SYNTHESIS AND HDAC INHIBITORY ACTIVITY OF PYRIMIDINE-BASED HYDROXAMIC ACIDS

V. Jakubkienė[1*], G. E. Valiulis[1], M. Žvirblis[1], G. Žvinys[1], A. Zubrienė[2], D. Matulis[2]

[1] *Institute of Chemistry, Faculty of Chemistry and Geosciences, Vilnius University, Naugarduko 24, 03225 Vilnius, Lithuania;*

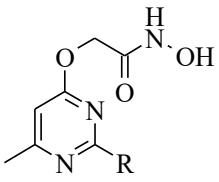
[2] *Institute of Biotechnology, Life Sciences Center, Vilnius University, Saulėtekio 7, 10223 Vilnius, Lithuania.*

**E-mail: virginija.jakubkiene@chf.vu.lt*

Pyrimidines represent an important group of heterocyclic compounds exhibiting broad spectrum of biological activity [1]. Pyrimidine moiety is a building block for several new drugs introduced to the market every year. Dabrafenib mesylate was approved in 2013 for the treatment of metastatic BRAF-mutant melanoma; macitentan and riociguat – for the treatment of pulmonary arterial hypertension; sofosbuvir – for the treatment of the hepatitis C virus across several genotypes [2]. On the other hand, compounds with moiety of hydroxamic acid serve as antibacterial [3], anti-inflammatory [4], anticancer [5], and other therapeutics. It is also known that pyrimidine-based hydroxamic acids possess diverse biological activities, for example, histone deacetylases (HDACs) inhibitory activity [6]. HDACs are promising targets for anticancer drug discovery and development [7].

Commonly, hydroxamic acids are prepared by coupling activated carboxylic acids with O/N-protected hydroxylamine [4] or by treatment of carboxylic acid esters with hydroxylamine [8, 9].

In consideration of diverse biological properties of this type of compounds and in continuation of our interest in the synthesis of biologically active heterocycles, a series of pyrimidine-based hydroxamic acids **1**, **2** was prepared and evaluated as inhibitors of HDAC8.



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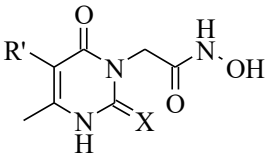

2

R: OH, SCH_3, SC_2H_5, $N(CH_3)_2$, , $NHCH_2CH{=}CH_2$, $NHCH_2C_6H_5$; R': H, Br; X: O, S.

The binding affinity of tested compounds towards HDAC8 was measured by fluorescent thermal shift assay.

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