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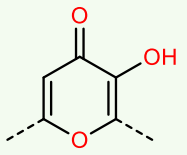
Ministero dell'Università e della Ricerca

Italiadomani
PIANO NAZIONALE DI RIPRESA E RESILIENZA

Bis-Maltol-Polyamine Family as potential anticancer agents

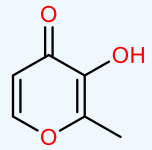
Università degli Studi di Urbino
23 maggio 2024

Introduction



3-hydroxy-4-pyrones

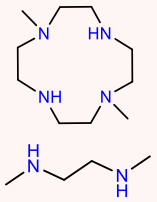
- high **synthetic** versatility
- high **affinity** for a range of **metal ions**
- **metallopharmaceuticals:**
  - **a)** sequestering action
  - **b)** improving absorption



Maltol

- **natural** product
- **anti-neoplastic** activity (DNA breaks; Apoptosis)
- **Metal complex (ROS)**
  - **a)** antimicrobial activity
  - **b)** anticancer activity

+



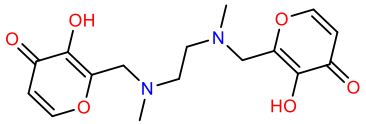
Macrocyclic & Linear polyamines

- **Antitumor** agents (Apoptosis)
- **Coordination** properties
- **water**-soluble

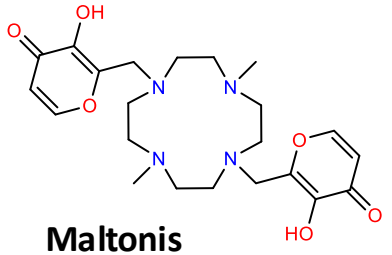
- **Dose-dependent reduction** in cell survival of different **tumor cell lines** (solid and haematopoietic)
- Activation of **cell cycle arrest**
- **Programmed cell death**
- Ability to induce **covalent binding** between **DNA** and **histones**

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

J. Org. Chem. 2012, 2207-2218



Malten



Maltonis

* *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*

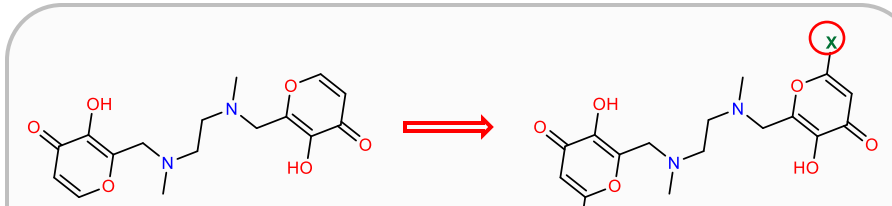
- **Maltonis** is **more effective** than **Malten**
  - Effective on **Sarcoma** (in vivo)
  - Effective on **multidrug & cisplatin-resistance** cell (in vitro)
  - **Ineffective** against **normal** human mesenchymal stem cells

