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Gold is the women's best friend: Au carbene complexes as promising anti-breast cancer agents

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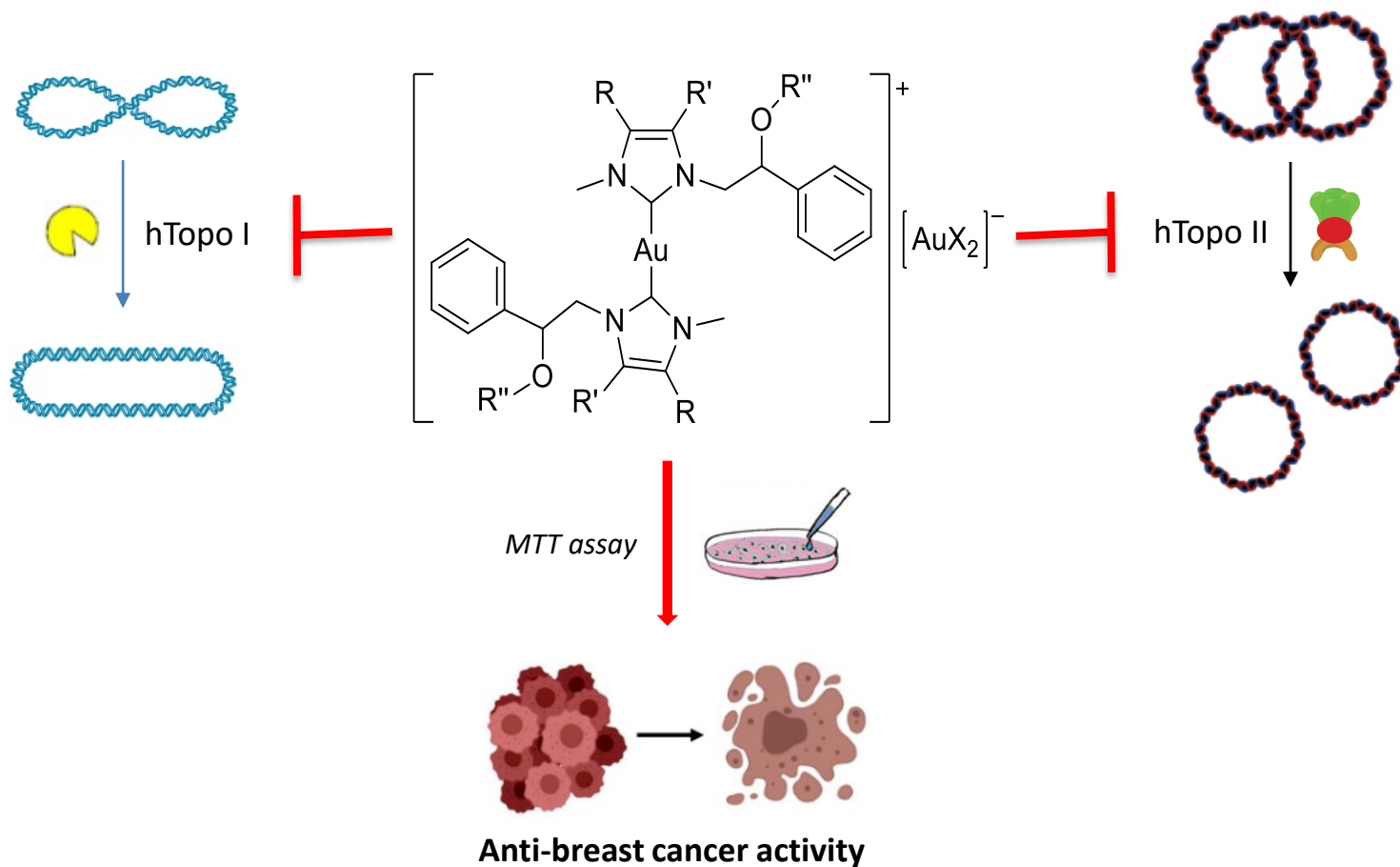
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Gold is the women's best friend: Au carbene complexes as promising anti-breast cancer agents



Abstract:

