ABSTRACT

of the dissertation for the degree of Doctor of Philosophy (PhD) in the specialty 6D072100 - "Chemical technology of organic substances"

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on the topic: "Synthesis and some transformations of new compounds based on N-, O-containing heterocycles"

Relevance of the research topic

This work is devoted to the development of a technology for the preparation and some transformations of new compounds based on N-, O-containing heterocycles – 3,5-substituted tetrahydropyranone and β-aminopropioamidoximes – and the search for biologically active compounds.

Among the variety of heterocycles, a number of compounds that potentially have pharmaceutical activity can be distinguished. O-containing heterocycles - tetrahydropyran-4-ones and their derivatives belong to the simplest, widely studied and used in medicine classes of heterocyclic compounds, which are building blocks for the synthesis of compounds with biological activity. Tetrahydropyran-4-one cycles, oximes, and Schiff bases derived from them have been found in biologically active natural compounds. Schiff bases are universal ligands that are synthesized by the condensation of primary amines with carbonyl groups. Most of them exhibit antibacterial, antifungal, and antitumor activity. On this basis, PASS prediction of the spectrum of biological activity of these compounds, as well as products of arylsulfochlorination of non-ionic β-aminopropioamidoximes, will make it possible to identify the most promising areas for testing new compounds. Predicting their toxicity and bioavailability will make it possible to draw a conclusion about the feasibility of their further testing and recommendations for their modification.

Among the new drugs approved by the FDA in 2021, almost 50% are substances with nitrogen-containing heterocycles. It is known that the sulfochlorination of amidoximes with six-membered N-containing heterocycles gives stable acylation products at the oxygen atom of the amidoxime group; at the same time, the reaction of sulfochlorination of derivatives of primary amidoximes can, depending on the structure of the starting amidoxime and the reaction conditions, leading to rearrangement products with the formation of ureas and substituted cyanamides. The formation of salts with a fragment of 1,5-diazaspiro-1-en-5-ium, obtained by arylsulfochlorination of β-aminopropioamidoximes, expands the understanding of the chemistry of amidoximes, and the resulting products have a great synthetic potential due to the enantiomeric advantage, regioisomeric composition, reactivity and tautomeric transformations. Previously, among the products obtained as a result of transformations of β-aminopropioamidoximes, compounds with complex anti-tuberculosis and anti-diabetic activity were isolated. The biological activity of pyrazoline compounds is well known, and therefore, in medicinal chemistry, the pyrazoline cycle is the subject of numerous structural modifications. Conducting *in vitro* tests of the antituberculous and antidiabetic activity of arylsulfo derivatives of β-aminopropioamidoximes obtained in this work should provide new samples with valuable biological properties.

Purpose of the work: development of a technology for obtaining new N-, O-containing heterocycles based on 3,5-substituted tetrahydropyran-4-one and arylsulfochlorination products of a number of β-aminopropioamidoximes and *in silico* and *in vitro* search for biologically active compounds.

Tasks:

1. Conduct research on the conditions for obtaining 3,5-dimethylenoxytetrahydro-4H-pyran-4-one and its derivatives – oxime, ether and Schiff bases;
2. Conduct research on the conditions for obtaining products of arylsulfochlorination of a number of β-aminopropioamidoximes;
3. Perform quantum-chemical studies of 3,5-dimethylenoxytetrahydro-4H-pyran-4-one and its derivatives, as well as the products of arylsulfochlorination of β-aminopropioamidoximes;
4. Perform computer prediction of the spectrum of biological activity of new compounds;
5. Perform tests analysis for antidiabetic activity and study of the bactericidal activity of the products of arylsulfochlorination of β-aminopropioamidoximes;
6. Present technological schemes for obtaining new promising compounds and calculate the material balance of production.

Research methods: Fine organic synthesis, IR and NMR spectroscopy, elemental analysis and microbiological screening for *in vitro* anti-tuberculosis activity on drug-susceptible (DS) and MDR strains of M. tb and *in vitro* anti-diabetic screening for α-amylase and α-glucosidase activity, *in silico* prediction of bioavailability and spectrum of biological activity, quantum chemical calculations by DFT at the B3LYP/6-31G++(d,p) level.

