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Finanziato dall'Unione europea
NextGenerationEU

Ministero dell'Università e della Ricerca

Italiadomani
PIANO NAZIONALE DI RIPRESA E RESILIENZA

Poliammino-bis-Maltoli

applicazioni e sviluppi futuri

Daniele Paderni

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Spoke 8 – WP**1** – Task **3**

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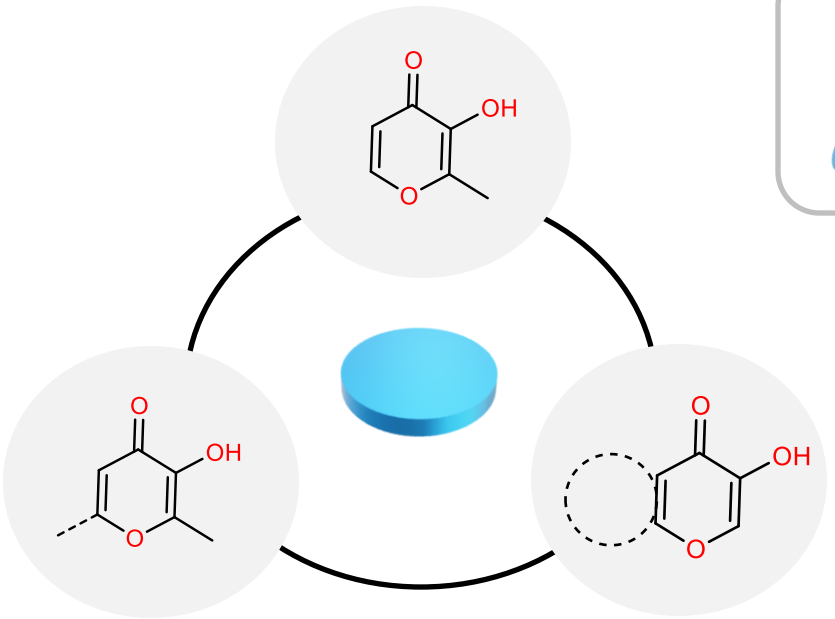
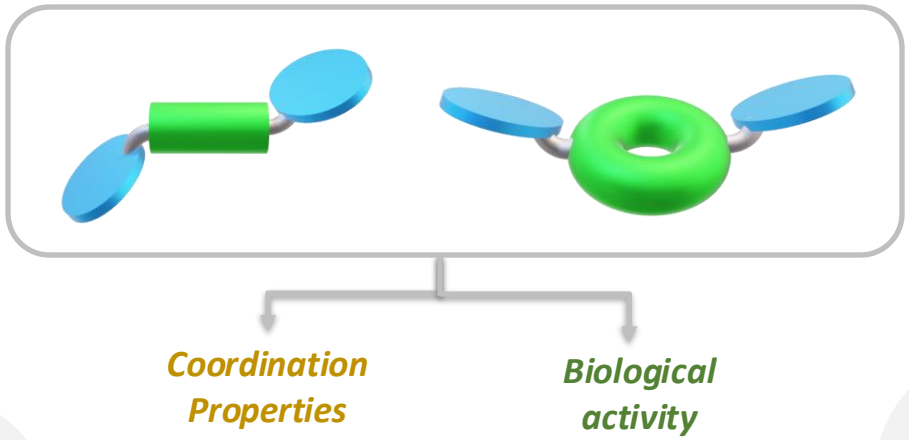
3-hydroxy-4-pyrones



- high **affinity** for a range of **metal ions**

- **metallopharmaceuticals:**
  - **a)** sequestering action
  - **b)** improving absorption



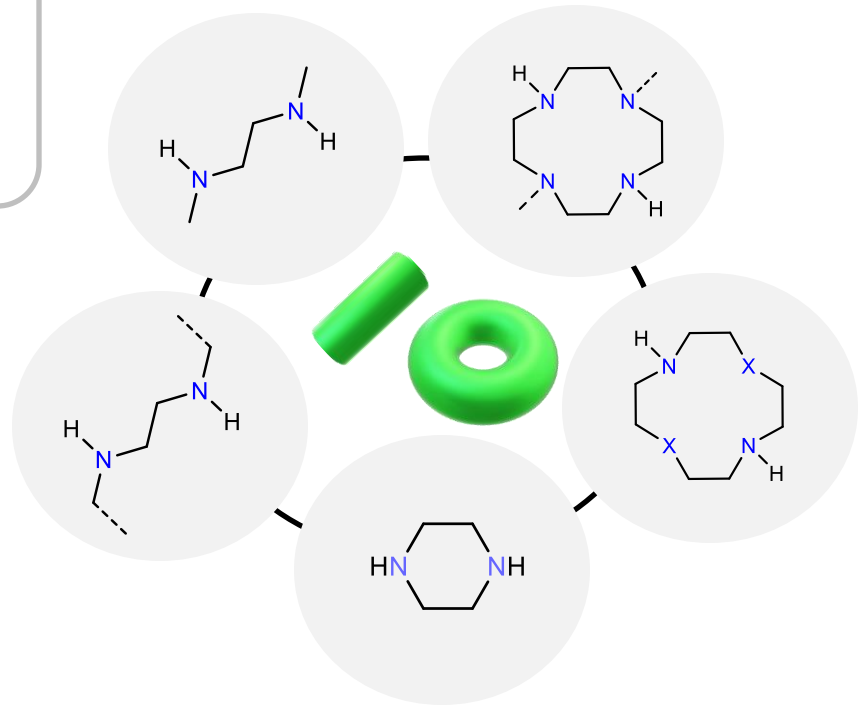
Maltol

- **natural** product

- **anti-neoplastic** activity (DNA breaks; Apoptosis)

