SYNTHESIS AND ANTICANCER ACTIVITY OF 2-(1,3,5-TRIAZIN-2-YLMETHYLTHIO)-*N*-(IMIDAZOLIDIN-2-YLIDENE)-5-METHYL BENZENESULFONAMIDE DERIVATIVES

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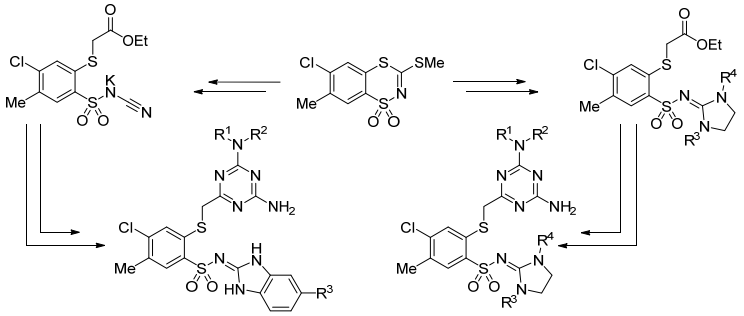
The project presents the synthesis of a series 2-(4-amino-1,3,5-triazin-2-ylmethylthio)-*N*-(imidazolidin-2-yl)benzenesulfonamide derivatives, which are hybrid structures of two pharmacophore fragments, i.e. 2,4,6-trisubstituted 1,3,5-triazine [1] and 2-mercaptobenzenesulfonamide (MBSA) [2-4] as new low molecular weight compounds with expected anticancer activity. The intended compounds were obtained in a multistep reaction, starting from 3-methylthio-1,1-dioxo-1,4,2-benzoditiazine, which was transformed into *N*-substituted 2-(ethoxycarbonylmethylthio)benzenesulfonamides, followed by cyclocondensation with the corresponding biguanide hydrochlorides in the MeONa/ MeOH lead to the target 2-(4-amino-6-R^1-1,3,5-triazin-2-ylmethylthio)-*N*-(imidazolidin-2-ylidene)-4-chloro-5-methyl benzenesulfonamide derivatives in moderate or good yields. Their structure was confirmed by spectroscopic methods (IR, ^{1}H, ^{13}C NMR), high resolution mass spectrometry (HRMS) and elemental analyse (C, H, N), and homogeneity – by TLC on silica gel and/or aluminum oxide.



Tests of in vitro anticancer activity was carried out using the MTT test against cell lines of cervical cancer (HeLa), colon cancer (HCT-116) and breast cancer (MCF-7), as well as non-cancer line of human keratinocytes (HaCaT) or human umbilical vein endothelial cell (HUVEC) confirmed the expected activity and selectivity against cancer cells.The highest sensitivity was found for the colon cancer line (HCT-116) against three compounds (IC_{50} = 6±0,1 μM). The cytotoxic activity of the remaining 20 out of 57 tested compounds was in the IC_{50} range of 7-16 μM. The selectivity of the most active compounds ($IC_{50} \leq 10$ μM) was confirmed by the selectivity index expressed as the ratio of IC_{50} HaCaT / IC_{50} HCT-116 was in the range of 4-8. Based on the molecular docking of the most active compounds, the hypothetical molecular target (Mdm-2 protein, pdb: 1RV1) was indicated.

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[1] *Liu B., Sum T., Zhou Z., Du L., Med. Chem. 2015; 5(3): 131-148.*

[2] *Sławiński J., Polish J. Chem. 2001;75:1309-1316*

[3] *Sławiński J., Polish J. Chem. 2002;76: 937-944.*

[4] *Sławiński J., Brzozowski Z., Eur. J. Med. Chem. 2006; 41: 1180-1189*