ABSTRACT

One of the biggest problems of the global public health is the increase number of cancer cases. In Poland every year the cancer is diagnosed in 155000 of people. Since the causes of some of the cancers have not been sufficiently well acknowledged, the most important task is to find an effective cancer treatment. A significant role may play the drug carriers which are able to form stable complexes with drugs and can change their bioavailability. In 2014 the research team from the Department of Organic and Applied Chemistry, University of Lodz synthesized two new molecules: 1,10-*N,N'*-bis-(β-D-ureidoglucopyranosyl)-4,7,13-trioxa-1,10-diazacyclopentadecane (molecule **L1**) and 1,10-*N,N'*-bis-(β-D-ureidocellobiosyl)-4,7,13-trioxa-1,10-diazacyclopentadecane (molecule **L2**). These molecules contain the sugar substituents which are linked by the urea bridges with the diaza-crown ether. It is known that, sugar units possess abilities to recognize the target tissue, while diaza-crown ethers are characterized by very good complexation abilities to the alkaline ions as well as to the neutral molecules. Additionally, they are characterized by the good solubility, high molecular weight and were experimentally proved to be non-toxic. Due to these properties the molecules L1 and L2 are considered as potential drug carriers. In the work [1], the authors show that L1 and L2 are able to form stable complexes with the drugs such as aspirin and paracetamol, which are very popular, analgesic, antipyretic and cheap medicines. However, they are characterized by the low water solubility, and the latter causes their low gastrointestinal absorption.

The aim of my doctoral thesis was to investigate the structural and energetic properties of L1 and L2 and their complexes with aspirin, paracetamol and busulfan (anticancer drug which is characterized the high toxicity and is used in the chemioteraphy against the leukemia) using theoretical methods. The dissertation is focused on finding structures which have the lowest energy as well as on the studies of intermolecular interactions between L1, L2 and the drugs in the complexes. For this purpose, configurational analysis of the molecules and their complexes was performed with the use of the approximate methods such as: molecular mechanics, semiempirical methods, computer simulation, followed by the more advanced calculations at the density functional theory (DFT) level. The calculated NMR chemical shifts are compared with the experimental data.

The results of my studies show that molecules L1 and L2 are characterized by very compact geometric structure which is mainly determined by formation of hydrogen bonds between the sugar units. The orbital analysis indicate that in both molecules the HOMO and LUMO orbitals are localized on the diaza-crown ether and sugar units, while the Natural Bond Analysis reveals that the most stabilizing interaction is localized in the area of urea.

It i also shown that, according to the B3LYP-GD2 results, the ligands L1 and L2 prefer to create the non-inclusion complexes with aspirin, paracetamol and busulfan. However, L2 can form the stable inclusion complexes, but only with the paracetamol molecule, and they are not energetically preferable. The supramolecular analysis indicates that molecules L1 and L2 form the most stable complexes with aspirin, despite the fact that the strongest interactions occur in the complexes with paracetamol. It is shown that complexation process is exothermic and spontaneous.