- **Metal complex (ROS)**
  - **a)** antimicrobial activity
  - **b)** anticancer activity

Polyamines



- **Coordination** properties

- **water**-soluble

- **Antitumor** agents (Apoptosis)

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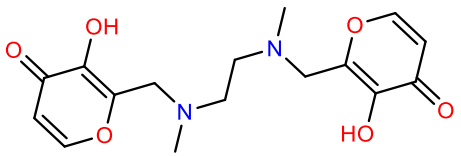
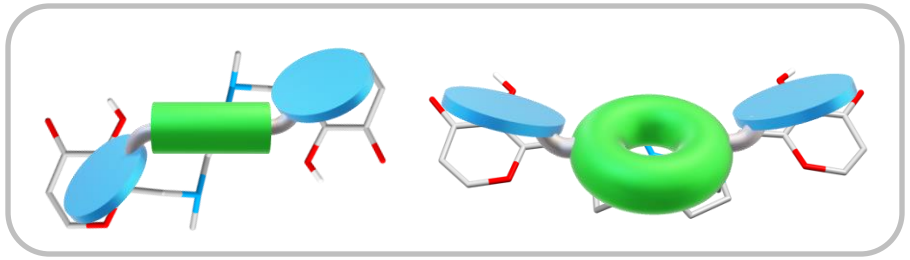
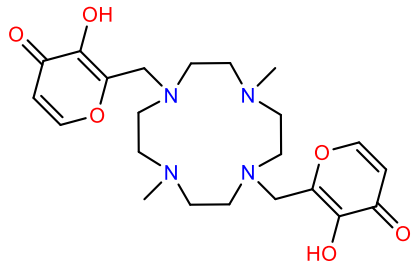


Malten





Maltonis

Biological activity

- **Dose-dependent reduction** in cell survival of different **tumor cell lines** (solid and haematopoietic)
- Activation of **cell cycle arrest**
- **Programmed cell death**
- Ability to induce **covalent binding** between **DNA** and **histones**

British Journal of Cancer 2010 (103), 239-248

J. Org. Chem. 2012, 2207-2218

* *M. Fanelli, V. Fusi, "Preparation of dimers of [(3-hydroxy-4-pyron-2-yl)methyl]amine as antineoplastic drugs", PCT Int. Appl. (2010), WO 2010/061282 A1 20100603*

* *M. Fanelli, V. Fusi, "Derivative of [(3-hydroxy-4-pyron-2-yl)-methyl]-amine and use thereof as anti-neoplastic drugs", US Patent (2015) US 9145381 B2 20150929*

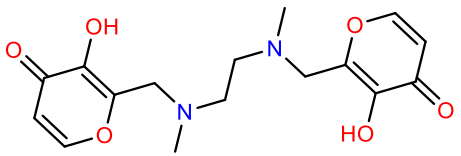
* *M. Fanelli, V. Fusi, "Pharmaceutical composition of [(3-hydroxy-4 -pyron-2-yl) methyl] -amine derivatives and DNA demethylating agents and their use as anti-neoplastic drugs", CT Int. Appl. (2018), WO 2018002896 A1 20180104*

- **Maltonis** is **more effective** than **Malten**
  - Effective on **Sarcoma** (in vivo)
  - Effective on **multidrug & cisplatin-resistance** cell (in vitro)
  - **Ineffective** against **normal** human mesenchymal stem cells

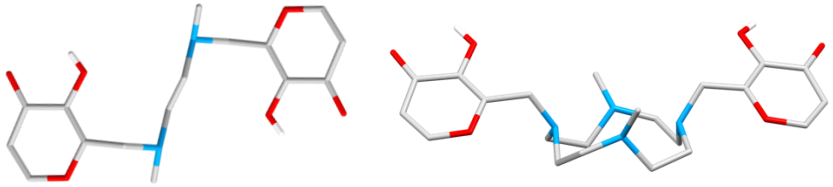
BMC Cancer 2014 (14), 137

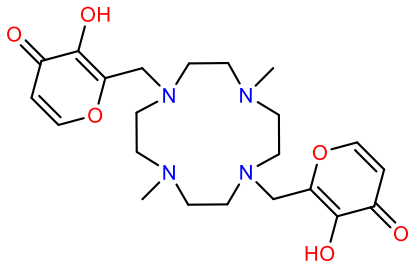
- **APL** (ACUTE PROMYELOCYTIC LEUKEMIA)
  - **Epigenomic reprogramming** of APL

