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Rhein to impart antimetastatic features to Pt(IV) complexes and to target brain

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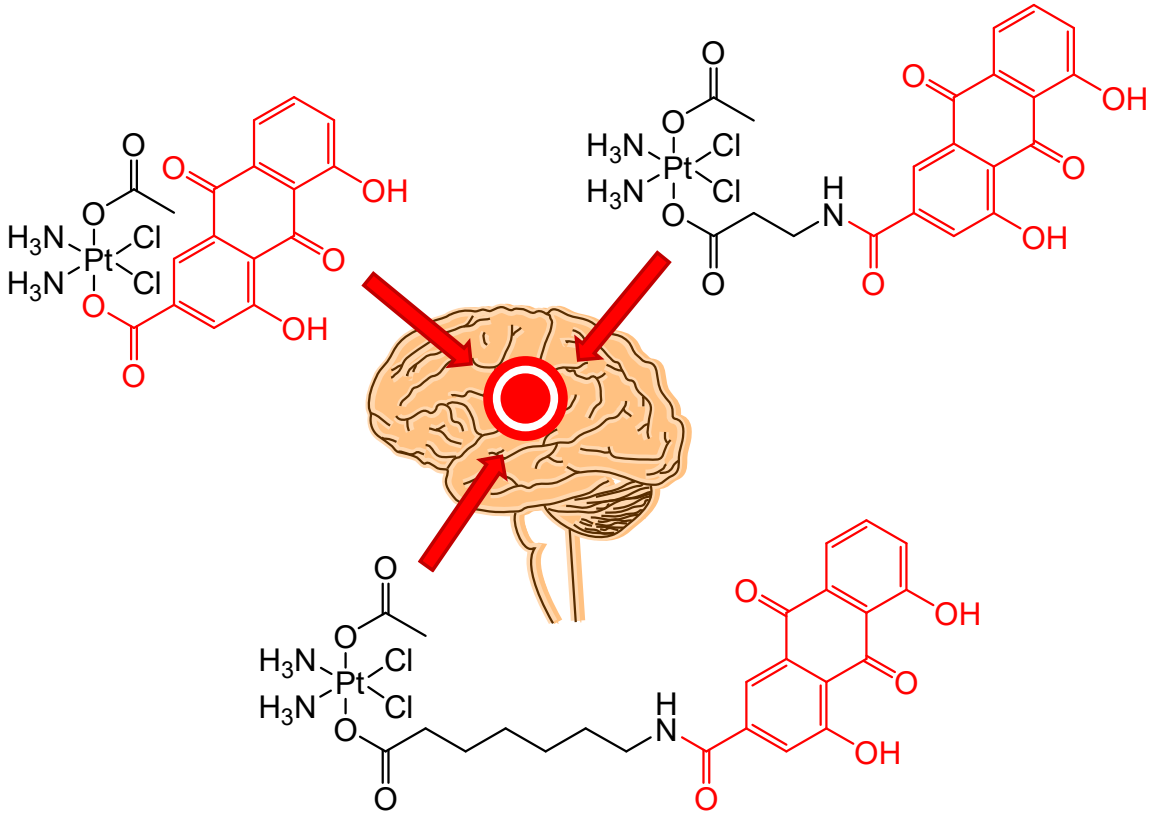
Rhein to impart antimetastatic features to Pt(IV) complexes and target brain

