytotoxic effects against various tumor cells [3]. Thus, POMs could be considered as a promising platform for developing next-generation chemotherapeutics.

The purpose of this study was to evaluate anti-tumor properties of monolacunary Wells-Dawson polyoxotungstate, α2-$K_{10}P_2W_{17}O_{61}{\cdot}20H_2O$ (mono-WD POM) (**Scheme 1.**) using human melanoma cell line, A375 as a model system. Mono-WD POM-induced cytotoxicity was compared with the anti-melanoma effect of cisplatin which has been used as a gold-standard chemotherapeutic in clinical practice

## METHODS AND MATERIALS

Mono-WD POM was synthesized by following a procedure described in the literature [4]. A stock aqueous solution (5 mmol/L) was prepared by mixing and heating at 30-40 °C. Appropriate concentrations of working solutions were prepared by diluting (with water) the stock solution. Human melanoma A375 cell line was purchased from the American Tissue Culture Collection (ATCC, Manassas, VA, USA) and cultured in high-glucose DMEM medium (Sigma-Aldrich, Steinheim, Germany) supplemented with 10% fetal bovine serum (Sigma-Aldrich), and penicillin/streptomycin (Sigma-Aldrich) in a humidified atmosphere of 5% CO2, at 37 °C (Heraeus, Hanau, Germany). A375 cells were seeded into flat-bottom 96-well plates, at a density of 2 × 103 cells/well. Then, exponentially growing cells were exposed to increasing mono-WD POM concentrations for 24, 48, and 72 hours. Mono-WD POM-induced cytotoxicity was determined by using sulforhodamine B (SRB) assay measuring cellular protein level [5]. A375 cells were in vitro exposed to mono-WD POM within the concentration range from 0.001 to 1 mmol/L.




**Scheme 1.** Structure of monolacunary Wells–Dawson polyoxotungstate (mono-WD POM), $\alpha_2$-$K_{10}P_2W_{17}O_{61}{\cdot}20H_2O$ (red balls–oxygen).

## RESULTS

The results were expressed as cell viability (% of control), as an indicator of cytotoxicity and anti-tumor potential of the investigated polyoxotungstate nanocluster, and showed as a function of mono-WD POM concentration (**Figure 1.**). The obtained results demonstrated a cytotoxic effect of mono-WD POM on tumor A375 cells by reducing the cell viability in a time- and dose-dependent manner. Indeed, after 24 hours exposure the highest studied concentration (1 mmol/L) induced a decrease of cell viability by 16%, whereas lower mono-WD POM concentrations did not affect A375 cells. During 48 hours treatment, the lowest studied concentration resulting in the decrease of A375 viability (9%) was 0.01 mmol/L, and a 55% decrease was obtained for 1 mmol/L mono-WD POM. The most significant effect (from 20 to 74% decrease compared to control) was observed for 72 hours exposure within the concentration range of 0.005-1 mmol/L. For cisplatin (positive control), significantly lower $IC_{50}$ values (in mM) were obtained: 0.09, 0.07, and 0.043, for 24, 48, and 72 hours, respectively. in cancer chemotherapy.

