

S p r e a d i n g   t h e

**M e d i c i n a l   C h e m i s t r y**   f r o n t i e r s :

N o v e l

**T h i o u r e a - M e t a l   C o m p l e x e s**

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**DE ESPAÑA**  **MINISTERIO**  
**DE ECONOMÍA**  
**Y COMPETITIVIDAD**

# Introduction



## Cancer

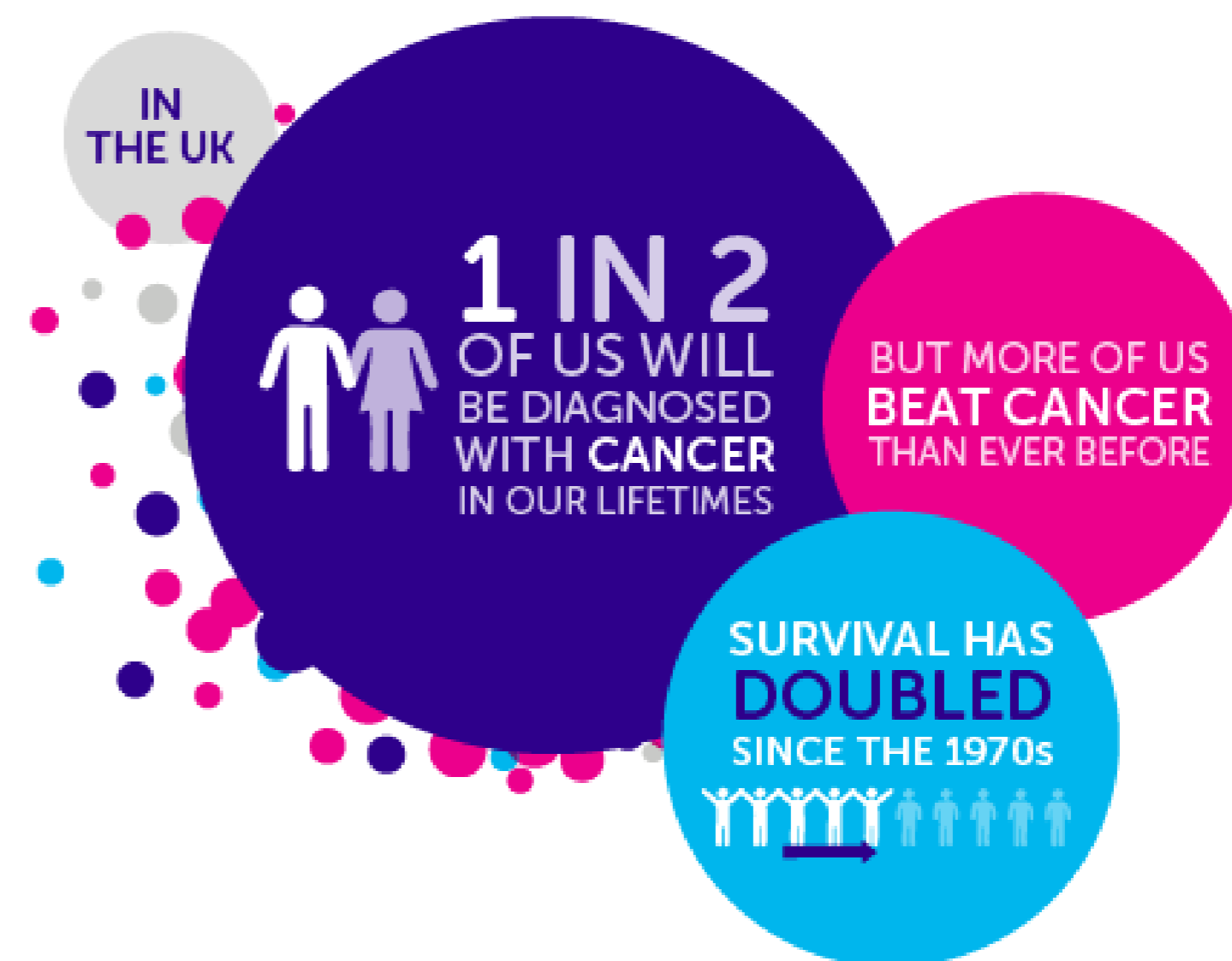
Cancer is one of the leading causes of death in the world.

In 2018, there were **18.1 million new cases** and **9.5 million cancer-related deaths** worldwide.

By 2040, the number of new cancer cases per year is expected to rise to 29.5 million and the number of cancer-related deaths to 16.4 million.

Generally, cancer rates are highest in countries whose populations have the highest life expectancy, education level, and standard of living.

