



3rd International Electronic Conference on Medicinal Chemistry

1-30 November 2017

chaired by Dr. Jean Jacques Vanden Eynde



Novel Gold Complexes with Nitrogen Acyclic Carbenes and their Applications as Anticancer Agents

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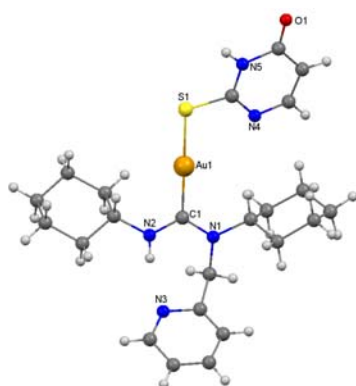
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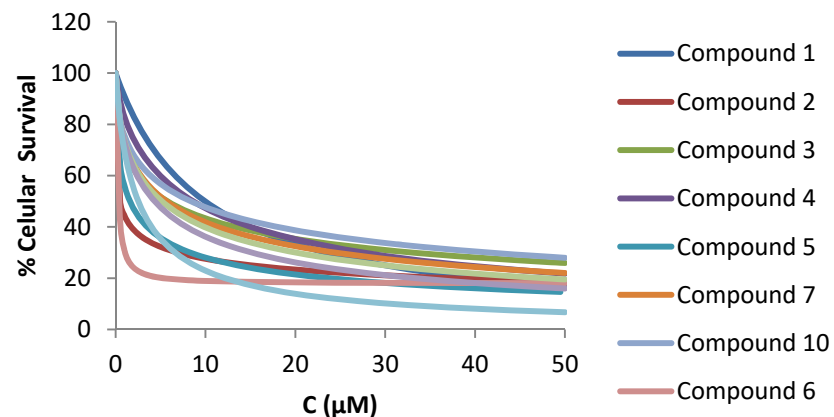
Novel Gold Complexes with Nitrogen Acyclic Carbenes and their Applications as Anticancer Agents

Graphical Abstract

Characterization



Synthesis



MTT Assay

IC₅₀



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Abstract:

Gold drugs are well known and have been widely studied for their potential chemotherapeutic properties in anticancer treatments, although they have some limitations.^{1,2}

Gold N-heterocyclic carbenes, especially NHC-Au(I) display high cytotoxicity in vitro (low micromolar to nanomolar) against a variety of human cancer cell lines with different degrees of selectivity. In the search for new alternatives, not only N-heterocyclic but N-acyclic carbenes must be explored.^{2,3,4}

N-acyclic carbenes are easily accessible via the reaction between isocyanide gold compounds and different amines. The reaction between one of those derivatives with different thiol groups, in presence of K_2CO_3 as an deprotonating agent, has led to a family of gold(I) NAC thioderivatives with high cytotoxicity.

Biological activity was measured by MTT assay for different human cancer cell lines: A-549 (lung cancer), MiaPaca2 (pancreatic cancer) for the different synthesized compounds, calculating their IC_{50} . The IC_{50} values found were in many cases less than the value six, being these results very promising.

Keywords: gold; N-acyclic carbenes; isocyanide; cytotoxic activity



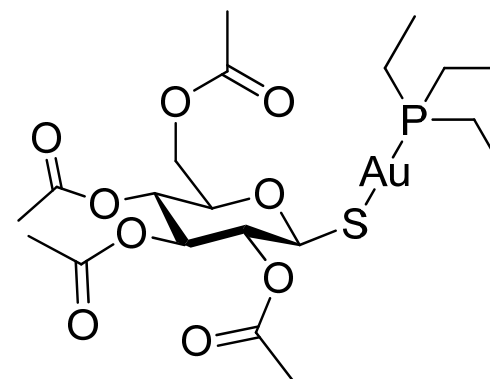
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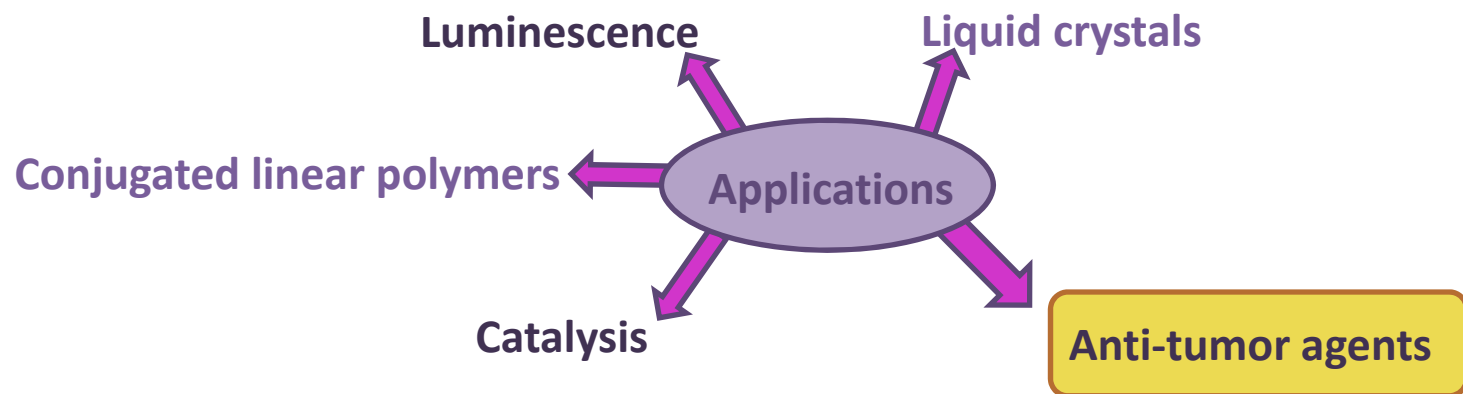


