DISSERTATIONES CHIMICAE UNIVERSITATIS TARTUENSIS
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The QSPR/QSAR approach for the prediction of properties of fullerene derivatives

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LIST OF ORIGINAL PUBLICATIONS

The present thesis consists of four articles listed bellow. All papers are denoted in the text by roman numerals I–IV.

I. Martin, Dana; Maran, Uko; Sild, Sulev; Karelson, Mati. **QSPR Modeling of Solubility of Polyaromatic Hydrocarbons and Fullerene in 1-Octanol and *n*-Heptane.** *J. Phys. Chem. B* **2007,** *111,* 9853–9857.

II. Martin, Dana; Sild, Sulev; Maran, Uko; Karelson, Mati. **QSPR Modeling of the Polarizability of Polyaromatic Hydrocarbons and Fullerenes**. *J. Phys. Chem. C* **2008***, 112*, 4785–4790.

III. Martin, Dana; Karelson, Mati. **The Quantitative Structure Activity Relationships for Predicting HIV Protease Inhibition by Substituted Fullerenes.** *Lett. Drug Des. Discov.* **2010**, *7*, 587–595.

IV. Martin, Dana; Karelson, Mati. **Quantitative Structure Activity Relationship for Describing the Inhibition of the β Amyloid Fibril Formation**, *Lett. Drug Des. Discov.* **submitted**.

Author's contribution

Publications I, II, III, IV: The author is responsible for the data sets, calculations, interpretation of the results and preparation of the manuscripts.

LIST OF ABBREVIATIONS

2D,3D	two, three dimensional
Aβ	β-amyloid peptide
AIDS	Aquired Immune Deficiency Syndrome
AM1	Austin Model 1
ANN	Artificial Neuronal Networks
APP	Amyloid Precursor Protein
BMLR	Best Multiple Linear Regression
CNT	Carbon Nanotubes
CODESSA	Comprehensive Descriptors for Structural and Statistical Analysis
CoMFA	Comparative Molecular Field Analysis
CoMSIA	Comparative Molecular Similarity Index Analysis
DFT	Density Functional Theory
DNA	Deoxyribonucleic acid
EC50	effective concentration at 50% value
F	Fisher criterion
fAβ	β-amyloid fibril
HIV	Human Immunodeficiency Virus
LOO	leave one out
LMO	leave many out
LSSVM	Least-Squares Support Vector Machine
MC	Monte Carlo
MD	Molecular Dynamics
n	refraction index
N	number of particles per volume
NLO	Nonlinear Optical devices
PAH	Polyaromatic Hydrocarbons
PCA	Principal Component Analysis
PLS	Partial Least Squares
PM3	Parameterized Model number 3
PRESS	Prediction Sum of Squares
R	the correlation coefficient of the regression
R^2	the coefficient of determination
R^2_{cv}	cross validation coefficient of the determination
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
RMSPE	the root-mean-square prediction error
RNA	Ribonucleic acid
s	the standard error of the multiple linear regression
s_0	the normalized standard error
SCAP	Solvent-dependent Conformational Analysis Program
sPRESS	Standardized Prediction Sum of Squares
STM	Scanning Tunneling Microscopy

SVM	Support Vector Machine
SWCNT	Single Wall Carbon Nanotubes
t	Student's test
QSAR	Quantitative Structure-Activity Relationship
QSPR	Quantitative Structure-Property Relationship
QSARModel	Quantitative Structure-Activity Relationship Model
σ	polarizability
γ	hyperpolarizability

INTRODUCTION

The discovery of fullerene by Kroto et al.[1] and of the carbon nanotubes (CNT) by Iijima et al.,[2, 3] extended the number of known forms of carbon allotropes. The shapes of some of these new compounds resemble geodesic domes, which were made popular by the well known architect Richard Buckminster Fuller and the naming of these new allotropic forms of carbon after the architect's name was a tribute to his visionary view.

