Description for the general public.

The emergence of pathogenic bacteria resistant to the majority of currently available on the market antibiotics is among the main public health concerns that may change drastically the shape of the modern human society by pushing it into the "*pre-antibiotic*" era or even to the Stone Age. The rise of resistance rate to existing antibiotics is rather not possible to hamper or to slow down by conventional means, since this process is indispensable part of the evolution directed to dominance of stronger and readily adjustable species. New resistance mechanisms, developed by certain bacteria, are becoming more and more often responsible for the failure of the current arsenal of antibiotics. In a view of the rising global health crisis and bacterial threat, the development of novel antibacterial agents with new mechanism of action and low resistance rate was recently set at several world major summits, including the G7 2015 meeting as a task of the highest priority which aim to secure existence of humanity. Because of the low economic profit in comparison to the manufacture and sales of other types of medicines, for instance, the ones that are related to major human health threats (such as cardiovascular disease, cancers, depression, diabetes, obesity etc), most of the major pharmaceutical companies have fully or partly abandoned or slowed down the discovery of new antibiotics. In particular, this impeded the influx of new medicines on the market and drug candidate into the clinical phases I-III. The significance of this problem was pointed out by awarding the 2015 Nobel Prize in Medicine for the discovery of antiparasitic drugs that combat the likes of malaria and river blindness. The innovation, deficit in large measure, provokes the current crisis in the branches.

The ultimate aim of this research proposal is the design, synthesis, functionalization and further biological evaluation of the series of fused pyridin-4(1*H*)-one, 4*H*-pyran-4-one and 4*H*-thiopyran-4-one derivatives as potential antimicrobial, antiviral and anticancer agents with the subsequent possibility to generate a set of preclinical drug candidates. It is known from the literature that co-drug systems, designed by combination of two or more pharmaceuticals or structural motifs responsible for the biological recall of these pharmaceuticals, often results in acquiring of new pharmacological profile, improved efficacy, improved pharmacokinetics and pharmacodynamics. This is a validated strategy for engineering of biologically active compounds with the enhanced rate of activity. Basing on these facts, one of the main objectives of present study will be the development of novel co-drug systems by linking to different classes of antibacterial drugs. More precisely, using so-called "*transition-metal-catalyzed aminocarbonylation*" reactions, we intend to tether the set of 4-quinolones and their isosteres with structural motifs of other drugs, including antibiotics, possessing an amino group suitable for this reaction. We are convinced that the present work will deliver to drug candidates with new mechanisms of action and low the resistance rate towards pathogenic bacteria over the long period of time.

Overall, the research presented in the current proposal conventionally can be divided into four main conceptual parts. The first part describes rational design and synthesis of diverse fused pyridin-4(1*H*)-ones, 4*H*-pyran-4-ones and 4*H*-thiopyran-4-ones (in other words 4-quinolones and their isosteres) as potential drug candidates. The goal of the second part is the development of novel straightforward and concise approaches towards transition-metal-catalyzed site-selective functionalizations of these heterocyclic scaffolds using the kit of available C-C, C-N and other C-heteroatom bond-forming reactions. The emphasis of the third part will be placed on the engineering of co-drug systems by merging the structural part of the fused heterocyclic systems developed in the course of part 1 (namely, 4-quinolones and their isosteres) with the set of pharmacologically relevant biogenic amines and structural motifs of several marketed drugs often prescribed for antibacterial treatments. Finally, in the fourth part we will be focused on the biological evaluation of obtained drug candidates and designed co-drug systems as well as on disclosing their pharmacological profiles having in a view the preclinical studies. This work will definitely have a visible impact in the field, namely within this study we intend to set the stage for the future research by developing the preclinical antibiotic candidates. We believe that the title research will open new scientific frontiers in the group of Dr. Iaroshenko and will trigger the development of novel scientific directions related to the fields of molecular design and design of new types of chemotherapeutics.