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Introduction



Organogold complexes known for over 100 years



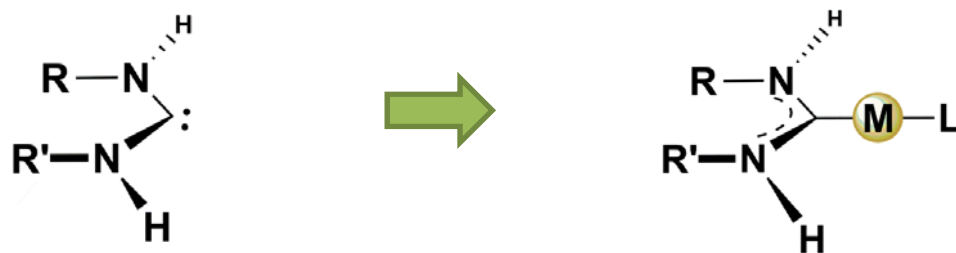
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Introduction

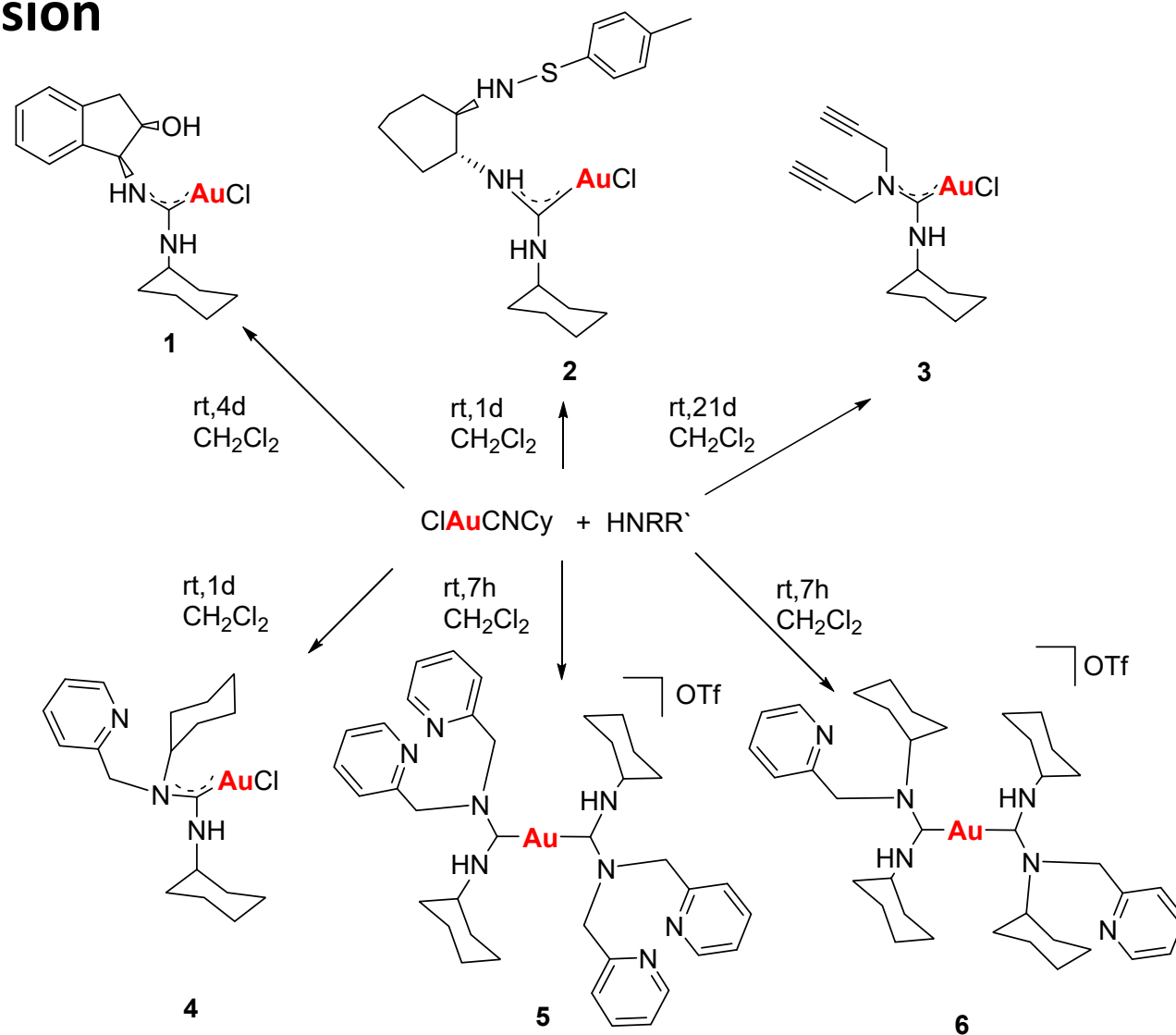


- First gold acyclic carbene **1971** (Bonati and Minghetti, *Synth. Inorg. Met.-Org. Chem.* **1971**, 1, 299) → **Addition of CH₃OH to Cl-Au-CNR**
