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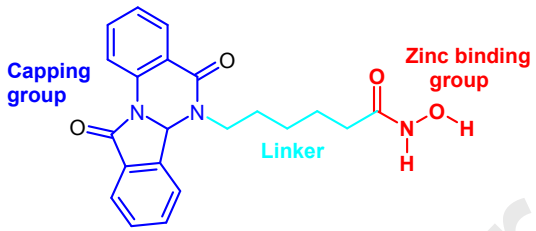

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Synthesis of new quinazoline-containing hydroxamic acids as potential HDAC/VEGFR inhibitors. Unusual rearrangements with pyrrolidone ring opening and dehydration of 3-N-hydroxyquinazoline fragment containing tetracycles.

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ABSTRACT

Synthesis pathways were developed and new hydroxamic acids were obtained as potential inhibitors of HDAC/VEGFR2, including tetracycles containing quinazolinone fragment as a "cap". Further biological testing of the obtained compounds will give an opportunity to estimate the real prospects of the chosen research direction.

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1. Introduction

One of the most promising strategies for the treatment of cancer, autoimmune and some neurodegenerative diseases is the use of targeted drugs. The basis of targeted therapy is the presence of a target in the cellular signaling pathway, which can be affected by applying a substance with a high degree of affinity to this target. To expand the arsenal of already known targeted drugs, many new compounds are synthesized and studied in the world. Among them the derivatives of quinazoline as well. They are known to have a number of important pharmacological effects and can be found as part of more than 100 drugs: antibiotics[1], pacemakers[2], vasodilators[3] and analgesics[4]. In addition, these derivatives actively inhibit the proliferation of tumor cells[5].

In the last decade, there are methods that develops rapidly to overcome multiple drug resistance (MDR) of malignant tumors, by creating a hybrid multi-functional inhibitors[6-9], combining two or more multidirectional ligands in one molecule, which are able to suppress tumor growth by different mechanisms. For example, hybrid inhibitors of histone deacetylase (HDAC) in combination with inhibitors of receptors of vascular endothelial growth factor[10,11] VEGFR2, multi-functional inhibitors of EGFR/HER2/HDAC[12-14], HDAC/TUBULINE[15] and others[5,16-18]. Most HDACi have a three-component structure consisting of a zinc-binding site (zinc binding group, ZBG), a linker, capable of occupying the enzyme channel, and a functional group interacting with amino acid residues at the entrance to the active HDAC center ("cap", capping group) (figure 1).

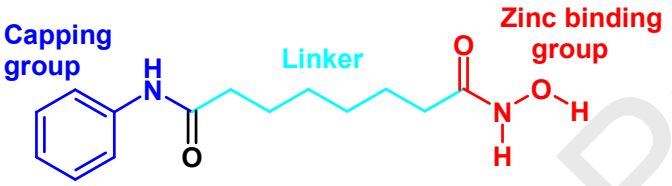

Figure 1. Pharmacophore structure of HDACi on the example of the drug Vorinostat.

A lot of research has been done to find different "caps" for HDACi. In particular, it is shown that the quinazoline cycle can act as an effective domain of surface interaction ("cap") with active sites of HDAC[19-23], matrix metalloproteinases[24,25] (MMPs) peptide deformylase[26] (PDF), and as novel inhibitors[10,11,27-29] of VEGFR–2.

2. Main

In this study, a number of new hydroxamic acids, which are connected through a linker with polycondensated heterocycles containing a quinazolinone fragment, are synthesized. Such bulk "caps" may become suitable structures for interaction with active HDAC sites and inhibit VEGFR2 receptors as well.

2.1. Synthesis

The synthesis of derivatives of quinazolinone by interaction of amides of anthranilic acid with appropriate aldehydes. Applying this methodology in present work, 6aH-isoindolo[2,3-a]quinazoline-5,11-diones and their 6-hydroxy-analogues were synthesized by the interaction of anthranilamides and 2-amino-N-hydroxybenzamides with 2-formyl benzoic acids. By further alkylation and treatment of the obtained esters with hydroxylamine we wanted to obtain target derivatives of hydroxamic acids connected to dihydroquinazolinone containing condensed tetracycles as a "caps" (figure **2**).

