SYNTHESIS OF PYRIMIDINES BEARING HYDROXAMIC ACID AND 1,3,4-OXADIAZOLE-2-THIONE MOIETIES AS POTENTIAL HDAC INHIBITORS

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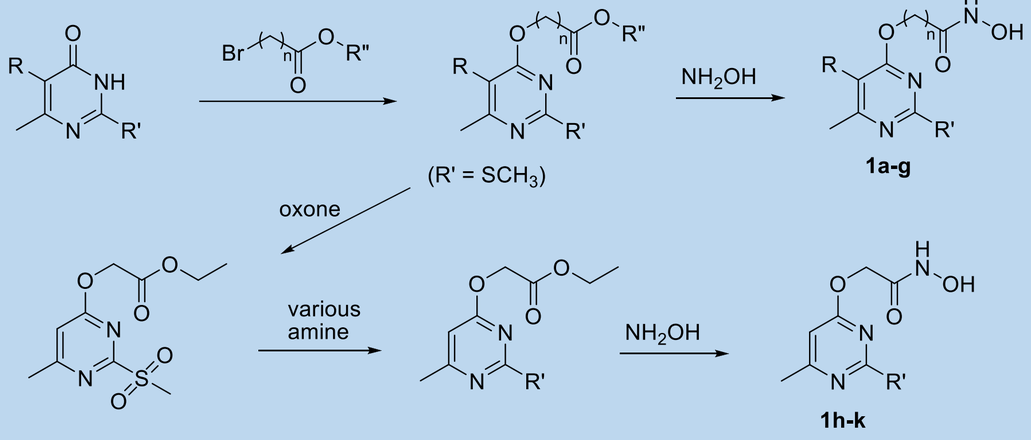
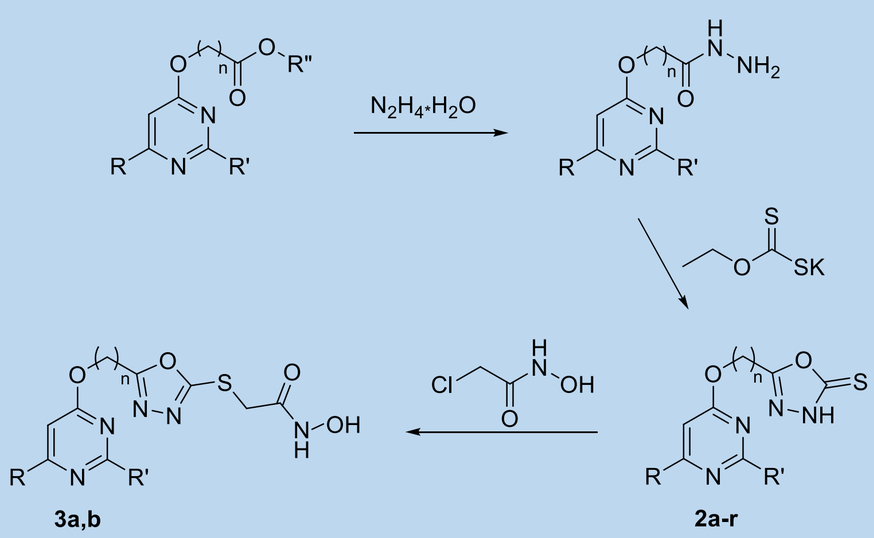
Introduction

Histone deacetylases (HDACs) are a family of enzymes that modulate the acetylation of histones and non-histone proteins. HDACs play an essential role in many biological processes such as gene regulation, transcription, cell proliferation, angiogenesis, migration, differentiation and metastasis [1]. HDACs have been proven to be promising therapeutic targets for cancer treatment, particularly of hematological malignancies, based on the successful clinical approval of six HDAC inhibitors to date: vorinostat, romidepsin, belinostat, panobinostat, pracinostat, and chidamide [2]. Pyrimidines are widely spread in nature and occupy an exclusive place, mainly due to their importance for living organisms and wide range of biological activities of their derivatives [3, 4]. Pyrimidine moiety is a building block for several new drugs introduced to the marked every year [5]. In this context and continuing our work dedicated to the development of efficient methods for the synthesis of functionalized pyrimidines [6, 7], we present herein the synthesis of pyrimidine-based hydroxamic acids 1a–k, 3a,b and 1,3,4-oxadiazole-2-thiones 2a–r.