- **1973** Bonati and Minghetti (*J. Organomet. Chem.* **1973**, 59, 403) → **Addition of NH₂R to Cl-Au-CNR**
- **Acyclic Aminocarbene Metal Complexes :**
 - Large σ -donor capacity
 - Wide angle N-C-N (adjustable)
 - Conformational flexibility
 - Wide range of nitrogen substituents



Results and discussion

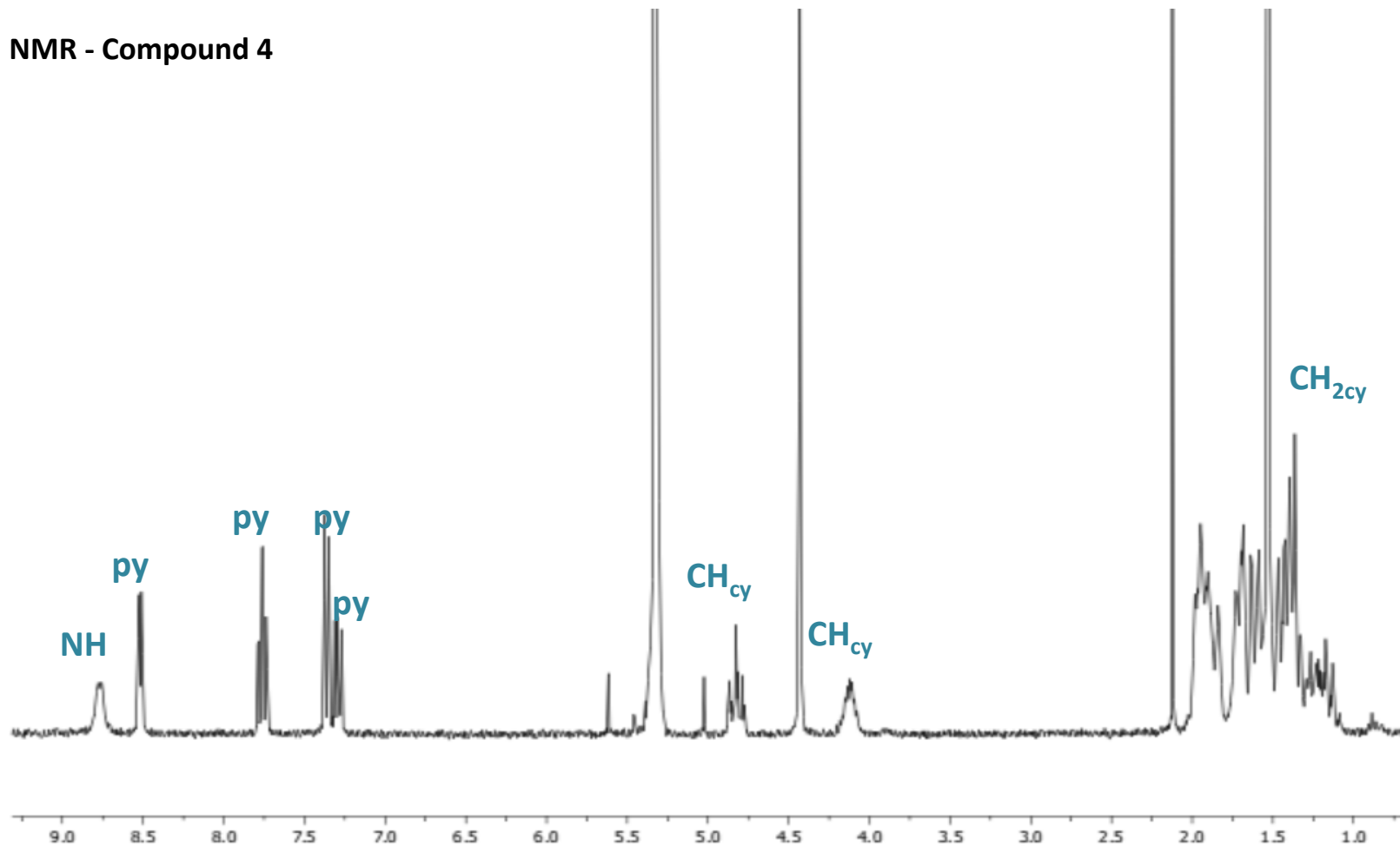
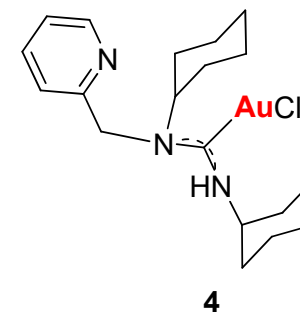
Synthesis and characterization of the new gold(I) NAC