Some cancer types, such as cervical cancer, the reverse is true, and the incidence rate is highest in countries in which the population ranks low on these measures.<sup>1</sup>



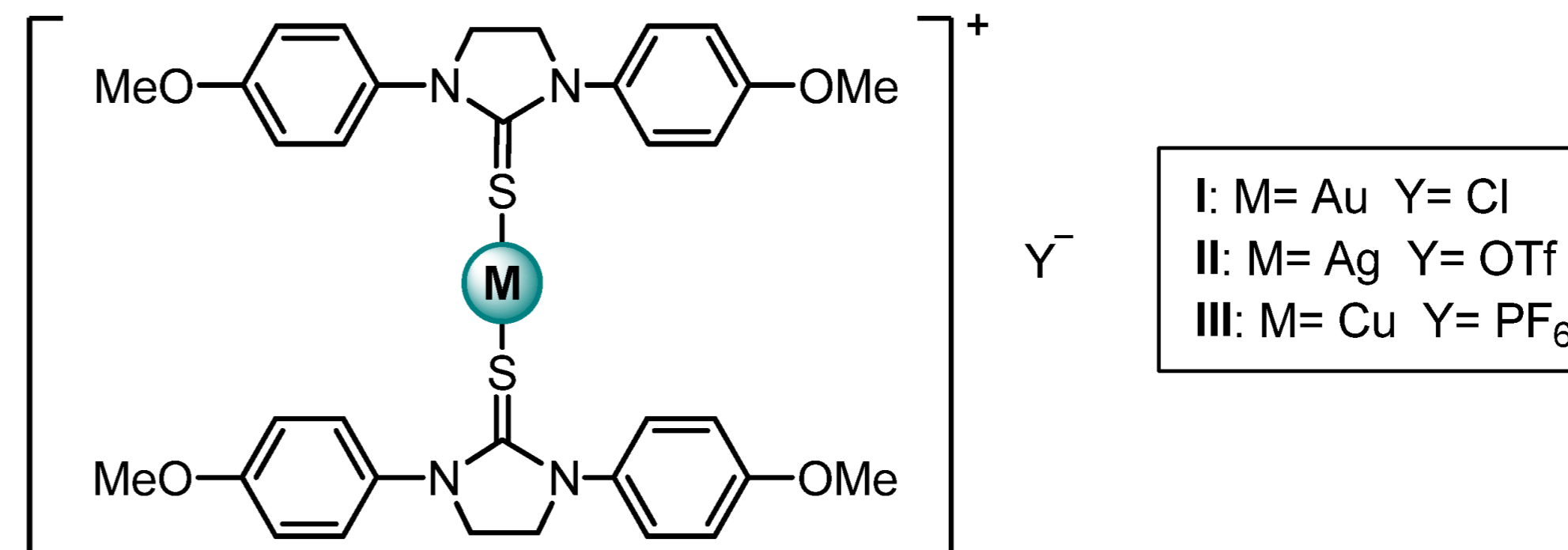
<sup>1</sup> National Cancer Institute. <https://www.cancer.gov/> (31<sup>st</sup> May 2022).

# Introduction



## Gold(I) and silver(I) complexes

Gold(I) and silver(I) complexes are known for their antitumor activities<sup>2</sup> and seem to avoid collateral effects in cancer treatment.<sup>3</sup> In 2010, Che and co-workers pioneered the use of thiourea-group 11 metal complexes with good cytotoxic activity and excellent TrxR inhibition.<sup>4</sup>

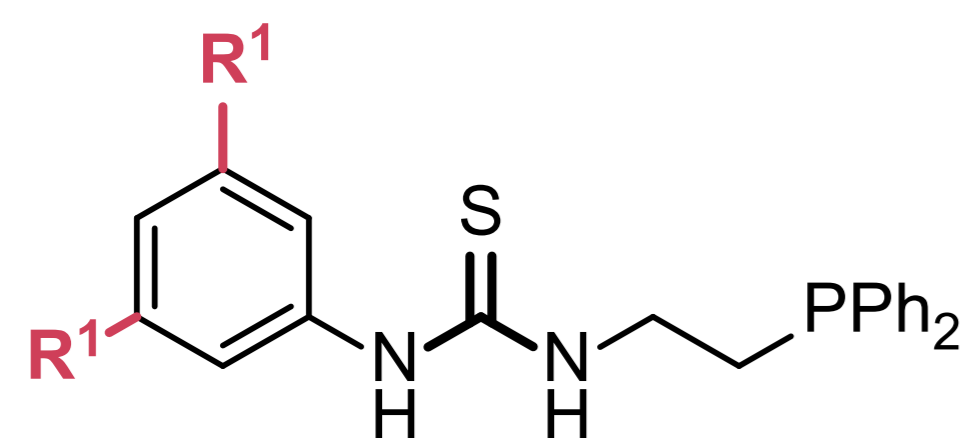


<sup>2</sup> I. Ott, *Coord. Chem. Rev.* **2009**, *153*, 1670.

<sup>3</sup> C. N. Banti, A. D. Giannoulis, N. Kourkoumelis, A. M. Owczarzak, M. Poyraz, M. Kubicki, K. Charalabopoulos, S. K. Hadjikakou, *Metallomics* **2012**, *4*, 545.