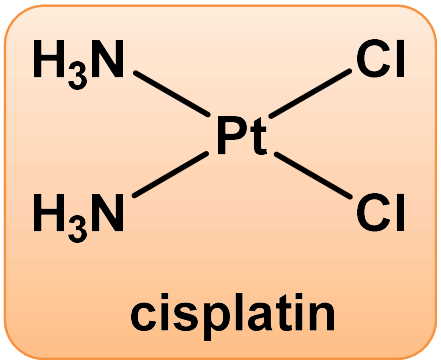
Graphical Abstract



Abstract:
The combination of an anticancer Pt drug and another coadjutant molecule with different biological targets is a promising therapeutic strategy. Octahedral Pt(IV) complexes allow to combine cisplatin-like moieties and a second anticancer agent in a single molecule to obtain potential bifunctional antiproliferative prodrugs. Indeed, in the hypoxic and reducing tumor environment Pt(IV) complexes are activated by a two-electron reduction to form an active Pt(II) metabolite with concomitant loss of the second agent, when linked to the metal in axial position. The natural anthranoid rhein or cassic acid has several pharmacological effects and exerts anticancer effects by modulating cellular proliferation, apoptosis, migration, and invasion. Moreover, it can inhibit in vivo glioma tumor progression. For this reason, cisplatin-based Pt(IV) derivatives were synthesized by differently linking rhein to the metal. The complexes proved to be similar to or more potent than cisplatin and rhein, and temozolomide (reference drug) on glioblastoma cells. The Pt(IV) complexes caused a significant decrease in the motility of cells, which can be related to inhibition of matrix metalloproteinases.

Keywords: antiproliferative activity; brain cancer; Pt(IV) complexes; rhein

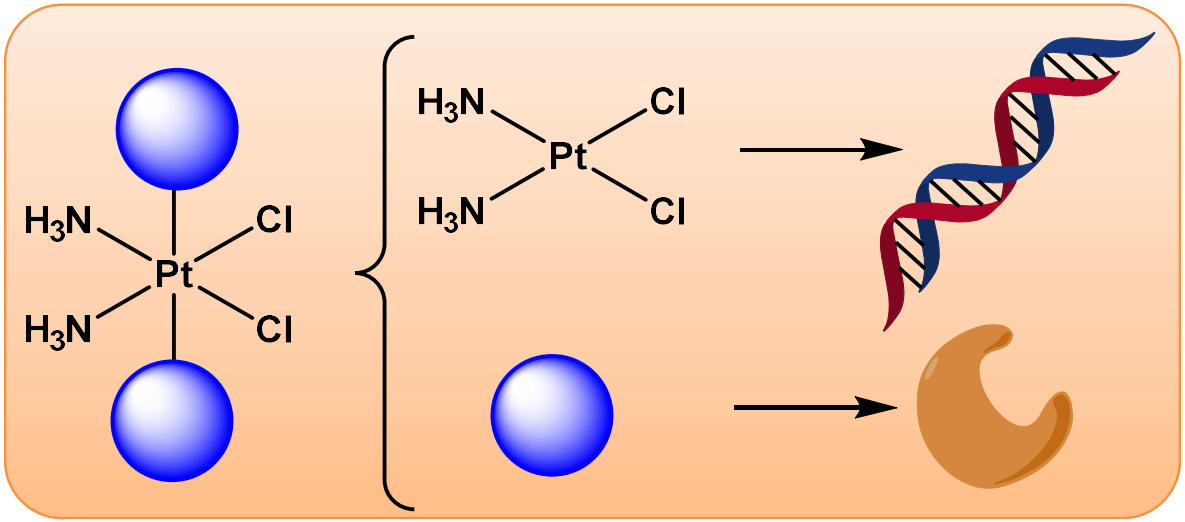
Introduction



Platinum-based anticancer drugs are widely employed but their use is limited by **drug resistance**, **systemic toxicity**, and **lack of antimetastatic properties**.

The **combination** of a platinum drug and another molecule with different biological targets is a promising therapeutic strategy.

