

Title	Nucleic Acids Alkylation by Mono and Bis-chloropiperidines
PI	Gatto Barbara
Research Group	Molecular Mechanism of Action of Drugs - Barbara Gatto - DSF
Curriculum	Scienze Farmaceutiche
Contact	web: http://www.dsfarm.unipd.it/barbara-gatto-0
	email: barbara.gatto@unipd.it

Project description:

This project aims to exploit the potentialities in drug development of easily accessible small molecules while building an interdisciplinary and international network. Mono and Bis-chloro-piperidines (M-CePS and B-CePS) are simplified analogues of natural products with potential therapeutic activity. They can be considered as piperidine-based analogues of nitrogen mustards, old drugs with valuable therapeutic activity despite severe side effects. In collaboration with the group of Prof. Dr. Goettlich at JLU - Giessen, we recently synthesized a large set of chloropiperidine derivatives intended to react covalently with nucleophilic sites on DNA, exploring the chemical space of B-CePS, elucidating their molecular mechanism of action (MMOA) and evaluating their potential as base alkylators in inducing cell death (1-3).

Beyond their ability to induce DNA damage, B-CePS derivatives exhibited the peculiar skill to differently react with RNA molecules inducing cross-linking of RNA strands. Opening new perspectives in the development of innovative antiviral agents targeting viral RNA structures, we aim to explore bis-chloropiperidines potential in inducing anti-HIV effects in vitro; and to elucidate their molecular mechanism of action by means of modern spectroscopic, electrophoretic and spectrometric methods.

Publications:

- Zuravka, I., R. Roesmann, A. Susic, W. Wende, A. Pingoud, B. Gatto and R. Gottlich (2014). "Synthesis and DNA cleavage activity of Bis-3-chloropiperidines as alkylating agents." *ChemMedChem* 9(9): 2178-2185.
- Susic, I. Zuravka, N.K. Schmitt, A. Miola, R. Göttlich, D. Fabris, and B. Gatto. "Direct and Topoisomerase II Mediated DNA Damage by Bis-3-chloropiperidines: The Importance of Being an Earnest G". *ChemMedChem*, 2017, 12, 1471 – 1479.
- Carraro, A. Francke, A. Susic, F. Kohl, T. Helbing, M. De Franco, D. Fabris, R. Göttlich, and B. Gatto. "Behind the Mirror: Chirality Tunes the Reactivity and Cytotoxicity of Chloropiperidines as Potential Anti-cancer Agents", *ACS Med. Chem. Lett.* DOI: 10.1021/acsmchemlett.8b00580.

Collaborations/Network:

The international partners of the BICePs network are Prof. Dr. Richard Goettlich, Institute of Organic Chemistry, Justus Liebig University (JLU) Giessen, Germany and Prof. Dan Fabris, The RNA Institute and Department of Chemistry, University at Albany, Albany, NY, USA.

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