Electrochemical Characterization of Imidazole-based Carboxamidrazones in Aqueous and Organic Solutions and Structure-Activity Relationship

Rui Rodrigues,[a,b] Daniela Dantas,[a] Filipe Carvalho,[a] Ana I. Ribeiro,[b] Andrea Zille,[b] Renata Silva,[c] Fernando Remião,[c] Alice Dias,[a] Eugénia Pinto,[d,e] Fátima Cerqueira,[d,f,g] and Dulce Geraldo[a]

[a] *Centre of Chemistry of University of Minho (CQ-UM), University of Minho, Campus de Gualtar, 4710-057 Braga.*
[b] *Centre for Textile Science and Technology (2C2T), University of Minho, Campus de Azurém, 4800-058 Guimarães.*
[c] *UCIBIO-REQUIMTE, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto.*
[d] *CIIMAR/CIMAR, Interdisciplinary Centre of Marine and Environmental Research, 4450-208 Matosinhos.*
[e] *Laboratory of Microbiology, Biological Sciences Department, Faculty of Pharmacy of University of Porto, 4050-313 Porto.*
[f] *Molecular Oncology and Viral Pathology Group, Research Center of IPO Porto (CI-IPOP)/RISE@CI-IPOP (Health Research Network), Portuguese Oncology Institute of Porto (IPO Porto)/Porto Comprehensive Cancer Center (Porto.CCC), 4200-072 Porto.*
[g] *FP-I3ID, FP-ENAS, CEBIMED, University Fernando Pessoa, Praça 9 de Abril, 349, 4249-004 Porto, Portugal and Faculty of Health Sciences, University Fernando Pessoa, Rua Carlos da Maia, 296, 4200-150 Porto.*
ruipvrodrigues@hotmail.com

The search for new antibiotics is an emergent topic in the scientific community due to the appearance of pathogenic organisms multiresistant to the available drugs and therapy [1]. The worrying increase in infections caused by pathogenic fungi in immunosuppressed patients prompted the search for new antifungal agents with new mechanisms of action and less side effects [2]. The imidazole ring is a crucial scaffold for drug design due to its vital role in various biological processes [3]. Thus, imidazole-based molecules have been widely used to synthetize promising heterocyclic ligands for several drug targets. Furthermore, amidrazones are known for their high reactivity, being useful intermediates for the synthesis of compounds with a wide range of biological activities, including antimicrobial action. The amidrazone derivatives have also been applied in different areas of chemistry, specifically in the synthesis of azo molecules [4].

In a previous work, novel imidazole based 5-aminoimidazole-4-carboxamidrazones were synthesized, which exhibited great antifungal activity evaluated against three yeast species, namely *Candida krusei, Candida albicans* and *Candida parapsilosis* [5].

In this communication, the electrochemical characterization of some carboxamidrazones performed by cyclic voltammetry in two different media is compared. The effects of substituent groups in the different carboxamidrazones on the variation of oxidation potential of these compounds in aqueous and organic media were also analyzed. To find a relationship between chemical structure and activity, the minimum inhibitory concentration was correlated with their oxidation potentials. The effect of the variation of pH on the oxidation potential of substituted carboxamidrazones was also analyzed. In addition, kinetic studies of the evolution of some carboxamidrazones in aqueous media characterized by UV-Vis spectroscopy were performed and the obtained results were correlated with the electrochemical and biological data.

Acknowledgments: We thank Fundação para a Ciência e a Tecnologia (FCT) for financial support through the Chemistry Research Centre of the University of Minho (UID/QUI/00686/2020), CIIMAR (UIBD/04423/2020), UID/Multi/04546/2019, and 2C2T (UID/CTM/00264/2021). FEDER funds through Portugal 2020 Competitive Factors Operational Program (POCI), and the Portuguese Government (OE, grant number POCI-01-0247-ERDF-047124). This work was also supported under the projects MEDCOR (PTDC/CTM-TEX/1213/2020) and UID/CTM/00264/2019, the Research Center of the Portuguese Oncology Institute of Porto (project no. PI86-CI-IPOP-66-2019), and PhD grant SFRH/BD/137668/2018 and 2021.08081.BD.

References:

[1] Morsy M. A.; Ali E. M.; Kandeel M.; Venugopala K. N.; Nair A. B.; Greish K.; El-Daly M. Antibiotics, 9 (**2020**), 221
[2] Cerqueira F.; Maia M.; Gabriel C.; Medeiros R.; Cravo S.; Ribeiro A. I.; Dantas D.; Dias A. M.; Saraiva L.; Raimundo L.; Pinto E. *Antibiotics*, *10* (**2021**), 183
[3] Arendse, M.; Khan, S.; Wani, M. Y.; Aqlan, F. M.; Al-Bogami, A. S.; Ahmad, A., *Braz J Microbiol*, (**2022**).DOI: https://doi.org/10.1007/s42770-022-00702-8
[4] Mazur, L.; Sączewski, J.; Jarzembska, K. N.; Szwarc-Karabyka, K.; Paprocka, R.; Modzelewska-Banachiewicz, B, *CrystEngComm*, *20* (**2018**), 4179–4193.
[5] Ribeiro A. I.; Gabriel C.; Cerqueira F.; Maia M.; Pinto E.; Sousa J. C.; Medeiros R.; Proença M. F.; Dias A. M., Bioorganic & Medicinal Chemistry Letters, 24 (**2014**), 4699-4702.