Results and discussion

Synthesis and characterization of the new gold(I) NAC

NMR - Compound 4



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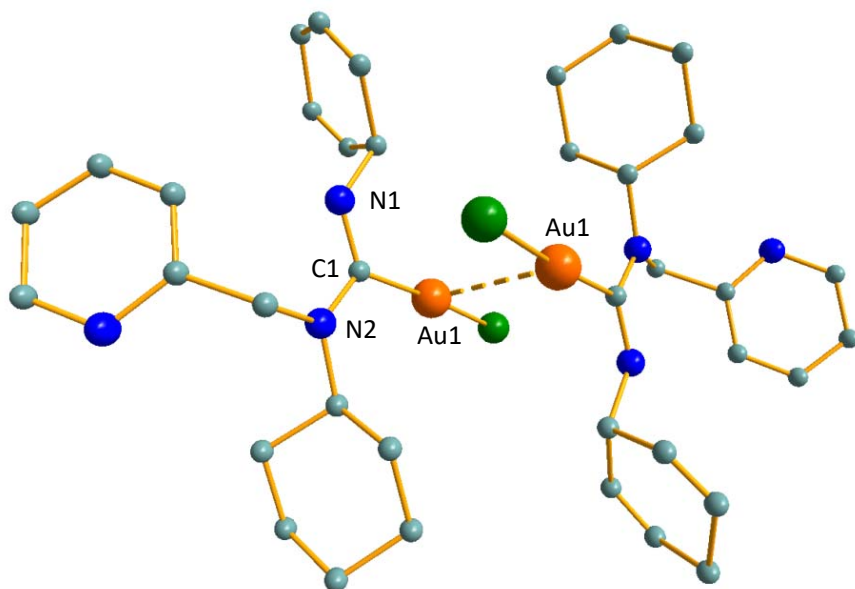


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Results and discussion

Synthesis and characterization of the new gold(I) NAC

Compound 4

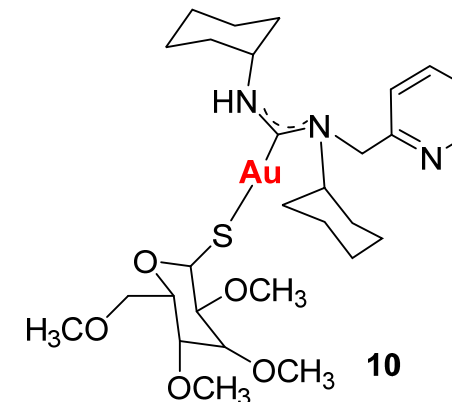
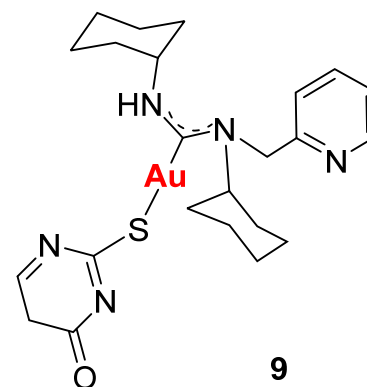
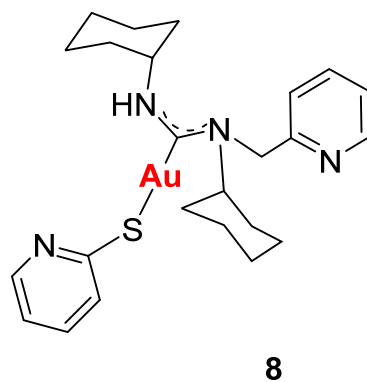
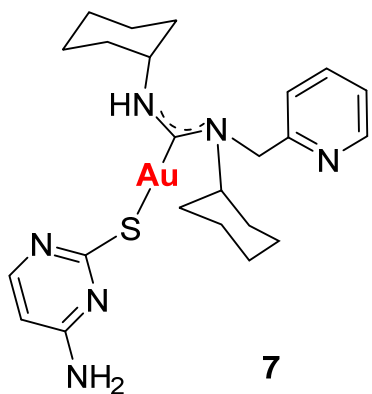
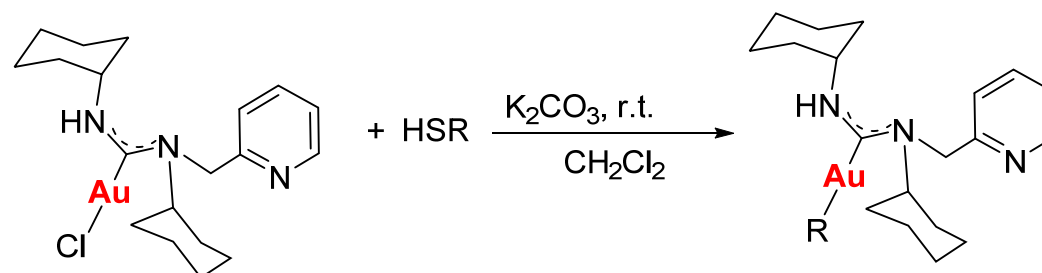