Canger Gene Therapy, 2023, (30) 671-682



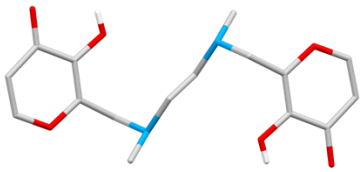
Malten





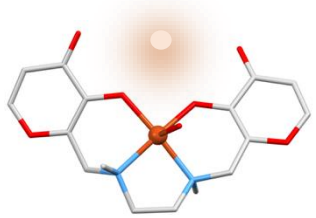
Maltonis

Coordination Properties



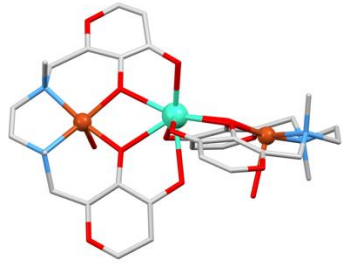
Malten

Cu(II)

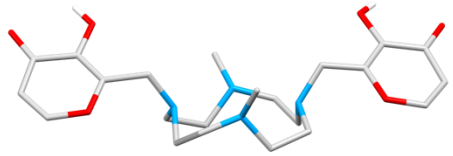


Mononuclear monomer

Gd(III)

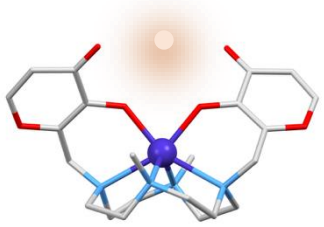


Heterotrinuclear dimer

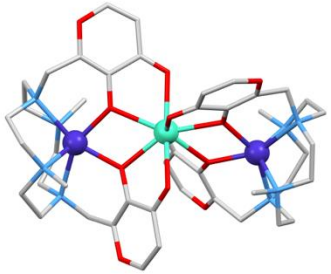


Maltonis

Co(II)



Gd(III)



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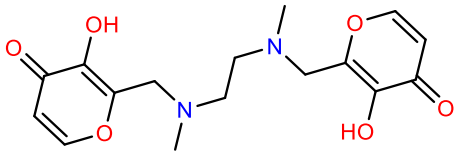
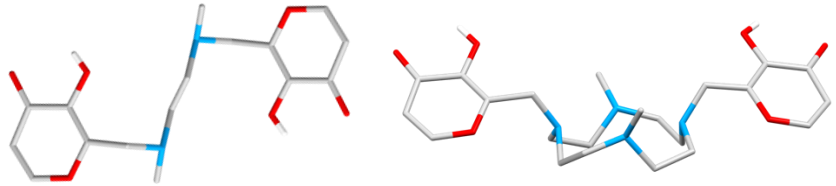
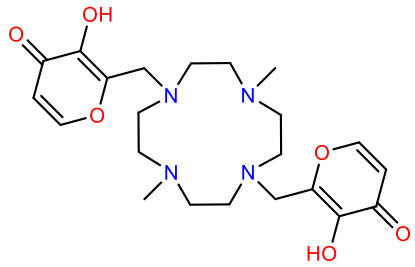
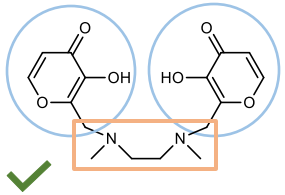