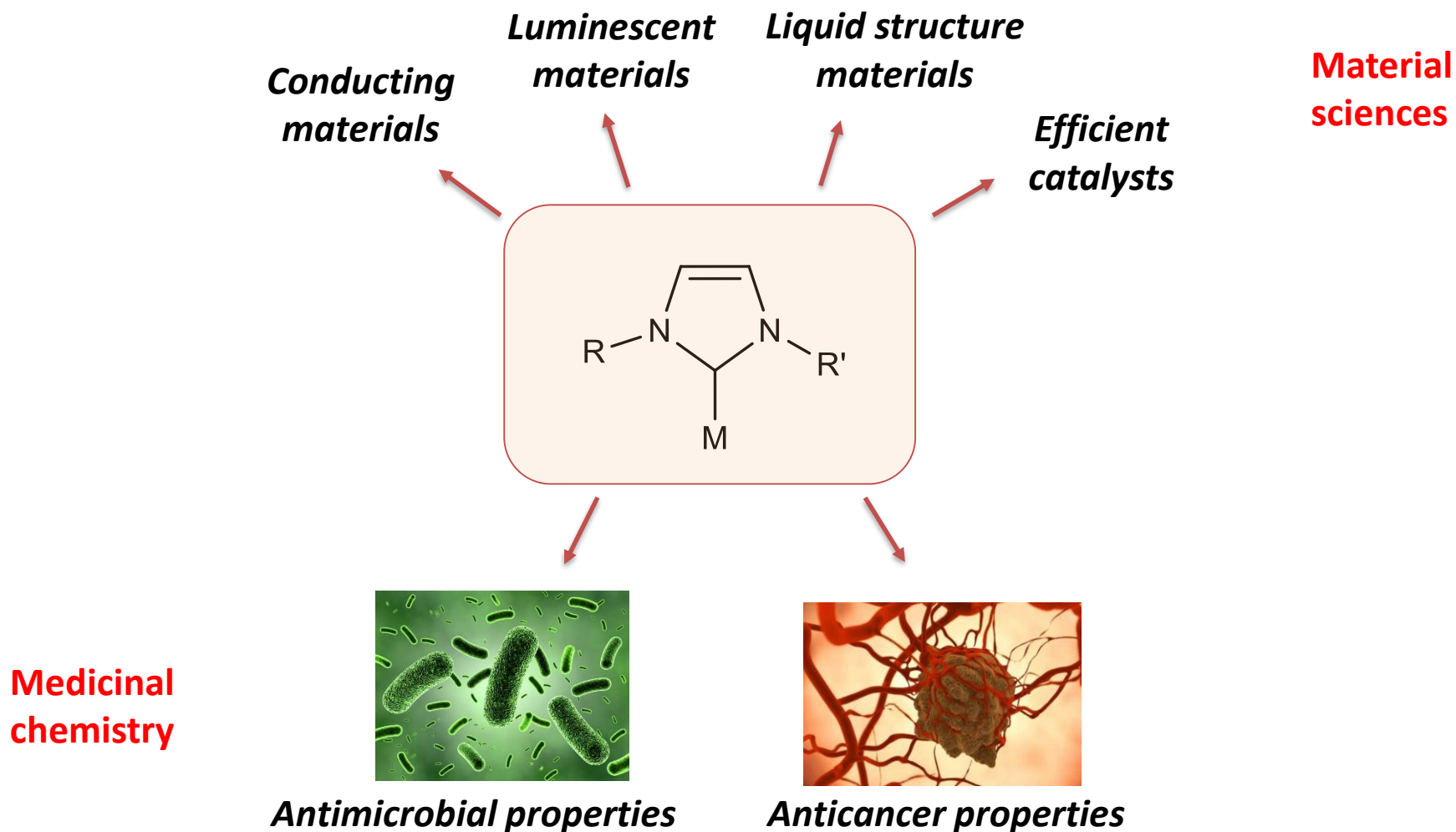
Over the past decade, metal complexes based on *N*-heterocyclic carbenes (NHCs) attracted great attention due to their wide and exciting applications in material sciences and medicinal chemistry. In addition to their well-known unlimited potential in several areas of the materials field and their use as highly efficient catalysts, more recently silver derivatives were employed as antimicrobial agents, while gold complexes were the focus of research efforts for the development of new anticancer compounds.

Interesting literature data and recent results obtained from some of us reported the design, the synthesis and the good anticancer activity of some silver and gold complexes with NHC ligands. Particularly, some of these complexes were more active towards some cell lines belonging to breast cancer, which represents the primary cause of death among young women. Considering these evidences, new Au and Ag NHC complexes were prepared in order to improve their solubility and biological activity. Among the new Au NHC compounds, **1** and **11** showed an interesting anticancer activity towards the breast cancer MDA-MB-231 and MCF-7 cell lines, respectively. In addition, *in vitro* and *in silico* studies demonstrated that they were able to inhibit the human topoisomerases I and II, essential enzymes involved in DNA metabolism and replication.

