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HYBRID EARLY TRANSITION METAL MATERIALS WITH ORGANIC SUBSTRATES AS POTENTIAL ANTICANCER AGENTS

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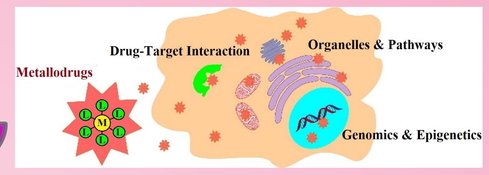
ARISTOTLE UNIVERSITY OF THESSALONIKI

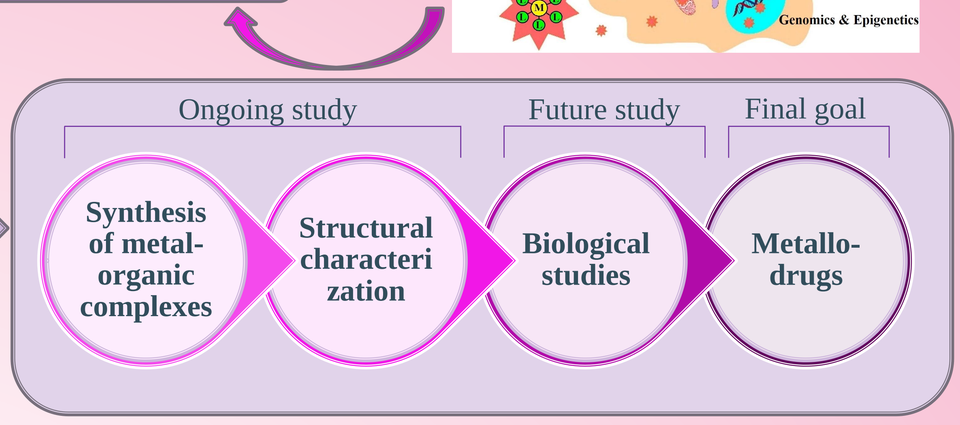
LABORATORY OF INORGANIC CHEMISTRY AND ADVANCED MATERIALS

Ti(IV)-flavonoids as potential metallodrugs



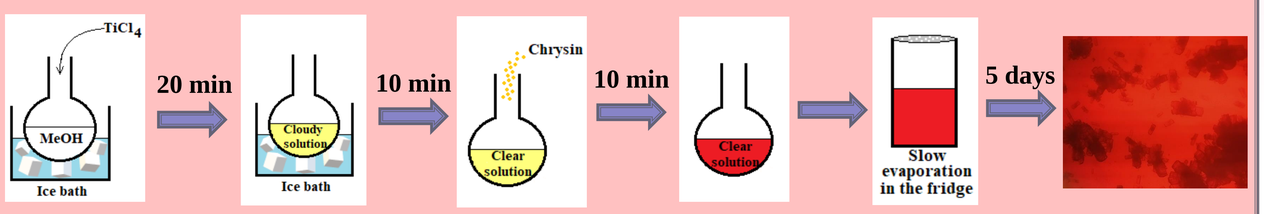
Abstract-Introduction

After platinum-based chemotherapy had proven effective in treating cancer, titanium(IV) complexes were the first ones to be tested as potential drugs in clinical trials. Their poor efficacy to toxicity ratio and formulation issues caused them to fail the trials. The complexes hydrolyze quickly, resulting in the production of several unclear aggregates, thus making it challenging to isolate and identify the specific active species and their exact cellular target.[1] In spite of that, these compounds still have potential in the field of pharmaceuticals due to their high efficacy and low toxicity in vivo, as well as the fact that in biological environments hydrolysis produces safe and inert titanium dioxide. The primary goal of this research is to develop resistant Titanium(IV) complex compounds that can be employed as metallodrugs to treat metabolic disorders or even prevent them altogether. Furthermore, incorporation of antioxidant, anti-inflammatory, and anti-cancer species[2] as organic ligands for complexation to a metal ion has come to be studied in our Lab as a very promising alternative to the already existing materials. To that end, Titanium(IV)-flavonoid systems have been investigated using chrysin and quercetin in both binary and ternary systems using 1,10-phenanthroline as reach chelator. The new materials unraveled for the first time in our Lab in binary and ternary systems have been fully characterized in the solid state and in solution.