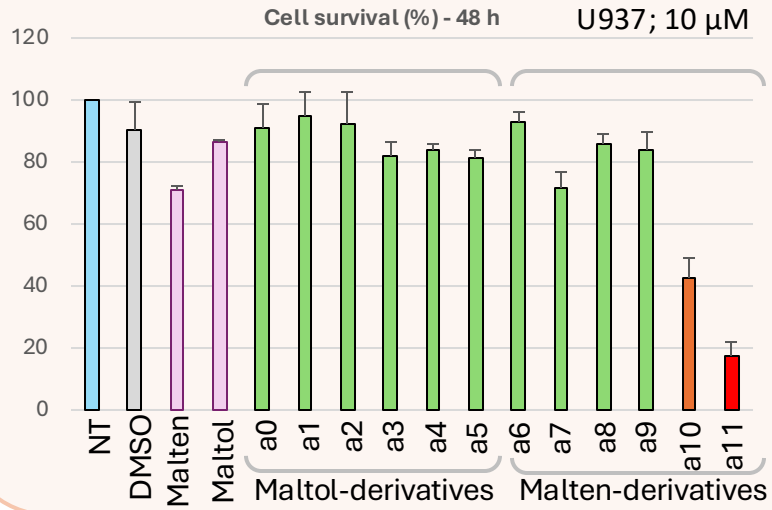
BMC Cancer 2014 (14), 137

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

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

New Malten derivatives





- 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

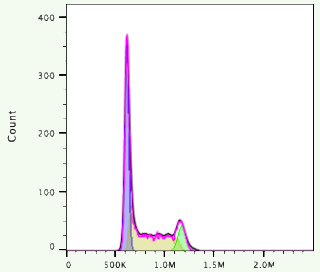
a11 - dose-response experiments

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

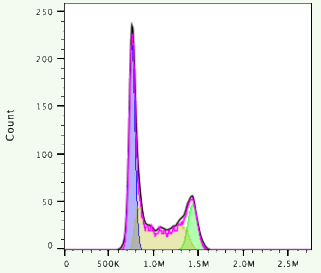
- **dose-response experiments** towards a panel of different tumor cell lines at 24h and 48h
- appreciable **selectivity** for **hematopoietic tumor** over solid tumor-derived cell lines
- less activity against a human normal fibroblast cell line (WI-38) respect to neoplastic cells.

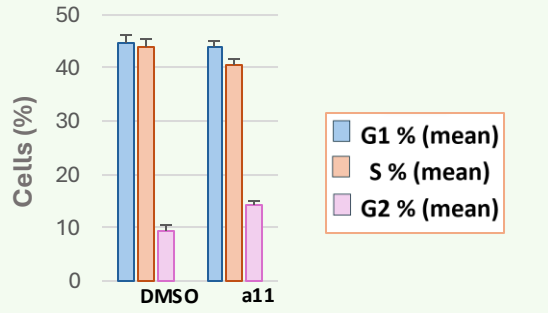
cell cycle (24 h) U937

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

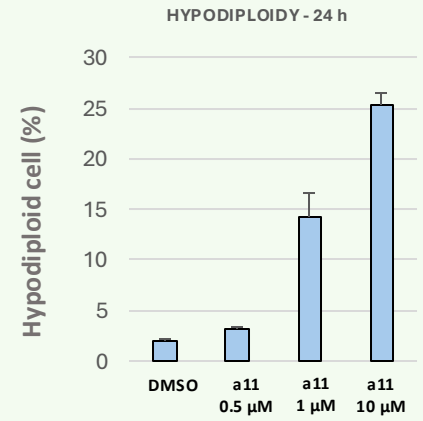


%G1	%S	%G2
43,8	39,7	15,0





	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%



New Malten and Maltonis derivatives

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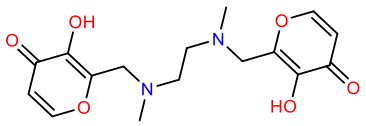
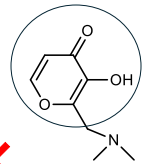
Malten derivatives