| | Å, ° |
|-----------|-----------|
| Au1---Au1 | 3.438(1) |
| Au1-C1 | 1.998(9) |
| Au1-Cl1 | 2.283(2) |
| N1-C1 | 1.328(12) |
| N2-C1 | 1.331(12) |
| C1-Au-Cl1 | 175.6(2) |
| N2-C1-N1 | 117.3(8) |



Results and discussion

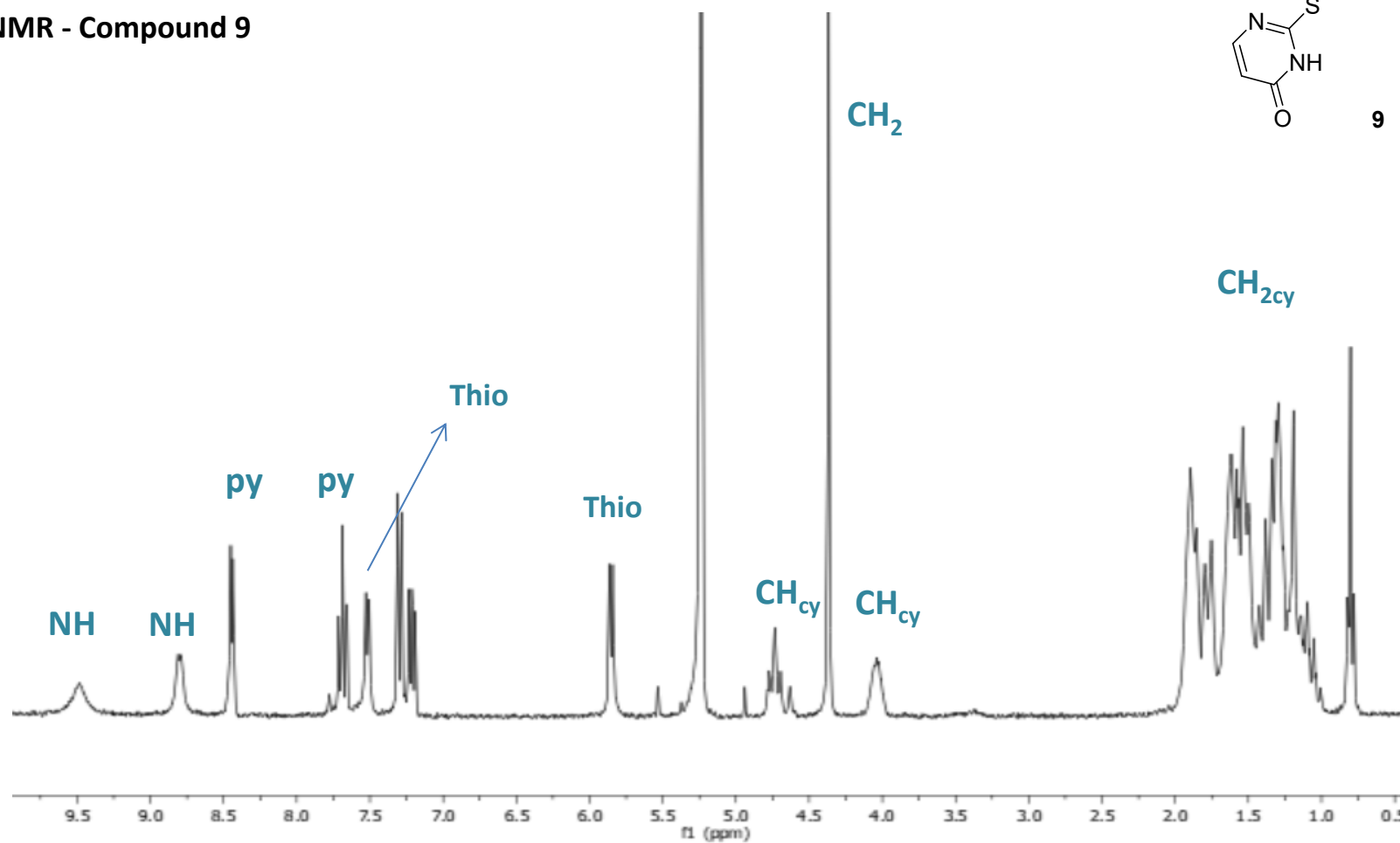
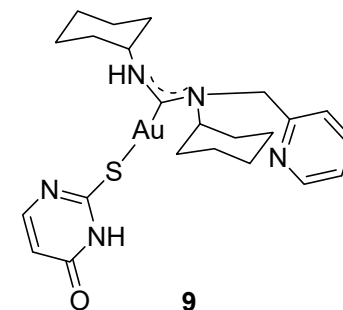
Synthesis and characterization of the thioderivatives