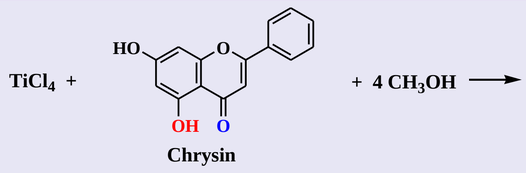


Ti(IV)-Chr

Synthesis Flow Diagram



Reaction

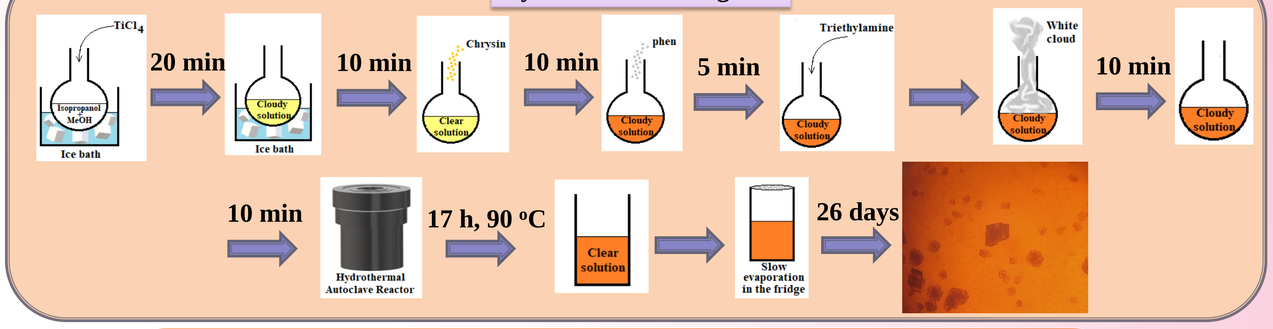


$[Ti(C_{15}H_9O_4)Cl(CH_3O)(CH_3OH)_2]^+Cl^- \bullet CH_3OH + 2\ HCl\uparrow$

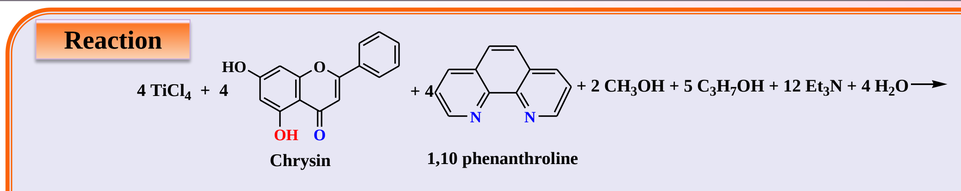
Materials and Methods

Ti(IV)-Chr-phen

Synthesis Flow Diagram



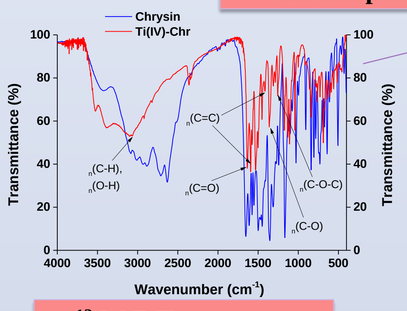
Reaction



$[Ti_4O_4(C_{15}H_9O_4)_4(C_{12}H_8N_2)_4] \bullet Cl_4 \bullet 2\ CH_3OH + 5\ C_3H_7OH + 12\ Et_3NHCl$

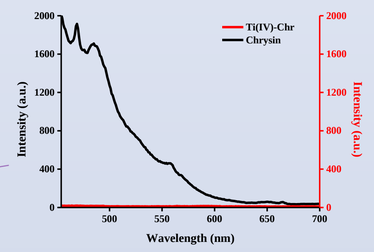
Physicochemical characterization – Results – Discussion

FT-IR spectrum



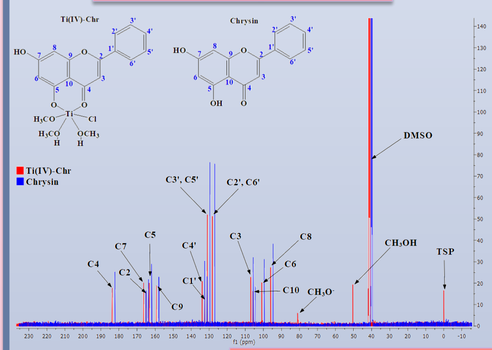
The absorption band at 1634 cm^{-1} corresponds to the ν(C=O) vibration and is shifted to lower frequency compared to chrysin, indicating that this group participates in the coordination of Ti(IV).