Keywords: breast cancer treatment; docking studies; metal complexes; *N*-heterocyclic carbenes; topoisomerases.



The wide applications of a *N*-heterocyclic carbene (NHC) metal complexes



Patil, S.A. et al. N-heterocyclic carbene metal complexes as bio-organometallic antimicrobial and anticancer drugs. *Future Med. Chem.* **2015**, 7(10), 1305–1333.



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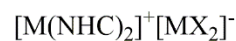
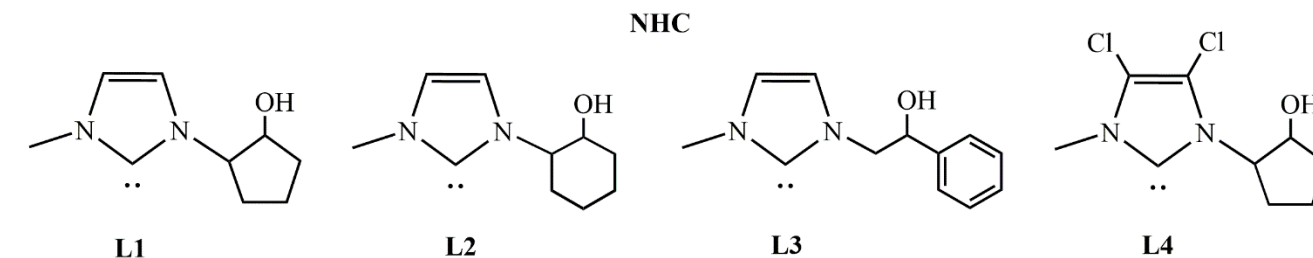


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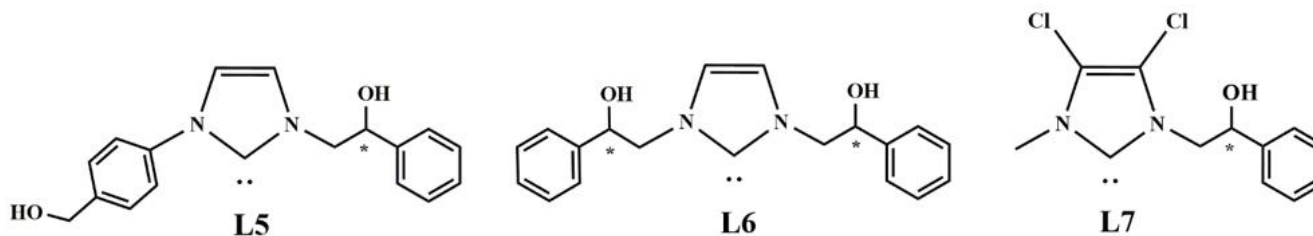
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N-heterocyclic carbene metal complexes as anticancer agents

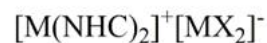


M = Ag or Au
X = I or Cl

AuL3
MCF-7 IC₅₀ = 1.0±0.7 μM



M(NHC)Br
M = Ag or Au



M = Ag or Au
X = I or Cl

AuL7
MDA-MB-231 IC₅₀ = 2.1±0.7 μM

[1] Saturnino, C. et al. N-heterocyclic carbene complexes of silver and gold as novel tools against breast cancer progression. *Future Med Chem* **2016**, *8*, 2213-2229.

[2] Iacopetta, D. et al. Novel Gold and Silver Carbene Complexes Exert Antitumor Effects Triggering the Reactive Oxygen Species Dependent Intrinsic Apoptotic Pathway. *ChemMedChem* **2017**, *12*, 2054-2065.

[3] Iacopetta, D. et al. Is the Way to Fight Cancer Paved with Gold? Metal-Based Carbene Complexes with Multiple and Fascinating Biological Features. *Pharmaceuticals* **2020**, *13*, 91.