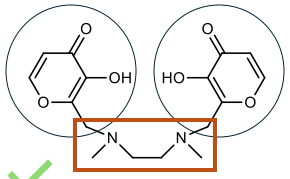


Design

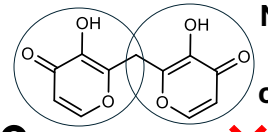
No effective against cancer cells



½ Malten



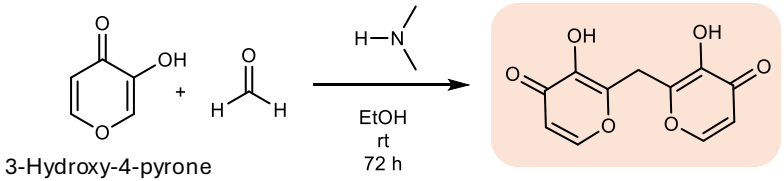
Malten

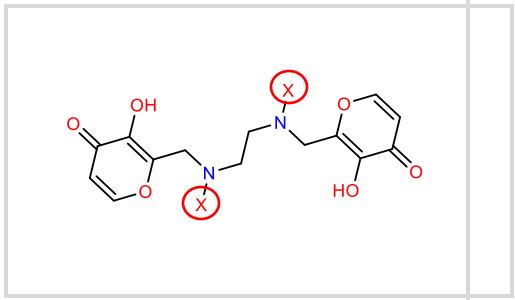


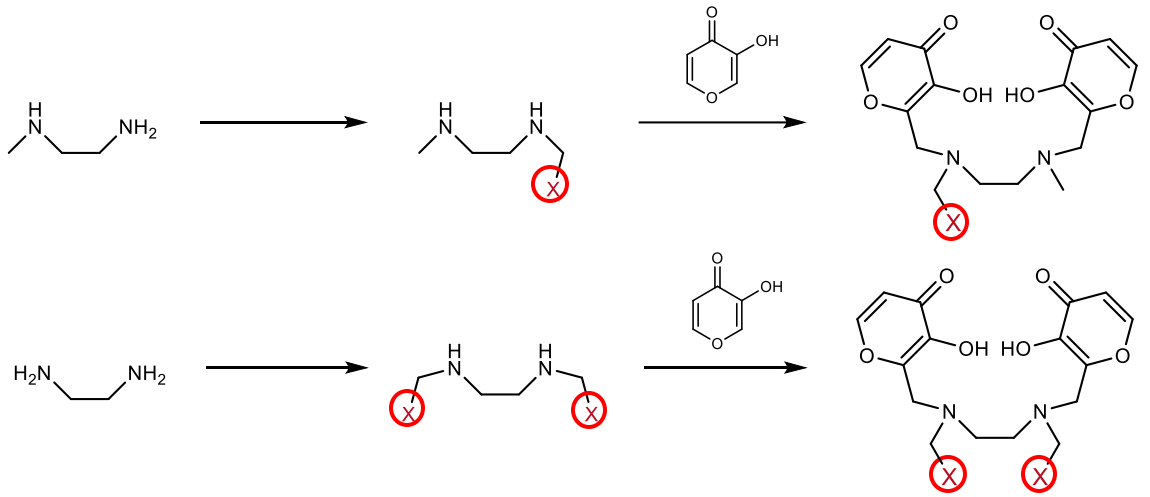
Di-Maltol

No effective against cancer cells

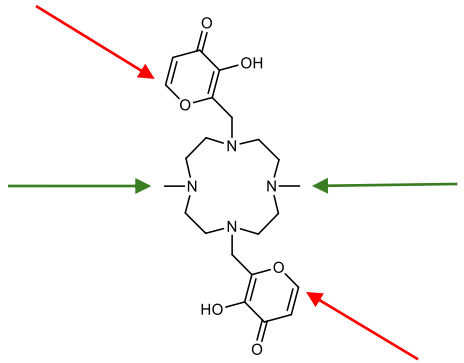
Synthesis





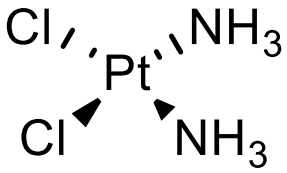


Maltonis derivatives



Ongoing work ...