Luminescence spectrum

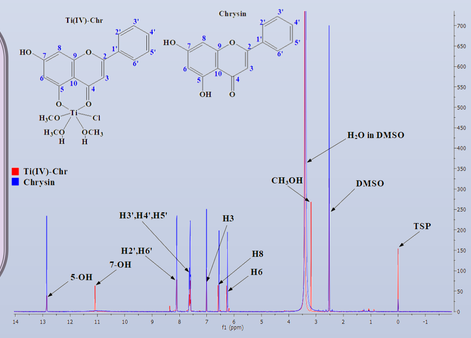


Quenching effect

^{13}C-NMR spectrum

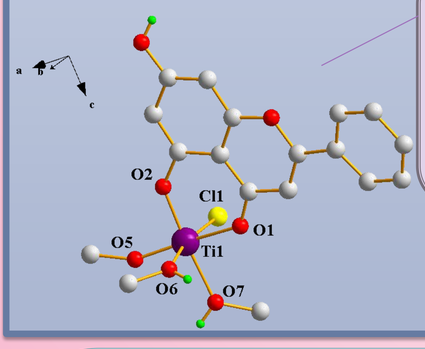


^{1}H-NMR spectrum



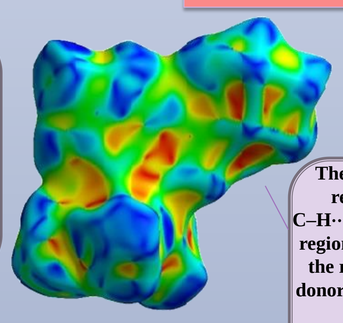
The deprotonation of the C5-OH group and deshielding caused by the complexation of the C4 and C5 carbons, suggest that the coordination sites are C5-OH and C4=O.
All carbon and hydrogen signals of the bound chrysin display downfield shifts, confirming coordination with the metal center.

X-ray structure



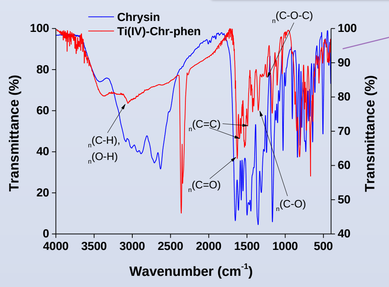
Space group: Monoclinic $P2_1/n$.
The complex has a Ti(IV) moiety connected to a singly deprotonated chrysin, a chloride anion, a methanol molecule, and two deprotonated methanol molecules.

Hirshfeld surface (Shape Index)



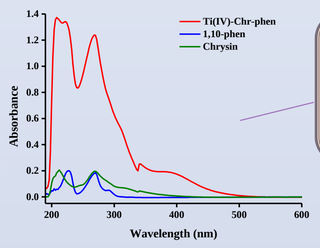
The blue-red "bow-tie" patterns represent C···C interactions. C–H···π interactions are shown as red regions of concave curvatures above the rings of chrysin, with the C–H donor interactions shown as opposite curvature in blue color.
Yellow ellipses confirm the presence of identical molecules above the ones being examined.

FT-IR spectrum



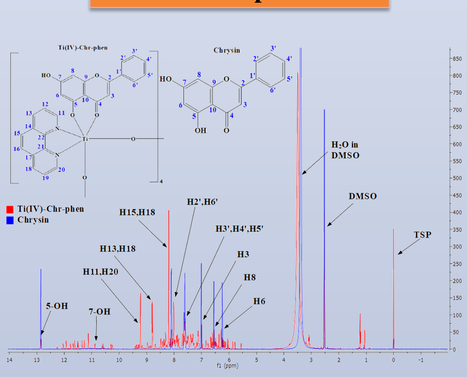
The absorption band at 1625 cm^{-1} correspond to the ν(C=O) vibration and is shifted to lower frequency compared to chrysin, indicating that this group participates in the coordination of Ti(IV).

UV-Visible spectrum

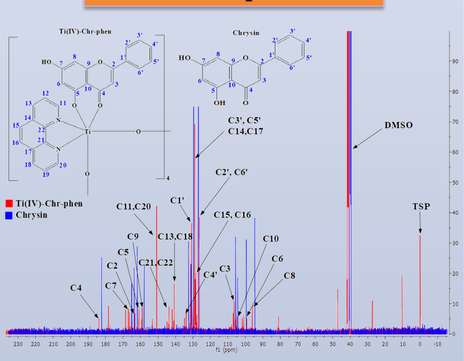


The peak associated with the coordination of Ti(IV) to C5=O and the phenolic group of ring A appears at 395 nm ($\varepsilon = 24.513\ M^{-1}\ cm^{-1}$).