Synthesis of compounds 1a–k



Synthesis of compounds 2a–r and 3a,b



Conclusions

A novel series of pyrimidine derivatives with hydroxamic acid and 1,3,4-oxadiazole-2-thione moieties were synthesized.

Several compounds were micromolar HDAC inhibitors. Compound 2d can be used as lead compound for design of more potent HDAC8 inhibitor.

References

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4. E. De Clercq, G. Li. Clin. Microbiol. Rev. **29** (2016) 695.
5. H. X. Ding, C. A. Leverett, R. E. Kyne (Jr.) K. K.-C. Liu et al. Bioorg. Med. Chem. 23 (2015) 1895.
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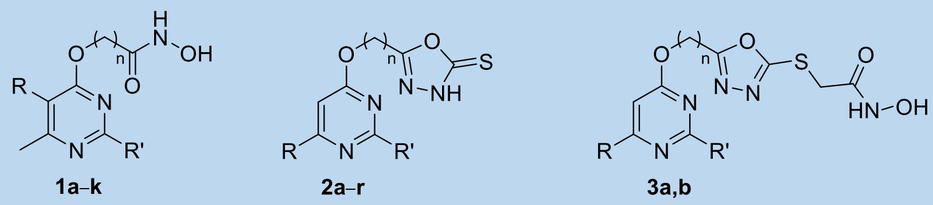
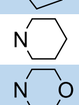
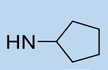
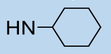
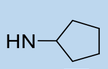
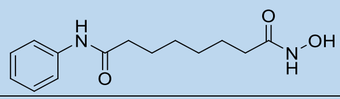
Inhibitory activities of synthesized compounds against HDAC4 and HDAC8



Compound	R	R'	n	IC_{50}, μM	
				HDAC4	HDAC8
1a	H	SC_2H_5	1	≥ 100	13
1b	H	SCH_3	1	38	28
1c	H	SCH_3	3	> 50	5.65
1d	H	SCH_3	5	> 50	2.05
1e	C_3H_7	SCH_3	1	38	1.4
1f	C_3H_7	SCH_3	3	> 35	2.4
1g	C_3H_7	SCH_3	5	16.6	1.2
1h	H	$NHCH_2CH{=}CH_2$	1	≥ 100	15
1i	H	$NHCH_2C_6H_5$	1	≥ 100	14
1j	H	$N(CH_3)_2$	1	≥ 100	35
1k	H		1	≥ 100	13
2a	CH_3	SCH_3	1	> 35	> 35
2b	CH_3	SCH_3	4	> 35	> 35
2c	CH_3		1	> 35	> 35
2d	CH_3		1	> 35	0.51
2e	CH_3		1	> 35	> 35
2f	CH_3	$NHCH_2C_6H_5$	1	> 35	9.6
2g	CH_3		1	> 35	12.49
2h	CH_3	$N(C_4H_9)_2$	1	12.57	> 35
2i	CH_3	NHC_4H_9	1	> 35	> 35
2j	CH_3		1	> 35	19.23
2k	CH_3		1	> 35	> 35
2l	C_3H_7		1	> 35	> 35
2m	C_3H_7		1	28.6	> 35
2n	C_3H_7	$N(C_4H_9)_2$	1	4.19	> 35
2o	C_3H_7	NHC_4H_9	1	> 35	> 35
2p	C_3H_7		1	24.59	6.8
2r	C_3H_7		1	> 35	> 35
3a	CH_3	SCH_3	1	> 50	> 50
3b	CH_3	SCH_3	4	> 35	12.7
Vorinostat				27*	5.3*

*Kleinschek, A., et al. *ChemMedChem*. **2016**, 11, 2598–2606.