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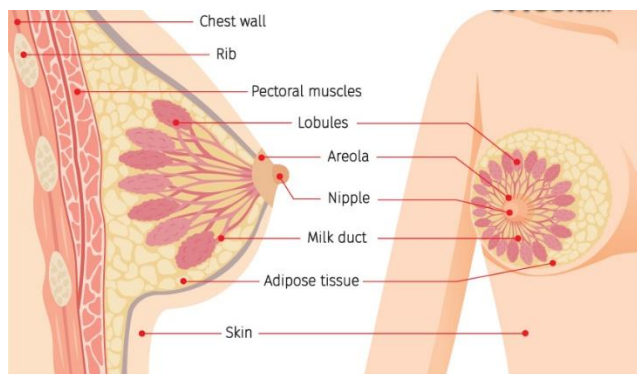
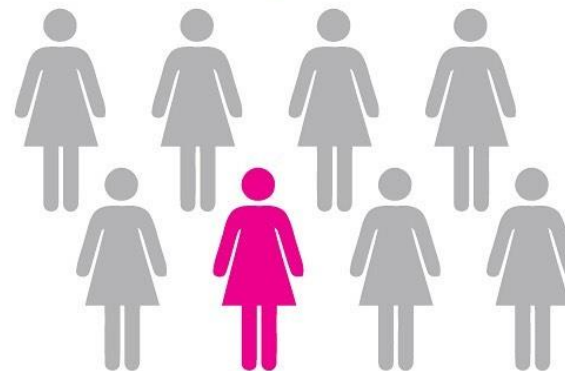
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Breast cancer: the primary cause of death among young women



DID YOU KNOW???

1 in 8 women will develop breast cancer in her lifetime

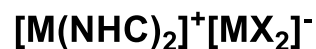
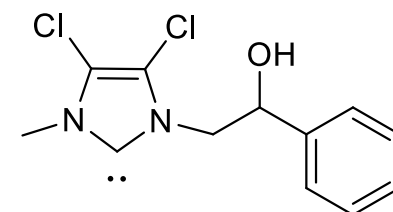
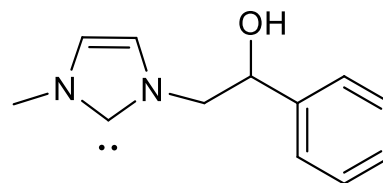
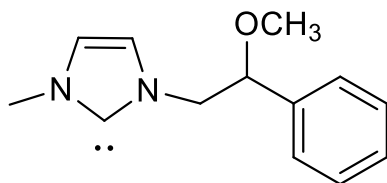
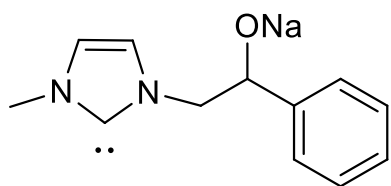


In Italy:

- 1 IN 40 WOMEN (less of 49 years)
- 1 IN 20 WOMEN (between 50 and 69 years)
- 1 IN 25 WOMEN (between 70 and 84 years)