Malten





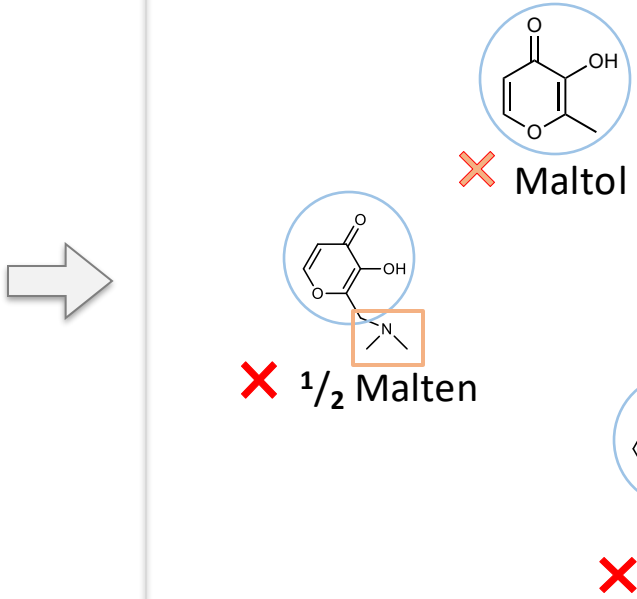
Maltonis



Malten

key for the biological activity

Simultaneous presence of **two amino-spaced maltol units**



Total loss of the Biological activity

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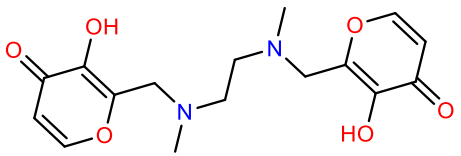
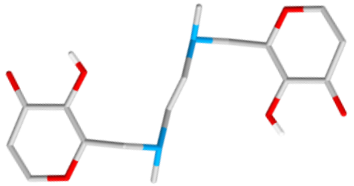
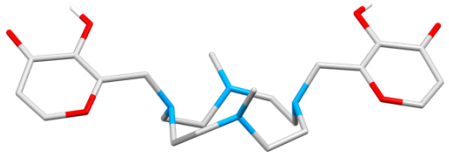
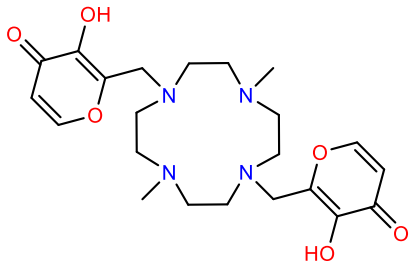






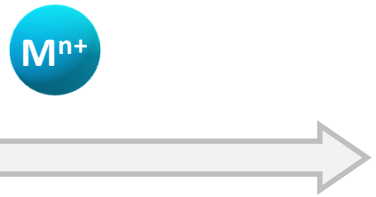


Malten

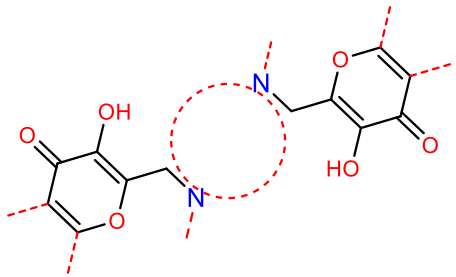
Maltonis

Coordination Properties

Anticancer Activity



Metal Complexes



Structure modifications

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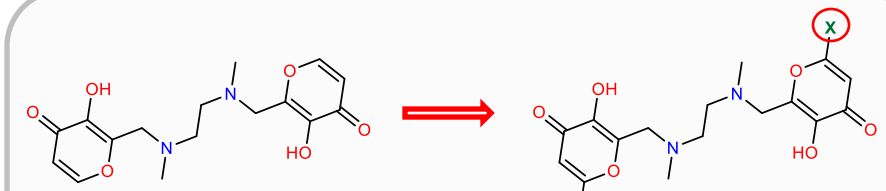
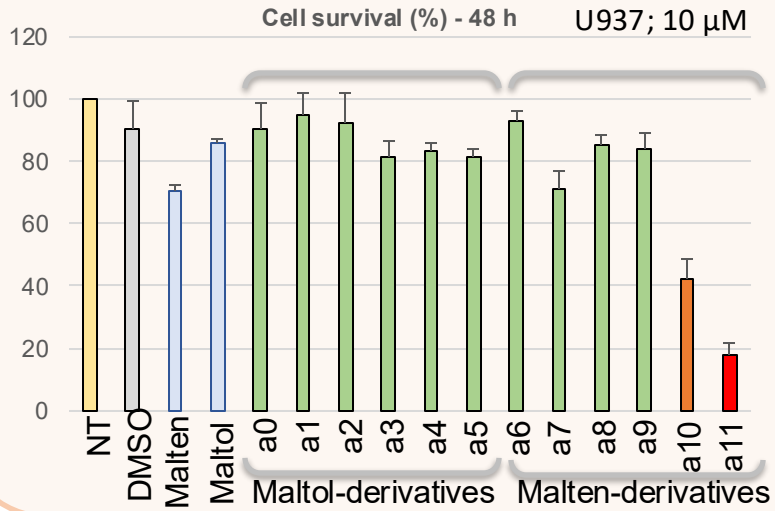




- 48 h treatments at the dose of 10 µM.
- Maltol and Malten, tested for comparison.
- Cells treated using the same volumes of DMSO used in the treatments as control.
- **a10** and **a11** showed a marked reduction of U937 cell survival compared to that caused by Malten

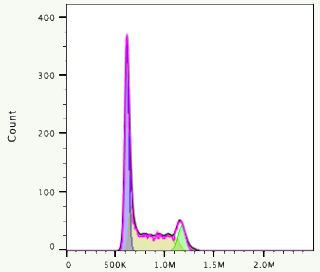
a11 - dose-response experiments

Cell lines	IC50 (24 h)	IC50 (48 h)
U937	0.76 µM	0.65 µM
K562	1.25 µM	1.18 µM
Jurkat	0.73 µM	0.28 µM
NB4	0.50 µM	0.37 µM
HeLa	1.97 µM	0.94 µM
U-373MG	6.67 µM	1.62 µM
WI-38	> 10 µM	7.58 µM

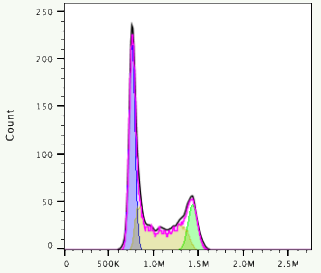
- **dose-response experiments** towards a panel of different tumor cell lines at 24h and 48h
- appreciable **selectivity** for **hematopoietic tumor** over solid tumor-derived cell lines
- less activity against a human normal fibroblast cell line (WI-38) respect to neoplastic cells.