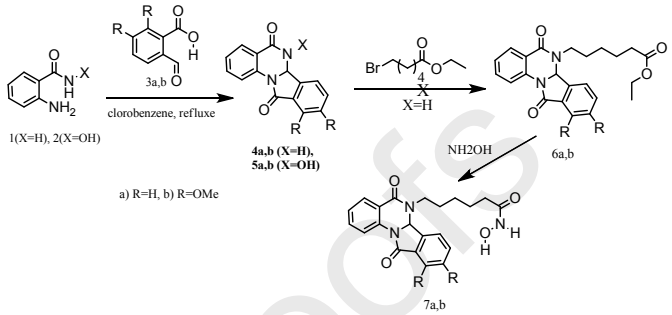

Figure 2. Scheme of synthesis of tetracyclic derivatives of hydroxamic acids.

It was found that the synthesis of quinazoline-containing tetracycles proceeds smoothly with high yields when anthranilamides **1** and **2** boils in chlorobenzene with 2-carboxybenzaldehyde **3a** and **3b**. The methods of synthesis, yield and physico-chemical data of the obtained tetracyclic amides **4a,b** and its hydroxy analogs **5a,b** are given in supplementary information.

Subsequently, it was unexpectedly discovered that amides **4a,b** in classical alkylation[31] conditions (RT, K_2CO_3 or Cs_2CO_3/DMSO or DMF) do not lead to esters **6a,b** (products of normal N-alkylation). When these processes carrying out with heating (80-100°C) uninterpretable mixture of products are obtained.

The cyclic hydroxamic acids **5a, b** under the same conditions are alkylated with ethyl 6-bromohexanoic acid giving low yield of esters **8a,b**. In the latter case, in a detailed analysis of the reaction mixtures, it was found that, along with the corresponding esters **8a,b**, they contain compounds with acidic functions, which were easily separated in crystalline form upon neutralization of the mother liquor with hydrochloric acid. A physicochemical study of the obtained acids showed that they have the structure of compounds **9a,b**. It is indicated by proton signals in the ^{1}H NMR spectrum and masses in mass spectra, as well as by comparison with known literature data[31, 32].

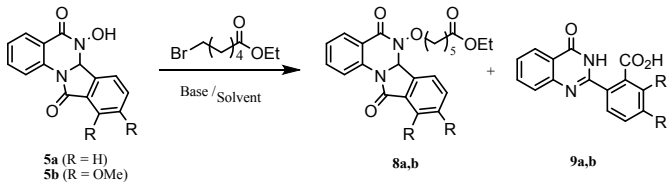

Figure 3. Scheme of the transformations of the tetracyclic hydroxamic acids **5a,b** in the compounds **8a,b** and **9a,b**.

By changing the conditions of alkylation reactions (the ratio of reagents, reaction temperature, solvents, etc.), we tried to direct the reaction towards the selective formation of target products **8a,b** (see table **1**). Determined that when reaction is carried out without alkylhalogenide (figure **4**) cyclic hydroxamic acid **5a** turns into the compound **9a** with almost quantitative yield (TLC of reaction mixture after the completion of the process indicates the absence of a spot of compound **5a** and the presence of a single product **9a**). By replacing potassium carbonate with cesium carbonate and carrying out the reaction in DMF at standard conditions we managed to direct the reaction towards the formation of the desired compounds **8a,b** with a sufficiently high selectivity (63% and 74%, respectively; see table **1**).

