# 742: Chiral 6,7-bis(hydroxymethyl)-1H,3H-pyrrolo[1,2-c]thiazoles as anticancer agents against breast cancer MCF7 and HCC1806 cell lines

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**Material and Methods:** The Y79 retinoblastoma cell line was propagated. 14 Balb/c nu/nu nude female mice were injected subcutaneously with a suspension of $10\times10^6$ Y79 cells. Animals were divided on two groups. One control group with 7 animals not submitted to PDT and other group with 7 animals treated with a bromated hydroxyphenyl porphyrin, being injected intraperitoneally (2 mg/kg) when tumor reached 200 $mm^3$ of volume. After the injection of the photosensitizer the animals were protected from the light. After 48 hours, animals were irradiated with a Ceramoptec laser system. Animals were monitored daily and registered any signs of disease, during 12 days. After the follow up the animals were killed.
**Results:** Heterotopic animal model of RB has proved to be reproducible and of simple obtainment and monitoring. In control group we observed a solid round tumor. In the group of treated mice, after irradiation we observed a significant difference in tumor volume related to control group. We verified that treated tumors growth is slower and in several cases it diminished until total remission. This process is accompanied by the appearance of necrosis and scarring.
**Conclusions:** This model allowed to conclude that the photosensitizer used has a significative effect over the growth of RB xenotransplants. Therefore, we intend to continue this study in an orthotopic animal model of retinoblastoma. This work may contribute for the acceptance of PDT in treatment of retinoblastoma, giving a new option for managing this disease.
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***No conflict of interest.***

### 741 PARP-inhibitor PJ34 potentiates the anticancer effect of chiral 6,7-bis(hydroxymethyl)-1*H*,3*H*-pyrrolo[1,2-c]thiazoles against breast cancer cell lines

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**Background:** PARP-inhibitor PJ34 has proved its potential to enhance chemosensitivity of breast cancer (BC) cell lines. The association of PJ34 with newly synthesized compounds with the potential to target DNA aims to increase tumor cells sensitivity to combination treatment mediated by sustained DNA damage and inefficient DNA repair.
**Material and Method:** The *in vitro* cytotoxic effect of PJ34, pyrrolo thiazole derivative 1 **(PT1)** and pyrrolo thiazole derivative 2 **(PT2)**, alone or in combined therapy was evaluated in MCF7 and HCC1806 cell lines. Cell cultures were plated and incubated for 24 h to allow cell attachment. Exposure to PARP-inhibitor PJ34 at concentrations of 0.5, 2, 10 and 25μM was 30 minutes prior to **PT1** and **PT2** administration at concentrations ranging from 0.1 to 200μM. The metabolic activity was determined by MTT assay and the results allowed to calculate the $IC_{50}$ values, the concentration required to inhibit cell proliferation by 50%.
**Results:** The $IC_{50}$ of the single therapy with **PT1** and **PT2** is 1.9 and 86.2μM for the MCF7 and 73.7 and 26.4μM for the HCC1806 cell lines, respectively, at 48 h. In the MCF7 cell line, the association of 10μM of PJ34 with **PT1** reduced the $IC_{50}$ to 210nM ($p = 0.015$). Considering 72 h of incubation of the MCF7 cell line with **PT2** the $IC_{50}$ is 53.9, being significantly reduced to 17.6 and 7.3μM in combination with PJ34 2μM and 10μM ($p < 0.001$), respectively.
In the triple negative HCC1806 cell line, when the concentration of PJ34 is 10μM, the $IC_{50}$ values are 65.9 (**PT1**) and 28.6μM (**PT2**), after 48 h of incubation. However, at 24 h the $IC_{50}$ value of **PT1** is significantly reduced from 80.3 to 53.7μM (PJ34 2μM; $p = 0.005$) and to 50.5μM (PJ34 10μM: $p < 0.001$), while at 72 h with **PT2** there is a reduction from 51.3 to 19.1μM (PJ34 2μM; $p = 0.031$) and to 11.4μM (PJ34 10μM: $p = 0.012$).
**Conclusions:** The effect of 10μM of PJ34 combined with **PT1** has a 5-fold significant reduction of the $IC_{50}$ value to nanomolar scale at 48 h and with **PT2** at 72 h, in the MCF-7 cell line. In the HCC1806 cell line, PJ34 with **PT2** decreased the $IC_{50}$ values, comparing to single therapy with **PT2**, at 24 h, yet PJ34 with **PT1** decreased the $IC_{50}$ values only at 72 h. These results suggest that **PT1** and **PT2** may target the DNA, and its repair is mediated by PARP. We conclude that different compounds should be considered towards more promising therapy response taking into account the biology of different types of cancer.
***No conflict of interest.***