Metal complexes as anticancer agents



cis-$[Pt(NH_3)_2Cl_2]$

1978 Medicinal Inorganic Chemistry

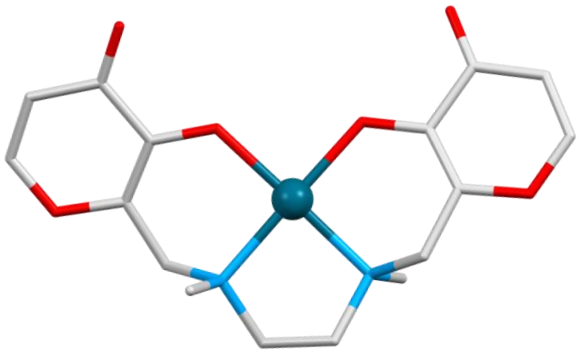
Disadvantages

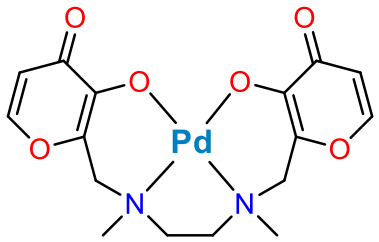
- Non-negligible side effects (non-specificity)
- Dose-limiting toxicity
- Resistance insurgence

Serch of new Anticancer agents based on different metal ions

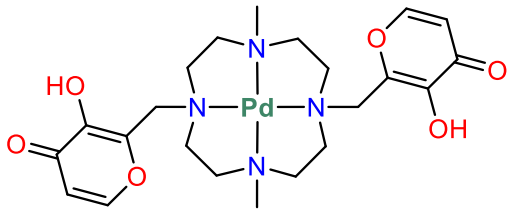
Pd^{2+}

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

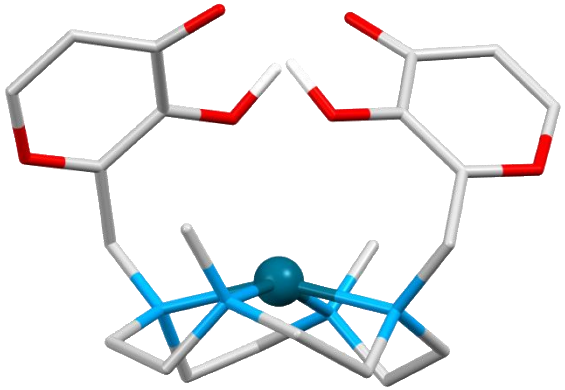




[H_{-2}**Malten**-Pd]



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



Malten and Maltonis-Pd(II) complexes Synthesis; ^{1}H NMR, UV-Vis and XRD studies

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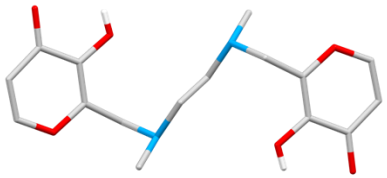
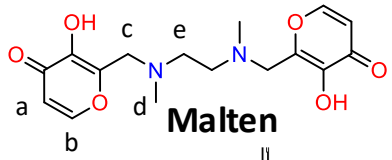
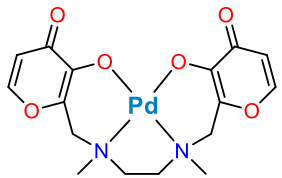