The main provisions for defense:

1. The formation of 3,5-dimethylenoxytetrahydro-4H-pyran-4-one by the interaction of acetone with formaldehyde under alkaline conditions has been established. It was found that the addition of potassium carbonate and heating the reaction mixture to 35°C leads to an increase in the yield of the product. The interaction of 3,5-dimethylenoxytetrahydropyran-4-one with hydroxylamine hydrochloride in the presence of pyridine leads to the formation of an oxime, the reaction of the latter with propionyl chloride yielded its tripropionate. The best yield of oxime at was obtained in the presence of sodium acetate at 75°C. The interaction of 3,5-dimethylenoxytetrahydro-4H-pyran-4-one with a number of amines - butylamine, 2-aminoethane-1-ol, aniline, o-toluidine, benzylamine - leads to the formation of Schiff bases.
2. The formation of 2-amino-1,5-diazaspiro[4.5]-dec-1-en-5-ammonium arylsulfonates was established under the conditions of arylsulfochlorination of a number of β-aminopropioamidoximes (with an N-containing heterocycle in the β-position); in the case of β-(benzimidazol-1-yl)propioamidoxime, the product was obtained at the oxygen atom of the amidoxime group; o-nitrobenzenesulfochlorination of β-(thiomorpholin-1-yl)propioamidoxime regioselectively at r.t. with the formation of two salts of spiropyrazolinium (ortho-

nitrobenzenesulfonate and chloride) and regiospecifically at b.p. solvent when only chloride is formed.

3. New compounds (2-amino-1,5-diazospiro[4,5]dec-1-en-5-ammonium tosylate, 3-(1H-benzo[d]imidazol-1-yl)-N'-(tosyloxy)propanimidamide, 2-amino-8-thio-1,5-diazospiro[4,5]dec-1-en-5-ammonium 4-nitrobenzenesulfonate and 3-(1H-benzo[d]imidazol-1-yl) -N'-(((4-nitrophenyl)sulfonyl)oxy)propane-imidamide) show in vitro α-glucosidase inhibition activity higher than that of the reference drug acarbose.

4. *In silico* assessment of the potential biological activity of new compounds based on 3,5-dimethylenoxytetrahydro-4H-pyran-4-one and arylsulfochlorination products of a number of nonionic β-aminopropioamidoximes shows their potential significance as leading compounds in the search for biologically active compounds.

Scientific novelty and main results of the study

For the first time, systematic studies were carried out to study the conditions for the synthesis of 3,5-dimethylenoxytetrahydro-4H-pyran-4-one and the synthesis of new compounds - oxime, ether, Schiff bases based on it was carried out.

For the first time, arylsulfochlorination of a number of β-aminopropioamidoximes was carried out to obtain 2-amino-1,5-diazaspiro[4.5]-dec-1-en-5-ammonium arylsulfonates and substitution products at the oxygen atom of the amidoxime group.

A theoretical study of the processes of arylsulfochlorination of β-aminopropioamidoximes was carried out on the basis of an assessment of the thermodynamic parameters of the corresponding reactions, an analysis of the HOMO–LUMO of the molecular structures of the reaction products by quantum chemistry methods.

For the first time, antidiabetic screening of the obtained products of arylsulfochlorination of a number of β-aminopropioamidoximes was carried out, which revealed promising samples (2-amino-1,5-diazospiro[4,5]dec-1-en-5-ammonium tosylate, 3-(1H-benzo[d]imidazol-1-yl)-N'-(tosyloxy)propanimidamide, 2-amino-8-thio-1,5-diazospiro[4,5]dec-1-en-5-ammonium 4-nitrobenzenesulfonate and 3-(1H-benzo[d]imidazol-1-yl)-N'-(((4-nitrophenyl)sulfonyl)oxy)propane-imidamide) with in vitro α-glucosidase inhibition activity higher than that of the reference drug acarbose.

For the first time, computer prediction of bioavailability and spectrum of biological activity for new compounds, derivatives of 3,5-substituted tetrahydropyran-4-one and non-ionic derivatives of β-aminopropioamidoximes using PASS online, Molinspiration Cheminformatics and ProTox-II was performed. According to the results of the forecast, the new compounds do not have toxicity and meet the bioavailability criteria.

The theoretical significance of the work. The work deepens the scientific understanding of the chemistry and methods of fine organic synthesis and the technology of obtaining N-, O-containing heterocycles, in particular, the conditions for the formation of 3,5-dimethylenoxytetrahydropyran-4-one by condensation of acetone with formaldehyde in an alkaline medium and the formation of salts of spiropyrazolilammonium under the conditions of arylsulfochlorination of β-

aminopropioamidoximes were studied; thermodynamic parameters of the reactions of their formation were calculated by quantum-chemical methods.

The practical significance of the work. In the ongoing research, a technology was developed for obtaining and conditions for the synthesis of 3,5-dimethylenoxytetrahydro-4H-pyran-4-one and its derivatives – oxime, ether, Schiff bases. The reactivity of b-aminopropioamidoximes has been studied; methods for the synthesis of new compounds have been developed; their structure was established using a complex of physicochemical and spectral methods; their valuable biological properties – antituberculous and antidiabetic – have been determined.