### 742 Chiral 6,7-bis(hydroxymethyl)-1*H*,3*H*-pyrrolo[1,2-c]thiazoles as anticancer agents against breast cancer MCF7 and HCC1806 cell lines

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**Background:** Small molecules are widely used in chemotherapy against DNA tumor cells. The current challenge is to find selective chemicals that induce DNA damage in cancer cells, thus preventing cell proliferation. Previously we showed great anti-tumor activity of compounds with 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole (**PT**) ring system, namely **PT1** (a derivative of PT) against MCF7 breast cancer cell line. With the aim of explore promising structure-activity relationship, the cytotoxic effect of newly synthesized compounds were evaluated *in vitro* against breast cancer (BC) cell lines MCF7 and HCC1806.
**Materials and Methods:** Metabolic activity was evaluated by the MTT assay after 24, 48, 72 and 96 h of exposure to several derivatives **PT2**, **PT3**, **PT4** or **PT5** in concentrations from 1 to 100μM, which allowed the calculation of $IC_{50}$. Further analysis of **PT1** and **PT4** was performed in order to evaluate cell viability, types of cell death, expression of Bax and Bcl2 and cell cycle. In order to determine the total protein variation SRB assay was performed. Possible DNA damage was assessed by the comet assay and long term survival was determined by the clonogenic assay.
**Results:** In MCF7 cell line the compounds **PT1**, **PT2**, **PT3**, **PT4** and **PT5**, had $IC_{50}$ values of 1.9, 0.54, 46.9, 86.2 and >100μM after 48 h of incubation, respectively. In HCC1806 cell line $IC_{50}$ values were 81.4, 63.1, 28.0, 26.4 and 41.7μM, respectively. In MCF7 cell line **PT1** induces cell cycle arrest in the S phase and cell death mostly by necrosis, no variation in the p53 expression and Bax/Bcl2 ratio. **PT1** decreases total protein production to 54.0±8.3% and the long term survival decreases to 25.8±1.8%. In HCC1806 cell line **PT4** reduces the long term survival to 1.40±0.3% and the total protein production decreases to 44.1±4.0%. **PT4** also induces a significant cell cycle arrest at the S phase and cell death mostly by necrosis, yet Bax/Bcl2 ratio is significantly augmented comparing to the control, however HCC1806 cell line does not express p53. In all treatments, for the concentrations tested, the comet assay showed no damage in the DNA.
**Conclusions:** **PT1** is the most promising compound in the MCF7 cell line, however in the triple negative HCC1806 cell line the new derivatives showed better activity, particularly **PT4**. The results allowed concluding that different chemical modifications should be considered towards more promising compounds taking into account the biology of different types of cancer.
***No conflict of interest.***

### 743 Gold nanoparticle conjugated lignan derivatives inhibited the proliferation of MCF-7 human breast cancer cells

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**Background:** In the last decade, phytoestrogen intake has considerable interest in relation to cancer prevention. Lignans are one of major structural classes of phytoestrogens as non-steroidal compounds. The anti-inflammatory and phytoestrogenic effects of lignans as well as their ability to inhibit proliferation render these compounds as important targets for cancer therapy. Gold nanoparticles (AuNPs) have been recently investigated for their interactions with cells since they are biocompatible materials. The aim of this study is to compare the antiproliferative effects of lignan derivatives, pinoresinol and lariciresinol with their AuNP-conjugated forms on breast carcinoma cells.
**Material and Methods:** AuNPs were synthesized by a chemical reduction method. AuNP was modified with a linking agent-thiolated β-cyclodextrin to achieve conjugation of AuNP and lignans. The human breast cancer cell lines MCF-7 (HTB-22) were treated with lignan derivatives lariciresinol and pinoresinol and their AuNP conjugated forms with concentrations ranging from $1\times10^{-4}$M to $1\times10^{-9}$M. The influence of lignan derivatives on MCF-7 cell viability was assessed using the MTT assay and the action of these compounds on cell proliferation was determined with bromodeoxyuridine (BrdU) assay.
**Results:** The AuNP conjugated forms of pinoresinol strongly inhibited the BrdU incorporation to the cells within the inhibition range was between 18.02% to 89.44% in descending sample concentration whereas it was 50.81% to 92.87% in free pinoresinol group. The inhibition of cell proliferation in AuNP conjugated lariciresinol group was also significantly higher than the free lariciresinol ($p < 0.05$). The cell viability was significantly decreased in both AuNP conjugated lignan groups as the results were 33.24% and 43.05%, respectively at $1\times10^{-4}$M dose.