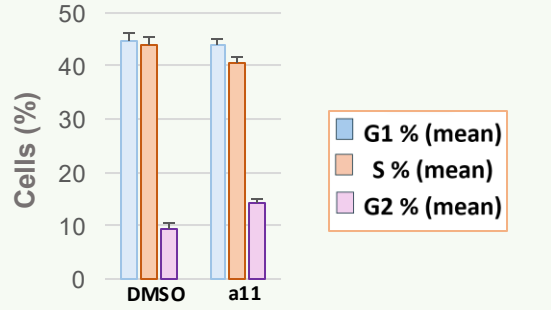
cell cycle (24 h) U937

%G1	%S	%G2
46,3	41,6	10,6

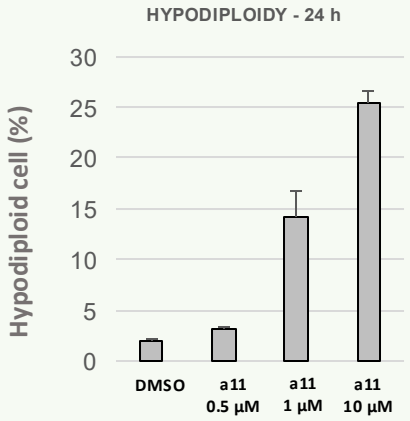


%G1	%S	%G2
43,8	39,7	15,0





	DMSO	a11 (0.5 µM)
G1 % (mean)	44.5 ± 1.7%	43.8 ± 1.3%
S % (mean)	43.8 ± 1.5%	40.6 ± 1.2%
G2 % (mean)	9.2 ± 1.4%	14.1 ± 1%



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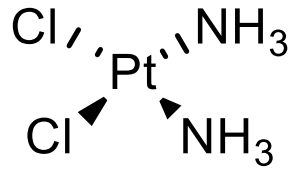
cis-[Pt(NH$_3$)$_2$Cl$_2$]



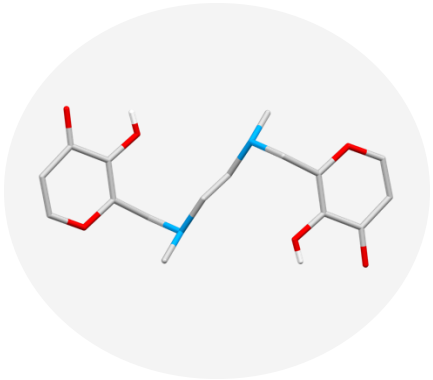
1978 **Medicinal Inorganic Chemistry**

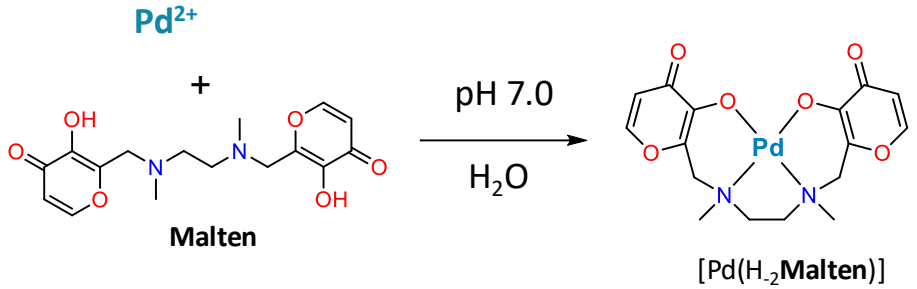
Disadvantages

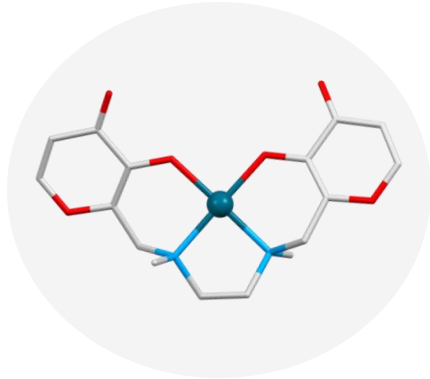
Search of new anticancer agents based on different metal ions