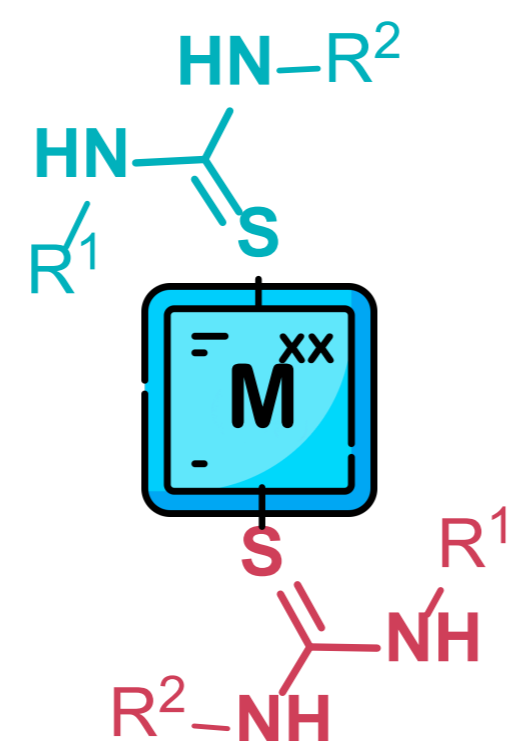
<sup>4</sup> K. Yan, C.-N. Lok, K. Bierla, C.-M. Che, *Chem. Commun.* **2010**, *46*, 7691.

# Workflow



## Ligands synthesis

Two thiourea ligands bearing a phosphine group in one arm and in the other a phenyl derivative group (**T1** and **T2**)



## Complexes synthesis

Gold(I) and silver(I) complexes with different ligands



## Structure determination

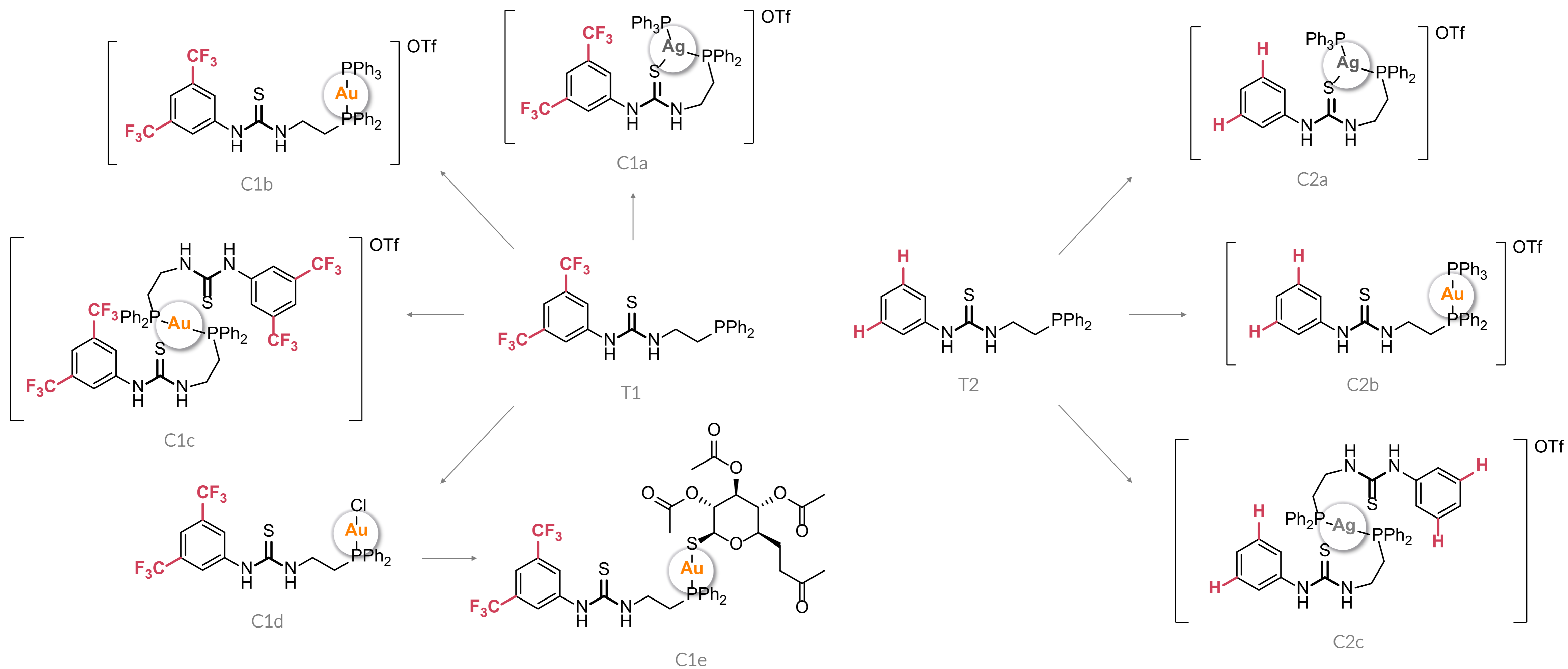
Characterization of the species and coordination studies by NMR, Mass Spectrometry and X-ray diffraction experiments