Further experimental and theoretical studies revealed more or less stable forms of spherical fullerenes,[4,5,6] carbon structures doped with B, N,[7,8] spherical fullerenes including metallic atoms[9] or structures similar to fullerenes and carbon nanotubes made entirely of B and N.[10,11]

All the above mentioned carbon structures have at least one dimension less than 100 nm and thus can be classified as nano compounds. The interest in nanomaterials is due to the fact that the properties stemming from the nano dimension can be quite different in comparison to those of the same material as bulk.

Nanomaterials have special mechanical, magnetical, electrical, optical and chemical properties and due to these properties are increasingly used as semiconductors, microelectronic devices, catalysts, cosmetic agents and medical substances for diagnosis, imaging and drug carrier.

The drawback of carbon nanostructures is that they can have adverse effects on human and animal health and are a matter of concern regarding environmental protection. Some nanostructures like C_{60} proved to be rather harmless,[12] while others like carbon nanotubes have an effect similar with asbestos on human health.[13] The Polyaromatic Hydrocarbons (PAH) which are the precursors of many larger carbon nanostructures are very toxic substances.[14] The toxicity and environmental pollution associated with carbon nanostructures are related to their solubility in water[15] and in solvents similar to body fluids,[16] a fact that makes the study of carbon nanostructure solvation a field of major interest.

As in the case of other substances the production, manipulation and use of carbon nanostructures should follow the EU legislation concerning: Safety at Workplace Directives,[17] The Directive on the Integrated Pollution Prevention and Control,[18] Waste Management Directives[19] and The European Regulation on the Registration, Authorization and Restriction of Chemicals(REACH) .[20]

Precise determination of the properties of carbon nanostructures may be difficult because some of these compounds are obtained in rather low quantity and the measurement of their properties can be carried out only by sophisticated experimental techniques.[21,22] An alternative method to determine the property values for nanostructures is to use computational methods.[23]

One of the computational techniques extensively used nowadays for obtaining the properties of different compounds is Quantitative Structure Property/ Activity Relationship (QSPR/QSAR) approach. This computational technique enables the building of theoretical models that relate the property of compounds

to their structural characteristics. Based on the models developed, the unknown properties of the compounds can be deduced from their molecular structure. Numerous computational programs for predicting properties that are missing for different substances have been developed based on QSPR/QSAR.

The purpose of the present thesis is to explore the applicability of QSPR/QSAR methodology for predicting properties of some carbon nano-structures, specifically the fullerene and its derivatives. Within this aim, computational models for predicting different physico-chemical and biological properties have been developed. These models enable the interpretation of the dependence of the particular properties on the structure of compounds through specific theoretical molecular descriptors. In Chapter I, the modeled properties and the methodology employed for modeling are overviewed. Chapter II presents the results obtained in modeling specific properties: solubility of PAH and fullerene in n-heptane and 1-octanol, polarizability of PAH and fullerenes, inhibition of HIV protease by different substituted fullerenes and the inhibition of amyloid fibril formation.

1. LITERATURE OVERVIEW

1.1. Properties of interest for carbon nanostructures

The discovery of new allotropic forms of C triggered an increased interest in their physical, chemical, biological properties and in possible practical applications based on these new compounds.

The special mechanical, electrical, optical and reactivity properties of the carbon nanostructures are due to the presence of the extended π electrons systems. This particular structure involving multiple π electrons induces the spherical aromaticity in the case of fullerenes[24] and is the source of the aromaticity induced special electronic properties of carbon nanotubes.[25]

Carbon nanotubes show high stiffness and axial strength as reflected by a high Young's modulus (~1 TPa),[26] and at the same time they have low density, which makes them suitable for the fabrication of strong, lightweight composite materials.[27]

According to the diameter and the helicity of carbon nanotubes these can be semiconducting or metallic,[28,29] which make them interesting compounds for nanosize electronic devices like transistors.[30] Another exceptional electronic property of carbon nanotubes is their ability to support ballistic electron transport.[31,32] Studies of fullerene C_{60} doped with K atoms revealed superconductivity at a temperature of 18K, which is among the highest observed for a molecular superconductor.[33]