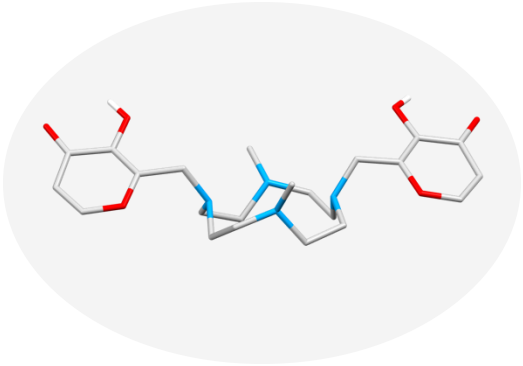
Pd^{2+}

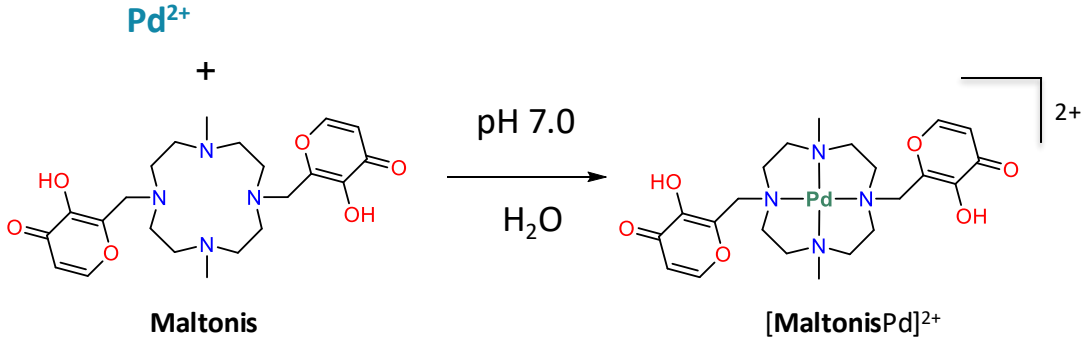
- **Same coord. N. (4)**
- **Same Geometry (square planar)**
- **Similar bond lengths and sizes**

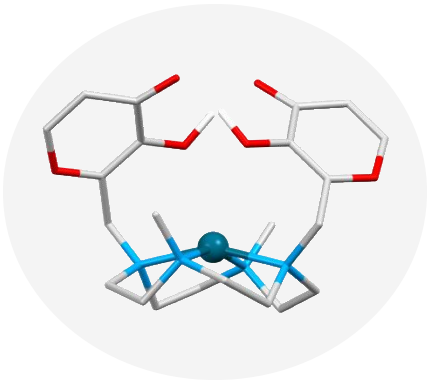












D. Paderni et al. *Dalton Transaction*, **2024**, 53, 14300-14314.
D. Paderni et al., *Journal of Inorganic Biochemistry*, **2025**, 262, 112758.

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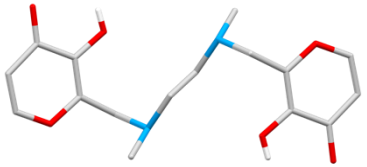
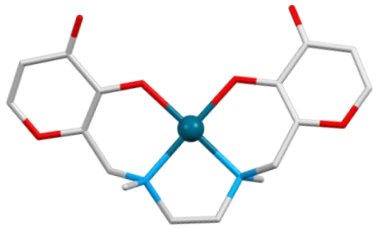
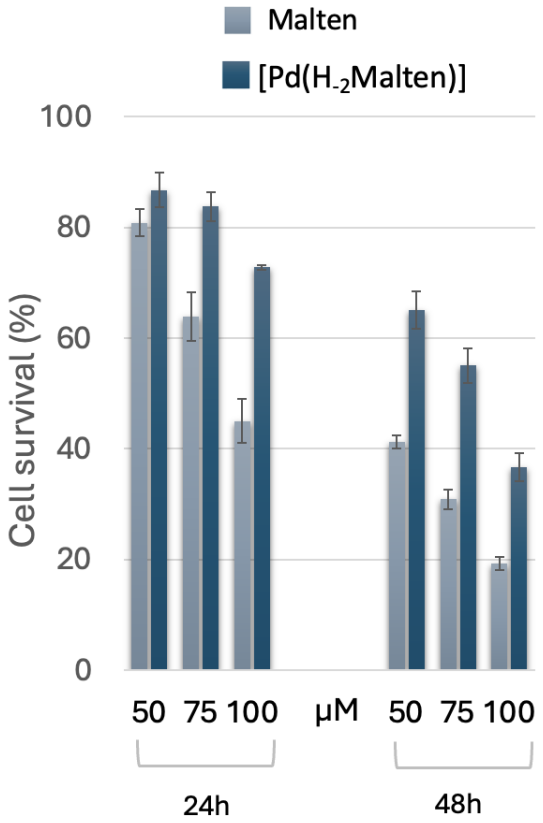
U937

