STRATAGEM

CA17104

New Diagnostic and Therapeutic Tools against Multidrug-Resistant Tumours

First Working-Group Meeting

WG 1 – WG 4

Abstract Book

Turin, Italy

30th – 31st January 2019

cost EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Funded by the Horizon 2020 Framework Programme of the European Union

DSTF DIPARTIMENTO DI SCIENZA E TECNOLOGIA DEL FARMACO UNIVERSITÀ DEGLI STUDI DI TORINO

UNIVERSITÀ DEGLI STUDI DI TORINO

Selected strategies used to design anticancer molecules.

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Recent progress in a biomedical research is focused, among others, on the synthesis of peptidomimetics; small peptide type molecules that reveal wide spectrum of biological activities. In our research we are focusing in particular on three key steps: the target validation and selection; chemical hit and lead generation; lead optimization to identify clinical drug candidates. In the first step of our studies, a therapeutic target proteasome was identified and several inhibitors with peptidomimetc structure were synthesized and validated as antitumor molecules. [1, 2] The next studies were devoted to peptidomimetic inhibitors of thioredoxin-thioredoxin reductase system [3,4]. One of our the most potent compound, SK053, triggers tumor cells apoptosis by oxidative stress-mediated endoplasmic reticulum stress. [5, 6] Subsequent experiments allowed us to identify peptidomimetic kinase inhibitors with high Cytostatic/Cytotoxic Activity. This effect was evaluated on tumor cell line (RAS-3T3) displaying overactivation of the MAP kinase RAS/MEK/ERK pathway in comparison to the parental, non-tumorigenic cells. [7] We intended to use gold and silver nanoparticles as anticancer molecules and revile the high instability of silver nanoparticles in buffers as well as low affinity of gold nanoparticles towards selected enzymes. [8]

Acknowledgements

We gratefully acknowledge the financial support from the Polish State Committee for Scientific Research project OPUS No. 2016/B/ST5/03307.

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Rational design of multi-target compounds with potential anticancer activity

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Multi-target compounds are designed to act on at least two targets in synergistic way, in order to produce stronger biological effect. The link between cancer and inflammation has been intensively studied in last years and inhibition of both COX-2 and 5-LOX enzymes may be an effective therapeutic approach for colon cancer treatment [1]. Acridines are known as DNA-topoisomerase II inhibitors. These compounds intercalate into the DNA and inhibit topoisomerase II by their side chain. Recent studies showed additional activities of acridine derivatives, depending on the side chain structure, such as inhibition of Src, MEK and VEGFR2 kinases [2,3]. Altered activity of PI3K/mTOR signaling pathway is one of the most common aberrations found in various forms of neoplastic lesions. Dual inhibition of PI3K and mTOR represents a reasonably attractive concept in potential cancer treatment [4]. In this paper, design of three groups of multi-target compounds with potential anticancer activity is presented. Designed compounds are potential inhibitors of COX-2 and 5-LOX, DNA-topoisomerase II complex and kinases (Src, MEK and VEGFR2), as well as dual inhibitors of mTOR and PI3K. A set of 27 compounds with published inhibitory activity on COX-2 and 5-LOX was formed and two QSAR models, for both activities, were created in Pentacle program. On the basis of models' interpretation, nine new compounds were designed and activity on both targets predicted by developed models. Twenty-three acridine derivatives were designed and their interactions with DNA-topoisomerase II complex, Src, MEK and VEGFR2 were tested using AutoDock Vina program. Nineteen designed compounds bind to DNA similarly to inhibitor amsacrine and among them, ten derivatives show key binding interactions with tested kinases and therefore possess potential to inhibit them. A dataset of eighty-five compounds with dual PI3K/mTOR inhibitory activities was formed, divided into two groups based on their structural analogy and 3D-QSAR analysis of each group was performed in Pentacle program,

resulting in four QSAR models. On the basis of these results, new compounds were designed and further evaluated by use of molecular docking, virtual screening and ADMET predictions. Finally, seven compounds were chosen as the most promising new dual mTOR/PI3K inhibitors.

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New ruthenium metallodrugs against cancer multidrug resistance

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The discovery of new potent and selective anticancer agents, able to decrease the noxious side effects of the chemotherapeutics in clinical use, and capable to overcome resistance mechanisms, is the driving force for research in this field.

In this frame we have been developing new of $[Ru(\eta^5\text{-}C_5H_5)(2,2'\text{-bipiridine})(PPh_3)]^+$ based compounds endowed with specific targeting components to take advantage of the singular characteristics of tumor cells and tissues, such as their permeability to macromolecules and overexpression of several receptors.[1-4] Thus, by introducing a biodegradable and biocompatible polymer and a biomolecule recognized by cancer cells in the structure of our compounds, one can benefit from a passive and active targeting, respectively. This family of ruthenium metallodrugs possess very attractive features: high cytotoxicity against several cancer cell lines with different degrees of aggressiveness, strong inhibition of several proteins known for their role in mechanisms of cell resistance, interference with proteins that regulate the microtubule or actin dynamics leading to cell death and low in vivo toxicity. Thus, this talk discloses the potential of these new ruthenium(II) compounds for the targeted therapy of metastatic and resistant cancers.

Acknowledgements: This work was financed by the Portuguese Foundation for Science and Technology (Fundação para a Ciência e Tecnologia, FCT) within the scope of project UID/QUI/00100/2013 and PTDC/QUI-QIN/28662/2017. Andreia Valente also acknowledges the Investigator FCT2013 and the CEECIND 2017 Initiatives for the projects IF/01302/2013 and CEECIND/01974/2017 (acknowledging FCT, as well as POPH and FSE - European Social Fund).

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