

Electrochemistry of Riminophenazines with High Antiproliferative Activity

Patrizia R. Mussini^a, Ivan Bassanini^b, Massimiliano Meli^b, Chiara Tognoli^b, Riccardo De Simone^b,

Anna Sparatore^c, Silvia Araneo^a, Chiara Margolfo^a, Alberto Vertova^a, Rebecca Galbiati^a

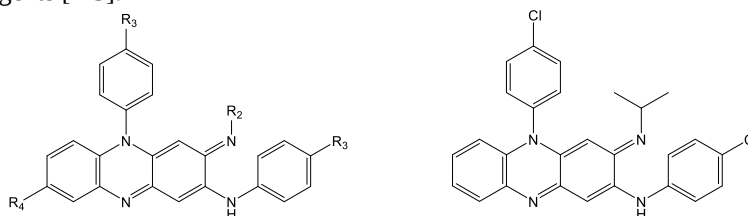
^a Dip. di Chimica, Università degli Studi di Milano, Via Golgi 19 20133 Milano;

^b Ist. di Scienze e Tecnologie Chimiche "Giulio Natta", CNR, Via Mario Bianco 9, Mi-20131(IT);

^c Dip. di Scienze Farmaceutiche, Università degli Studi di Milano, Via Mangiagalli 25, Mi-20133(IT).

patrizia.mussini@unimi.it

Riminophenazines are a dye family, synthetic but related to the natural phenazine building block, continuously growing and intensively studied as of utmost interest in pharmacology [1-5]. Clofazimine (see scheme below) can be considered a prototype of this family of bioactive small molecules and it was at first FDA-approved for the treatment of multi-drug resistant tuberculosis and leprosy. Medicinal chemistry research effort has now highlighted the high potentialities of the riminophenazine scaffold as antiproliferative agents. Accordingly, Clofazimine repositioning strategies have prompted the development of synthetic analogues endowed with (i) powerful growth inhibitory activity against Gram-positive bacteria and protozoa; (ii) interesting anti-inflammatory effects; and (iii) promising profiles as Wnt-targeting anticancer agents [1-5].



Left: a generic riminophenazine structure.

Right: clofazimine

In this context, many research groups, including some of us [3,4], are currently investigating the structure-activity relationships (SAR) of this scaffolds to enhance specific pharmacological activities or/and reduce undesired side effects related to clofazimine administration, like skin pigmentation.

Although riminophenazines are highly electrochemically active on both the oxidation and the reduction side, only a few related electrochemical studies are to our knowledge so far available (for example [2,6]). Quite recently we have however realized that electrochemistry can be regarded as a powerful asset in this key research field. Not only electrochemistry can help in understanding the electronic properties as a function of riminophenazines molecular structure but it can help to relate them to their *in vitro* performances as antiproliferative agents, to understand and rationalize their mechanism of action against specific parthenogens and, last but not least, to improve synthetic pathways. Very attractive preliminary results will be presented and discussed.

[1] C.E.J. Van Rensburg, R. Anderson, J.F. O'Sullivan, Riminophenazine compounds: pharmacology and anti-neoplastic potential, *Critical Reviews in Oncology/Hematology* 25 (1997) 55.

[2] M. V. Bvumbi, C. van der Westhuizen, E. M. Mmutlane, A. Ngwane, Riminophenazine Derivatives as Potential Antituberculosis Agents: Synthesis, Biological, and Electrochemical Evaluations, *Molecules* 26 (2021) 4200.

[3] I. Bassanini, S. Parapini, N. Basilico, A. Sparatore, Novel Hydrophilic Riminophenazines as Potent Antiprotozoal agents, *ChemMedChem* 14 (2019) 1940.

[4] A. Koval, I. Bassanini, J. Xu, M. Tonelli, V. Boido, F. Sparatore, F. Amant, D. Annibali, E. Leucci, A. Sparatore, V. L. Katanaev, Optimization of the clofazimine structure leads to a highly watersoluble C3-aminopyridinyl riminophenazine endowed with improved anti-Wnt and anti-cancer activity in vitro and in vivo, *Eur. J. Med. Chem.*, 222 (2021) 113562.

[5] M. Tonelli, A. Sparatore, I. Bassanini, V. Francesconi, F. Sparatore, K. Maina, S. Delbue, S. D'Alessandro, S. Parapini, N. Basilico, In Vitro Screening of an In-House Library of Structurally Distinct Chemotypes Towards the Identification of Novel SARS-CoV-2 Inhibitors, *Pharmaceuticals* 17 (2024) 1668.

[6] A. Fakier-Lesch, R.F. Ngece-Ajayi, N. Mohamed, C. Cupido, Electrochemical Determination of Clofazimine Using A Carbon Dot Polythionine Nanocomposite-Modified Screen-Printed Electrode, *Electroanalysis* 37 (2025) e202400278.