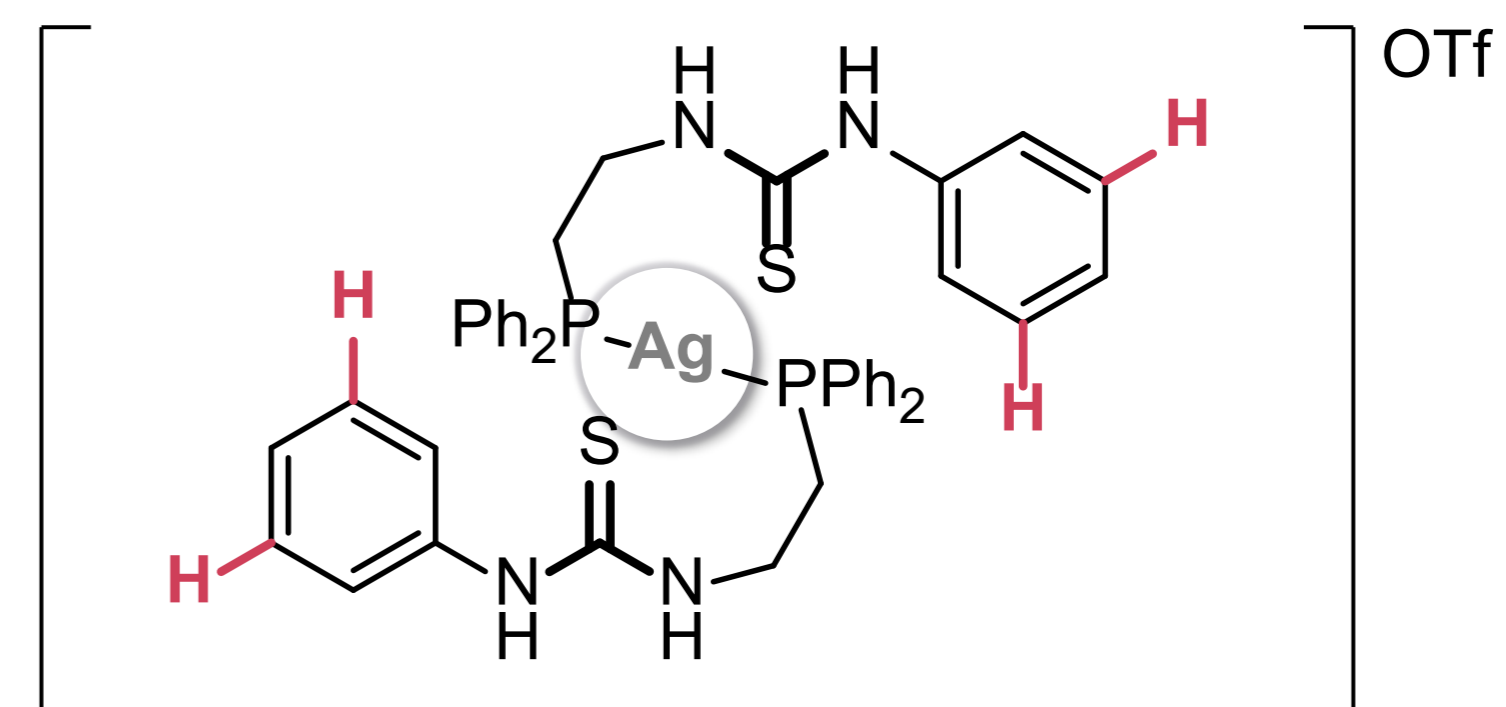
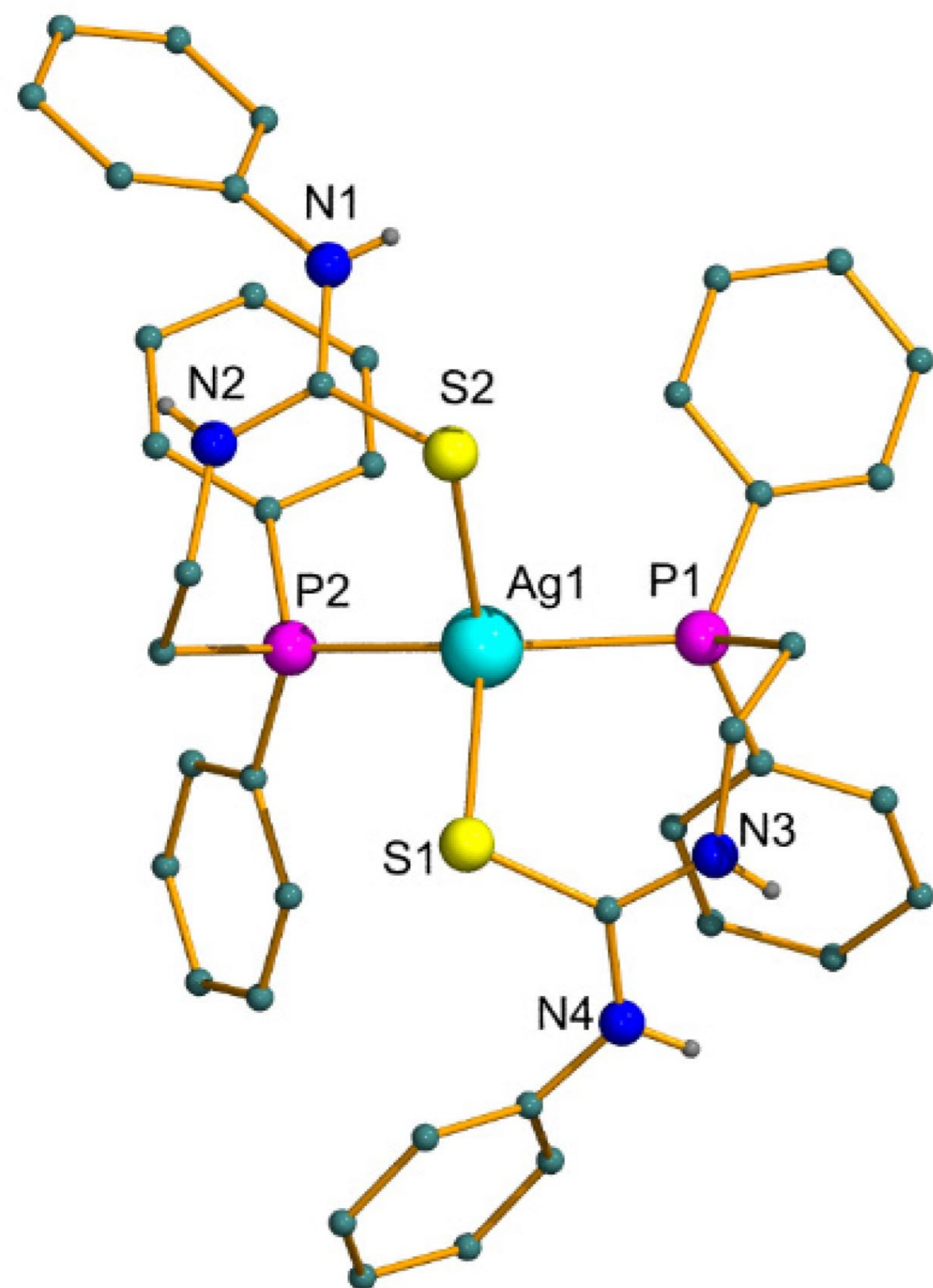
## *In vitro* assays

