

Novel silver(I) compounds display strong activity towards resistant colorectal and ovarian cancer cell lines

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BACKGROUND

Carboplatin (CBP) is used to treat several types of cancers including ovarian carcinoma (OC). However, drug resistance is a frequent obstacle for successful treatment. In the quest for new (metallo)drugs to treat OC with acquired resistance, we have explored the use of silver(I)-based compounds containing 2,2'-bipyridine derivatives and triphenylphosphane (PPh₃) or 1,2-bis(diphenylphosphino)ethane (dppe) co-ligands as prospective anticancer agents. Their cytotoxic activity was tested in two human OC models (SKOV-3 and MESOV),

their carboplatin-resistant counterparts and non-malignant fibroblasts F331. To evaluate the impact of p53, HCT116 and HCT116/p53ko colon carcinoma (CC) cells were also tested (data not shown here). Herein, we show our preliminary results focused on drug-resistant OC cells which indicate that the dppe-Ag(I) compounds have a high tumor selectivity for special cancer types, making them interesting drug candidates.

Synthesis and characterization

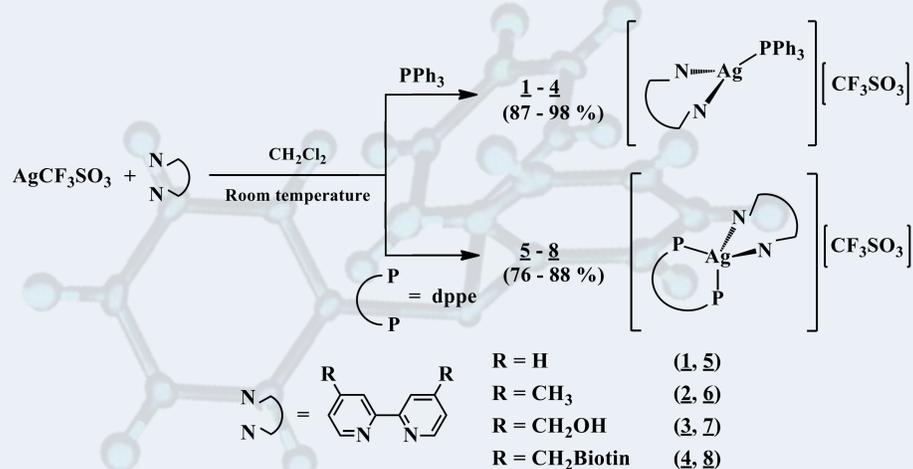


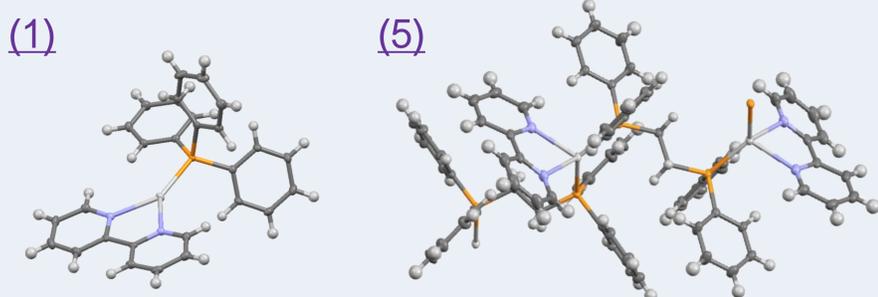
Figure 1. Synthesis of compounds **1-8**.

NMR

Table 1. ³¹P{¹H} NMR data for compounds **1** and **5** (dms_o-d₆).

Compd	δ (³¹ P{ ¹ H} NMR), ppm
(1)	13.52 (broad d, ¹ J _{AgP} = 578 Hz, PPh ₃).
(5)	3.49 (d, ¹ J ¹⁰⁹ _{AgP-dppe} = 265.7 Hz), 3.49 (d, ¹ J ¹⁰⁷ _{AgP-dppe} = 230.0).

Single crystal X-ray Diffraction



Polymeric in the solid state

Figure 2. Molecular structure of compounds **1** (left) and **5** (right).

- Eight compounds were synthesized and characterized by several techniques, including SC-XRD.
- All compounds are stable over 24 h in 100 % DMSO solutions.