New synthesized Au and Ag *N*-heterocyclic (NHC) carbene complexes



1 M=Au; X=Cl⁻

2 M=Au; X=CH₃COO⁻

3 M= Ag; X=Cl⁻

4 M=Ag; X=CH₃COO⁻

5 M=Au; X=I⁻

6 M=Au; X=CH₃COO⁻

7 M= Ag; X=I⁻

8 M=Ag; X=CH₃COO⁻

9 M=Au; X=CH₃COO⁻

10 M=Ag; X=CH₃COO⁻

11 M=Au; X=CH₃COO⁻

12 M=Ag; X=CH₃COO⁻



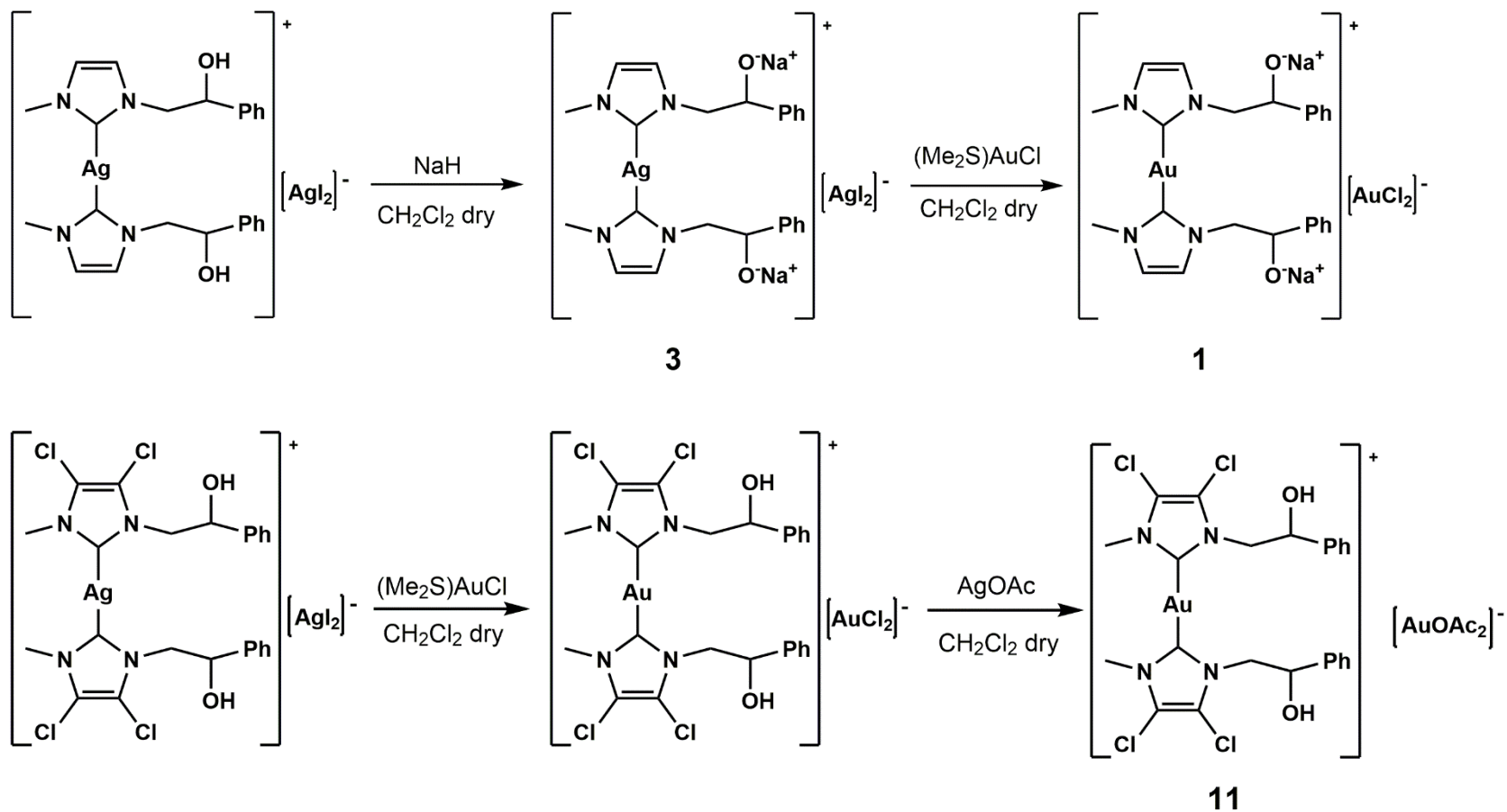
Anticancer activity towards breast cancer cell lines Au NHC complexes

Table 1. IC₅₀ values of Au metal complexes and Cisplatin, expressed in μM. The means ± standard deviations are shown.

Compounds	MDA-MB-231	MCF-7	MCF-10A
<i>Cisplatin</i>	28.7±0.4	35.8±0.7	81.3±0.6
1	15.8±0.7	29.9±1.1	>200
2	22.6±1.1	30.6±0.7	39.6±0.5
5	2.2±1.1	3.3±1.4	13.3±1.0
6	3.0±0.7	9.4±0.6	5.2±0.9
9	58.5±1.2	21.9±0.5	27.8±0.7
11	16.8±1.2	1.2±0.3	24.4±0.9