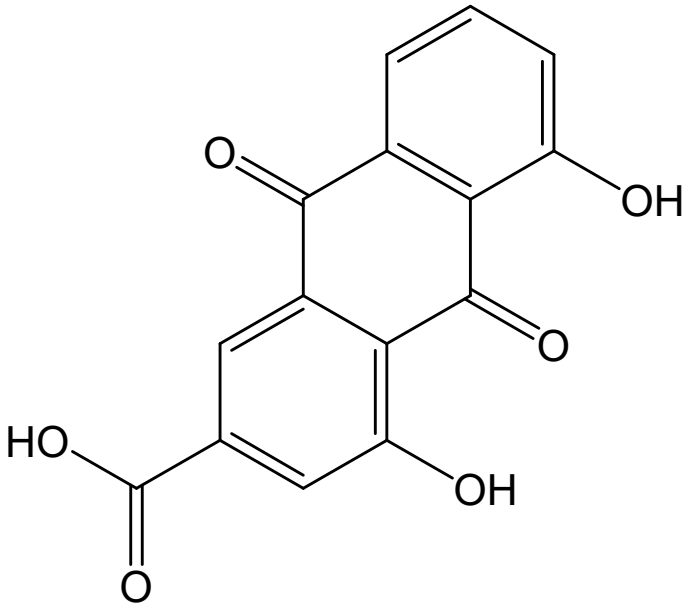
Pt(IV) complexes represent an effective way to combine cisplatin-like moieties and a second bioactive molecule to get potential **bifunctional antiproliferative prodrugs**.



M. Ravera, E. Gabano, M. J. McGlinchey, D. Osella, Inorg. Chim. Acta, 492 (2019) 32–47.

Introduction

- Cassic acid or rhein belongs to the anthraquinone group present in root and leaf of Rheum, Senna, and Cassia species.
- It is used as Chinese herbal medicine to cure or improve of several deseases.
- It exerts **anticancer effects** by modulating cellular proliferation, apoptosis, migration, and invasion.
- It **inhibits** the **migration** of ovarian cancer cells through down-regulation of matrix metalloproteinases.
- It can **inhibit** in vivo **glioma tumor progression**.



E. Blacher et al., Int. J. Cancer, 136, 2015, 1422–1433. B. Ren et al., Biol. Pharm. Bull., 42, 2019, 568–572.

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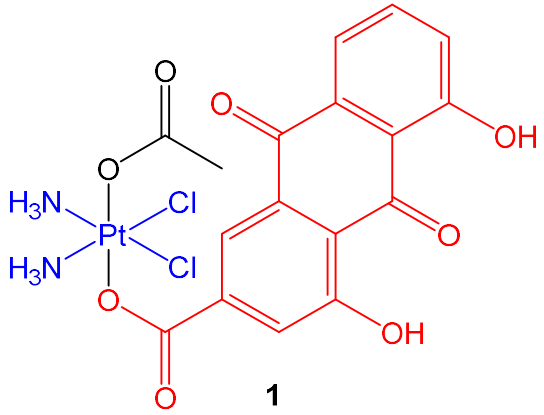
Introduction

- ✓ **Glioma** is a most common brain tumor and **glioblastoma** multiforme (GBM) is the most **aggressive** glioma.
- ✓ The standard care consists of surgical resection followed by radiotherapy and chemotherapy (temozolomide).
- ✓ Pt drugs have a checkered history in the treatment of GBM patients, featuring hints of success but mostly limited amounts of drugs that crosses the **blood–brain barrier** (BBB) and/or major **systemic toxicities**.



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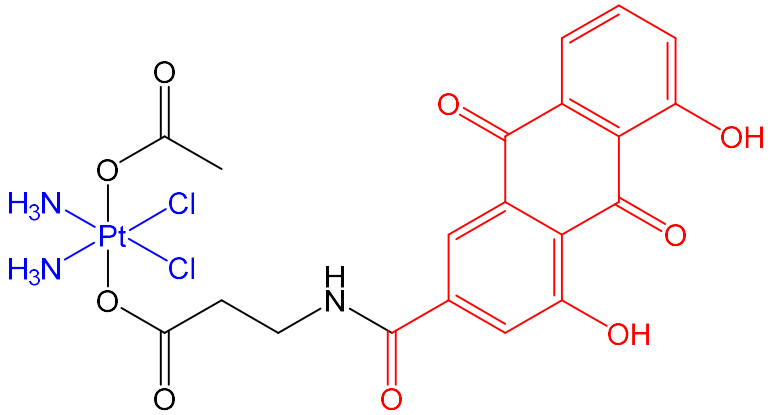