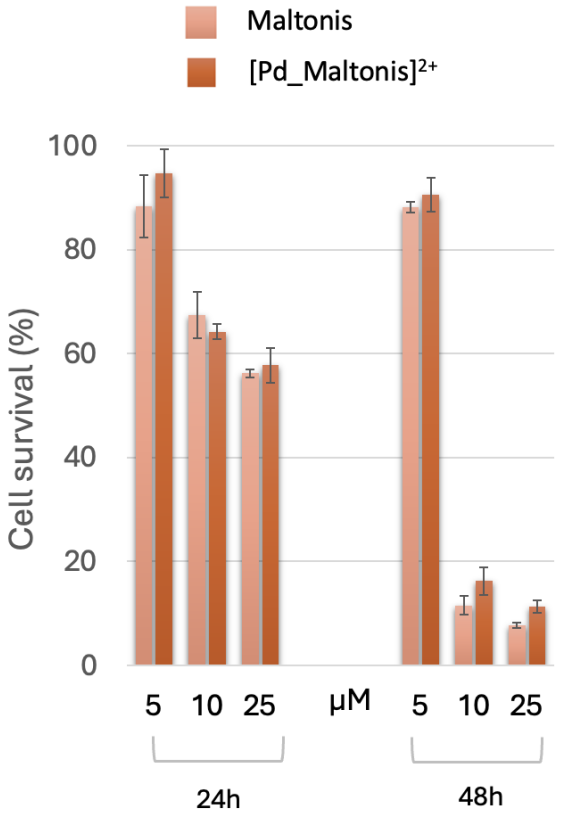


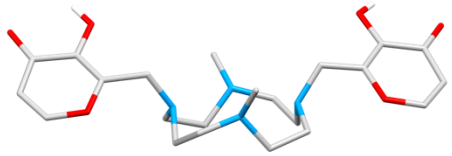
Malten



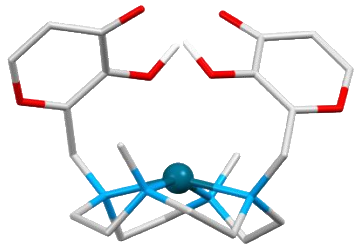
[Pd(H$_{-2}$**Malten**)]







Maltonis



[**Maltonis**Pd]$^{2+}$

D. Paderni et al. *Dalton Transaction*, **2024**, 53, 14300-14314.
D. Paderni et al., *Journal of Inorganic Biochemistry*, **2025**, 262, 112758.

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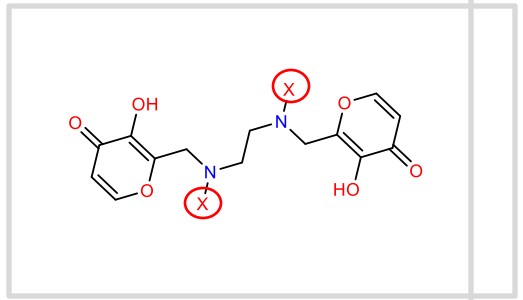
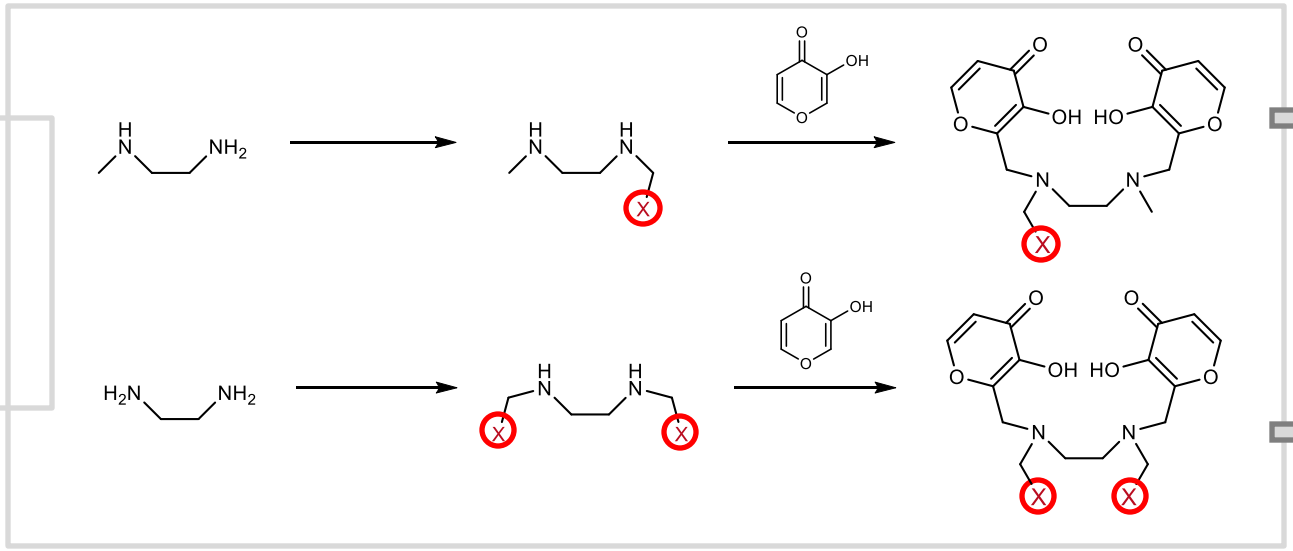
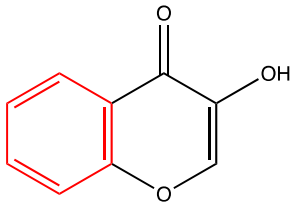


