Structure-activity relationships of a series of self-assembling compounds on 1,4-dihydropyridine core as delivery agents

Aiva Plotniece1,*, Klavs Pajuste1, Martins Rucins1, Aleksandra Vezane2, Irena Timofejeva2, Oksana Petrichenko1,3, Brigita Vigante1, Velta Ose2, Mara Plotniece1,4, Dace Bandere4, Marina Gosteva3, Arkadij Sobolev1, Tatjana Kozlovskā2, Karlis Pajuste1

1Latvian Institute of Organic Synthesis, Riga, Latvia
2Latvian Biomedical Research and Study Centre, Riga, Latvia
3University of Latvia, Riga, Latvia
4Riga Stradiņš University, Riga, Latvia

*aiva@osi.lv

Recently development of new non-viral vectors as DNA or drug delivery systems has resulted in elaboration of various nanopharmaceutical applications. Polyfunctional pyridinium derivatives on the 1,4-dihydropyridine (1,4-DHP) scaffold form liposomes and efficiently act as gene delivery agents, for example, 1,4-DHP1,2. The influence of lipid head-groups3 and linker structure4 on transfection activity as well as properties of 1,4-DHP1 formed liposomes4 were studied.

The aims of the work are: 1) modification of substituents on the 1,4-DHP cycle; 2) studies of biological activity and physical-chemical properties; 3) characterisation of nanoparticles formed by modified delivery agents; 4) clarification of the structure-activity relationships.

A series of amphiphiles as putative gene delivery agents differing in the substituents of 1,4-DHP core have been designed and synthesised. It can be concluded that structure of substituents of at positions 2 and 6 of 1,4-DHP molecule are important for radical scavenging properties. The buffering capacity of studied N-unsubstituted 1,4-DHPs were in the pH range 6.8–8.8. All amphiphiles possessed self-assembling properties, formation of nanoparticles with the average size 79–273 nm, which was dependant from the structure of compound. 1,4-DHPs with modifications at the positions 2 and 6 or 4 of 1,4-DHP molecule showed highest transfection activity of pEGFP-C1 plasmid DNA delivery into the BHK-21 cell line.

Acknowledgements The financial support of the Latvian National Research Programme BIOMEDICINE and the internal LIOS grant (IGP-2015-AP); the internal LIOS grant (IGP-2015-AP).