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# Spectroscopic Studies of Cu<sup>2+</sup> and Zn<sup>2+</sup> Binding to Prodigiosin Analogs and Tambjamines

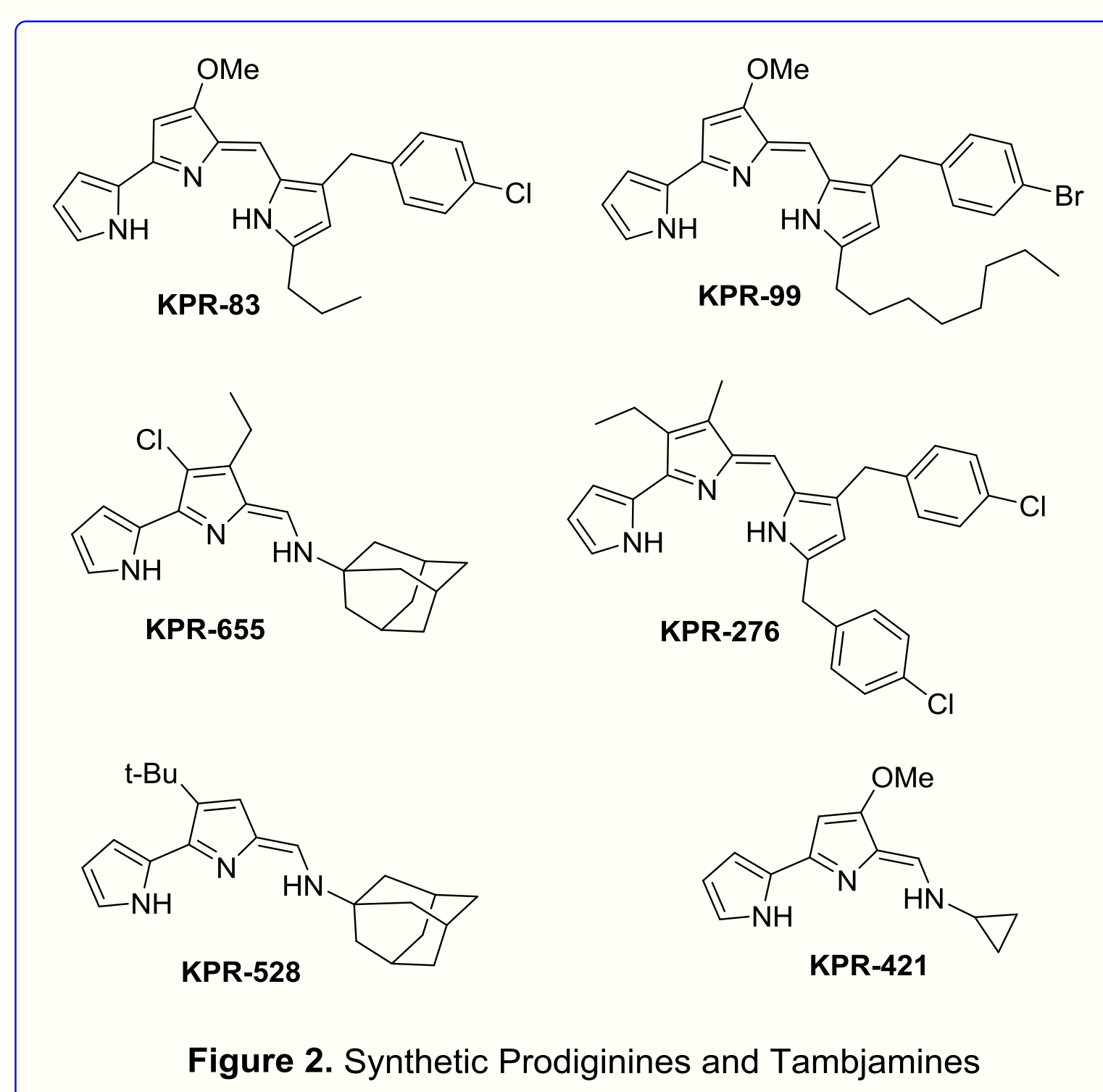
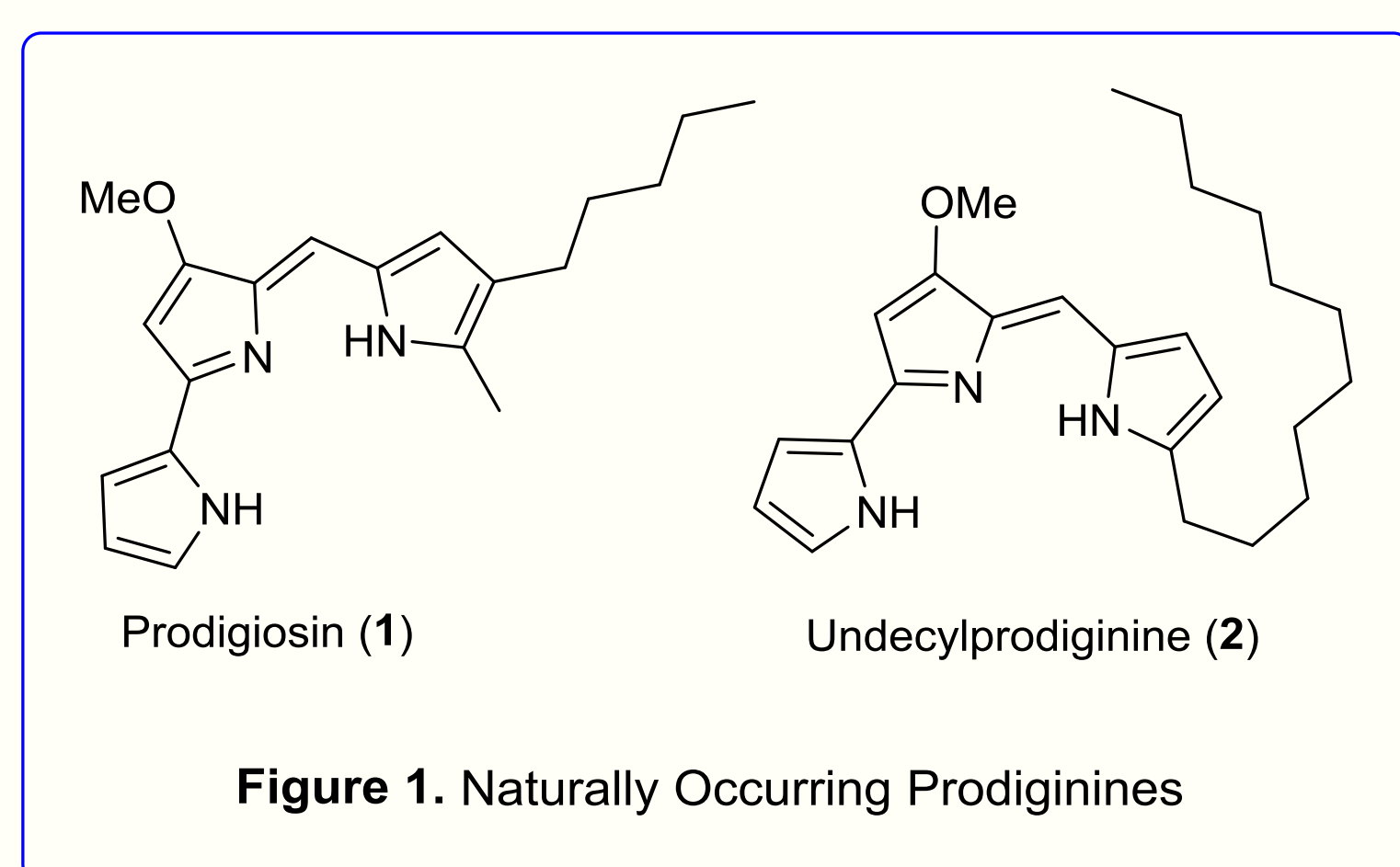
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## UV Binding Studies