Compliance with the directions of scientific development or state programs

The dissertation work was carried out in accordance with the priorities for the development of science, approved by the Higher Scientific and Technical Commission under the Government of the Republic of Kazakhstan: 5. Scientific research in the field of natural sciences.

The work was carried out within the framework of the grant funding program of the SC MES RK under the project AP08856440 "Study of the regioselectivity of the reaction of arylsulfochlorination of β-aminopropioamidoximes; *in vitro* anti-diabetic and anti-tuberculosis product screening" (2020–2022).

Approbation of work. The main results of the dissertation were reported and discussed at conferences: "Chemistry and chemical technology in the XXI century: materials of the XXIII International Scientific and Practical Conference of Students and Young Scientists named after outstanding chemists L.P. Kulyova and N.M. Kizhner", Tomsk, May 16–19, 2022 and May 17–20, 2021, LVI-LVII International Scientific and Practical Conference "Chemistry, Physics, Biology, Mathematics: Theoretical and Applied Research", 2022. "Trends, Prospects and innovative approaches to the development of chemical science, production and education in the context of globalization", Almaty, November 3, 2021, IV International Scientific-Practical Conference "The Europe and the Turkic World: Science, Engineering and Technology" May 1–3, 2019.

Publications. As a result of research on the topic of the dissertation, 18 scientific papers were published in co-authorship, including 1 article in the international journal Molecules (Q2, percentile 83%), 1 article in the international journal Acta crystallographica Section C, Structural chemistry (Q3, percentile 40%), 1 article in the international journal Acta Crystallographica Section E: Crystallographic Communications (Q3, percentile 36%), 1 article in the international journal Journal of Structural Chemistry (Q4, percentile 28%), 2 utility models of RK, 4 articles in Chemical Journal Kazakhstan, Bulletin of KazNU and International Journal of Biology and Chemistry, included in the list of journals recommended by the Committee for Control in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan, 2 articles in republican and foreign journals, 1 monograph, as well as materials and abstracts of 5 reports on international scientific conferences.

Personal contribution of a doctoral student to the preparation of each article

The doctoral student was directly involved in obtaining experimental data, processing and interpreting experimental results for the design of the article "Reaction products of β-aminopropioamidoximes nitrobenzenesulfochlorination: linear and rearranged to spiropyrazolinium salts with antidiabetic activity" in the journal Molecules (2022, Vol. 27, no. 7, P. 2181-2197, Q2).

The doctoral student was directly involved in obtaining experimental data, processing and interpreting experimental results for the design of the article "Crystal structure and antidiabetic activity of 2-aminospiropyrazolinium tosylates and the product of O-tosylation of β-(benzimidazol-1-yl)propioamidoxime" in the journal Acta Crystallographica Section C: Structural Chemistry (2022, Vol. 78, P. 542–551, Q3).

The doctoral student was directly involved in obtaining experimental data, processing and interpreting experimental results for the preparation of the article "Redetermination of the structure of 2-amino-8-thia-1, 5-diazaspiro[4.5]dec-1-en-5-ium chloride monohydrate" in Acta Crystallographica Section E: Crystallographic Communications (2022, Vol. 78, No. 2, P. 164–168, Q3).

The doctoral student was directly involved in obtaining calculated data, processing and interpreting the results for the preparation of the article "Computational studies of para-toluensulphoclorination and para-nitrobenzenesulphoclorination products of β-aminopropioamidoximes" in the Journal of Structural Chemistry (2021, Vol. 62, P. 1969– 1975, Q4).

The doctoral student was directly involved in obtaining experimental data, processing and interpreting the experimental results for the issuance of a patent for utility model No. 6887 "Method for obtaining β-(morpholin-1-yl)propioamidoxime" (publ. 25.02.2022, Bull. No. 8) and a patent for utility model No. 6926 "Application of products of arylsulfochlorination of beta-aminopropioamidoximes as compounds with antidiabetic activity" (publ. 21.10.2022, Bull. No. 42).

The doctoral student was directly involved in obtaining experimental data, processing and interpreting experimental results for the design of 4 articles in the journals Chemical Journal of Kazakhstan, Bulletin of KazNU and International Journal of Biology and Chemistry, included in the list of journals recommended by Committee for Quality Assurance in the Sphere of Education of the Ministry of Education of the Republic of Kazakhstan, 2 articles in republican and foreign journals, 1 monograph, as well as materials and abstracts of 5 reports at international scientific conferences.