Ligands and complexes were explored against different cancer cell lines (HeLa, A549 and Jurkat)

# Synthesis



# Crystal structure of C2c



The crystal structure corroborates that the silver atom is coordinated by **two thiourea T2 ligands** in a chelated form, through the sulfur and phosphorus atoms. The silver center has a somewhat distorted tetrahedral geometry, mainly due to the chelation angles of the ligand.

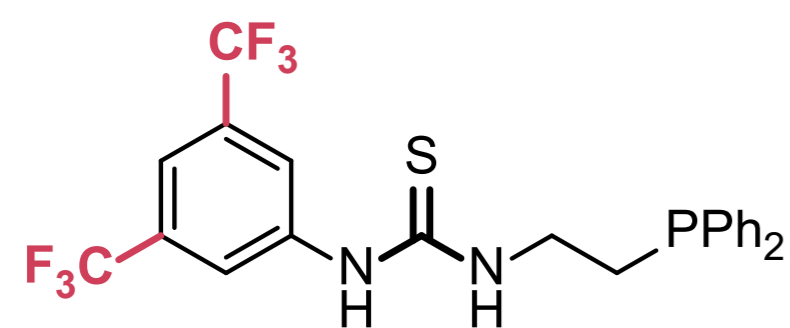
# *In vitro* assays (MTT - 24 h)