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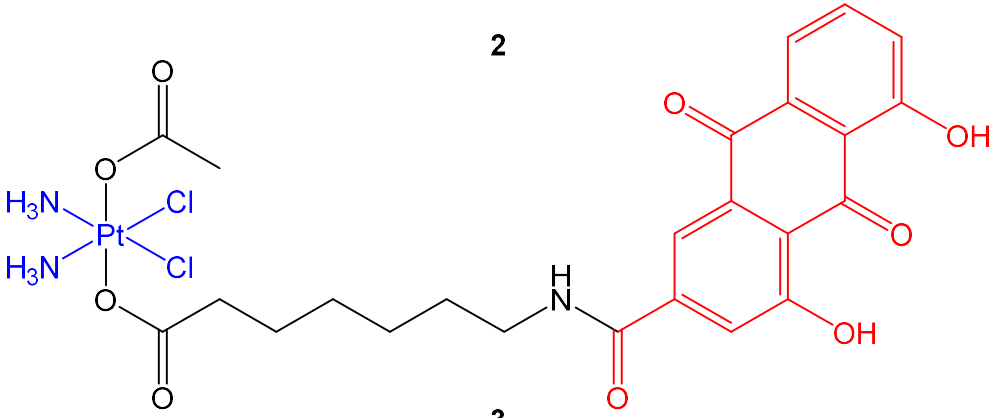

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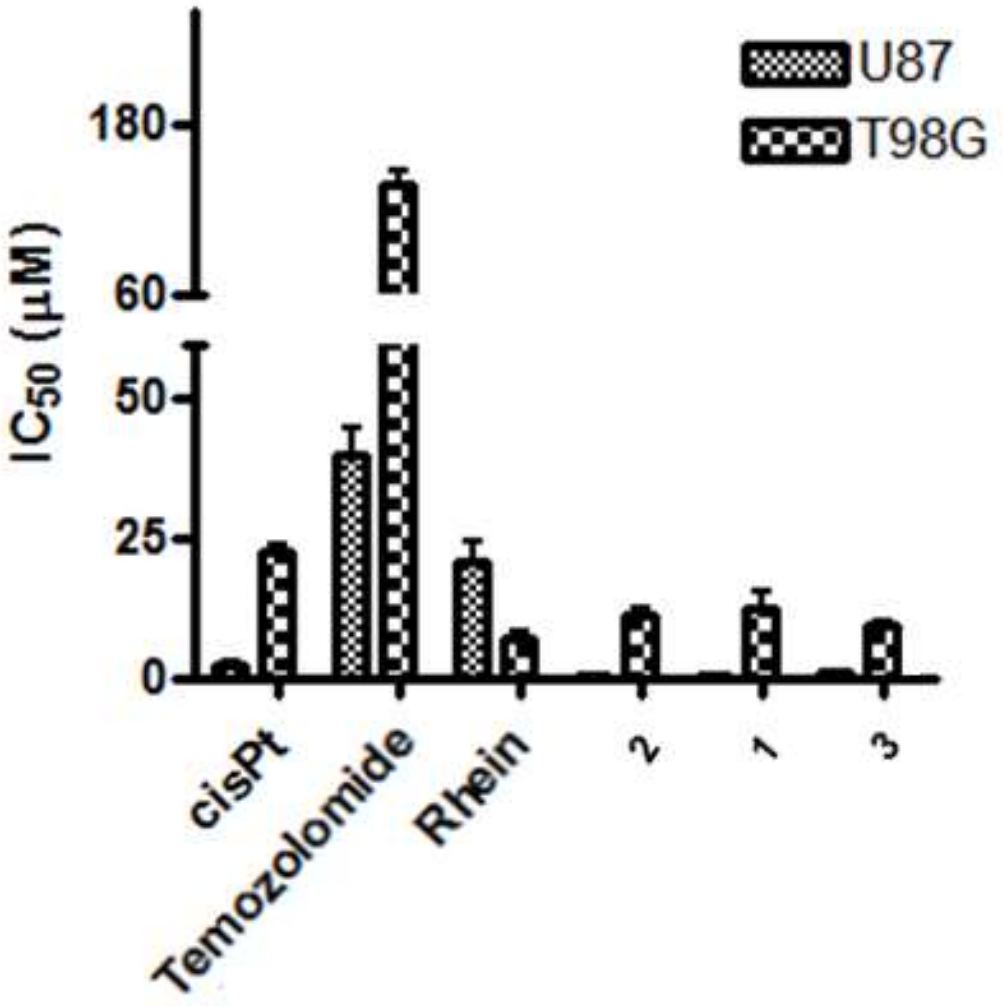
Results and discussion

