Development of Mn^{2+}-based MRI contrast agent candidates
Investigation of structure-activity relationships of new bispidine derivatives

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1. INTRODUCTION

The idea for the project arose in response to the safety and environmental concerns associated with currently used Magnetic Resonance Imaging (MRI) contrast agents, particularly compounds containing Gd^{3+}-ions. The toxicity of Gd^{3+}-ions – specially in patients suffering from renal failure – has been linked to the development of Nephrogenic Systemic Fibrosis (NSF). Furthermore, due to the positive gadolinium anomaly, these substances may also have harmful environmental impacts. These issues have provided strong motivation to investigate alternative, biologically compatible metal ions – such as Mn^{2+} ion complexes – as potential new contrast agent candidates.

2. AIMS

The aim of the project is to synthesize and physicochemically characterize a new type of Mn^{2+}-ion complexing bispidine derivative with potential application as an MRI contrast agent. The main scientific question of the project is whether the stability, inertness, and relaxation effect of Mn^{2+} complexes can be increased by appropriate structural modifications. The aim is that the modifications preserve the biocompatibility of the complexes and reduce their potential toxicity.

3. METHODS AND MATERIALS

The bispidine scaffold and its derivatives are not commercially available, therefore I had to synthesize them myself. In the first step, I carried out a three-component Mannich reaction, which was followed by the introduction of a 2,4-dimethoxybenzylamine (DMB) protecting group. In the third step, the carbonyl group was reduced using sodium borohydride, after which the alkylation of the side chain was performed. In the final step, the methyl ester was hydrolysed with 6 M hydrochloric acid (HCl) in a microwave reactor **[Fig. 1]**.

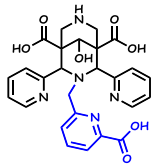

Figure 1. Formula of the test compound BisPid-N3PA

4. RESULTS

The protonation constants of the ligand and the thermodynamic stability constants of the complex were determined by the pH-potentiometric method (pMn = 6.84) **[Table 1].**

The relaxivity value – determined by relaxometric measurements – was >1.5 $mM^{-1}s^{-1}$, which suggests the presence of a coordinated water molecule, a requirement for clinical application.

However, the half-life of the exchange reaction with Zn^{2+} ions is 22.5 seconds, indicating that further fine-tuning is necessary.

	BisPid-N3PA	BisPid-BA
Σ log K_3^H	18.05	16.15
pMn	6.84	6.65

Table 1. Properties of the contrast agent candidate I produced compared with the reference compound Bispid-BA

From a scientific perspective, the project advances knowledge on MRI contrast agents, particularly Mn^{2+}-based derivatives. It may also support the development of safer, cheaper, and more environmentally friendly alternatives to Gd^{3+}-based agents.

5. CONCLUSIONS

In the first phase of the project, I successfully synthesized and characterized a new bispidine derivative that complexes Mn^{2+} ion. Based on the results, the compound has potential applications as an MRI contrast agent; therefore, improvement of kinetic inertness is still needed. The next phase of the research is aimed at the synthesis of BISPIDIN-N7PA and BISPIDIN-N3,7PA ligands and the investigation of their complexes.

6. ACKNOWLEDGEMENT

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7. REFERENCES

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