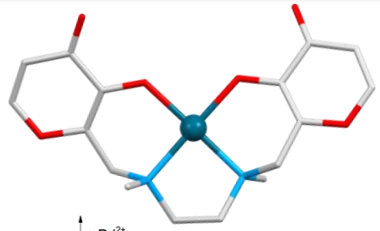
Malten

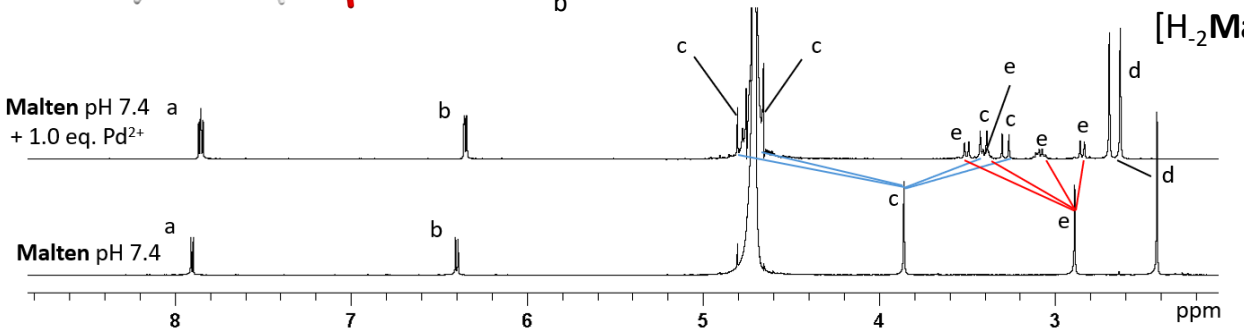
Pd^{2+}

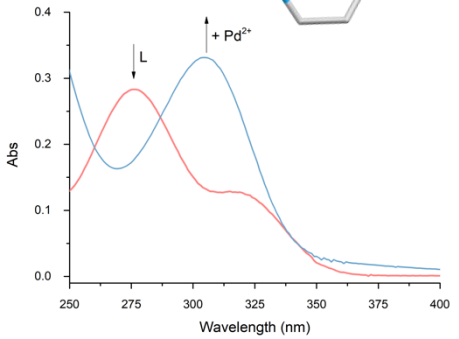
pH 7.0

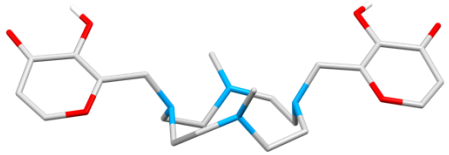


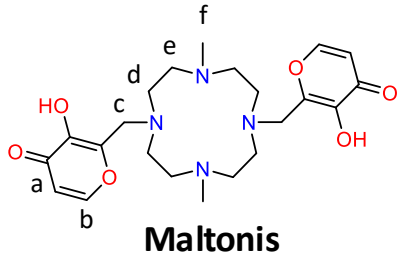
[H_{-2}**Malten**Pd]







