University of Victoria | Graduate Studies

PROGRAMME

The Final Oral Examination
for the Degree of

DOCTOR OF PHILOSOPHY
(Department of Chemistry)

Paria Parvizi

2007	Amirkabir University of Technology	MSc
2005	Amirkabir University of Technology	BSc

"Pyridinium-based cationic lipids: correlations of molecular structure with transfection efficiency"

Friday, December, 12th, 2014
9:30 AM
University Centre, Room A207a

Supervisory Committee:
Dr. Tom Fyles, Department of Chemistry, UVic (Supervisor)
Dr. Fraser Hof, Department of Chemistry, UVic (Member)
Dr. Jeremy Wulff, Department of Chemistry, UVic (Member)
Dr. Terry Pearson, Department of Biochemistry, UVic (Outside Member)

External Examiner:
Dr. Vance Williams, Department of Chemistry
Simon Fraser University

Chair of Oral Examination:
Dr. Rustom Bhiladvala, Department of Mechanical Engineering, UVic

Abstract

A series of pyridinium cationic lipids was designed, synthesized and characterized. These lipids varied in the lipophilic part, bearing C9 to C20 saturated, unsaturated, straight and branched hydrocarbon chains.
The lipid shape parameter was calculated from the molecular structure of these lipids based on the partial molar volumes of the atoms, and standard bond lengths and bond angles, using fragment additive methods. The shape parameter controls the lamellar/hexagonal phase balance in lipoplexes of the lipid with DNA. The lipid phase behaviour of the lipoplexes was derived from small-angle X-ray scattering experiments and was successfully correlated with the calculated lipid shape parameter.
The synthesized pyridinium lipids were co-formulated (1:1) with 1,2-dimyristoyl-sn-glycero-3-ethylphosphocholine (EPC) as the co-cationic lipid in 1:1 ratio, and the mixed cationic lipids were co-formulated (3:2) with the neutral lipids 1,2-dioleoyl-sn-glycero-3-phosphatidylethanolamine (DOPE) or cholesterol. The effect of variation in cationic lipid structure and lipoplex formulation on the transfection of nucleic acid (β-galactosidase and GFP) into CHO-K1 cells and the cytotoxicity of these formulations was assessed.
Initial studies on the synthesized lipids bearing saturated and terminally unsaturated C16 chains showed that a Transfection Index (TI_{PSV}) which encompasses the variation in the lipid shape parameter, the phase packing in a hexagonal lipoplex and the partition of these lipids into the lipoplex successfully correlated with transfection efficiency. To further investigate the effect of the variation of the partition of these lipids to the lipoplex, transfection studies were done on a series of pyridinium lipids with straight saturated and unsaturated chains of varied lengths, with similar shape parameters but varied partition coefficients (logP). The correlation of these experimental transfection data with the initial TI_{PSV} was unsuccessful, but the data suggested that chain length as it relates to chain mixing and chain melting behaviours of pure lipids played a role in transfection. A refined transfection index (TI_{PSVM}) was proposed which contained terms for the lipid shape parameter, the phase packing into a hexagonal lipoplex, the partition of these lipids into the lipoplex and a chain melting term. TI_{PSVM} gave an acceptable correlation with the experimental transfection efficiency for the range of compounds. Additional experimental transfection data was obtained for compounds with widely variable lipid shape parameters, either as pure compounds, blends of two pure compounds, or statistically produced mixtures of mixed-chain compounds. Although very short-chain compounds (C9) and very lipophilic compounds (C20) performed poorly, the results from the

blends allow the assessment of the role of the shape parameter in the TI. Since the shape parameter and the volume filling term are both calculated with same molecular parameter, the experimental work demonstrated that only one of these terms is required. Thus a three parameter transfection index (TI_{PVM}) was proposed and found to correlate the entire set of comparable data.
A QSAR study was done on the cytotoxicity of the transfection formulations utilized. The toxicity of the synthesized pyridinium lipids was shown to correlate with the shape parameter, the lipid mixture partition co-efficient (logP) and the charge ratio of the lipoplex formulation.
Taken together, the developed transfection index TI_{PVM} and the cytotoxicity correlation uncovered can be used in the design of low-toxicity, high activity pyridinium lipids for transfection.