IC_{50} values obtained by MTT assay in U87-MG and T98G cells following 72 h treatment with rhein and its Pt(IV) derivatives **1**-**3**. Temozolomide and CDDP were used as reference compounds.

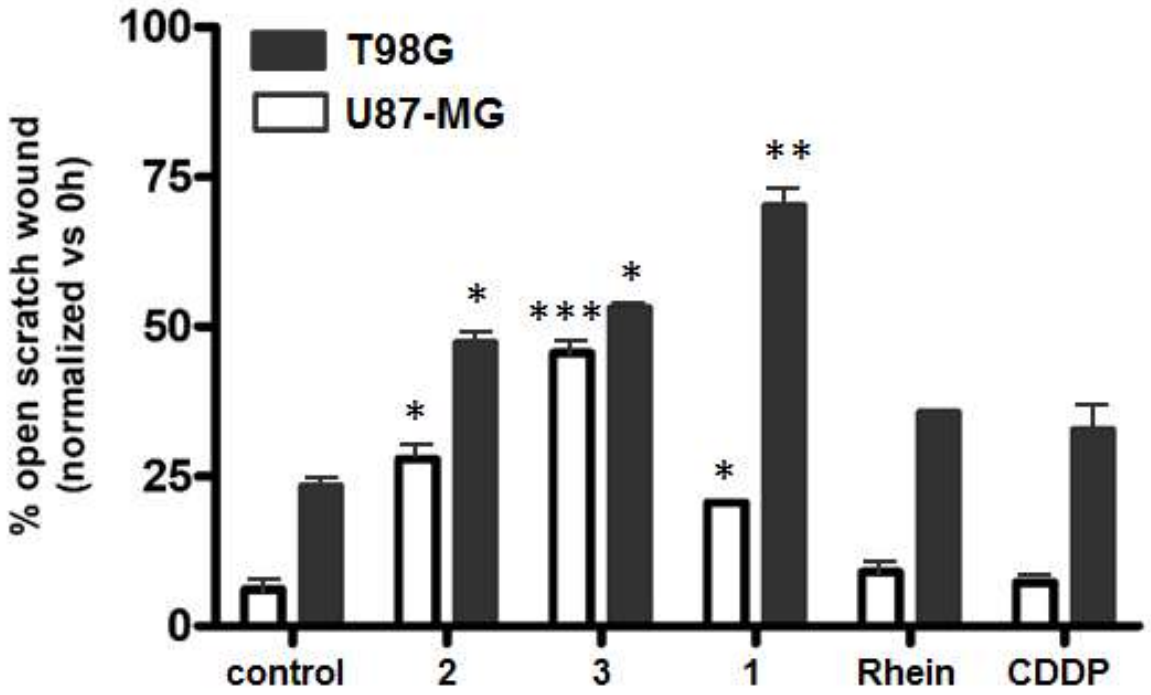
Both cell lines were more sensitive to all Pt complexes and rhein than temozolomide.

Similar activity was maintained for the Pt complexes in both cell lines either **under hypoxia or normoxia**.