Cisplatin

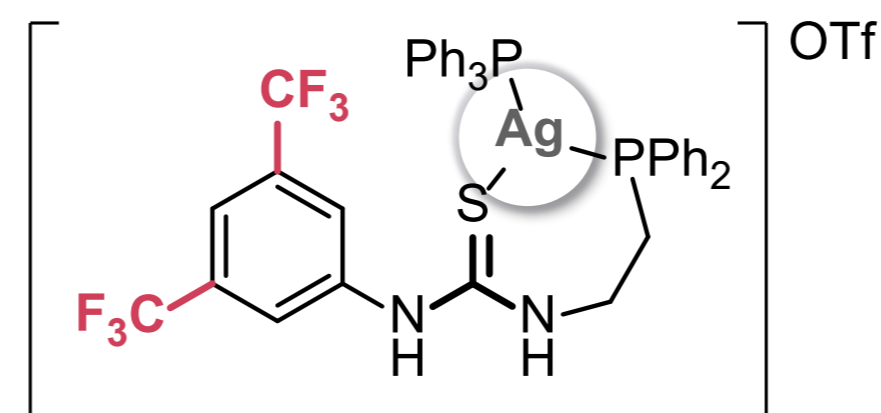
55 ± 9

114.2 ± 9.1

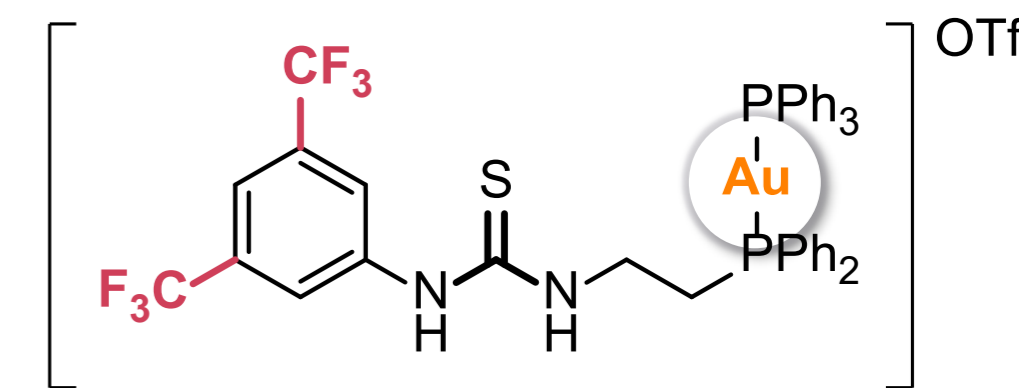
10.8 ± 1.2



T1



C1a



C1b

HeLa

&gt; 25

10.17 ± 1.74

2.09 ± 0.17

A549

13.89 ± 4.0

7.06 ± 1.95

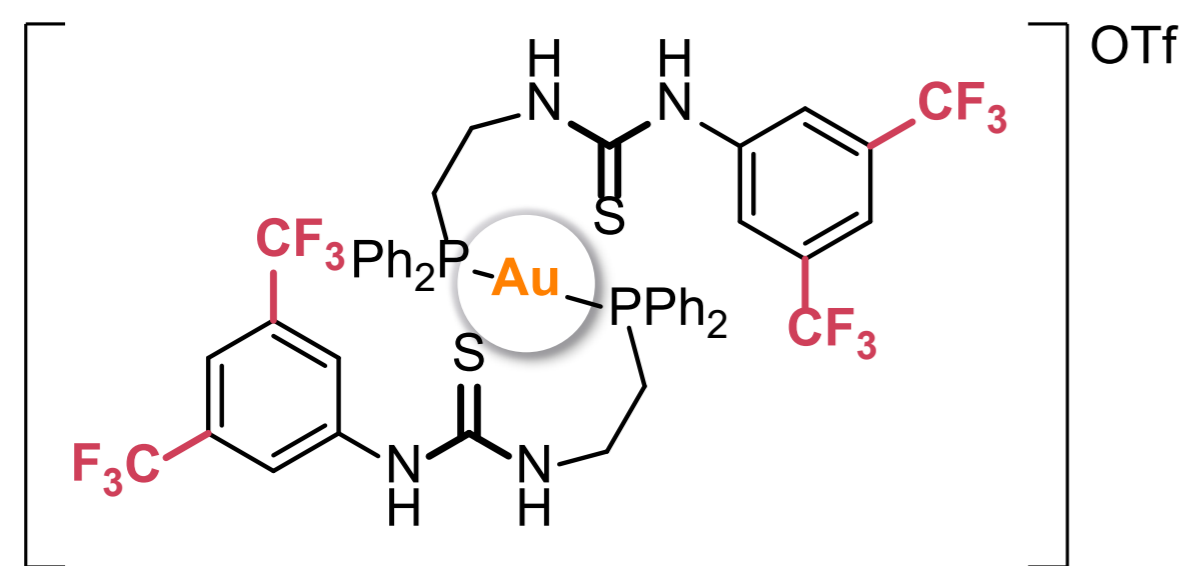
&gt; 25

Jurkat

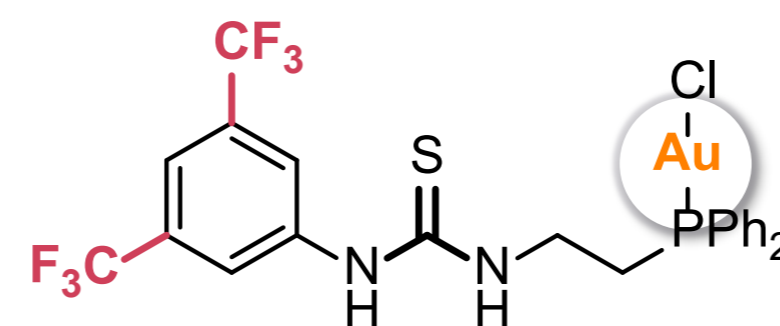
&gt; 25

3.89 ± 0.19

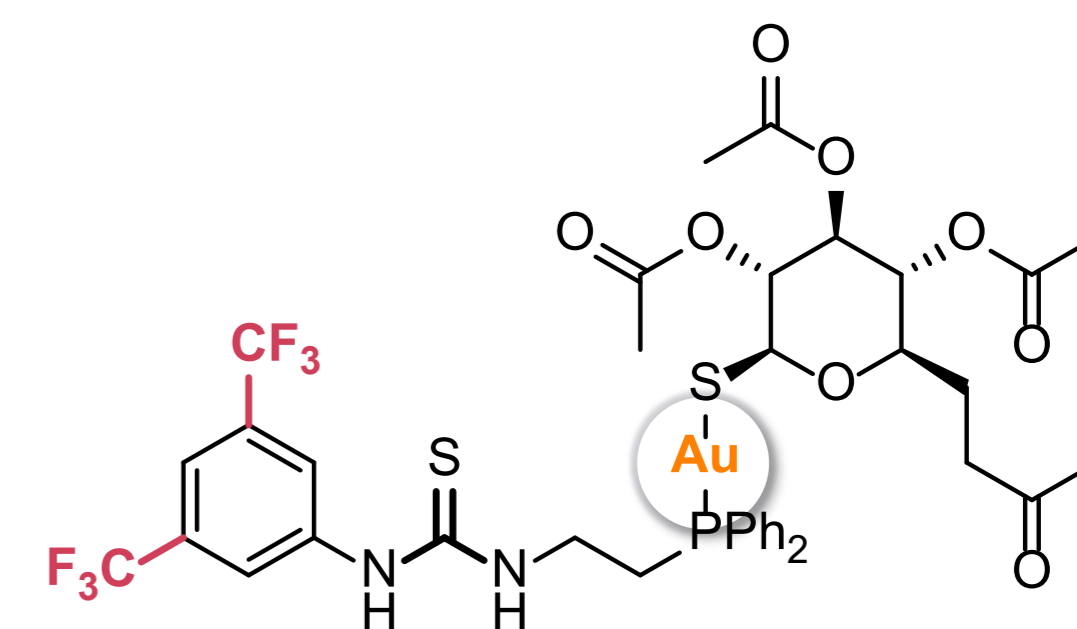
0.62 ± 0.03



C1c



C1d



C1e

HeLa

0.25 ± 0.12

&gt; 25

4.52 ± 0.23

A549

&gt; 25

&gt; 25

5.98 ± 1.18

Jurkat

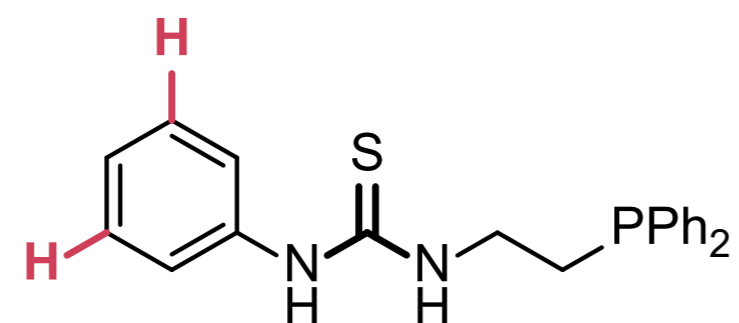
0.70 ± 0.06

19.80 ± 0.46

2.57 ± 0.15

