Title: **New scaffolds for extension of structure-activity relationship studies of metal-based anticancer drugs**

Acronym: **METDRUG**

Project code: **PN-III-P1-1.1-PD-2016-1027**

Contract: **5/02.05.2018**

Project Manager: **Dr. Mirela-Fernanda Zaltariov**

Contract Authority: **Executive Agency for Higher Education, Research, Development and Innovation Funding**

Contractor: **"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania**

Project duration: **02.05.2018-30.04.2020**

Budget: **250 000 lei (**2018: 79 856 lei; 2019: 141 141 lei; 2020: 29 003 lei)

ABSTRACT

The present proposal is concerned with the development of new metal complexes based on a library of specifically modified indolo[2,3-c]quinolines and new indolo[3,2-d]benzazepines to be evaluated as anticancer drugs.

We propose to extend our studies on structure-activity relationships on these frameworks and to elucidate the effects of location of the lactam group in azepine ring, and orientation of indole basic unit with respect to quinolone-2-(1H)-one entity. The rationale behind our proposal is to design new metal complexes which can allow their application at very low doses due to the highly cytotoxicity, at nanomolar concentrations.

Thus the enormous potential impact of these new classes of metal-based drugs relies in their possible site-specific delivery in localized tumors, strongly improving their cellular uptake and minimizing unwanted side-effects, which could offer a significant advantage over platinum-based chemotherapeutics.

OBJECTIVES

- Synthesis of proligands based on indolo[2,3-c]quinoline and indolo[3,2-d]benzazepine derivatives and their metal and organometallic complexes, establishment of their structure in solid state and in biological media, investigation of physico-chemical and spectroscopic properties.

- Determination of their antiproliferative activity in different cancer cell lines and in a normal noncancerous cell-line, establishment of SARs.

- Estimation of their ability to inhibit enzymes that can be considered as possible targets in anticancer chemotherapy.

- Attempts to get an insight into the molecular basis for antiproliferative activity and enzyme inhibition by studying adducts enzyme-inhibitor using advanced methods of mass spectrometry, molecular modeling calculations, protein X-ray crystallography.

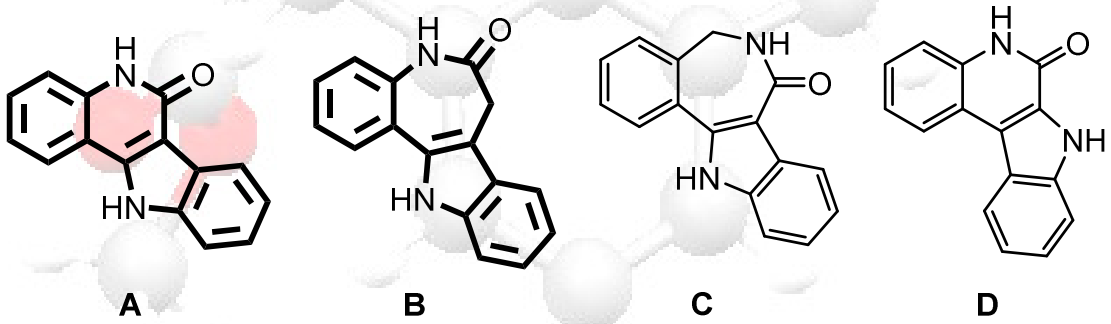
- Encapsulation of metal complexes into liposomes as carriers to study their in vivo selective tumor delivery.

- Investigation of the drug accumulation in the tumor and comparison with usual formulations.

Stage 2018 - Indolo[2,3-*c*]quinoline and indolo[3,2-*d*]benzazepine derivatives

Specific aims:

- *Synthesis of frameworks **C** and **D** based on reported synthetic procedures*
- *Synthesis of modified indolo[2,3-c]quinolines and new indolo[3,2-d]benzazepines containing metal-binding sites*
- *Purification and characterization of the obtained compounds*



Deliverables: **Stage 2018:** At least four well characterized proligands; Scientific Report;

Stage 2019 - Metal-complexes of modified indolo[2,3-*c*]quinolines and new indolo[3,2-*d*]benzazepines

Specific aims:

- *Synthesis of metal-based indolo[2,3-c]quinolines and new indolo[3,2-d]benzazepines*
- *Purification and characterization of the obtained metal complexes*
- *Studies on solution equilibria and hydrolytic stability of the proligands and metal complexes in biological environments*
- *Study of antiproliferative activity of proligands and metal complexes in several cancer cell lines and normal cells*
- *Dissemination of the results*

Deliverables: **Stage 2019:** At least four well-defined metal complexes based on new indolo[2,3-*c*]quinolines and indolo[3,2-*d*]benazepines containing metal-binding sites; results of antiproliferative activity assays for four proligands and four metal complexes; at least one research article submitted at an ISI journal; Scientific Report.

Stage 2020 - Metal-complexes (further studies)

Specific aims:

- *Study of the ability of potential drugs to inhibit enzymes that can be considered as possible targets in anticancer chemotherapy*
- *Study of the encapsulation of the metal complexes into liposomes and their use for in vivo targeted delivery*
- *Dissemination of the results*

Deliverables: **Stage 2020:** Results of the enzyme inhibition tests; results of encapsulation of at least two complexes into liposomes; at least one full-paper submitted at an ISI journal; Scientific Report.

Scientific results -Papers

1. Synthesis, structural characterization and biological studies of new Schiff bases containing trimethylsilyl groups, Mirela-Fernanda Zaltariov*, Mihaela Avadanei, Mihaela Balan, Dragos Peptanariu, Nicoleta Vornicu, Sergiu Shova, *Journal of Molecular Structure* 1175, 624-631(**2019**);

2. ATR-FTIR and thermal behavior studies of new hydrogel formulations based on hydroxypropyl methylcellulose/poly(acrilic acid) polymeric blends, Mirela-Fernanda Zaltariov*, Daniela Filip, Cristian-Dragos Varganici, Doina Macocinschi, *Cellulose Chemistry and Technology*, 52 (7-8), 619-631 (**2018**).

Scientific results -Conferences

1. Metal complexes as R2 ribonucleotide reductase inhibitors: elucidation of structure-activity relationship, Mirela-Fernanda Zaltariov, A XXXV-a Conferinţă Naţională de chimie Călimăneşti-Căciulata, 02-05 octombrie **2018**-comunicare orala

2. Interaction of platinum(IV) ions with polydentate N, O-donor ligands: complex formation ability, stability and cytotoxicity, Mirela-Fernanda Zaltariov, Mihaela Avadanei, Dragos Peptanariu, A XXXV-a Conferinţă Naţională de chimie Călimăneşti-Căciulata, 02-05 octombrie **2018**-poster

METDRUG - Team

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