E. Gabano, M.B. Gariboldi, G. Caron, G. Ermondi, E. Marras, M. Vallaro, M. Ravera, Dalton Trans., 51 (2022) 6014.

Results and discussion



Migratory activity of U87-MG and T98G cells following treatment with subtoxic concentrations (IC_{20}) of rhein, CDDP and **1**-**3** derivatives.

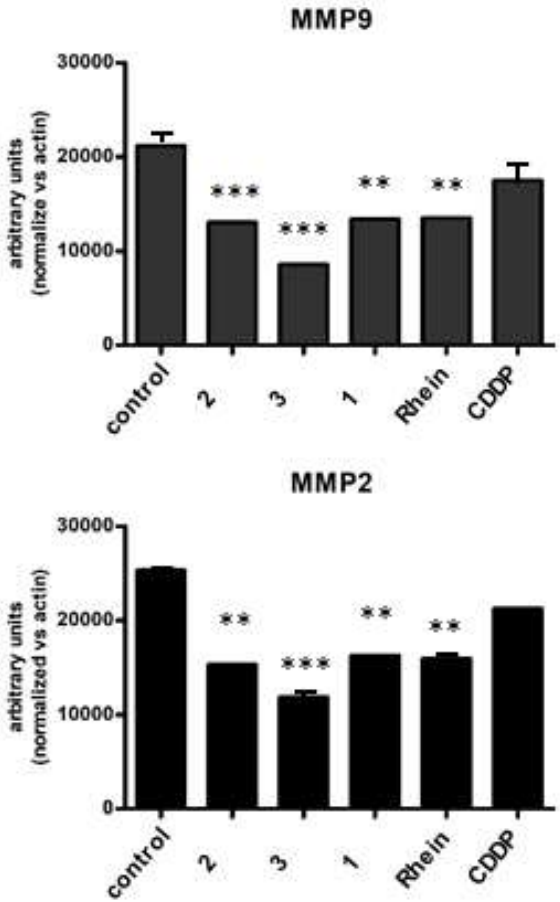
Percentage of open scratch wound, normalized *vs* 0 h, in U87-MG and T98G cells following 24 h incubation with IC_{20} concentrations of rhein, CDDP and **1**-**3**.

Results and discussion

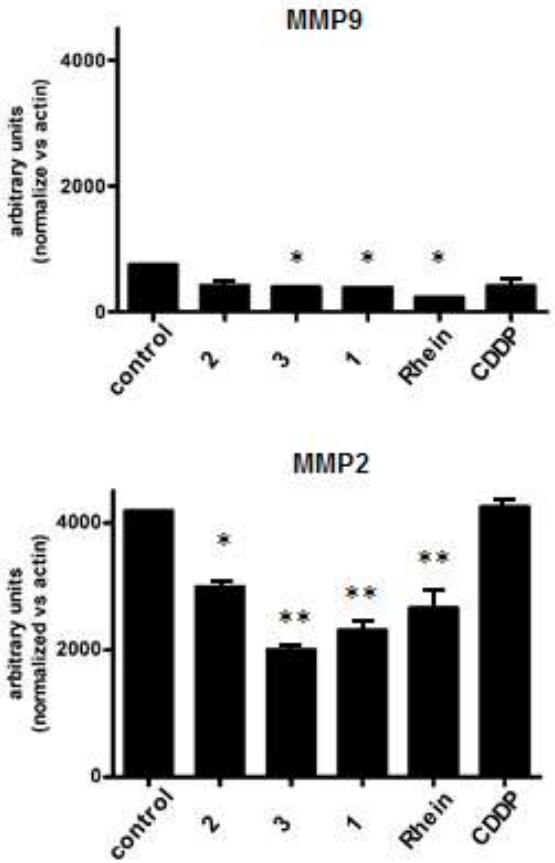
Densitometric analysis of the **MMP9 and MMP2 protein levels** in cells treated 72 h with CDDP, rhein and **1-3** at their IC_{20}.

The effect on cell migration could be, at least in part, attributed to **inhibitory activity against matrix metalloproteinases MMP2 and MMP9**.