CONCLUSIONS

- A series of silver(I) compounds were evaluated towards OC and CC cell lines
- All compounds were highly active against both sensitive and resistant cell lines
- Compounds **1** and **5** are able to surmount carboplatin resistance in OC

RESULTS

In vitro screening

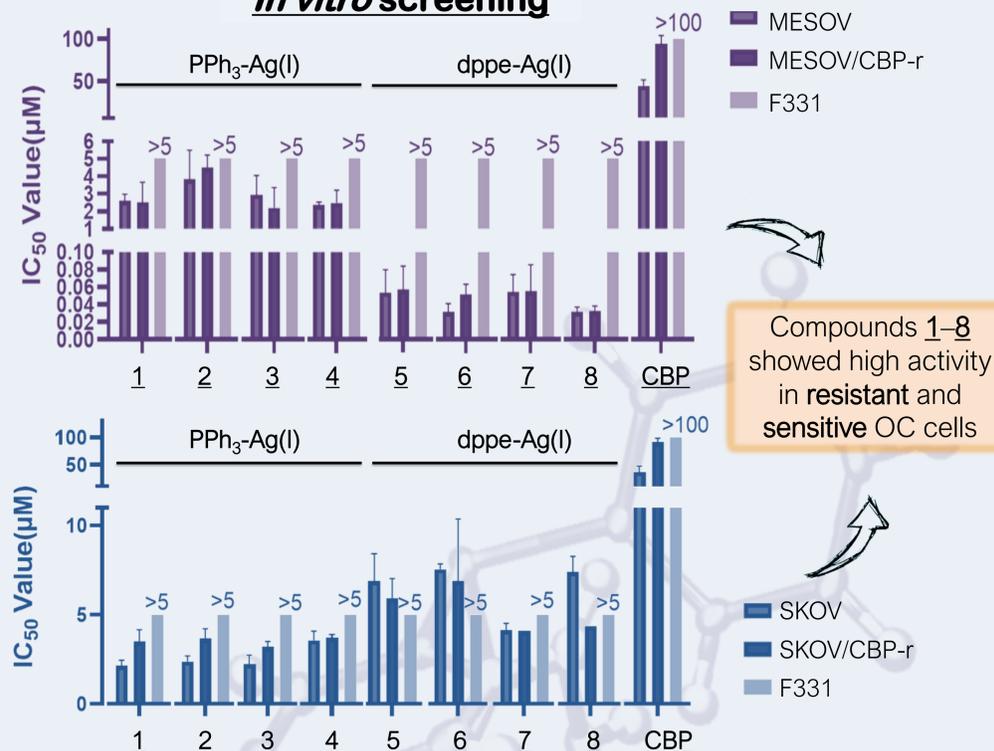


Figure 3. IC₅₀ (µM) of the Ag(I) compounds and carboplatin (CBP) in the cell lines analyzed after 72 h of incubation (MTT assay). MESOV/CBP-r and SKOV/CBP-r represent the CBP-resistant cell lines, respectively.

Annexin V / PI assay

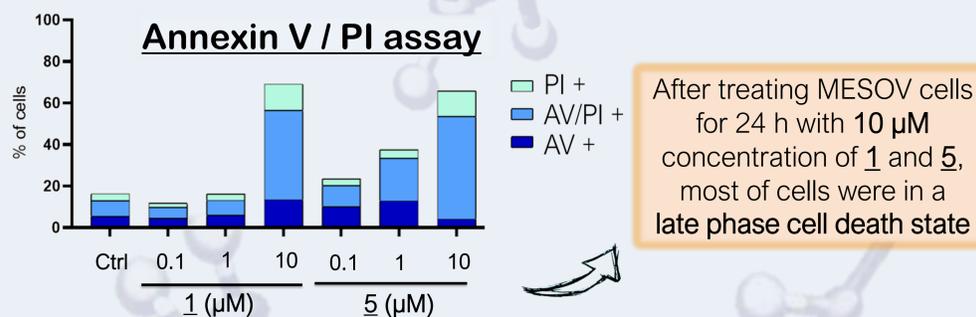


Figure 4. Cell cycle analysis (via FACS) of **1** and **5** in MESOV cell line after 24 h treatment. (AV = annexin V; PI = propidium iodide)

Compounds **1** and **5** induced cleavage of PARP and generation of γH2AX at 10 µM

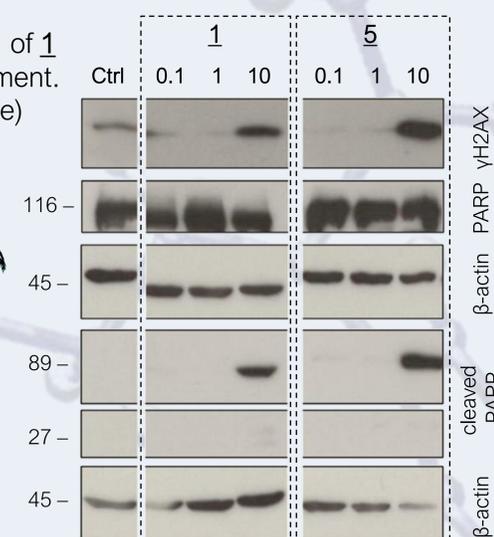


Figure 5. Western blot analysis of **1** and **5** in MESOV cell line after 24 h treatment.

Acknowledgements

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References

[1] A Citta *et al.*, *Metallomics*, 12, 2020, 1863-1877; [2] SJ Allison *et al.*, *Cancer Letters*, 403, 2017, 98-107.