Due to their extended π electron systems carbon nanostructures also find applications as materials for Nonlinear Optical Devices (NLO). The phenomenon behind NLO devices is the photorefractive effect described by the spatial modulation of the refractive index. The behavior of refractive index is controlled by the polarizability (σ) and the second-order hyperpolarizability (γ) which renders these properties important to be measured in the case of carbon nanostructures used as compounds for NLO devices.[34,35]

The discovery of the Bingel reaction[36] allowed the introduction of pendant arms to the sphere of fullerene thus modifying many of the fullerene properties and inducing new potential technological and biological applications.[37]As in the case of fullerenes, CNT can also be side-wall derivatized by different reactions[6] rendering them thus more appropriate for different applications.[38]

One of the most studied biological applications of fullerene is their ability to inhibit different types of enzymes. Enzymes have a crucial role in organisms from viruses to mammals and their inhibition can cure a wide range of diseases from viral infections to cancers. Substituted fullerenes proved effective inhibitors of enzymes like: HIV protease,[39,40] HIV reverse transcriptase and Hepatitis C RNA polymerase,[41] carbon anhydrase,[42] acetyl cholinesterase,[43] and neuronal nitric oxide synthase.[44]

When exposed to light, fullerenic compounds produce singlet O species [45] with cytotoxic effect on cells.[46,47] This reactive O induced cytotoxicity could have practical applications in treating different forms of cancers by destroying

abnormal cells. However O reactive species can also have undesirable side effects on healthy cells like: DNA cleavage,[48] mutagenicity,[49] genotoxicity[50] or hemolytic effects.[51] On the other hand, the fullerols that are polyhydroxylated fullerens have been shown to be effective as free radical scavengers[52] and can be used to treat ischemic, neuronal and rheumatoid degenerative diseases which are due to overproduction of free radicals in the tissue.

Fullerene derivatives also have bactericidal effects[53–59] because of their capacity to intercalate in the biological membrane of different sorts of bacteria and to disrupt the bacteria cell's wall thus causing the microorganism's death.

The 1,2-(dimethoxymethano)fullerene proved to be an efficient compound for preventing the aggregation of β-amyloid peptide thus being a potential drug for Alzheimers' disease treatment.[60]

Endohedral fullerenes[61] which are the fullerenes with metal ions trapped inside the fullerene cage proved to be effective tools in medical diagnosis as MRI agents.[62] Highly-iodinated C_{60} molecules are good contrast agents for X-ray imaging[63] having a lower toxicity than other commercially available X-ray agents.

1.2. Properties studied in the present thesis

Solubility of carbon nanostructures

Solubility is a fundamental property for all chemical compounds mainly because most reactions and biological processes take place in solution. For carbon nanostructures solubility is important in fields like: separation of carbon nanostructures after synthesis, synthesis of substituted carbon nanostructures, environmental protection and bioavailability of compounds.

In comparison with other allotropic forms of carbon, like diamond and graphite, which are not soluble in any solvents, fullerenes can be dissolved at room temperature mostly in aromatic solvents. Further studies of C_{60} dissolved in a variety of solvents confirmed the fact that "like dissolves like" and that the most important parameters in evaluating the capacity of a solvent to dissolve C_{60} are: the solvent's polarity, polarizability, molecular size and Hildebrand solubility parameter.[64]

The unsubstituted fullerene is insoluble in water, the maximum concentration that can be achieved as a hydrated fullerene is 4mg/mL.[65] The hydrated fullerene $C_{60}(H_2O)_{24}$ consists of the C_{60} cage surrounded by 24 water molecules, which act for the fullerene cage as electron donors through the O atoms, and constitute the first hydration shell.