Results and discussion

Synthesis and characterization of the new gold (I) NAC

NMR - Compound 9



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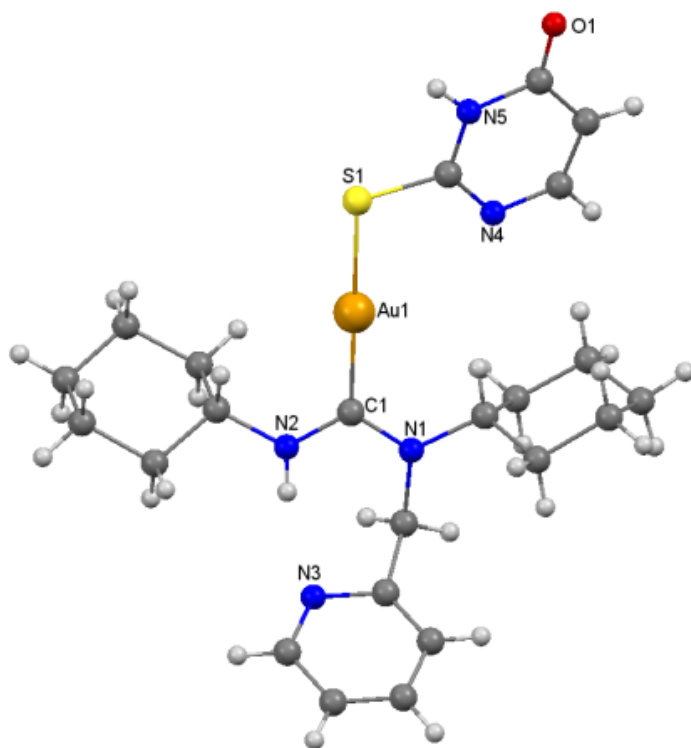
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Results and discussion

Synthesis and characterization of the new gold (I) NAC
Compound 9



| | Å, ° |
|----------|-----------|
| Au1-C1 | 1.999(15) |
| Au1-S1 | 2.305(4) |
| N1-C1 | 1.343(16) |
| N2-C1 | 1.358(16) |
| C1-Au-S1 | 176.2(4) |
| N2-C1-N1 | 115.0(13) |



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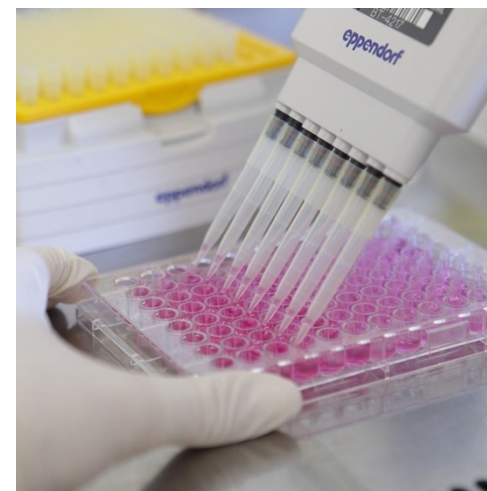
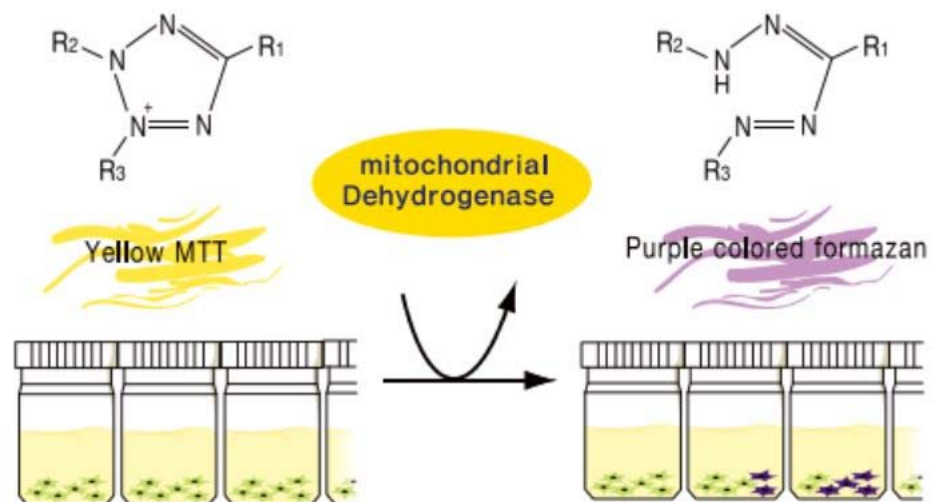
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Results and discussion

