**PO-411** NOVEL HIF1α INHIBITORS SUPPRESS CANCER CELL GROWTH AND CIRCUMVENT MULTIDRUG RESISTANCE

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**Abstract**

**Introduction** Hypoxia is one of the causes of the resistance of tumours to various therapeutic agents. Most solid tumours contain hypoxic regions and adapt to low levels of oxygen by producing hypoxia-activated molecules, among which HIF-1α (Hypoxia-Inducible Factor 1-alpha) is key. HIF-1α is upregulated in many types of solid cancers and contributes to tumour progression by stimulation of VEGF-A expression and subsequent neoangiogenesis. The goal of the study was to synthesise a series of novel hypoxic cytotoxins and to evaluate their anticancer potencies.

**Material and methods** A series of 3-aryl/heteroaryltriquinoxaline-2-carbonitrile 1,4-dioxides was synthesised by Beirut reaction. Cancer cell lines were purchased from ATCC. The cytotoxic activity of quinoxaline 1,4-dioxides was evaluated in normoxia (21%O2) and hypoxia (1%O2). The cytotoxicity was assessed by MTT test (72 hour growth with compounds). HIF-1α and p53 activation was assessed by reporter analysis. The presence of ROS in MDA-MB-231 breast cancer cells was detected using the fluorescent probe 2’,7’-dichlorofluorescin diacetate.

**Results and discussions** Lead compounds in series new quinoxaline 1,4-dioxides demonstrated better cytotoxicity and comparable hypoxia selectivity for human breast adenocarcinoma cell lines MCF-7 and MDA-MB-231 than the reference agent tirapazamine. In contrast to reference antibiotic doxorubicin, quinoxaline 1,4-dioxides inhibited hypoxia-mediated HIF-1α activation and showed potent cytotoxicity against multidrug resistant human chronic myeloid leukemia K562/4 cells with overexpression P-glycoprotein (Pgp). Selected compound LCTA-2809 (6,7-dichloro-3-phenylquinoxaline-2-carbonitrile 1,4-dioxide) inhibited of cancer cell growth through p53-independent mechanisms. Compound LCTA-2809 showed no effects on p53-dependant lucerase activity, when doxorubicin revealed high potency to activate p53-dependant reporter in MCF-7 cells. Our results revealed that compound LCTA-2809 sensitised MCF-7 cells to bignonide metformin in hypoxia. Short-term treatment with LCTA-2809 resulted in the fast increase of ROS accumulation in cancer cells.

**Conclusion** HIF-1α inhibitor LCTA-2809 can be considered as the lead compound for further anticancer drug design, evaluation, and development of new potent antitumor agents. The biology experiments of the research were supported by RSF 14-15-00362.

**PO-412** NOVEL DRUG DISCOVERY APPROACHES FOR CANCER WITH THE INSPIRATION OF A NATURAL PRODUCT – METHYL JASMONATE

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**Abstract**

**Conclusion** Cancer is one of the well-known illnesses leading to death. Clinical validations prove that protein kinases are an attractive class of therapeutic drug targets for cancer as demonstrated with the recent approval of six protein kinase inhibitors. The Warburg effect describes the particular reliance of cancer cells on glycolysis for energy. Increased glycolysis and acid resistance have been postulated to be an essential part of carcinogenesis, conferring a significant growth advantage as well as promoting typical tumour progression. Targeting accelerated glycolysis in cancer cells is a new promising modality for treatment of cancer. Inhibition of glycolysis can be done without significant side effects, and such treatment will be additive to most known cancer therapies.

**Results and discussions** In our research laboratory, we designed and synthesised handful of novel methyl jasmonate analogues. We will highlight the biological activity results of those novel analogues as anti-cancer agents as well as their toxicologic profiles will be highlighted.

**Conclusion** As a result of this study, we have identified several novel methyl jasmonate analogues that are much more potent in biological assays. Based on the synthetic feasibility and freedom of operation of methyl jasmonate molecule, additional druggable analogues are also being investigated in our research.

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**PO-413** ESTIMATION OF ANTITUMOR ACTIVITY OF AMINO DERIVATIVES OF QUINOXALINE-2-CARBONITRILE 1,4-DIOXIDE

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**Abstract**

**Introduction** Tumour hypoxia and its key mediator the HIF-1α contributes to tumour aggressiveness and responsible for major distinguishing features of cancer including metastasis, invasion...
and treatment resistance. Derivatives of quinoxaline 1,4-dioxide are known as hypoxia-selective antitumor agents. Previously described quinoxaline-2-carbonitrile 1,4-dioxides are water insoluble; this complicates their biological evaluation. Therefore, search of new water-soluble derivatives in this class can be perspective direction for development of novel selective cytotoxins.

**Material and methods** A series of new 3-phenyl-quinoxaline-2-carbonitrile 1,4-dioxides bearing the amine residues was obtained via Beirut reaction [RU2640304]. The cytotoxic activity of newly synthesised compounds was tested (MTT-assays) in MCF-7 and MDA-MB-231 breast carcinoma cell lines after 72 hour incubation in normoxia (20% O2) or hypoxia (1% O2). The antitumor efficacy of the selected compound was evaluated in BDF1 (C57BL x DBA2) male mice (20–22 g) with i.p. transplanted P388 leukemia. Animals were injected i.p. with a solution (0.2%) of the hit compound (24 hour after tumour cell transplantation) daily for 5 days. The antitumor efficacy was estimated by measurement of increasing life span (ILS) of animal.

**Results and discussions** All new derivatives of 3-phenylquinoxaline-2-carbonitrile 1,4-dioxide were water soluble and able to inhibit growth of two breast cancer cell lines at micromolar to submicromolar concentrations. Moreover, the cytotoxicity of new quinoxaline 1,4-dioxides increased under hypoxia. Among the new quinoxaline 1,4-dioxides with various structure of the amine moiety, LCTA-2645 (7-(3-amino-pyrrolidinyl)-3-phenylquinoxaline-2-carbonitrile 1,4-dioxide) was exceptionally potent for cells in normoxia/hypoxia. This derivative demonstrated highest hypoxic cytotoxicity ratios (HCR=32 and 22 for the MCF-7 and MDA-MB-231, respectively) among all series of compounds. The results of estimation of an efficiency in vivo on murine tumour model P388 shown, that LCTA-2645 at the daily dose 25 mg/kg increased the lifespan of mice (ILS=20%, p<0.01) with good tolerance.

**Conclusion** The amino derivatives of quinoxaline-2-carbonitrile 1,4-dioxide are a promising class of hypoxia-selective agents for development of antitumor drugs. Further studies of LCTA-2645 include dose optimisation and tests on animal models of solid tumours. Experiments with cell cultures were supported by RSF grant 14-15-00362.

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**PO-415**

NEW ANTI-MIGRATORY AND ANTI-INVASIVE EFFECTS OF A FASCIN INHIBITOR ON COLORRECTAL CANCER CELLS

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**Introduction** Serrated adenocarcinoma (SAC) is a histological subtype of colorectal carcinoma characterised by its poor prognosis, prominent invasive front and over-expression of fascin, the key protein involved in actine bundling needed for cell migration and invasion. Given that the frequency of KRAS or BRAF mutations in SAC are higher than in conventional colorectal carcinoma, this tumour type is usually resistant to anti-EGFR therapy. For these reason, anti-fascin treatment could be an interesting approach to treat SAC and other tumours over-expressing fascin. In this work we have characterized the anti-migratory and anti-invasive properties of compound G2 (N-(1-(4-