Carbon nanostructures have many potential applications in medicine which are conditioned by their solubility in body fluids. Thus one field of major interest is the functionalization of carbon nanostructures with pendant arms that will render them soluble in different solvents. The functionalization of C_{60}, resulting in a dendrimeric fullerene derivative bearing 18 carboxylic groups can significantly improve its solubility in water up to 34mg/mL at pH=7.4.[66]

The Single Wall Carbon Nanotubes (SWCNT) also have potential applications in medicine but the major problem is their insolubility in all solvents. The covalent functionalization of SWCNT[6] is not always as successful as in the case of fullerenes, sometimes the band electronic structure is disrupted by these modifications or even the full structure of SWCNT is damaged.[67] The dissolution in water of the SWCNT is achieved by using polymers and surfactants.[68]

The solubility of PAH with a small number of cycles is well studied due to the importance of these compounds in many industrial processes like the production of dyes and drugs. On the other hand the PAH with a large number of cycles are not readily available for analysis, these compounds being obtained mostly in small quantities in combustion processes. The PAH are very toxic compounds and their solubility in water has been studied[69,70] as mostly related to issues like human health and environmental protection.

In the present thesis, the QSPR approach has been applied for modeling the solubility of C_{60} and carbon nanostructures' precursors, the polyaromatic hydrocarbons (PAH), in two solvents – the n-heptane and 1-octanol.

Polarizability

The increasing number of applications based on nonlinear optical (NLO) effects in fields like telecommunications, computer storage devices and optical devices triggered the necessity to measure and compute as precisely as possible the properties on which the NLO effects depend, the refractive index and implicitly the polarizability and hyperpolarizability of different compounds used in NLO devices.

The electric polarizability reflects the ease of distortion of the electron cloud of a molecular entity by an electric field (such as that due to the proximity of a charged reagent). As defined in the dictionary, the electrical polarizability is "the electrical dipole moment induced in a system such as an atom or molecule, by the electric field of unit strength".[71]

Richard Feyman[72] modified the Clausius-Mosotti equation to adapt it for bulk materials thus establishing the relationship between polarizability and the refraction index:

$$N\alpha = 3\frac{n^2 - 1}{n^2 + 2} \tag{1}$$

where N is the number of particle per unit volume, α is the atomic polarizability and n is the refractive index.

Polarizability consists on isotropic and anisotropic components.[73] The isotropic part of the molecular polarizability is mostly an additive quantity that can be calculated by summation of individual polarizability of atoms or bonds of a certain molecule. The anisotropic polarizability is mostly due to the fact that atoms are not isolated in molecules and their electronic distribution is influenced by the chemical neighborhood. The polarizability, especially its

anisotropy is important in many ligand-receptor, enzyme-substrate and other biological interactions.[74–76]

Encompassed in the thesis is a QSPR model for polarizability of a set of fullerene and PAH compounds.

HIV protease inhibition

Acquired Immune Deficiency Syndrome (AIDS) is a disease caused by the human immunodeficiency virus (HIV) and it has as effect the collapsing of the human immune system. The failure of the immune system leaves the organism pray to the opportunistic infections which otherwise wouldn't have been dangerous.

The most important step in the cure of AIDS is preventing the HIV virus from reproducing itself and also to inhibit the viruses already present in the infected organisms. Up to now a large number of compounds have been tested to inhibit the virus in different stages of its development.[77] There are inhibitors for practically every phase of virus' life cycle: adsorption, fusion, uncoating, reverse transcription, integration, replication, transcription, translocation, maturation and budding. [78]

One successful method of reducing the amount of HIV viruses in infected organisms is to inhibit the respective aspartyl protease, which has the role of producing the HIV structural proteins called gag and implicitly determines the production of HIV mature virions. The HIV protease inhibitors bind specifically to the active catalytic site where they remain stuck thus blocking the enzyme. There are several protease inhibitors approved as drugs: Saquinavir, Indinavir, Amprenavir, Fosamprenavir, Tipranavir, Darunavir.

Fullerene C_{60} is an interesting molecule for blocking the HIV protease[79] due to its size of around 10 Å which is similar to the inside diameter of the protease channel. Another reason for the C_{60} efficacy against HIV protease is its hydrophobicity which makes it compatible with the hydrophobic amino acids that line the protease channel. To increase the efficiency of the C_{60} fullerene in inhibiting the protease all sort of pendant arms, which react with the catalytic site, have been added.[80,81] Actually such a substituted fullerene named Fulevir, which is the sodium salt of fullerene-polyhydropolyamino-caproic acid is currently used clinically for the treatment of HIV infection.[82]

Included in the present work is a QSAR approach for predicting the activity of substituted fullerenes in inhibiting the HIV protease.

