

Abstract



1

2

3

4

5

6

7

8

9

10

11

12

35

36 37

38

39

Silver(I) complexes as potential anticancer drugs: synthesis, characterization, and *in vitro* studies

<u>Zulima Aguado</u>¹, Ricardo Rodríguez², Guillermo Cásedas¹, Pilar García-Orduña², M Pilar del Río ^{3,*} and Cristina Moliner ^{1,*}

- Department of Pharmacy, Faculty of Health Sciences, Universidad San Jorge, 50830 Villanueva de Gállego (Zaragoza), Spain; <u>zaguado@usj.es</u> (Z.A.); <u>gcasedas@usj.es</u> (G.C.); <u>acmoliner@usj.es</u> (C.M.)
 Institute de Síntesia Ouíniera e Católicia Llene e ín ca (ISOCIL). CCC Universidad de Zaragoza
- ² Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC-Universidad de Zaragoza, Departamento de Química Inorgánica, Pedro Cerbuna 12, 50009 Zaragoza. <u>riromar@unizar.es</u> (R. R), <u>mpgaror@unizar.es</u> (P. G-O), <u>780213@unizar.es</u> (A. S).
- ³ Centro Universitario de la Defensa, Ctra. Huesca s/n, 50090 Zaragoza ; mpdelrio@posta.unizar.es (M.P.R.)
- Correspondence: mpdelrio@posta.unizar.es (M.P.R); <u>acmoliner@usj.es</u> (C.M.); Tel.: +34 976 060 100

Abstract: To address the challenge of mitigating the adverse effects and drug resistance associated13with Pt(II) chemotherapeutic compounds, significant efforts have been devoted to designing metal-14based drugs with diverse anticancer mechanisms. Exploring alternative organometallic complexes,15such as those incorporating silver, is an interesting approach in the pursuit of more effective and16safe treatments.17

This study aims to develop a new family of silver(I) complexes with nitrogen donor ligands that18exhibit antitumor properties, and to determine the mechanism by which these compounds induce19cell death, such as the generation of reactive oxygen species (ROS)."20

A novel family of eight silver complexes was synthesized using a newly developed imine, (E)-N-21 (3,5-bis(trifluoromethyl)benzyl)-1-(4-(piperidin-1-yl)phenyl)methanamine, which was formed by 22 condensing two pharmacophores. This study employed two tumor cell lines: cervical cancer (HeLa) 23 and hepatocellular carcinoma (Hep-G2). To assess their antitumor potential, MTT assays were conducted. Additionally, the generation of ROS in HeLa cells was measured as possible mechanism of 25 action to understand their effects. 26

The results indicate that, with one exception, new compounds exhibit activity against both assayed 27 lines. Higher cytotoxic activity of the compounds was observed against the HeLa cell line, except 28 for compound ZAG-14.2, which showed greater efficacy against Hep-G2. Regarding the production 29 of ROS, it was observed that exposure to the compounds increased ROS levels in HeLa cells compared to control cells. 31

The potential of these new complexes as anticancer drugs is evident through their significant cytotoxic activity in both cell lines. Further studies are needed to fully understand their mechanism of action. 34

Keywords: Ag (I) complexes, cytotoxicity, ROS.

Supplementary Materials:

Citation: Lastname, F.; Lastname, F.; Lastname, F. Title. *Med. Sci. Forum* 2023, 2, x. https://doi.org/10.3390/xxxxx

Academic Editor: Firstname Lastname

Published: date

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2023 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licens es/by/4.0/).

Author Contributions: All authors have read and agreed to the published version of the manuscript.	1 2
Funding: This research was funded by NAME OF FUNDER, grant number XXX" and "The APC was funded by XXX". Check care-fully that the details given are accurate and use the standard spelling of funding agency names at https://search.crossref.org/funding. Any errors may affect your future funding.	3 4 5 6
Institutional Review Board Statement: Not applicable.	7
Informed Consent Statement: Not applicable.	8
Acknowledgments: We thank the MCIU/AEI/FEDER-(PID2021-122406NB-100), Gobierno de Aragón (E05-20R and B44_20D) and CUD (CUD-2023_04) for financial support.Conflicts of Interest: The authors declare no conflict of interest.	9 10 11 12
	13