### Background

Prodigiosins (prodiginines) are a family of secondary metabolites that were first isolated from the bacterium *Serratia marcescens*. These natural compounds are red pigmented and characterized by a tri-pyrrole skeleton with a C-4 methoxy group (Figure 1). They have been reported to have good biological properties that include anticancer, antimalarial, antimicrobial and immunosuppressive activities. In continuation of our drug discovery program on efficient antimalarial agent, we have synthesized a library of novel analogs of the natural prodigiosins and tambjamines (Figure 2). Most of these analogs exhibited enhanced antimalarial activity against chloroquine-sensitive (CQ<sup>S</sup>) D6 and chloroquine-resistant (CQ<sup>R</sup>) Dd2 and 7G8 strains of *P. falciparum* and improved toxicological profiles in human liver hepatocellular carcinoma cell line (HepG2). In this work, we studied the interaction between prodiginines and Cu<sup>2+</sup> and Zn<sup>2+</sup> using UV and Mass Spectroscopy techniques. Early results show that our prodigiosin analogs have good metal binding properties with dissociation constants (K<sub>d</sub>) in the micromolar range. Understanding metal binding activities of prodiginines can be key in understanding their pharmacological action. With some drug-metal complexes already in use for the management of conditions such as cancer, diabetes, ulcers and rheumatoid arthritis there is increased interest in this area.