^{13}C-NMR spectrum

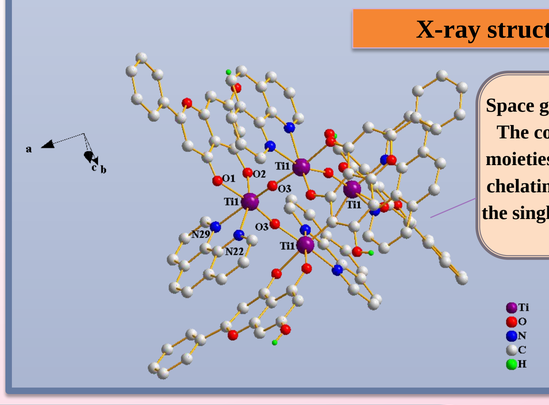


^{1}H-NMR spectrum



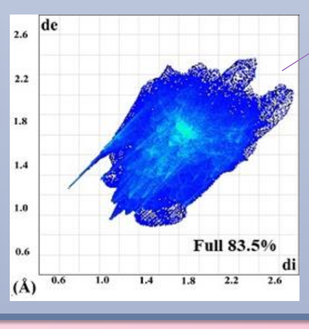
The deprotonation of the C5-OH group and the deshielding caused by the complexation of the C4 and C5 carbons, suggest that the coordination sites are C5-OH and C4=O.
All carbon and hydrogen signals of the bound chrysin and phen ligands display downfield shifts, confirming coordination with the metal center.

X-ray structure



Space group: Tetragonal $P4_2/n$.
The complex has four Ti(IV) moieties, each one linked to the chelating N,N'-donor phen and the singly deprotonated chrysin.

Hirshfeld fingerprint



The 2D fingerprint shows that the H···H, O-C-H···π and H···O intermolecular interactions are well defined and fill 83.5% of the Hirshfeld surfaces.

Conclusions

- By changing the conditions of the experiments, and the ratio of reactants and solvents, it is possible to get the desired result. In the case of the synthesis of the binary material Ti(IV)-Chr, the optimal conditions for conducting the experiment were 25 ºC and 1 atm, the ratio of reactants 5:1 and methanol (10 mL) as solvent, while for crystallization it was necessary to drop the temperature at 4 °C. In the case of the synthesis of the ternary material Ti(IV)-Chr-phen, the optimal conditions for conducting the experiment were 90 ºC for 17.0 h, the ratio of reactants 1/2:1/2:1/2:1/2 and as solvent mixture methanol - isopropanol (1:1), while for crystallization it was necessary to drop the temperature to 4 °C.
- Both materials have retained some structural features of chrysin, such as the similar infrared and UV-visible absorption bands, as well as the magnetic resonance of the ^{13}C and ^{1}H nuclei. Nevertheless, both compounds show a strong luminescence quenching behavior compared to free chrysin and phenanthroline substituents. Therefore, we have two well-characterized crystalline complexes with a unique structure, particularly in the case of the tetranuclear flavonoid-metal arrangement, which was synthesized for the first time in our laboratory.
- It is possible to synthesize the ternary material by redissolving the binary compound and reacting it with phenanthroline and triethylamine in a mixture of methanol - isopropanol (1:1). After 23 days of slow evaporation in the refrigerator, thin spikes formed, which appear to have the same structure as the Ti(IV)-Chr-phen material. From that, we conclude that the ternary material can be produced and crystallized in different ways while maintaining its basic structure, thereby indicating stability.

Future goals

- In vitro and in vivo biological studies of the antioxidant, antifungal, anti-inflammatory and anticancer properties of Ti(IV)-Chr and Ti(IV)-Chr-phen.
- Study of magnetic properties of Ti(IV)-Chr and Ti(IV)-Chr-phen materials, if intended for biological applications.
- Water solubility of Ti(IV)-Chr and Ti(IV)-Chr-phen complexes, to optimize their activity in biological systems, where hydrolysis is necessary.
- Design and synthesis of binary and ternary systems with quercetin and metal titanium(IV) ion, because it is a flavonoid with many beneficial actions that, in combination with the specific metal, can be a material of high biological interest.

References

[1] Tshuva EY, Miller M. (2018). *Metallo-Drugs: Development and Action of Anticancer Agents, Metal Ions in Life Sciences*, 18.

[2] Halevas E, Matsia S, Hatzidimitriou A, Geromichalou E, Papadopoulos TA, Katsipis G, Pantazaki A, Litsardakis G, Salifoglou A. (2022). *A unique ternary Ce(III)-quercetin-phenanthroline assembly with antioxidant and anti-inflammatory properties. Journal of Inorganic Biochemistry*, 235, 111947.