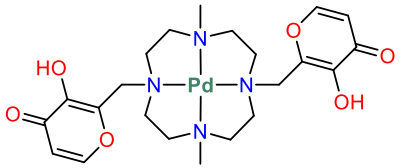




Maltonis

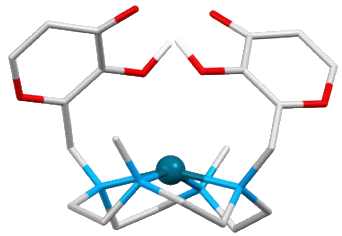
Pd^{2+}

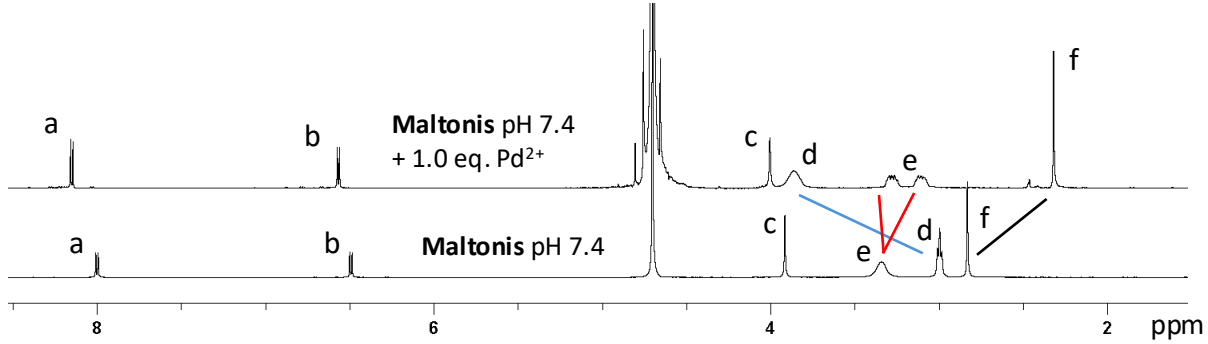
pH 7.0

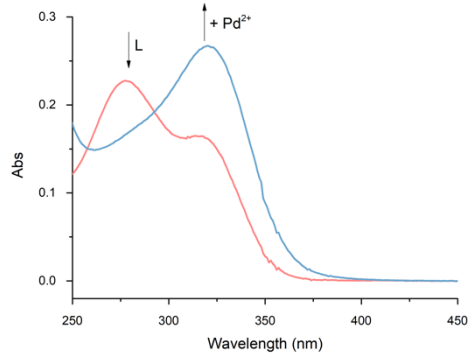


[**Maltonis**-Pd]$^{2+}$

2+

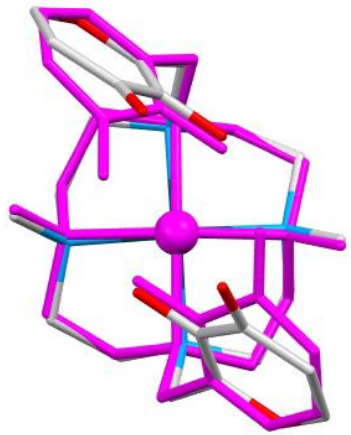






Results of solution studies

- 1:1 stoichiometry L:Pd^{2+}
- Water-soluble
- stable at pH 7.4, 37°C over 5 days
- Maltol units in Maltonis complex are involved in an intramolecular hydrogen bond



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Thank you for the attention

Daniele Paderni

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Università degli Studi di Urbino
23 maggio 2024

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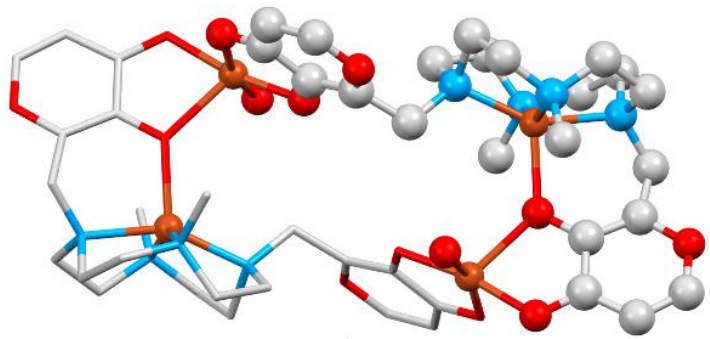
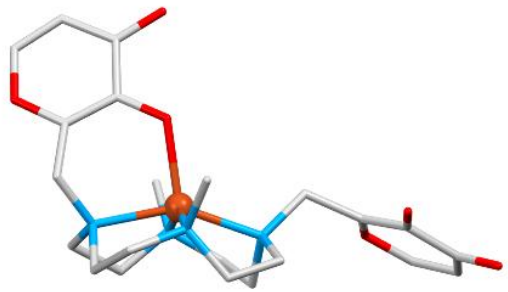
a



b_1



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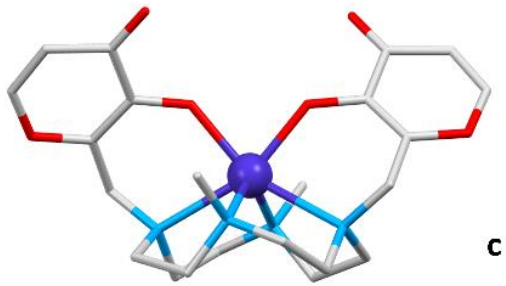