Awards, Scholarships, Fellowships

2009- Graduate Entrance Award at University of Victoria
2005- Graduate Entrance Award at Amirkabir University of Technology

Presentations

1. **248TH ACS NATIONAL MEETING, AUGUST 10-14, 2014.** (San Francisco, California, US)
   •**P. Parvizi**, E. Jubeli, L. Raju, N. Abdul Khalique, A. Almeer, H. Allam, M. Al Manaa, H. Larsen, D. Nicholson, M. D. Pungente, T. M. Fyles,"***Synthesis and study of pyridinium based cationic lipids as gene delivery vectors***".
2. **7TH FRENCH-CANADIAN WORKSHOP IN SUPRAMOLECULAR CHEMISTRY, JUNE 6, 2014.** (Vancouver, British Columbia, CANADA)
   •**P. Parvizi**, M. Zheng, T. M. Fyles, "***Predicting and controlling "limit size" lipid nanoparticles using lipid packing parameters***".
3. **97TH CANADIAN CHEMISTRY CONFERENCE AND EXHIBITION, JUNE 1-5, 2014.**(Vancouver, British Columbia, CANADA)
   •**P. Parvizi**, M. Zheng, T. M. Fyles, ***"Predicting and controlling "limit size" lipid nanoparticles using lipid packing parameters"***.
4. **96TH CANADIAN CHEMISTRY CONFERENCE AND EXHIBITION, MAY 26-30, 2013.**(Quebec, Quebec, CANADA)
   •**P. Parvizi**, J. Mendez Campos, E. Jubeli, L. Raju , N. Abdul Khalique, A. Almeer , H. Allam , M. Al Manaa , M. D. Pungente, T. M. Fyles, "***Synthesis and study of pyridinium based cationic lipids as gene delivery vectors***".
5. **6TH FRENCH-CANADIAN WORKSHOP IN SUPRAMOLECULAR CHEMISTRY, MAY 24, 2013,** (Montreal, Quebec, CANADA)

•**P. Parvizi**, J. Mendez Campos, E. Jubeli, L. Raju , N. Abdul Khalique, A. Almeer , H. Allam , M. Al Manaa , M. D. Pungente, T. M. Fyles, ***"Synthesis and study of pyridinium based cationic lipids as gene delivery vectors"***.

6. **95TH CANADIAN CHEMISTRY CONFERENCE AND EXHIBITION, MAY 26-30, 2012.**(Calgary, Canada, CANADA) •**P. Parvizi**, A. Neal, T. M. Fyles, ***"Synthetic cationic lipids".***

Publications

1. **NATURE COMMUNICATIONS, 2014, 5, 4142-4150.**
   M. Barboiu, Y. Le Duc, A. Gilles, P. Cazade, M. Michau, Y. Legrand, A.van der Lee, B.Coasne, **P. Parvizi**, J. Post & T. Fyles "An artificial primitive mimic of the Gramicidin-A channel".
2. **INTERNATIONAL JOURNAL OF PHARMACEUTICS, 2014, 461, 145-156.**
   P. Parvizi, E. Jubeli, L. Raju , N. Abdul Khalique, A. Almeer , H. Allam , M. Al Manaa , H. Larsen, D, Nicholson, M. D. Pungente, T. M. Fyles "Aspects of nonviral gene therapy: correlation of molecular parameters with lipoplex structure and transfection efficacy in pyridinium-based cationic lipids**".**
3. **JOURNAL OF ORGANIC & BIMOLECULAR CHEMISTRY, 2013, 11, 4359-4366.**
   D. Bowie, **P. Parvizi**, D. Duncan, C. J. Nelson, T. M. Fyles, "Chemical-genetic identification of the biochemical targets of polyalkylguanidinium biocides".
4. **JOURNAL OF THE CHINESE CHEMICAL SOCIETY, 2009, 56, 1035-1042.**
   •**P. Parvizi**, A. Khosravi, S. Moradian, K. Gharanjig," Synthesis and Application of Some Alkali-clearable Azo Disperse Dyes Based on Naphthalimide Derivatives".