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EVALUATION OF UREA/THIOUREA DERIVATIVES AS ADJUVANTS IN CANCER CHEMOTHERAPY

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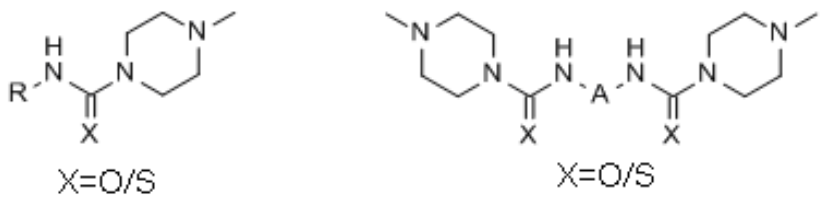
Malignant diseases present a significant burden to healthcare systems worldwide, the major types of cancers are the leading causes of death among the 18-64-year-old population [1,2]. The mortality associated with lung and colorectal cancer amid the EU countries is the highest in Hungary.[3] Combination chemotherapy as a viable treatment of various malignancies has been described in the clinical practice as well as in a research setting. The additional problem of cancer multidrug resistance (MDR) and tumour cell heterogeneity further confirms the relevance of multiple drug treatment.[4] The activity of urea, thiourea and selenourea derivatives against various cancer cell lines has been demonstrated by the literature.[5]

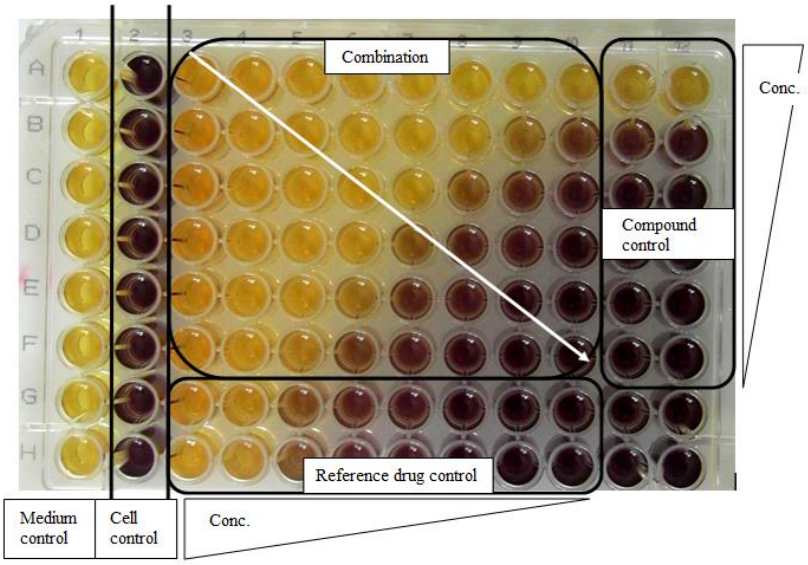
The aim of our study was to evaluate the efficacy of novel urea and thiourea derivatives (1-10) as anticancer agents in combination chemotherapy, using various *in vitro* model systems.

Figure 1.: General structure of the tested compounds (1-10)



The antiproliferative and cytotoxic activity of the compounds against tumoral and non-cancerous cell lines was assessed by MTT method, the inhibition of the MDR transporter P-glycoprotein (ABCB1) was studied by rhodamine 123 accumulation assay using flow cytometry [6,7]. A checkerboard microplate method was applied to evaluate the effect of drug interactions between the tested compounds and the reference drugs (doxorubicin, cisplatin, 5-fluorouracil, topotecan, methotrexate and verapamil), the interactions were categorized based on combination index (CI) values, using the Chou-Talalay method [8].

Figure 2.: Setup of the plates in the checkerboard combination assay



Apart from a benzyl-substituted thiourea-derivative, the tested compounds did not present potent cytotoxicity, while all derivatives showed moderate antiproliferative activity in the concentration range of 11.9-90.5 μM. The compounds were slightly selective towards the tumoral cell lines. The tested compounds did not show effectual efflux pump inhibitory activity in the tested concentrations. Some of the (thio)ureas showed favourable interactions with 5-fluorouracil (*pyrimidine-antagonist*) and verapamil (*efflux pump inhibitor*), while strong synergism was observed in relation to topotecan (*topoisomerase-I-inhibitor*) and doxorubicin (*topoisomerase-II-inhibitor*). In contrast, in case of cisplatin (*alkylating agent*) and methotrexate (*folate-antagonist*), antagonism was predominantly observed.

While the tested compounds did not show remarkable anticancer and efflux pump inhibitory activity, the ureas/thioureas presented potent synergistic activities with the anticancer drugs acting on the topoisomerase enzymes. The design of further experiments and the involvement of additional chemotherapeutic drugs are warranted to fully assess their potency as adjuvants.

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