EUROPEAN FEDERATION FOR MEDICINAL CHEMISTRY
SOCIETÀ CHIMICA ITALIANA - DIVISIONE DI CHIMICA FARMACEUTICA

European School of Medicinal Chemistry

(XXXVI Advanced Course of Medicinal Chemistry
and "E. Duranti" National Seminar for PhD Students)

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Urbino, June 26 - July 1

PROCEEDINGS OF PhD STUDENT POSTER SESSION

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NEW BENZOTHIAZOLAMINE DERIVATIVES AS INDUCERS OF AN EARLY APOPTOSIS IN MCF-7 HUMAN BREAST CANCER CELL LINE

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Background

Cancer is the second leading cause of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer-related deaths in 2012.[1] Current chemotherapy targets the proliferative advantage of tumor cells over healthy cells, but the lack of selectivity of chemotherapeutic agents usually leads to serious side effects. A major challenge in the development of effective and safe cancer treatment is to identify the agents that could affect cellular processes essential for, or greatly enhanced in, malignant cells only.

Aims

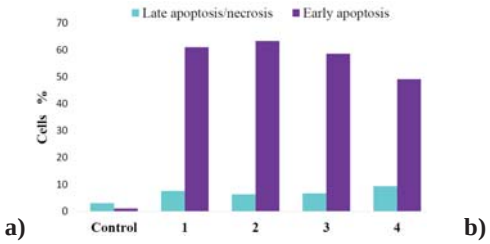
Benzothiazole derivatives represent a series of compounds of an undoubted interest because of the broad spectrum of biological effects associated with this scaffold.[2] In addition, benzothiazoles have attracted considerable attention in anticancer research and a lot of structural modifications on their core nuclei have been made to improve the antitumor activity. Therefore, we have synthesized novel benzothiazolamine derivatives and investigated their anticancer potential against MCF-7 human breast cancer cell line.

Methods

We have synthesized a series of novel benzothiazolamine carbamates and amides starting from 1-chloro-4-nitrobenzene and an appropriate alkylthiol,[3] followed by cyclization to benzothiazolamine and further derivatization of amino-group. The selected compounds were subjected to a panel of NCI-60 cell line for *in vitro* determination of antitumor activity. For better insight into possible mechanism of antiproliferative activity, we have examined the cell cycle phase distribution and apoptosis in MCF-7 human breast cancer cell line using flow cytometry methods, after treatment with synthesized compounds. Our research continued towards examination of our compounds' influence on the reactive oxygen species level, mitochondrial membrane potential, as well as cell cycle regulators.

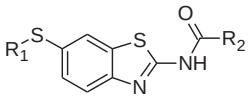
Results

The cell cycle phase distribution and apoptosis in MCF-7 human breast cancer cell line were investigated after exposure to IC_{50} concentrations, obtained *in vitro*, of four selected compounds (Figure 1.b) for 24 and 48 hours, respectively.



a)

b)



1) R_1= Pr, R_2= OPr
2) R_1= ^{i}Bu, R_2= OEt
3) R_1= ^{i}Bu, R_2= OPr
4) R_1= Pr, R_2= Bu

Figure 1. **a)** Apoptosis measured by bivariate Annexin V/PI flow cytometry in control cells and cells treated for 48 h with selected benzothiazolamine **(b)** derivatives

Using flow cytometry after PI staining we showed that our compounds affect cell cycle distribution in a time dependent manner. After 24 h treatment, the portion of cells in G2/M phase increased, suggesting cell cycle arrest in mitosis. After 48 hours, the number of sub G1 phase cells increased, which indicates apoptosis.
Following incubation with selected compounds for 48 hours, the proapoptotic effect was reflected by the increase of portion of early apoptotic cells up to 63 % measured by bivariate Annexin V/PI flow cytometry (Figure 1.a). Moreover, we observed the loss of mitochondrial membrane potential, which could indicate that our compounds promote apoptosis via the mitochondrial pathway in MCF-7 cells. In addition, reactive oxygen species level in MCF-7 cells significantly decreased after treatment with benzothiazolamine derivatives.

Conclusion

Benzothiazolamine carbamates and amides showed great potency for promoting highly specific programmed cell death apoptosis in MCF-7 cancer cell line. Further examination will eventually provide identification of molecular targets of benzothiazolamines. Our data offer a significant contribution to the search for medicinally active compounds and may lead to discovery of a new potent antitumor agent.

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