MTT assay

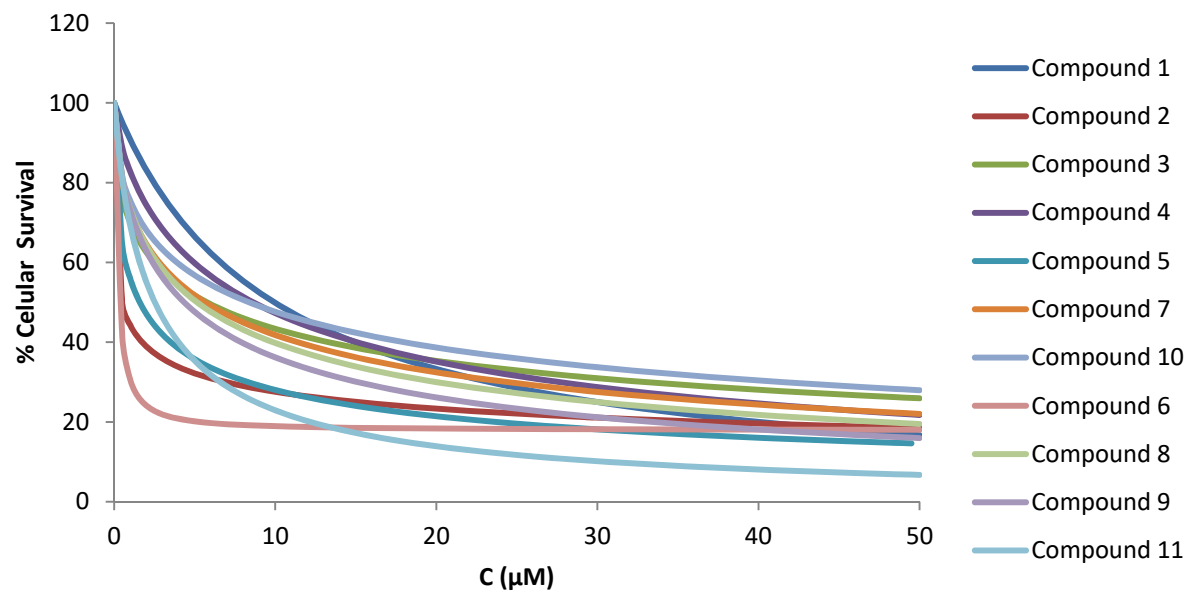


Results and discussion

MTT assay

| Compound | IC ₅₀ | error |
|----------|------------------|-------|
| 1 | 18.92 | 2.93 |
| 2 | 0.49 | 0.19 |
| 3 | 5.75 | 1.99 |
| 4 | 8.63 | 2.88 |
| 5 | 1.59 | 0.39 |
| 7 | 5.64 | 1.02 |
| 10 | 6.04 | 3.50 |
| 6 | 0.23 | 0.07 |
| 8 | 5.14 | 0.58 |
| 9 | 4.34 | 0.60 |
| 11 | 2.52 | 0.89 |

Cellular line: A-549



The IC₅₀ values found were in many cases less than the value six, being these results very promising.



