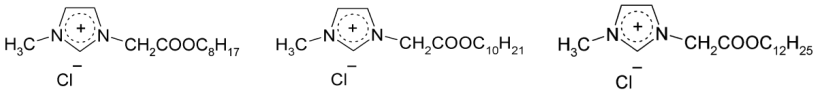
ASSESSMENT OF THE SELECTIVE CYTOTOXIC EFFECT OF LONG-CHAIN IONIC LIQUIDS ON HUMAN TUMOR CELL LINES

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The discovery of new pharmacological drugs for the treatment of cancer remains an urgent problem. In current oncological practice there are three main traditional methods of treatment of oncological pathology – surgical, radiation therapy and chemotherapy. Low efficacy and/or high toxicity of these traditional treatments of malignant tumors requires the search for new methods and new tools in the fight against oncogenesis. One of the promising areas in modern oncology is the investigation of new cytotoxic agents that will combine both, effective inhibition of the tumor progression and inactivity against non-malignant ones.

For the last decades, the attention of the pharmaceutical industry was drawn to ionic liquids (ILs) as a potential target in search of new therapeutic agents. ILs are currently widely used as antimicrobials with high cytotoxic activity and low toxicity. ILs possess flexible physicochemical properties due to their structure that can be easily modulated by a combination of various organic cations and organic or inorganic anions. An effective method of reducing the toxicity of ILs is their chemical functionalization through incorporation of polar functional groups (hydroxyl, carboxyl, ester, amide) into the alkyl chains [3-4]. The antitumor properties of ILs have not yet been studied in detail. The main research in this area is limited to assessing the effect of ILs on cell viability, and only a few reports show in-depth research. An in-depth understanding of the cellular mechanisms of the antitumor effect of ILs may favor the research of compounds with targeted antitumor activity and higher selectivity or can help to improve the existing chemotherapeutic agents.

In the current study, we demonstrate the effect of ester-functionalized imidazolim ILs with different alkyl chains (Fig. 1).



IL-1 **IL-2** **IL-3**

Fig. 1. Name and structures of test ILs

The cytotoxic effect was assessed on the cell lines of chronic human myelogenous leukemia K-562 (ATCC CCL-243), human neuroblastoma SK-N-DZ (CRL-2149). For the evaluation of compounds selectivity over cancer cells, human embryonic kidney cells HEK293 (ATCC CRL-1573) was used For the assessment of compounds growth inhibition effect, we used a colorimetric method that measures the metabolic activity of cells with a redox indicator – resazurin. Compounds were assessed at the final concentrations ranging from 0.46 μM to 1000 μM (8 points, 3-fold serial dilutions).

All test compounds showed a dose-dependent cytotoxic effect on both cancer cell lines K562 and SK-N-DZ (Fig. 2 and Table 1).

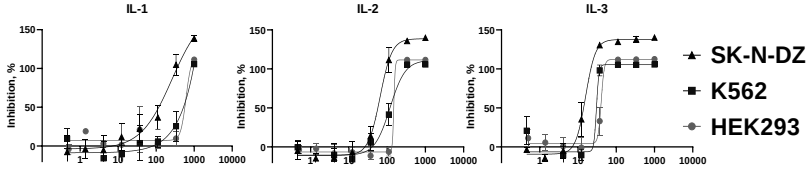


Fig. 2. Dose-response curves for test ILs in dose-response against SK-N-DZ, K562 and HEK 293 cell lines

Table 1. IC_{50} values (uM) for the compounds tested for cytotoxic effect against SK-N-DZ, K562 and HEK 293 cell lines

Compound name	HEK293(human embryonic kidney)		K562 (myelogenous leukemia cell line)		SK-N-DZ (neuroblastoma cell line)	
	IC50	HillSlope	IC50	HillSlope	IC50	HillSlope
IL-1	609.7	6.2	NA	NA	260.2	1.1
IL-2	149.7	24.2	119.2	2.2	65.6	2.8
IL-3	40.5	11.0	30.4	13.3	15.8	3.3

The obtained results indicated that long-chain imidazolium ILs comprising polar ester groups in the alkyl chains are promising objects for the development of new drugs with antitumor properties. It should be noted, that the ionic structure of ILs creates extremely wide opportunities for compounds with the optimal combination of high and/or anticancer activity and low cytotoxicity.

Literature

1. Burrell, Rebecca A., and Charles Swanton. "Tumour heterogeneity and the evolution of polyclonal drug resistance." Molecular oncology 8.6 (2014): 1095–1111.

2. R. Ferraz, L. C. Branco, C. Prudêncio, J. P. Noronha, Ž. Petrovski, ChemMedChem 2011, 6, 975–985.

3. Przestalski S., Sarapuk J., Kleszczyńska H., Gabrielska J., Hładyszowski J., Trela Z., Kuczera J. Influence of amphiphilic compounds on membranes. Acta Biochim Pol. 2000, 47:627-638.

4. Trush M., Metelytsia L., Semenyuta I., Kalashnikova L., Papeykin O., Venger I., Tarasyuk O., Bodachivska L., Blagodatnyi V., Rogalsky S. Reduced ecotoxicity and improved biodegradability of cationic biocides based on ester-functionalized pyridinium ionic liquids. Environ. Sci. Poll. Res. 2019, 26: 4878–4889.