### Cu<sup>2+</sup> Titration

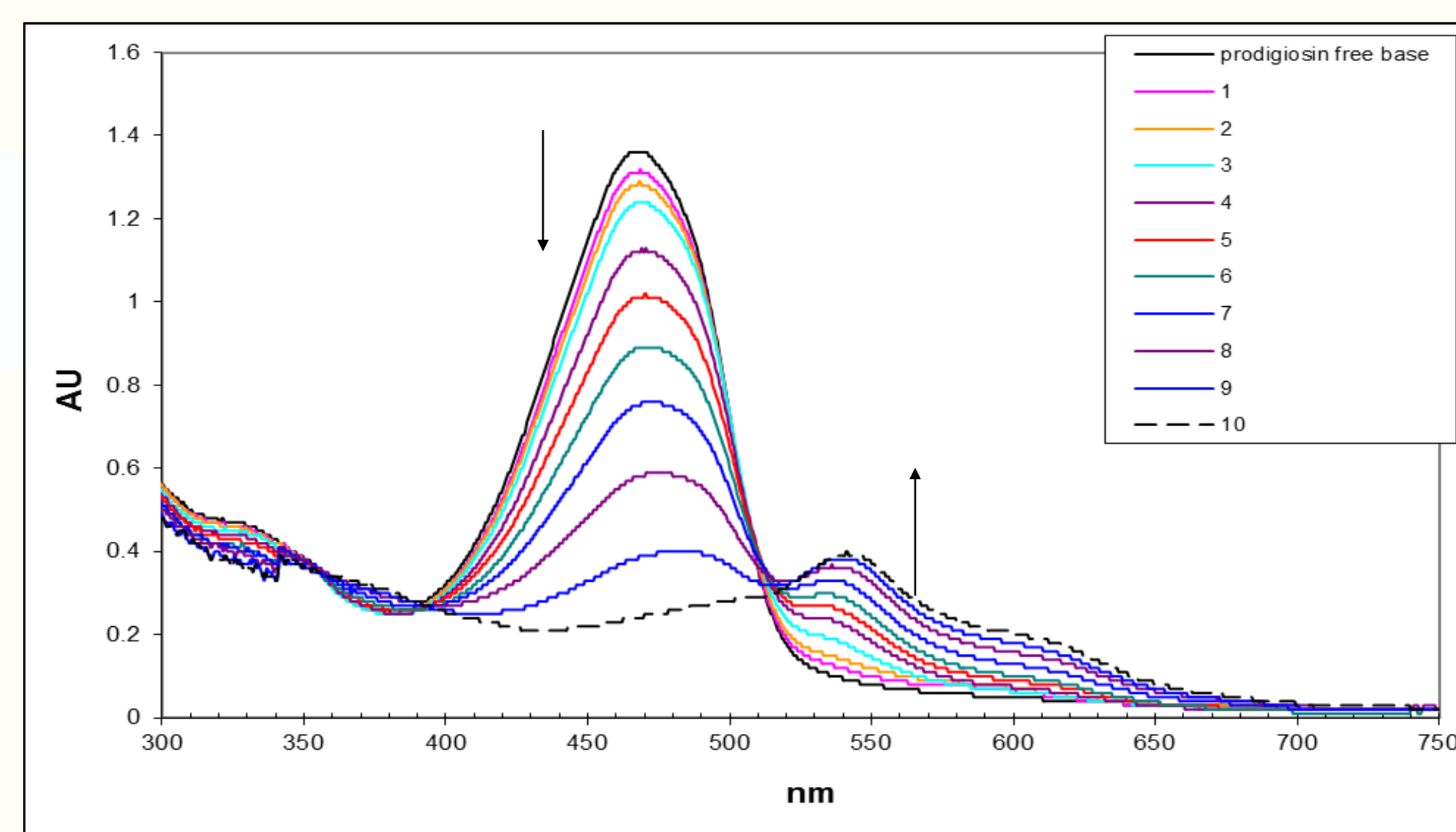


Figure 3. UV-Vis titration of **1** (19 μM) with Cu(OAc)<sub>2</sub> added in 0.1 equiv at 25 °C. The UV-Vis titration studies confirmed the binding of Cu<sup>2+</sup> to **1** to form **1**-Cu complex as indicated by loss of absorbance of **1** at 467 nm and gain of absorbance at 550 and 600 nm.