Synthesis of compounds 1 and 11

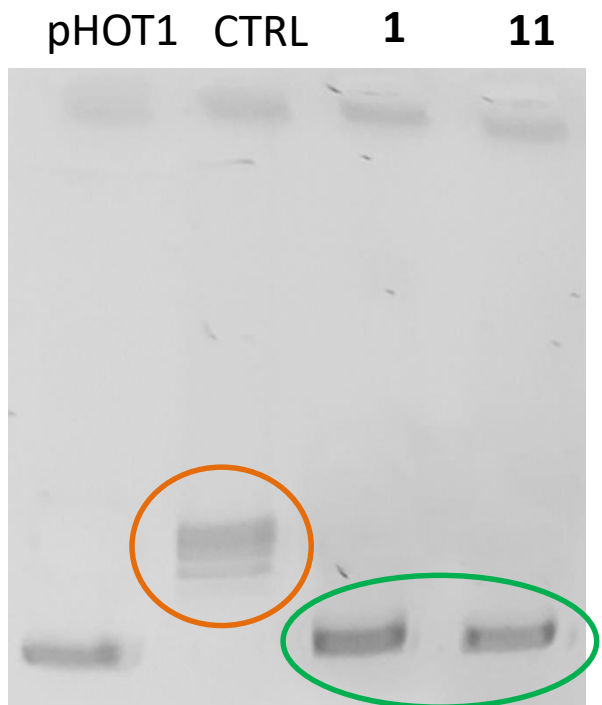


Characterization by ¹H-NMR, ¹³C-NMR and mass spectroscopy

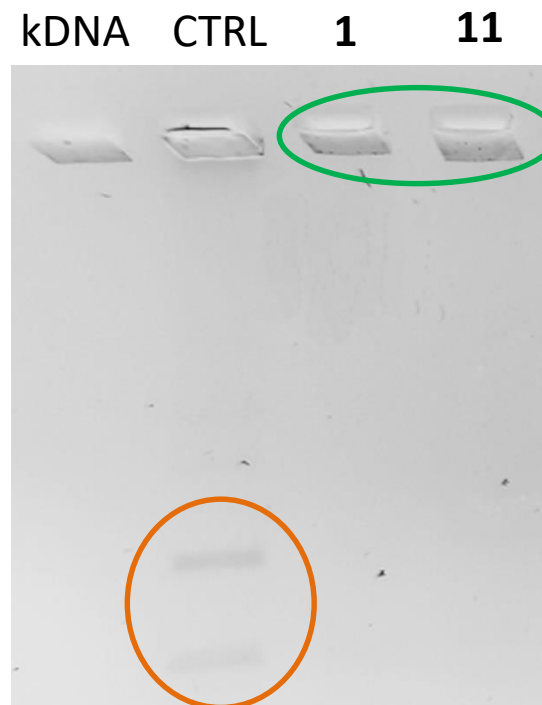


Human topoisomerases I and II inhibition

*Human Topoisomerase I
Relaxation Assay*



*Human Topoisomerase II
Decatenation Assay*



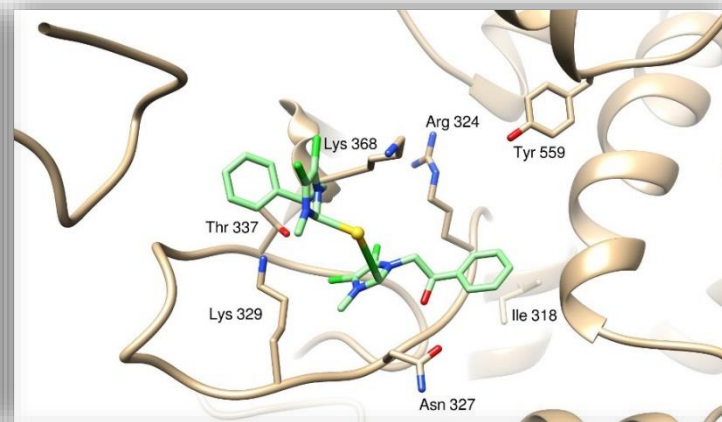
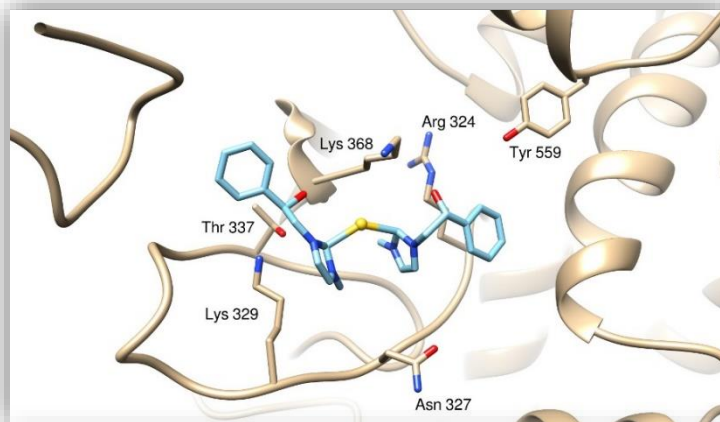
Docking studies: Au NHC complexes *and* topoisomerases I and II

