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Aluminum(III) interactions with α-synuclein and a hydrazonic metallophore: potential implications for the treatment of parkinsonism syndrome

Dayanne Martins[1], Hellora Caroline Izidoro Rodrigues[1], Roberta Lamosa[1], Carolina B. P. Ligiero[2], Daphne S. Cukierman[3] and Nicolás A. Rey[1]

[1] Chemistry Department, Pontifical Catholic University of Rio de Janeiro, Brazil
[2] Department of Inorganic Chemistry, Federal Fluminense University, Brazil
[3]Department of General and Inorganic Chemistry, State University of Rio de Janeiro, Brazil

E-mail: dayanne.martinspppp@gmail.com

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Aluminum is a well-known neurotoxic element.[1] In the context of Parkinson's disease, this metal has been identified as a promoter of oxidative stress and α-synuclein (αSyn) aggregation.[2,3] In this sense, the study of new chelating agents against aluminum is of interest. In the present work, the ligand 2-hydroxy-3-methylbenzaldehyde isonicotinoyl hydrazone (**hdz-CH$_3$**) was synthesized, characterized using solid-state and solution spectroscopic techniques, and its toxicity was evaluated by exposing increasing concentrations to *Saccharomyces cerevisiae*. The binary interactions of αSyn and **hdz-CH$_3$** with Al^{3+} were studied in solution. The nature of the αSyn-metal interplay was described at a residue-specific level of resolution (Fig. 1A). Aggregation kinetics experiments correlated well with the αSyn-Al^{3+} interaction profile. Regarding **hdz-CH$_3$**, preliminary results indicate that it is stable against hydrolysis (followed for 12 hours at 25 °C), and non-toxic to yeast at concentrations as high as 900 µM. Spectrophotometric studies revealed the formation of an ML complex in solution (Fig. 1B), while the neutral ML_2 compound was obtained in the solid state. ESI-MS(+) measurements in fact detected the presence of different ML (m/z^+ 326.3, 344.3 and 372.4) and ML_2 species (m/z^+ 282.2).

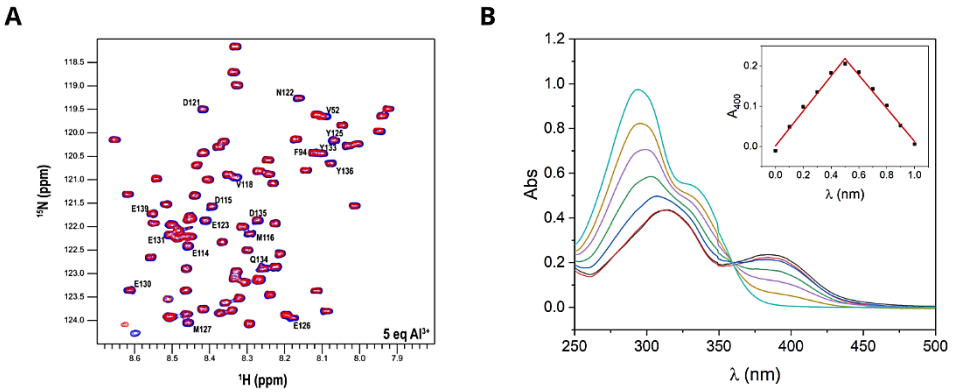

Figure 1. (**A**) Overlaid contour plots of the ^{1}H-^{15}N HSQC spectra of 100 mM αSyn in the absence (blue) and presence (red) of 5 eq. of Al^{3+}. (**B**) UV-Vis spectra and Job plot of different ligand-to-metal molar fractions.

Due to the promising toxicity prospect of **hdz-CH$_3$** and its affinity for Al^{3+} ions, *in vivo* studies involving an experimental model of aluminum-related parkinsonism are being carried out.

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