### Zn<sup>2+</sup> Titration

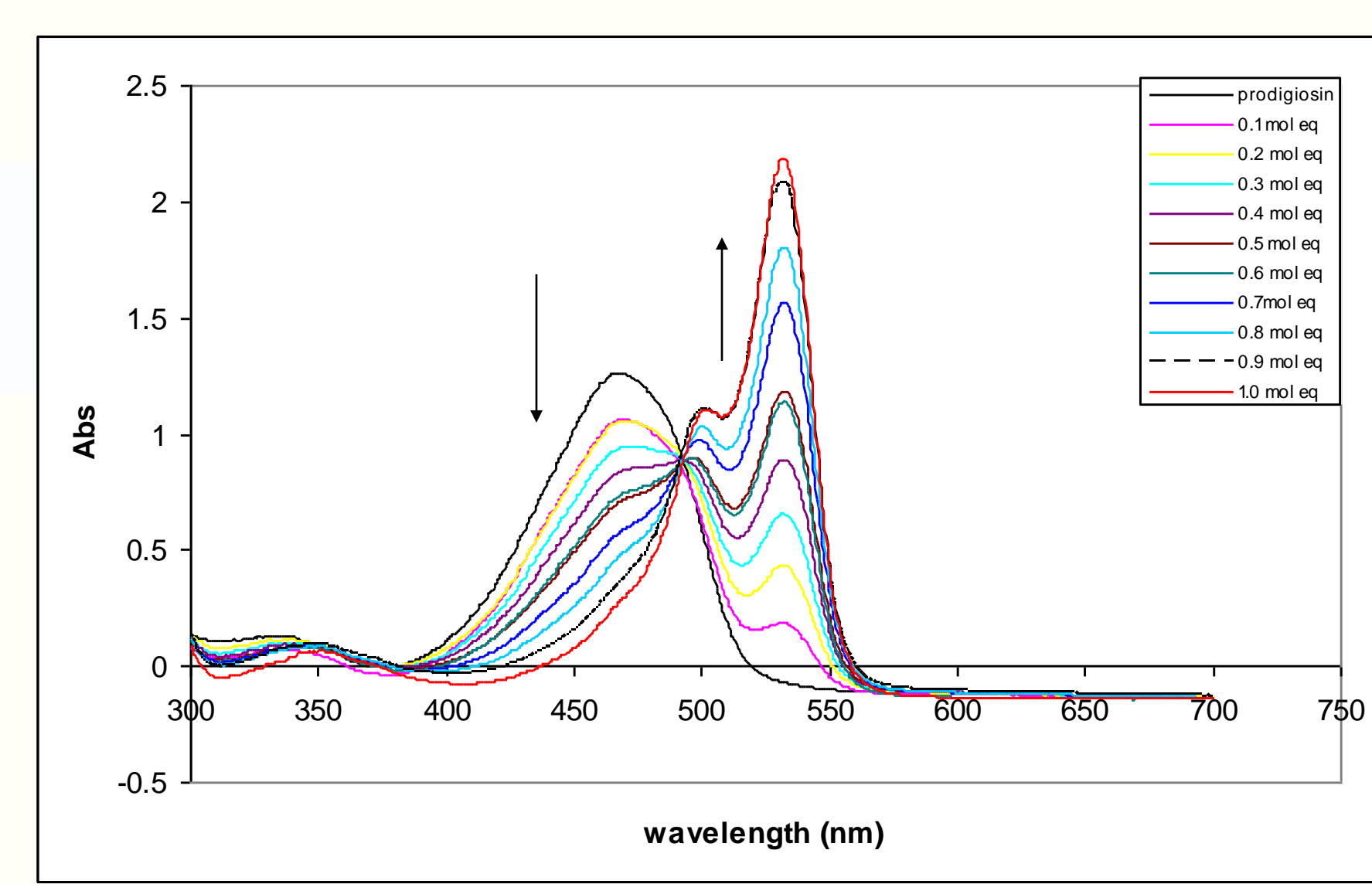


Figure 4. UV-Vis titration of **1** (19 μM) with ZnCl<sub>2</sub> added in 0.1 equiv at 25 °C. The UV-Vis titration studies confirmed the binding of Zn<sup>2+</sup> to **1** to form **1**-Zn complex as indicated by loss of absorbance of **1** at 467 nm and gain of absorbance at 505 and 527 nm.

Table 1. Experimental K<sub>d</sub> values for metal ion binding to synthetic prodiginines and tambjamines. Data shown is mean ± std dev.

Compound	Cu <sup>2+</sup> K <sub>d</sub> , μM	Zn <sup>2+</sup> K <sub>d</sub> , μM
KPR-83	14.84 ± 2.1	10.85 ± 6.1
KPR-99	4.25 ± 1.2	1.85 ± 0.7
KPR-276	13.27 ± 2.2	No binding
KPR-421	7.36 ± 0.9	No binding
KPR-528	6.46 ± 0.01	No binding
KPR-655	19.14 ± 4.9	No binding