Binding energies (kcal/mol)		
Compounds	h Topo I	h Topo II
1	-8.42	-6.63
11	-9.58	-8.65

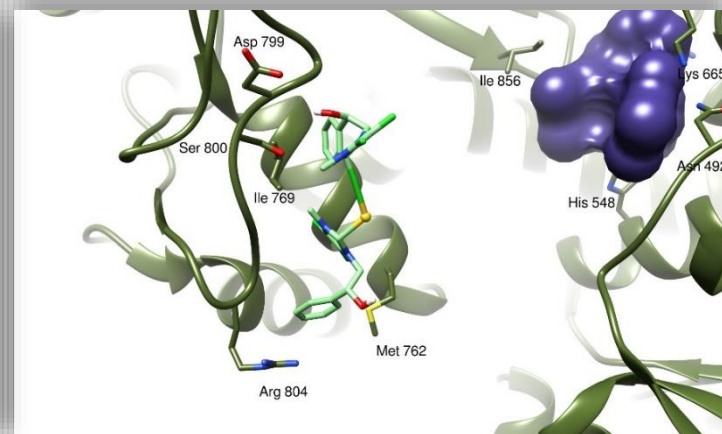
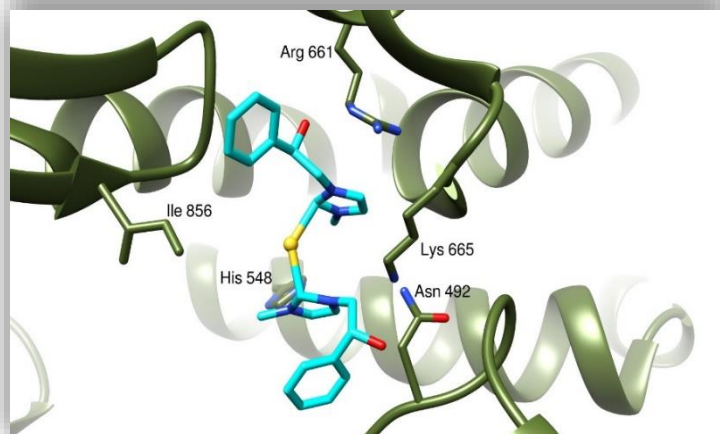
Compound 1

Compound 11

h Topo I



h Topo II



Anticancer activity towards breast cancer cell lines Ag NHC complexes

Table 1. IC₅₀ values of Ag metal complexes and Cisplatin, expressed in μM. The means ± standard deviations are shown.

Compounds	MDA-MB-231	MCF-7	MCF-10A
<i>Cisplatin</i>	28.7±0.4	35.8±0.7	81.3±0.6
3	43.5±0.6	36.2±1.1	71.7±1.3
4	7.0±0.4	18.3±0.8	>200
7	52.6±0.3	31.8±0.8	>200
8	20.9±1.1	30.7±0.7	>200
10	>100	18.4±0.6	>200
12	38.1±0.8	13.2±0.3	>200



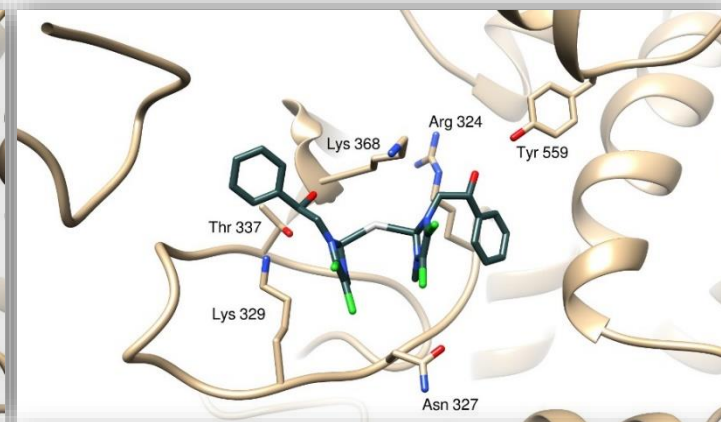
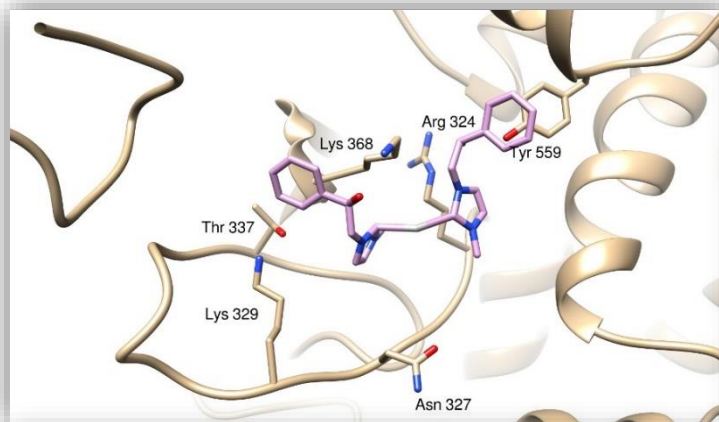
Docking studies: Ag NHC complexes *and* topoisomerases I and II

