ABSTRACT

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

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«New materials – heterocyclic derivatives of β-aminopropioamidoximes for solving health problems in Kazakhstan (treatment of tuberculosis and diabetes)»

Relevance of the research topic. There is a sharp increase in the incidence of diabetes mellitus in the world, and tuberculosis, especially its MDR (multiple drug resistance) form, has been and remains a national and international public health problem. As a result of tuberculosis and diabetes, patients lose their ability to work for a long time and may become disabled or die. Treating cross-pandemics of tuberculosis and diabetes is a lengthy process. The creation of new multifunctional low-toxicity, highly effective, and economically affordable medicines is relevant for pharmaceuticals and medicine. At the same time, high social and economic effects can be expected, associated with a decrease in the burden of two chronic diseases and the fact that their treatment should be shorter.

Amidoximes are an attractive class of compounds in terms of their ambident reactivity with the possibility of carrying out reactions at the nitrogen atoms of the imine and amine groups and at the oxime oxygen atom. In the laboratory of chemistry of synthetic and natural medicinal substances of JSC "A.B. Bekturov Institute of Chemical Sciences" in the group of the supervisor of the presented dissertation work of Doctor of Chemical Sciences, Professor L.A. Kayukova is studying a number of β-aminopropioamidoximes; accumulated experience in the methods of synthesis, reactivity, rearrangements of the studied substances.

Among β-aminopropioamidoximes and 5-substituted phenyl-3-[β-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles, compounds have been identified that simultaneously have two types of biological activity: with pronounced anti-tuberculosis properties on drug sensitive and MDR strains of *M. Tuberculosis* and antidiabetic activity.

The discovery of relevant multifunctional biological properties of anti-tuberculosis and anti-diabetic properties in the studied new derivatives of β-aminopropioamidoximes will be a milestone in the development of new drugs with a lower risk of drug interactions, improved drug compliance, and a more predictable pharmacokinetic profile.

Scientific novelty of the research. The following results were achieved in the dissertation for the first time:

− 1,2,4-oxadiazoles under hydrolysis conditions led to rearranged spiropyrazoline compounds.

- The interaction of β-aminopropioamidoximes with phenacyl bromides in acetone led to new compounds - substituted 1,2,4-oxadiazines-(5-phenyl-3-[β-(dialkylamino)ethyl]-6H-1,2,4-oxadiazines). From these compounds, pharmacologically acceptable salts were obtained: oxalates and citrates.

– *In vitro* screening of the synthesized compounds for anti-tuberculosis and anti-diabetic activity was carried out. Highly active compounds have been identified that exceed the activity of the reference substances used in medical practice.

– *In silico* analysis of the biological potential of the synthesized PASS compounds for derivatives of β-aminopropioamidoximes: O-esters of amidoximes, 3,5-disubstituted 1,2,4-oxadiazoles, and 3,5-disubstituted 1,2,4-oxadiazines was performed. Anti-tuberculosis activity is predicted with a low probability, which indicates a relatively high novelty of our molecules in relation to known anti-tuberculosis substances; activities are predicted with a high probability: treatment of phobic disorders, anti-neurotic, anti-dyskinetic, stimulating kidney function and anti-alcohol action. These activities may be the subject of further experimental studies.

A search in the ChemSpider, CSLS, and Integrity databases revealed that none of the molecules we studied is present among the known structures, which also indicates the relative novelty of our results.

Thus, derivatives of β-aminopropioamidoximes with proven anti-tuberculosis and anti-diabetic properties significantly enriched information on structure-activity relationships in these pharmacotherapeutic areas.

Communication with the research plan. The dissertation work was carried out in accordance with the research plans: “Fundamental foundations and scientific approaches and methods for creating a new generation of unique innovative biologically active polyfunctional saturated carbo- and hetero(aza-, oxa- and/or thia) cyclic systems for practical medicine, veterinary medicine and plant growing" (2012–2014), "Development of anti-tuberculosis and antidiabetic drugs based on new derivatives of β-aminopropioamidoximes" (2015–2017), "Synthetic design of complex molecular systems based on basic initial both natural and synthetic compounds with composite functional groups by classical and green methods of fine organic synthesis" (2015–2017), "Physical and chemical bases for the creation of inorganic, organic, polymeric compounds, systems and materials with desired properties" (2018-2020).

Methodological base for research support. Material and technical base of JSC "A.B. Bekturov Institute of Chemical Sciences" includes operating own equipment; stock of reagents and solvents for syntheses manufactured by Sigma, Aldrich, CIS companies, qualification "chemically pure", "purified", "analytical grade", routine chemical equipment of different years of production, the Institute’s Laboratory of Physical Methods has an IR spectrometer "Nicolet 5700 FTIR". The necessary NMR spectral data were obtained at the National Laboratory for Collective Use (East Kazakhstan State University named after S. Amanzholov, Ust-Kamenogorsk). The material and technical base of co-executors includes operating modern equipment. Microbiologists of the Reference Laboratories of the National Center for Tuberculosis Problems of the Ministry of Health of the Republic of Kazakhstan have equipment, premises and a vivarium, which are maintained at a high level, mainly by the world sponsoring organizations for the fight against tuberculosis (WHO, Global Fund, ExpandTB) and the Ministry of Health of the Republic of Kazakhstan. Pharmacologists of the Center for Life Sciences of

Nazarbayev University have high-quality equipment for pharmacological research of world manufacturers of laboratory equipment not older than 2012.