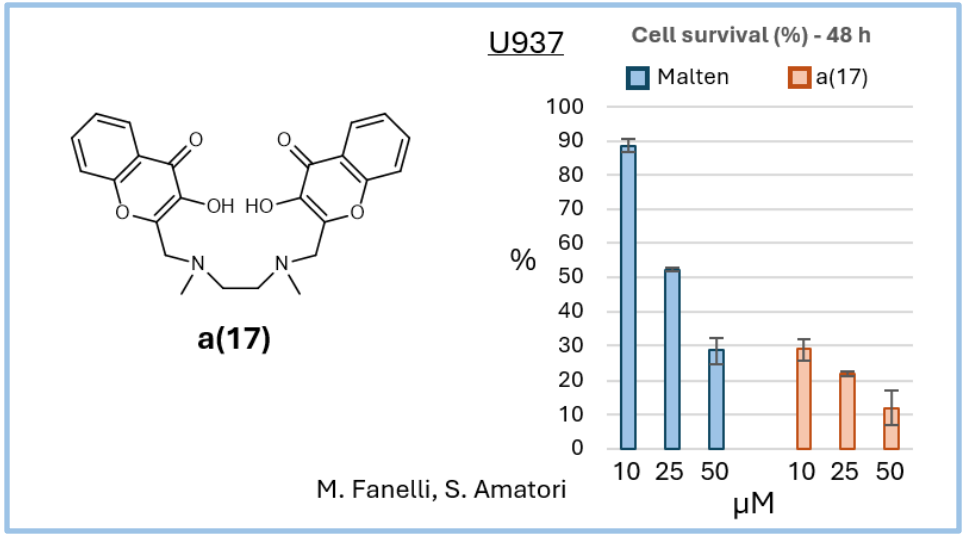


- Investigation of biological activity

- By Increasing the number of **donor atoms** for new metal complexes

By changing the ***maltol*** units with other ***3-hydroxy-4-pyrones***





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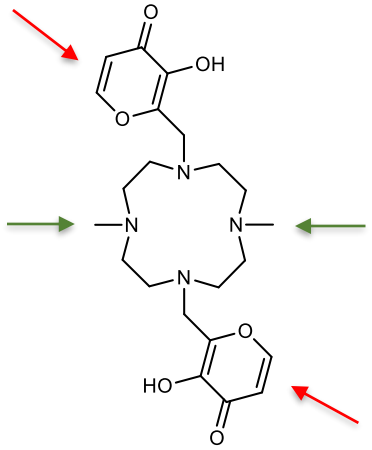
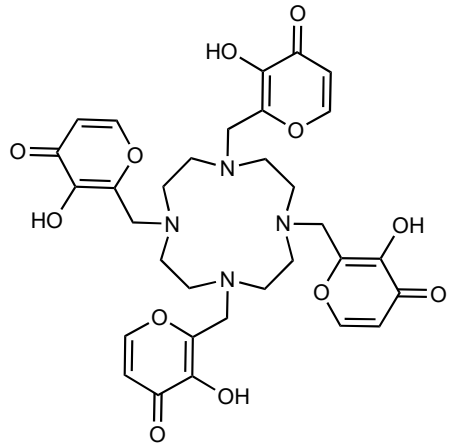


Maltonis



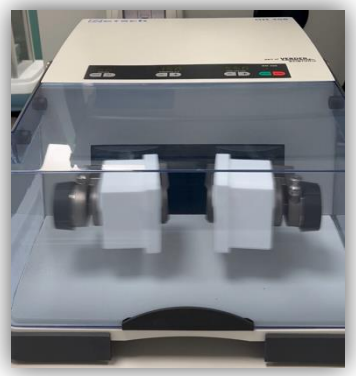
Super Maltonis

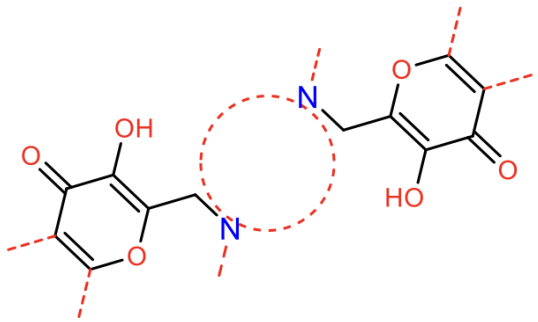
M^{n+}

Work in progress

New Synthesis of Maltonis

- Green
- Easier
- Faster
- Cheaper
- Higher yeald





A New set of **Maltonis** Derivatives

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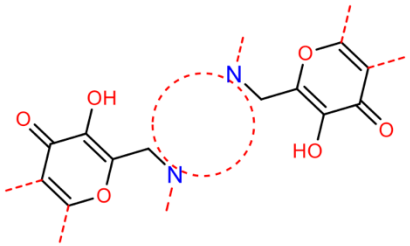
- **Conclusioni**

Gli studi Biologici sono ancora in corso

Le nuove molecole saranno testate per la loro attività biologica

Sono in corso gli studi di caratterizzazione di nuovi complessi metallici



- **Ringraziamenti**

VITALITY

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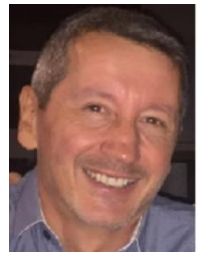




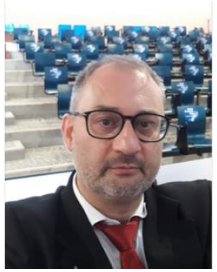



Grazie per l'attenzione