Binding energies (kcal/mol)		
Compounds	h Topo I	h Topo II
4	-10.3	-8.34
12	-7.84	-7.96

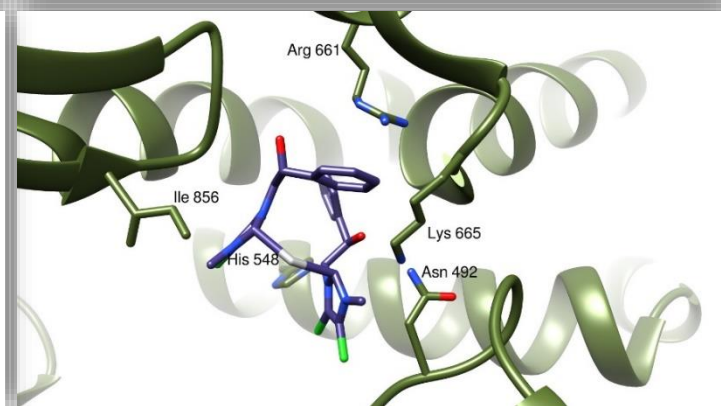
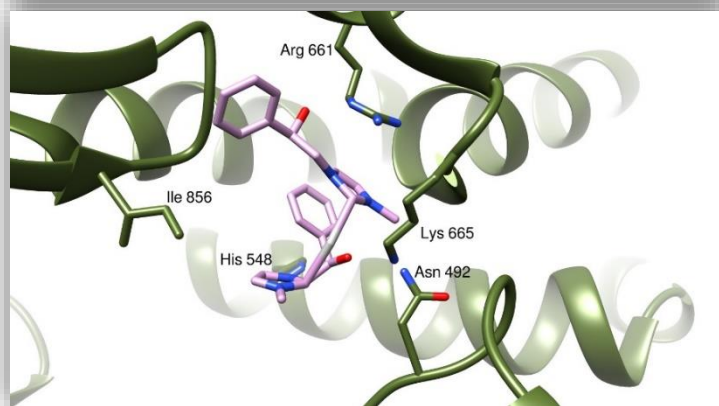
Compound 4

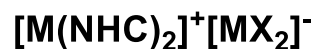
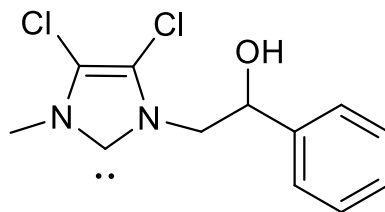
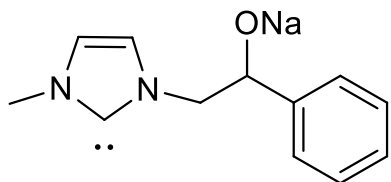
Compound 12

h Topo I



h Topo II





1 M=Au; X=Cl⁻

4 M=Ag; X=CH₃COO⁻

11 M=Au; X=CH₃COO⁻

12 M=Ag; X=CH₃COO⁻

Au NHC complexes

Compounds	MDA-MB-231	MCF-7	MCF-10A
1	15.8±0.7	29.9±1.1	>200
11	16.8±1.2	1.2±0.3	24.4±0.9

Ag NHC complexes

Compounds	MDA-MB-231	MCF-7	MCF-10A
4	7.0±0.4	18.3±0.8	>200
12	38.1±0.8	13.2±0.3	>200

Work in progress...



In-depth investigations about:

- possible mechanisms of cell death;
- ability to interfere with ROS production or with cell migration and angiogenesis.





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BEST FRIEND**



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