The compounds **9a,b** occurs is due to the opening of the pyrrolidinone tetracycle fragment under the action of a strongly basic solution (almost super-basic solution) with sequential dehydration and hydration or vice versa according to the scheme:

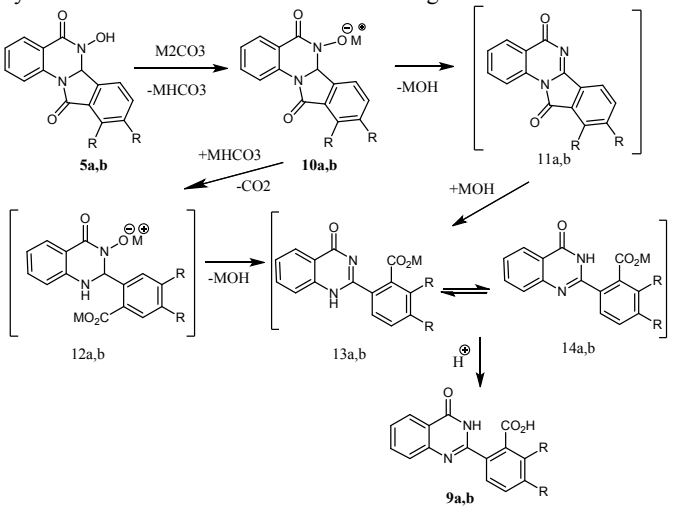

Figure 4. Probable directions for deriving by-products **9a,b**.

As noted above, the direct alkylation of amides **4a,b** didn't lead to positive results and for the synthesis of compounds **7a,b** we had to design another way, consisting in the initial preparation of anthranilamide, corresponding to the amino acid ester, followed by the construction of tetracycles **6a,b** with the already replaced amide group in the "one-pot" reaction:

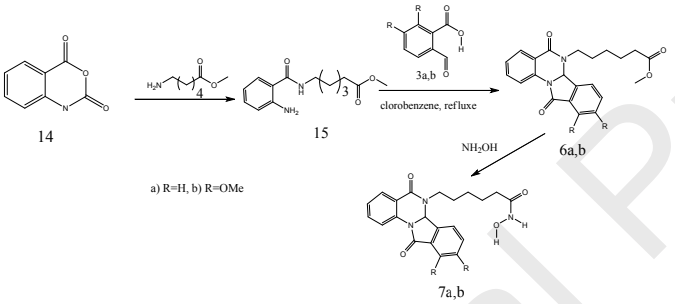

Figure 5. Scheme of the synthesis of the tetracyclic hydroxamic acids **7a,b**.

It should be noted that the implementation of this pathway was very successful and the target products **7a,b** (hydroxamic acids bound through a linker with a tetracycle containing a quinazolinone fragment) were obtained with satisfactory total yields (70-80%) and with high purity (more than 96% by LSMS).

Conclusion

Thus, in the course of research, synthesis pathways were developed and new hydroxamic acids were obtained as potential inhibitors of HDAC/VEGFR2, including tetracycles containing quinazolinone fragment as a "cap". Further biological testing of the obtained compounds will give an opportunity to estimate the real prospects of the chosen research direction.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/

№ exp.	Initial tetracycle	Molar ratio of *1: 2: Base	Base	Temp., °C (Time, h)	Solvent	Yield, % 8 (a or b)	Yield, % 9 (a or b)
1	5a	1.05: 1: 2	K_2CO_3	RT (16), 75 (2)	DMSO	35(**a**)	57(**a**)
2	5b	1.10: 1: 2	K_2CO_3	RT (23)	DMSO	16(**b**)	63(**b**)
3	5b	1: 1.15: 1	$NaH_{60\%\ (in\ oil)}$	RT (50)	DMF	48(**b**)	24(**b**)
4	5b	1: 1.5:1.25	Cs_2CO_3	RT (9)	DMF	74(**b**)	-**
5	5a	1: 1.5:1.25	Cs_2CO_3	RT (20)	DMF	63(**a**)	-**
6	5b	1: 1.5:1.25	K_2CO_3	RT (6)	DMF	55(**b**)***	13(**b**)
7	5a	1: 0: 2	K_2CO_3	70 (1)	DMSO	-	83(**a**)

* **1** – compound **5a** or **5b**; **2** – ethyl 6-bromohexanoate
** Compound **9** by TLC was observed in the mother liquor (didn't isolate)
*** + **1:1** mixture of compounds **8b** and **9b** (not separated from each other)

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