U87-MG cells



T98G cells



Results and discussion

Lipophilicity and **ionization** are related to the ability of compounds to cross blood-brain barrier (BBB).

The main molecular property affecting drug BBB passage is the **ability to form H bonds** with BBB components.

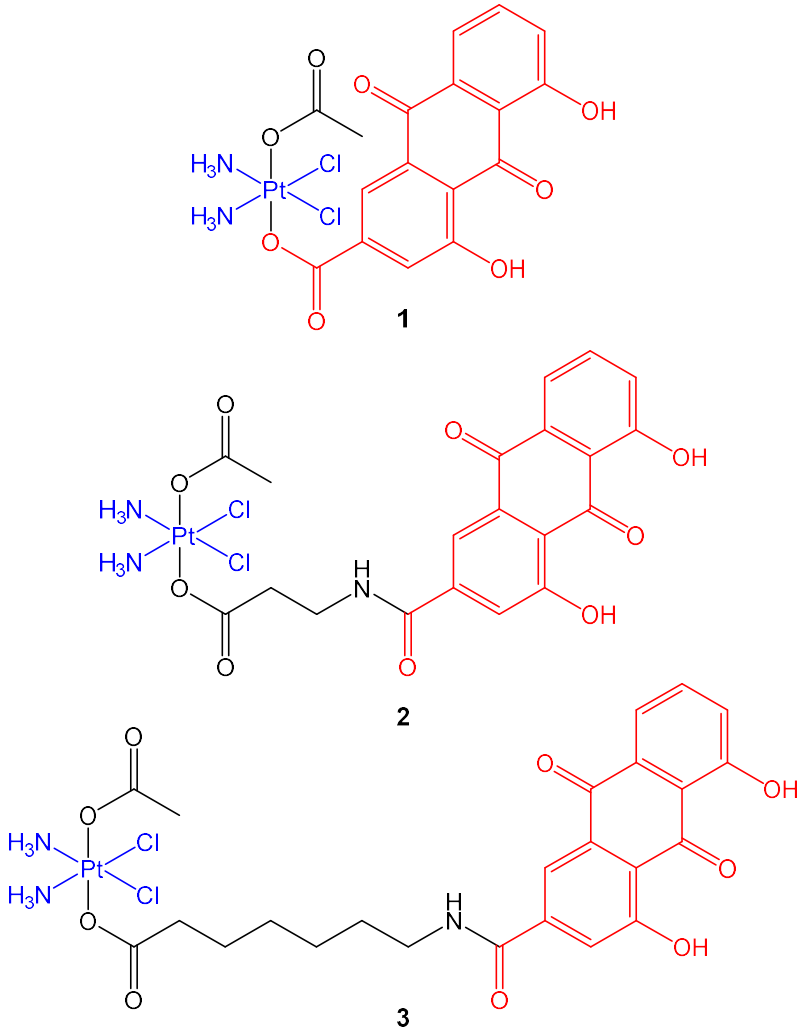
The features of the molecules were studied by means of:

- ✓ potentiometric titrations: ionization behavior
- ✓ lipophilicity measurements in n-octanol/water and toluene/water systems
- ✓ chromatographic lipophilicity index with immobilized artificial membrane (IAM) columns (a monolayer of phospholipids covalently linked to silica)
- ✓ molecular modeling

1-**3** are considered to be more **prone to cross BBB** than rhein.

Conclusions

- The Pt(IV) complexes showed **better activity** on U87-MG and T98G cells **than CDDP**.
- They were **comparable to or better than rhein** and **more potent than temozolomide** (one of the standard treatments for GBM).
- Thanks to rhein the Pt(IV) complexes are able to **inhibit cancer cell migration**.
- In mice intracranially injected with glioma cells, rhein inhibited tumor progression, showing its ability to cross the BBB. Pt(IV) complexes **1-3** are likely more **prone to cross BBB** than rhein.
- These compounds could represent an interesting improvement for GBM treatment.



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Acknowledgments

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