Synthesis of thio- and selenohydantoins and complexes based on them with potential anticancer activity

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Relevance of the research topic and degree of development. The discovery of the anticancer properties of cisplatin in 1965 led to the development of numerous metal-containing drugs for the treatment of malignant neoplasms. However, the widespread and safe use of platinum-containing drugs is limited by dose-dependent side effects and, in addition, hereditary or acquired resistance to therapy with such drugs. It can be expected that coordination compounds based on endogenous metals Cu (II), Co (II), Zn (II), Fe (II) will become less toxic compared to platinum analogues. Based on this, detailed studies in the field of synthesis of metal complexes with organic polydentate ligands and the identification of the spectrum of their physiological activity in the human body in recent decades have become the basis for the development of strategies for the creation of new drugs and the search for acceptable experimental methods of synthesis.

Based on substituted 2-thiohydantoins, new types of antibacterial drugs are synthesized, to which microorganisms demonstrate low resistance even at low concentrations; thiohydantoins can also act as herbicides and fungicides .

Complex compounds of transition metals with a 2-thiohydantoin type ligand exhibit greater antitumor activity. In turn, 5-substituted thiohydantoins also exhibit various types of pharmacological activity, including anticonvulsant, antithrombotic and antitumor.

Such systems, we believe, are of great interest not only in the field of pharmacy, but also in a number of other areas far from pharmacy, since the introduction of a transition metal ion into supramolecular crystalline systems gives such systems the optical, conductive and magnetic properties of the introduced ion, which makes the created materials are promising for use not only in pharmacy, but also in nonlinear optics, as conductors and ferromagnets.

Consequently, the development of methods for the preparation of coordination compounds based on functionalized derivatives of 2-thioxo-tetrahydro-4H-imidazol-4-ones, 2-alkylthioimidazolin-4-ones and 2-aminoimidazolin-4-ones and their seleno analogues, as well as the study of their physico-chemical properties and biological activity is an urgent task.

Goals of work. The objectives of this dissertation are: Synthesis and identification of biologically active compounds in a series of ligands and metal complexes, where the ligands are derivatives of 2-thioxo-tetrahydro-4H-imidazol-4-ones, 2-alkylthioimidazolin-4-ones and 2-aminoimidazoline-4-ones and their selenium analogues.

Tasks solved in the course of achieving the goal. 1) Development of synthetic approaches to the preparation of 2-thio(seleno)hydantoins containing pyridine substituents in the 5-position; 2) Study of the possibility of alkylation of such 2-thiohydantoins to obtain a series of bi- and tetradentate N-, S-containing ligands and study of the features of the reaction mechanism leading to high stereospecificity of the formation of the desired products; 3) Study of complex formation reactions of the obtained compounds with salts of a number of metals and study of the molecular and crystal structure of the synthesized complexes by X-ray diffraction analysis; 4) Study of the

physicochemical characteristics of ligands and their complexes using IR , NMR spectroscopy and mass spectrometry and quantum chemical modeling of node structures; 5) Study of the cytotoxic activity of the obtained compounds in in vitro on cell cultures of various origins: A549, VA 13, MCF-7, HEK293T.

Scientific novelty. 1) New and optimized known methods for the directed synthesis of 2-thioxotetrahydro-4H-imidazol-4-ones, 2-aminoimidazolin-4-ones have been proposed; 2) A preparatively convenient lick reaction between an azide and an alkyne was proposed for the introduction of vector fragments into the 3rd position of the thiohydantoin ring, which made it possible to obtain **7** 5-(*Z*)-pyridylmethylene-substituted-2-thiohydantoins **16–22** containing in the third position of the thiohydantoin ring alkyl azide and propargyl moieties; 3) Based on the analysis of the IR and NMR spectra, the high lability of the electronic system of the thiohydantoin cycle is shown, leading to a change in the force constant bonds. The change in the position of the band 1660-1690 cm^{-1} in amides strongly depends on the substituents at the nitrogen atom, and alkylation of the sulfur atom leads to an increase in the aromaticity of the ring and a weakening of the C=O bond; 4) A method has been proposed for the synthesis of new bis (seleno- and imidazolone) derivatives containing alkyl and aromatic substituents at the N(3) atom of the ring; 5) Assessment of the cytotoxicity of the obtained 5-alkyliden- and 5-arylidene-substituted compounds based on dimerized 2-selenohydantoins using cellular lines A549, VA 13, MCF-7, HEK293T identified a number of promising compounds that require further study; 6) It was shown for the first time that the electrostatic interaction of the centroids of the NEP of bromine and sulfur atoms leads to a significant deformation of the bond angles of the complexing agent atom, expressed in a change in the square (planar) coordination of the copper atom to tetrahedral; 7) In the thiohydantoin complexes in the crystalline state, the phenomenon of conformational chirality; 8) For the first time, the reasons and details of the condensation mechanism leading to the formation of one of two probable stereoisomers have been established.

The following provisions are submitted for defense: 1) Optimization and modification of the structure of new substituted biologically active compounds based on derivatives of 2-thioxo-tetrahydro-4H-imidazol-4-ones, 2-alkylthioimidazolin-4-ones and 2-aminoimidazolin-4-ones and their selenium analogues and synthesis of complex compounds with transition metals and synthesized compounds as ligands; 2) The nature of the stereospecificity of the formation of condensation products of thio- and selenohydantoins with pyridylaldehyde; 3) Features of the crystal packing of conformationally isomeric compounds in the series of thiohydantoins; 4) The existence of molecular coordination compounds of different valences in the series of thiohydantoins; 5) Biological activity of derivatives of 2-thioxo-tetrahydro-4H-imidazol-4-ones, 2-alkylthioimidazolin-4-ones and 2-aminoimidazolin-4-ones, their selenium analogues.

Theoretical and practical significance of the work. Using quantum chemistry methods of structural calculations, the reasons for the stereoselectivity of condensation of thiohydantoins with functionally substituted aldehydes were substantiated for the first time, which expands our understanding of the details of the mechanism of condensation at the active methylene group - the

solvents used take part in the formation of the reaction complex. The boundaries of use have been expanded click reactions of derivatives of 2-alkylthio-5-(pyridylmethylene)imidazolin-4-ones.

The complex formation of the resulting ligands with copper(II) bromide was studied to obtain binuclear coordination compounds containing atoms of the coordinating metal in different oxidation states, which introduces new data into the mechanisms of functioning of copper-containing oxidases.

The cytotoxicity of a number of the obtained substances was studied and the prospects for the development of work in the direction of both the synthesis of new compounds and the synthesis of metal complexes with such ligands were shown. This part of the work was carried out jointly with Ph.D. Skvortsov D.A., Department of Chemistry of Natural Compounds, Faculty of Chemistry, Moscow State University.

The previously demonstrated ability of the structure of the binuclear Cu (II),(I) coordination compound based on 2-alkylthioimidazolin-4-one to penetrate the cell membrane and accumulate in the cell nucleus has been expanded by the synthesis of a new complex based on copper dibromide. This result opens up the possibility of obtaining selective DNA-interacting drugs.