### Mass Spec. analysis of undecylprodiginine(2)-Cu complex

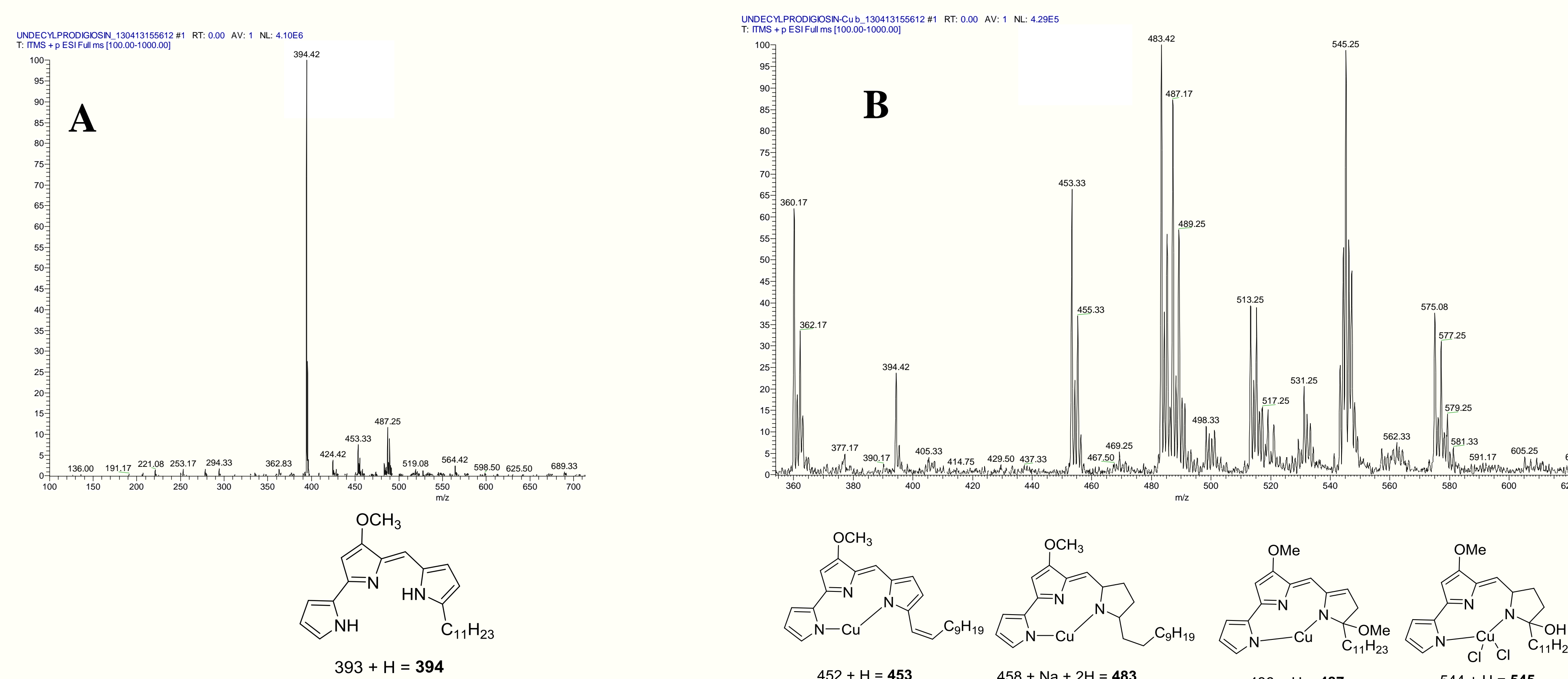


Figure 5. (A) ES<sup>+</sup> of undecylprodiginine, and (B) undecylprodiginine-Cu complex

### Discussion

- UV titration of prodigiosin with Cu and Zn confirm previous work by Park *et al.*, 2003 in which prodigiosin was shown to form complexes with the two metal ions.
- Prodigiosin analogues are more selective towards Cu<sup>2+</sup> than Zn<sup>2+</sup>.
- The differences in selectivity for metal binding could be a result of selection by preferential binding geometry of the 2 metal ions.
- Cu<sup>2+</sup> binds to most ligands more strongly than Zn<sup>2+</sup> and it has a preference for tetragonal geometry which arises from the Jahn-teller effect, a result of its d<sup>9</sup> configuration. Zn<sup>2+</sup> has d<sup>10</sup> configuration and a preference for tetrahedral geometry.
- MS analysis of the **2**-Cu complex suggests formation of a mixture of different Cu complexes.
- More work needs to be done with the synthetic prodiginines and tambjamines to determine the nature of the complexes they form with Cu<sup>2+</sup> and Zn<sup>2+</sup> and the geometry of the metals in these complexes in order to fully understand their selectivity.

### Acknowledgements

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