# *In vitro* assays (MTT - 24 h)

Cisplatin

 $55 \pm 9$  $114.2 \pm 9.1$  $10.8 \pm 1.2$ 

T2

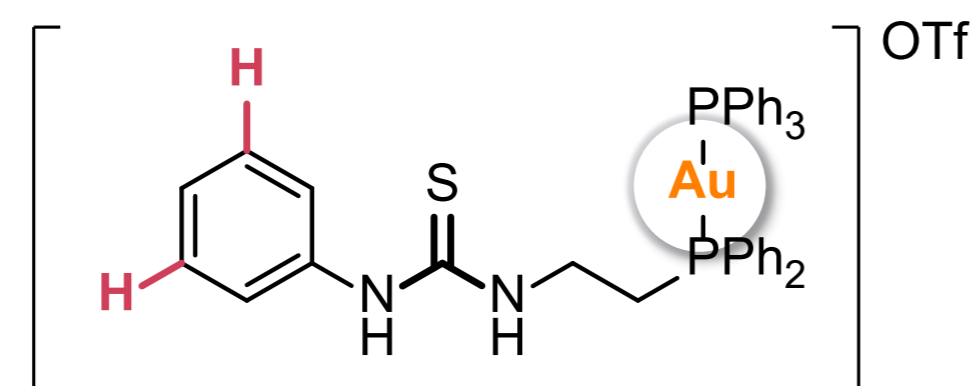
HeLa

 $8.16 \pm 0.15$ 

A549

&gt; 25

Jurkat

 $14.20 \pm 0.72$ 

C2b

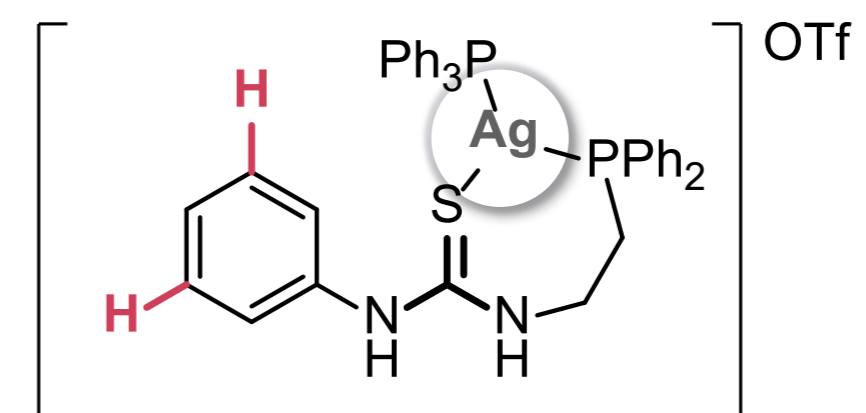
HeLa

 $1.48 \pm 0.15$ 

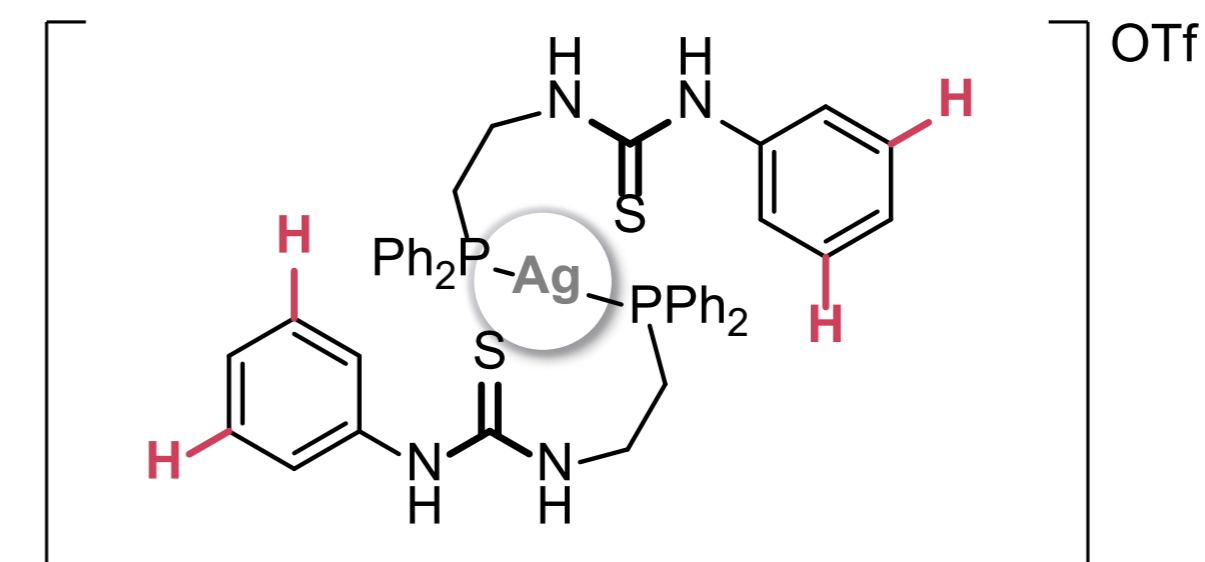
A549

 $4.91 \pm 0.23$ 

Jurkat

 $5.15 \pm 0.32$ 

C2a

 $0.87 \pm 0.06$  $0.79 \pm 0.04$  $0.64 \pm 0.04$ 

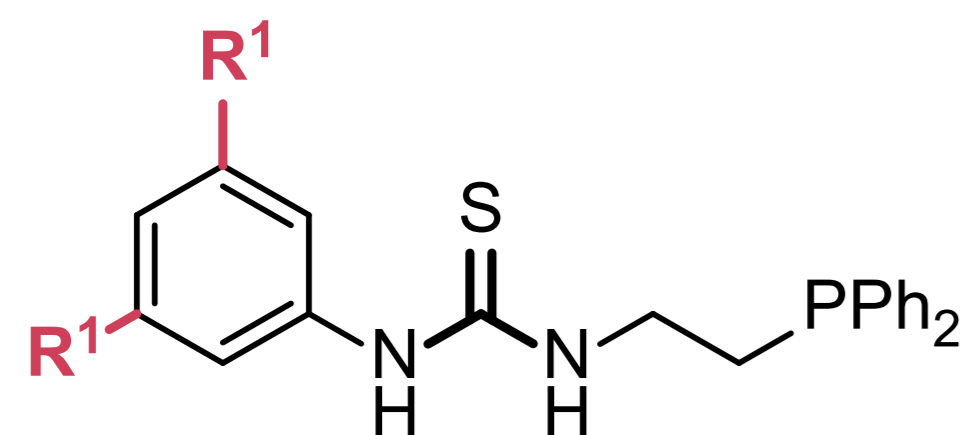
C2c

 $1.52 \pm 0.09$  $0.58 \pm 0.02$  $1.53 \pm 0.31$



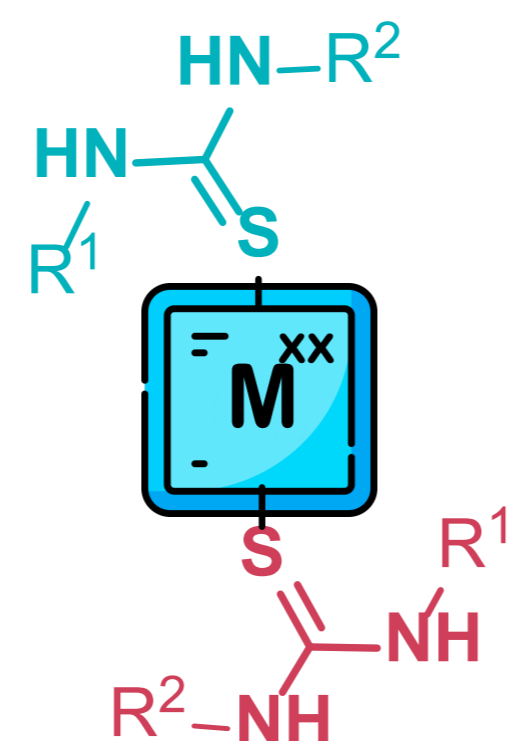
# Conclusions

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## Ligands synthesis

Two thiourea ligands bearing a phosphine group were synthesized



## Complexes synthesis

Gold(I) and silver(I)-thiourea complexes were obtained in excellent yields



## Structure determination

Structures and coordination geometries were performed by NMR, Mass Spectrometry and X-ray diffraction experiments



## *In vitro* assays

Ligands and complexes were explored against different cancer cell lines (HeLa, A549 and Jurkat) with promising  $IC_{50}$  values

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