The purpose of the work: Development of methods for the synthesis, fine structure, reactivity of new multifunctional organic compounds – derivatives of β-aminopropioamidoximes: 1) 1,2,4-oxadiazoles; 2) 1,2,4-oxadiazines and their pharmacologically acceptable salts of oxalates and citrates to obtain data on the possibility of their use as drugs in the treatment of tuberculosis and diabetes mellitus. Also assess the correspondence between the *in vitro* experimental data of the synthesized compounds on biological activity and the *in silico* data obtained by chemoinformatics methods.

Research objectives:

− Implementation of a systematic study to study the conditions of the Boulton-Katritzky rearrangement for a series of 3-(β-piperidin-1-yl)-5-alkyl(aryl)-1,2,4-oxadiazoles;

− With the use of catalytic systems **a:** $3K_2CO_3$, 18-crown-6, $C_6H_5CH_3$, 50°C, **b:** $Pd_2(dba)_3$, Xantphos, K_2CO_3, dioxane, 100 ^oC and **c:** $(Et)_4NI$–$(Et)_3N$, acetone, at room temperature, perform catalytic alkylation with substituted phenacyl bromides of a number of β-aminopropioamidoximes (β-amino group: piperidin-1-yl; morpholin-1-yl; benzimidazol-1-yl; 4'-phenylpiperazin-1-yl; thiomorpholin-1-yl);

– Increasing the bioavailability of a potential drug by improving the solubility of biologically active substrates 5-phenyl-3-[2-(dialkylamino)ethyl]-*6H*-1,2,4-oxadiazines with the formation of their oxalates, citrates;

− Analysis of the potential biological activity of new β-aminopropioamidoximes by *in silico* chemoinformatics;

− Conducting *in vitro* screening of the synthesized compounds for anti-tuberculosis and anti-diabetic activity.

Research methods: Fine organic synthesis, IR and NMR spectroscopy, elemental analysis and in vitro microbiological screening for anti-tuberculosis activity on drug-susceptible and multidrug-resistant (MDR) *M.tuberculosis* strains and *in vitro* antidiabetic screening on α-amylase and α-glucosidase activity.

Objects of study: Boulton-Katritzky rearrangement products of 3-(β-piperidin-1-yl)-5-alkyl(aryl)-1,2,4-oxadiazoles *in silico* screening of synthesized compounds, products of alkylation of β-amidoximes with phenacyl bromide – 5-phenyl-3-[2-(dialkylamino)ethyl]-*6H*-1,2,4-oxadiazines and their pharmacologically acceptable oxalate and citrate salts.

Provisions for defense:

1. Synthesis and structure of the starting hydrochlorides and bases of O-aroyl-β-piperidinepropioamidoximes, 3-(β-piperidin-1-yl)-5-alkyl(aryl)-1,2,4-oxadiazoles;
2. Rearrangement of 3-(β-piperidin-1-yl)-5-alkyl(aryl)-1,2,4-oxadiazoles to spiropyrazolinium structures when exposed to hydrogen chloride and water;
3. Synthesis and structure of 5-phenyl-3-[2-(dialkylamino)ethyl]-*6H*-1,2,4-oxadiazines and their salts: oxalates and citrates;
4. High *in vitro* antituberculous and antidiabetic activity of some new derivatives of β-aminopropioamidoximes.

5. *In silico* screening of 5-phenyl-3-[2-(dialkylamino)ethyl]-6H-1,2,4-oxadiazines and their salts: oxalates and citrates.

The author's personal contribution to the dissertation work consists in compiling a literature review on amidoximes and their biological properties, in carrying out the synthesis of new derivatives of β-aminopropioamidoximes and participating in the interpretation of the results obtained.

Approbation of work. The main results of the work were presented and discussed at scientific, practical and international conferences, seminars: All-Russian conference with international participation "Modern achievements in the chemistry of unsaturated compounds: alkynes, alkenes, arenes and heteroarenes" dedicated to the scientific heritage of Mikhail Grigorievich Kucherov (St. Petersburg, 2014) ; VI International scientific and practical conference "Problems of innovative development of the oil and gas industry" KBTU (Almaty, 2014); XXII Russian National Congress "Man and medicine" (Moscow, 2015); International conference "Anatolian Conference on Synthetic Organic Chemistry" (Turkey, 2015); International scientific conference "Perspective directions of development of chemistry and chemical technology", dedicated to the 70th anniversary of the Order of the Red Banner of Labor JSC "Institute of Chemical Sciences named after A.B. Bekturov" (Almaty, 2015); IXth Joint Meeting in Medicinal Chemistry (Greece, 2015); International scientific conference "OrgChem-2016" (St. Petersburg, 2016); XXV Russian National Congress "Man and medicine" (Moscow, 2018); International Symposium "Astana Biotech 2018" (Astana, 2018); International scientific and practical conference "Science, education and production in the conditions of the fourth industrial revolution" (Karaganda, 2018); 2nd Alpine Winter Conference on Medicinal and Synthetic Chemistry (Austria 2020). International scientific and practical conference "Modern aspects of chemical science and chemical education: theory and practice" (Almaty, 2021-2022).

The practical significance of the work. In present studies, the reactivity of β-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.

Publications

The results of the work performed are reflected in 29 scientific publications, including:

– 7 articles published in journals recommended by the Committee for Control in the Sphere of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan;

− 3 patents of the Republic of Kazakhstan for innovation (1) and utility model (2);

– 4 articles published in international scientific journals included in the Scopus and Web of Science databases;

– 15 abstracts published in collections of proceedings of international, foreign and republican scientific conferences, seminars.

Structure and scope of the dissertation: The dissertation consists of an introduction, three sections, the first of which provides a brief literature review on synthesis methods, structure and biological properties; the second section discusses the results of our own experiments; the third section (experimental part) presents methods for the synthesis of new compounds; conclusions; list of references; applications. The dissertation is presented on 106 pages, has 21 tables, 10 figures, the list of references consists of 123 titles.