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 were obtained via Reutur 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 (C5-Bl 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 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 anticancer 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.

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 aproach 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-
(trifluoromethyl)benzyl–1H-indazol-3-yl)furan-2-carboxamide), a patented anti-fascin molecule and compared its effect with migmastatin, a typical fascin inhibitor.

**Material and methods** We have used molecular modelling to predict the fascin amino acids involved in G2 binding. A qPCR assay was carried out to find out which from eight different colorectal cancer cell lines expressed the highest amount of fascin. After cell viability assay, scratch and IBIDI assays were performed to evaluate the anti-migratory effect of the compounds. Immunofluorescence for fascin was used for assessing lamellipodia formation. Anti-invasive effect was evaluated using cell invasion assay Transwell with matrigel and a myoma organotypic invasion model.

**Results and discussions** Molecular modelling using blind docking calculations identified a region in fascin possibly involved in G2 binding. HCT116 cells expressed the highest fascin levels and its migration capacity was clearly reduced by migmastatin and G2, the latter even at lower concentrations. Still, G2 inhibited the migration of all the cell lines demonstrating that G2 affected fascin functional capacity.

Invasion and confocal studies were performed with HCT116 cells and both inhibitors strongly abolished the protrusion of lamellipodium (p=0.003). The Transwell Matrigel invasion assay also evidenced the anti-invasive effects of migmastatin and G2. Myoma discs showed that both compounds were similarly able to significantly decrease both the invasion depth and invasion area of HCT116 cells at 50% (p<0.001).

**Conclusion** This study demonstrates an interesting anti-migratory and anti-invasive effect of G2 in a similar extent to migmastatin and provides significant evidence that G2 is an interesting candidate for further investigation/chemical modifications to develop new fascin-specific therapies for colorectal cancer.

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**PO-416 CYTOTOXICITY OF RU (II) AND RU (III) SALEN COMPLEXES AGAINST BREAST AND COLORECTAL CANCER CELL LINES**

**Introduction** Breast and colorectal cancer are the most common cancers, and are therefore responsible for a high mortality rate worldwide. The search for new anticancer drugs has increased in the last decades since chemotherapeutic drugs used nowadays show many adverse effects and cancer resistance. Previous studies have shown that metallic salen complexes exhibit antitumor activity. Additionally, Ru complexes have revealed cytotoxic activity, proving greater selectivity for tumour cells. They are less toxic relatively to Pt complexes, being for this reason pointed out in the literature as a credible alternative to current drugs used in chemotherapy. The aim of this study is to synthesise four novel Ru(III) and Ru(II) chlorinated salen complexes and test their cytotoxicity on breast and colorectal cancer cell lines.

**Material and methods** Ru salen complexes were synthesised from camphoric acid derivatives. MCF-7 and HCC1806 breast cancer cell lines and LS1034 and WiDr colorectal cell lines were cultured in appropriate culture medium. The effect of the compounds on cell metabolic activity was evaluated by colorimetric MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) test. For this study, the cells were seeded in 48-well plates and after 24 hour were incubated with increasing concentrations of the complexes (0.5 to 200 µM). After 48 hour, cell proliferation was evaluated through MTT assay. Dose response curves were plotted and IC50 (half maximal inhibitory concentration) values for each ruthenium complex were determined.

**Results and discussions** All compounds induced a decrease in cell proliferation in a dose-dependent way. For breast cancer MCF-7 and HCC1806 cell lines the tetrachlorinated Ru(III) complex presents greater cytotoxicity (IC50 <4 µM) than the other compounds which have IC50 values between 10 and 20 µM. Similar results were observed for the colorectal cancer cell lines in the presence of the same complex (IC50 <4 µM) and, for the remaining compounds, IC50 values were between 15 and 30 µM. The tetrachlorinated Ru(III) complex is, consequently, the most promising, showing similar cytotoxic activity in all cell lines.

**Conclusion** All compounds revealed dose-dependent anti-proliferative effects. The tetrachlorinated Ru(III) complex was found to be the most promising, exhibiting high anticancer activity in all cell lines, namely in the HCC1806 and LS1034 chemoresistant cell lines.

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**PO-417 SYNTHESIS OF CU(II) COMPLEXES DERIVED FROM IMIDAZOLE AND CYTOTOXIC ACTIVITY EVALUATION AGAINST BREAST AND COLORECTAL CANCERS**

**Introduction** Despite the existence of new therapeutic options, breast (BC) and colorectal (CC) cancers remain the leading causes of cancer death and the most commonly diagnosed in worldwide. Studies have reported that imidazole derivatives show antitumour, antimicrobial, antibacterial, antifungal and antioxidant activities. Furthermore, recently it has been found that the association between imidazole ligands and copper increases their DNA binding affinity giving potential anticancer activity. Therefore, we synthesised three novel Cu(II) complexes using heterocyclic nitromidazole derivatives as ligands. The aim of this study is to evaluate the cytotoxic activity of these complexes in two BC and two CC cell lines.

**Material and methods** Nitroimidazole derived ligands containing cyclohexylamine, morpholine and piperidine and the respective Cu(II) complexes were synthesised. MCF-7, HCC1806, LS1034 and WiDr cell lines were cultured and grown in proper conditions. To evaluate the cytotoxic activity of these Cu(II) complexes on four cell lines, MTT colorimetric assay was used. Cells were seeded in 48 well-plates and then were treated with increasing concentrations of the complexes, from 0.5 to 200 µM. After 48 hour of incubation, medium was removed and MTT was added. Two hours later, isopropanol was added in order to dissolve formazan crystals. The