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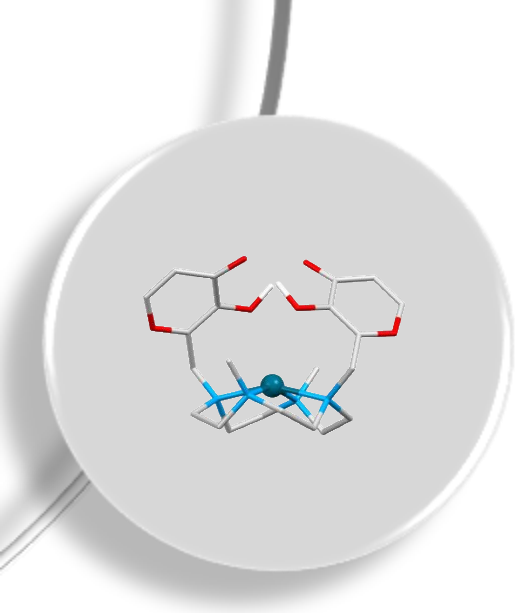
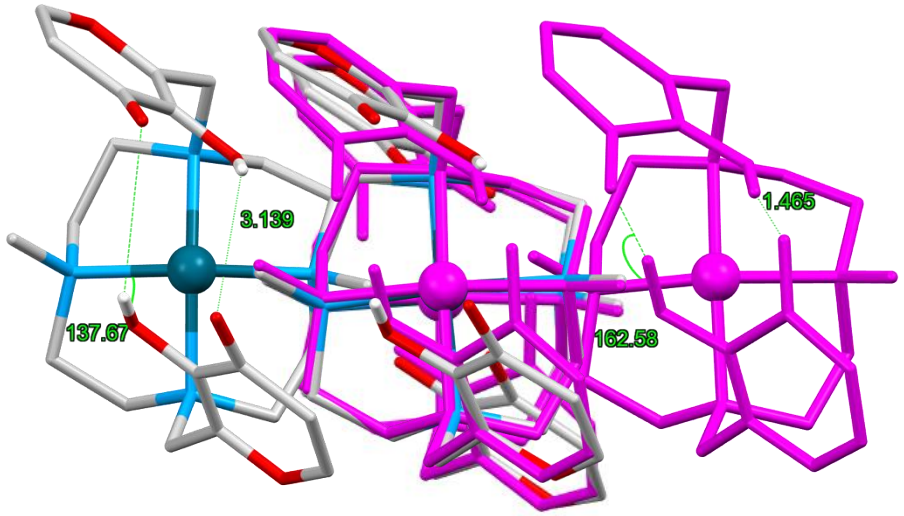


RMSD: 0.4469 Å

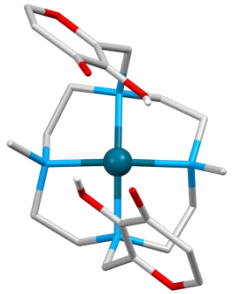


crystal structure

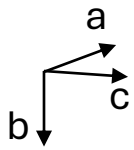
Oxygen atoms not involved in the coordination but «closed» conformation

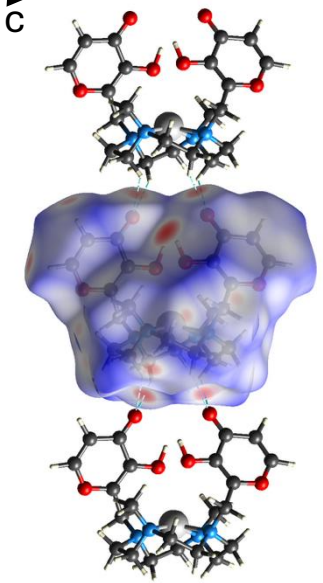
Conformer	ΔG (kcal/mol)
Open	0.00
Closed	-1.6
Partially open	1.8

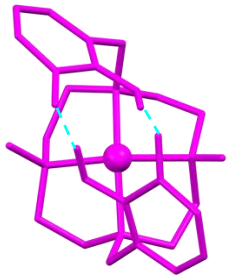
optimized structure
DFT/B3LYP/sdd/TZVP method



O···HC ***intermolecular*** *hydrogen bonds*







O···HO ***intramolecular*** *hydrogen bonds*