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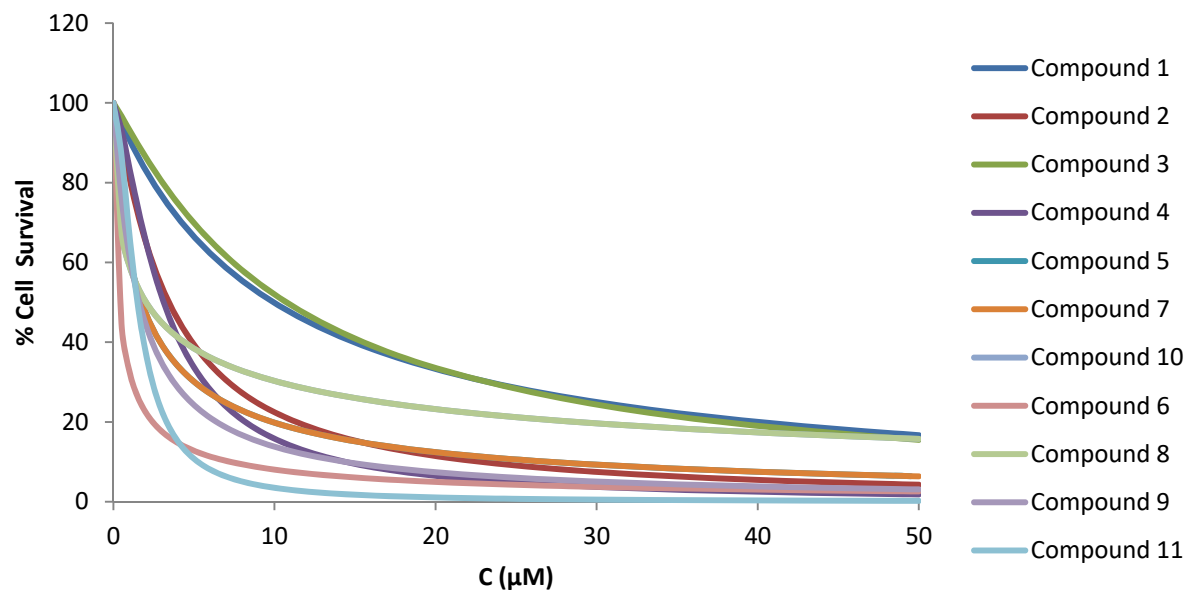
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Results and discussion

MTT assay

| Compound | IC ₅₀ | error |
|----------|------------------|-------|
| 1 | 9.94 | 2.07 |
| 2 | 3.45 | 0.56 |
| 3 | 10.74 | 2.57 |
| 4 | 3.12 | 0.76 |
| 5 | 1.75 | 0.15 |
| 7 | 3.30 | 0.26 |
| 10 | 2.03 | 0.53 |
| 6 | 0.38 | 0.10 |
| 8 | 2.03 | 0.53 |
| 9 | 1.60 | 0.17 |
| 11 | 1.49 | 0.24 |

Cellular line: MiaPaca2



The IC₅₀ values found were in many cases below 6µM, Showing these compounds a high cytotoxicity in both cellular lines.



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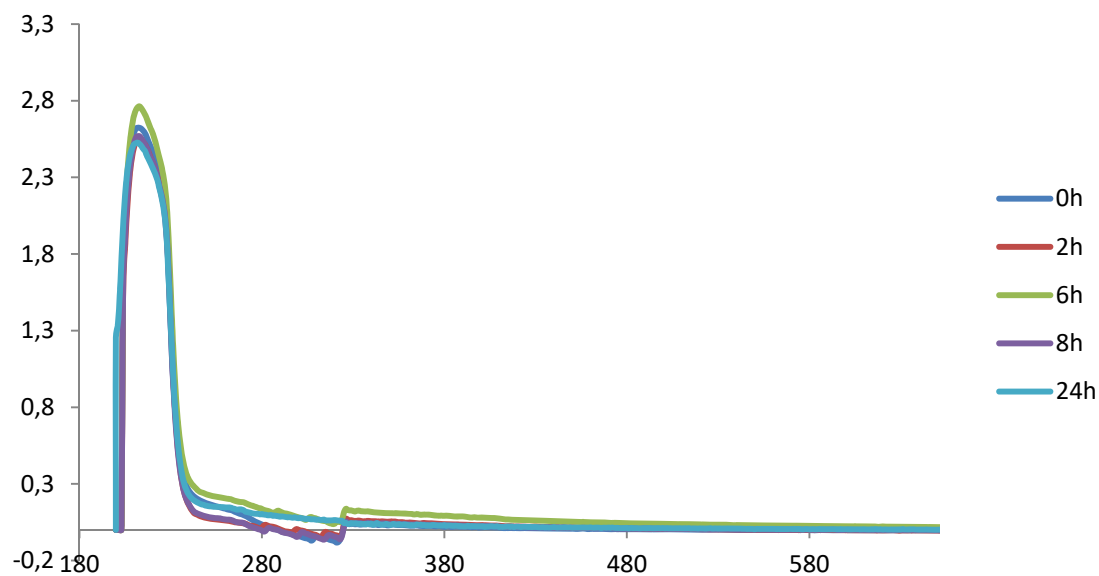
Results and discussion

Stability

- 20mM solutions in DMSO were prepared
- Solutions 10^{-4} M in PBS (buffer solution)
- Samples incubated at 37°C, measured by UV over 24h



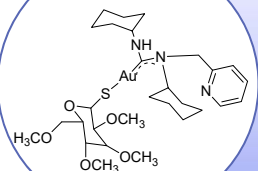
All the compounds were stable under biological conditions



Conclusions



New gold(I) N-acyclic carbenes were synthesized.



Thioderivatives were coordinated to gold(I) NAC.



New complexes were tested through MTT assay, cell lines: A-549 (lung cancer), MiaPaca2 (pancreatic cancer). The IC_{50} values found very promising



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