PROJECT SUMMARY

Project number	FR/154/6-420/13
Project Title	New Derivatives of Biological Active N-Adamantyl-, N-Adamantoylaminobenzene and 2-,5(6)-Adamantylbenzimidazole: Synthesis, Reactions and Investigation
Research subdirection/ subdirections	6-420 Organic Chemistry;
Name of the leading organization	Ivane Javakhishvili Tbilisi State University
Web	tsu.edu.ge
Name of the co-participating organization	
Web	
Project Budget (Lari)	150000
Project duration (in month)	36

Personnel

	Surname, name (affiliation, position)	Position in the project	Academic degree	Date of birth
1	Marina Trapaidze	Principal Investigator	Doctor	1950-08-20
2	Davit Zurabishvili	Head Scientist	Doctor	1945-01-06
3	Medea Lomidze	Leader of a group, Senior researcher Scientist	Doctor	1950-01-07
4	Ivane Gogolashvili	Senior Research Scientist	Master	1952-01-14
5	Nino Samsonia	Senior Research Scientist	Doctor	1966-08-16

Project Summary

The goal of the project: the project is aimed to synthesise new derivatives of biological active N-adamantyl-, N-adamantoylaminobenzenes and 2-, 5(6)-adamantylbenzimidazoles in order to create a wide variety of biologically active compounds (antiviral, anticarcinogenic, antimicrobial, acto-protector, adaptogen, anthelmintic, immunotropic etc.) that meet the modern requests.
Creation of new generation of medications is one of the keen problems in the modern world. Deterioration of ecological situation in many countries, increase of viral and infectious deceases, stress situations connected with professional activities and other factors significantly increase demand for medical products that can control functional activities of neuron and immune systems, increase of neuroendocrine homeostasis, physical and mental activities, resistance to viral and bacterial infections. Development of nontoxic chemical compounds, which can prevent penetration of microorganisms into cells, or their reproduction, is one of the main problems in therapy. Searching for new means is also very important because of high drug resistance of microorganisms and other reasons.
Such unique properties are characteristic to adamantane line preparations (Amantadine, Amantol, Simmetrel, Mantadix, Rimantadine, Paramantine, Protexin, Viregite, Betsovet, Neoride, Bromantane, Kemantane etc.). They display simultaneously antiviral, antimicrobial, cytotoxic, psychoneuro immunoregulatory and other actions, increase energy of organism, significantly improve emotional and physical conditions of patients. Prophylactic and therapeutic effects of adamantane containing medications can be explained by unique molecular composition and biological properties of adamantane itself, which creates the basis of therapeutic effect for their vide variety.
It is proved experimentally that including of adamantane fragment in a medication can fully change, or partially enhance its biological activity; often decreases toxicity takes place. This can be explained by change of spatial organization of the preparation, hydrophobicity, and lipophilicity, as well as by creating favorable conditions for transportation through the biological membranes, effect of the preparation action prolongation, high immunotropicity etc.
The strategy of selection adamantane containing benzimidazoles for the study by our research team is based on the following assumption: it is well known that benzimidazoles are characterized with wide range of biological activities. Preparations created on their base are widely used in medicine, veterinary and agriculture. Benzimidazole-2-carbamates, such as Parbendazole, Oxybendazole, Albendazole (USA), Flubendazole (Belgium), Fenbendazole (Germany), and others belong to the group of most effective preparations. Their pharmacological effectiveness can be explained by influence of the carbamate group, which imparts lipophilicity, resistance to the fermentative hydrolysis to the compound and maintains its prolonged action. On the other hand, a number of compounds of this group have revealed teratogenic, embriotoxity and other side effects.
The project participants believe that replacement of the carbamate group (-NHCOOR) by adamantane pharmacophore will eliminate above mentioned negative effects and improve biological characteristics of the molecule. This assumption is corroborated with experiments described in related scientific literature and also by results of performed by us virtual screening (via internet software systems: www.Pharmaexpert.ru/ passonline/, which has shown that specified in our project adamantane containing compounds are with high probability expected to have the following effects in experiment: Antiviral (Influenza, Picornavirus, Adenovirus); Anthelmintic; Antineoplastic (brain cancer); Antiparkinsonian, Cytostatic; Nootropic; Neurotrophic factor enhancer etc.
All members of the project main staff have many year experience of working in the field of synthesis and study of adamantane line derivatives. They have synthesized adamantane line amines, alkoxyanilides, aminoacids, hydrazides, benzimidazoles, indoles, oxadiazoles (1994-2012) and compounds that exhibit different degrees of antimicrobial, biocide, anthelmintic, antitumor and anti-AIDS activities.
After antiviral (EBOV-eGFP, Marburg Ci67, VEE, EEE, RVFV, CCHF) and antibacterial (B. anthracis, S. aureus, Mycobacteria smegmatis, F. tularensis, F. novicida, Pseudomonas aeruginosa, Escherichia coli, Burkholderia thailandensis, Y. pestis, Burkholderia cepacia, Acenitobacter baumanii complex, Klebsiella pneumoniae, Burkholderia pseudomallei, B. mallei, Yersinia pestis) bio screening of some of nitrogen containing adamantane derivatives (36 compounds) there were determined that some group of compounds have wide range of activities. They inhibit virus and bacterial strains at the same time. There were distinguished the basic structures, which derivatives are perspective in creation of new effective compounds against variety bio agents (USAMRIID, 2011-2012).
According to the information given above, the synthesis and studying of active compounds of considered groups and also nitrogen containing new structures of adamantane derivatives for creation of new antiviral, antibacterial and other biological

active agents is perspective and actual.

The present project is aimed to solve the following problems:

* Synthesis of new derivatives of 5(6)-(1-adamantyl)-2-amino-(methylamino, phenylamino)-benzimidazoles and 2-(1-adamantyl)-5(6)-amino-(carboxy, hydrazido, alkoxy, acyl)benzimidazoles and determination of their structures, preparation of laboratory samples and bioscreening.
* Elaboration of the synthetic procedures.
* Study of electron donor adamantyl radical on reactivity of the obtained compounds and their specific biological activities.
* Study of the relation between chemical structure and biological activity.

The results obtained within the frames of this project, will make certain contribution in further development of adamantane and pharmaceutical chemistry and as well as in scientific research of infectious diseases, cancer chemotherapy, bio-security and other spheres.

The objectives of the project are to be realized using methods of organic synthesis and physical-chemical methods of investigation (spectral, chromatography, etc.).
Works on syntheses will be performed by the project staff in Iv. Javakhishvili Tbilisi State University.
Also, it is intended to execute biological screening of the synthesized compounds (off-budget) in:

• U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID).
• National Cancer Institute (NCI/DTP), USA.
• Richard G. Lugar Center for Public Health Research, Tbilisi.