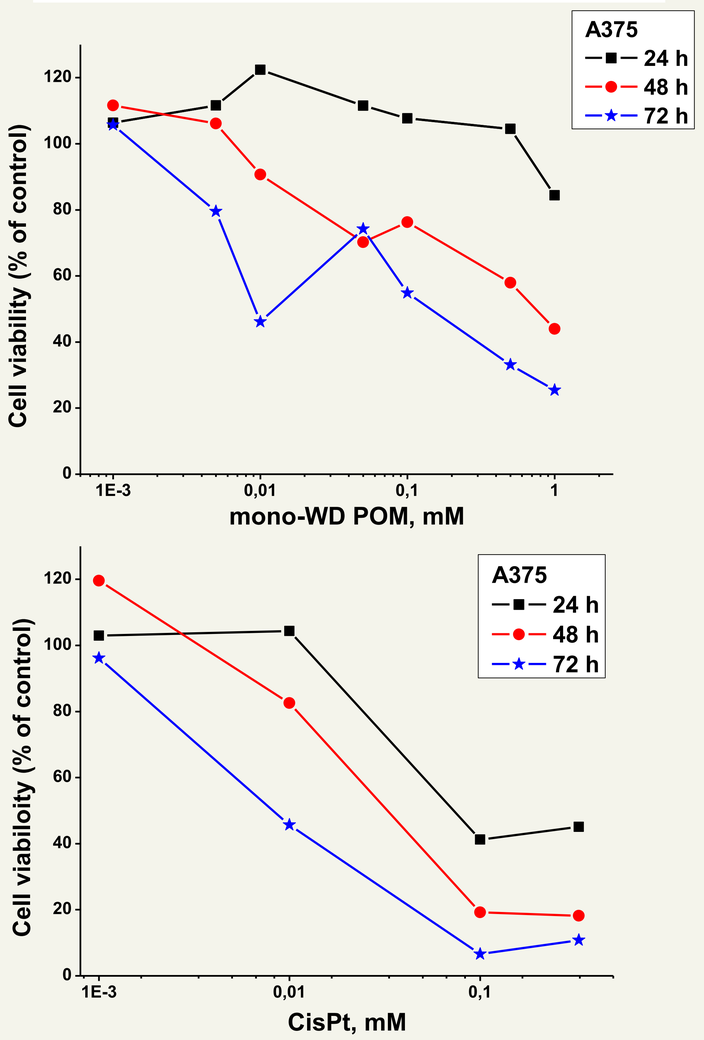



**Figure 1.** The effect of mono-WD POM and cisplatin on the viability of human melanoma A375 cells, after 24, 48, and 72 hours exposure. Cell viability was presented as % of untreated (control) cells (100%). Results are expressed as mean ± S.E.M. from at least 2 independent experiments done in triplicates.

## DISCUSSION

This is first the study investigating potential anti-tumor action of a tungsten-based WD nanocluster, against human melanoma cell line, A375 that were found as resistant tumor cells. In comparison with Fe-containing analog of mono-WD POM (data not shown), the studied mono-WD POM exhibited weaker cytotoxic affects. Indeed, mono-WD POM–induced $IC_{50}$ values (in mM) were as follows: >1, 0.72, and 0.14 (**Figure 1.**), whereas the corresponding values for Fe-WD POM were: 1, 0.58, and 0.51, for 24, 48, and 72 hours exposure, respectively. However, both investigated WD analogs were not found as superior anti-human melanoma agents compared to cisplatin that has been the most frequently prescribed chemotherapeutic. On the contrary, our previous research on a series of Pd-based POMs [3] reported this class of POMs as even superior than cisplatin. Furthermore, cervical carcinoma HeLa cells were less resistant to the studied mono-WD POM (data not shown). Anti-HeLa $IC_{50}$ values were lower more than 10 times in respective with A375 cells and similar to the gold-standard cisplatin. In accordance, tungste-based nanoclusters deserve attention as a promising base for the design of potential anti-cancer candidates and further relevant studies on antitumor properties and toxicity are worthy to be carried out.

## CONCLUSIONS

The studied polyoxotungstate, mono-WD POM demonstrated significant time- and dose-dependent cytotoxic effects against the human melanoma A375 cell line at micromolar concentrations. Nevertheless, its anti-tumor potency was not superior compared with cisplatin, the gold standard in cancer chemotherapy.

## REFERENCES

1. M. B. Čolović, M. Lacković, J. Lalatović, A. S. Mougharbel, U. Kortz, D. Krstić, Curr. Med. Chem., 27 (2020) 362.
2. J. Iqbal, M. Barsukova-Stuckart, M. Ibrahim, S. Usman Ali, A. Ahmed Khan, U. Kortz, Med. Chem. Res., 22 (2013) 1224.
3. A. M. Isakovic, M. B. Čolović, T. Ma, X. Ma, M. Jeremić, M. Gerić, G. Gajski, S. Misirlic-Dencic, U. Kortz, Z. Krstić, J. Biol. Inorg. Chem., 26 (2021) 957.
4. A. P. Ginsberg, Inorganic Syntheses, John Wiley and Sons, New York, USA, 1990.
5. P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J. T. Warren, H. Bokesch, S. Kenney, M. R. Boyd, JNCI-J. Natl. Cancer I., 82 (1990) 1107.

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