B-Amyloid peptides aggregation inhibition

Alzheimer's disease that mostly affects the elderly population is characterized by dementia and at the physiological level by cerebral atrophy and loss of synapses and neurons.[83] One of the main causes of Alzheimer's disease is the overproduction of β-amyloid peptides (Aβs) and their deposition in the brain as amyloid extracellular plaque[84] thus damaging the neuronal cells.

The main Aβs that result from cleaving the amyloid protein precursor (APP) are Aβ(1–40) and Aβ(1–42).[85] The two Aβs have almost identical amino acid

sequence but differ in which concerns the aggregation behavior, with Aβ(1–42) deposing faster and thus having increased neurotoxicity.[86]

The potential strategies for the treatment for Alzheimer's diseases include blocking the enzymes that cleave the APP[87] or anti aggregation agents against amyloid fibril (fAβ) formation.[88,89] Many different types of molecules have been experimentally tested as anti amyloid aggregation agents.[60,90–100]

Included in the present thesis is a QSAR approach for evaluating the inhibition power of different compounds against Aβs aggregation.

1.3. Computational approaches used for predicting the properties of carbon nanostructures

The techniques mostly used to compute the properties of carbon nanostructures include: quantum chemistry, force field methods and molecular dynamic simulations. The preferred technique depends on the size of carbon nanostructure: for compounds with up to several hundred atoms, simplified quantum mechanical based techniques like Density Functional Theory (DFT) are used, while in the case of nanostructures with thousands of atoms, statistical mechanics based methods are applied. Most computations in the field of carbon nanostructures are made for the prediction of the physical properties (mechanical, optical, electrical and magnetic) while calculations of biological activities and toxicities are less numerous.

The mechanical and electronic properties of carbon nanotubes have proved important from the technological point of view. That raised the interest in developing a variety of techniques for predicting the properties of these structures. The thermo-mechanical and transport properties of carbon nanotubes have been modeled by computational techniques like molecular dynamics (MD), Monte Carlo (MC) simulation and *ab initio* quantum chemical methods.[101,102] Before it was proved experimentally by Scanning Tunneling Microscopy (STM) that CNT can be metallic or semiconductors,[103] their electrical properties were predicted by using first-principle, self-consistent, all-electron Gaussian-orbital based local-density-functional approach[104,105] and tight-binding band-structure calculations.[106] Also the ballistic conductance in carbon nanotubes was anticipated by using a tight-binding model.[107]

Different computational techniques like the finite field approach with PM-3 parametrization,[108] atom monopole-dipole interaction models,[109,110] time-dependent density-functional theory,[111] point-dipole interaction model[112] have been used to compute polarizability and hyperpolarizability. These computational methods proved to be a good alternative to the experimental techniques in determining polarizability and hyperpolarizability, properties that indicate how suitable different carbon nanostructures are for NLO devices.

Computational tools proved also useful in evaluating and predicting the biological properties of substituted fullerenes. Docking is a valuable technique showing its utility in evaluating the potential of substituted fullerenes to inhibit

enzymes like HIV protease[79] and mammalian carbon anhydrase.[42] 3D QSAR techniques like Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similarity Index Analysis (CoMSIA) have also been employed for proposing a series of C_{60} fullerene-based inhibitors of HIV protease.[113,114] Theoretical studies revealed the relationship between cytotoxic and hemolytic properties of water-soluble fullerene C_{60} derivatives and the hydrophilic and hydrophobic areas of these compounds.[51] A structure-activity study on six different carboxyfullerene superoxide dismutase (SOD) mimetics also showed that the neuroprotection efficacy depends on the number and the symmetry of distribution of the carboxylic groups attached to the fullerenic cage.[115]

The modeling of the solubility of carbon nanostructures in different solvents has been made by QSPR modelling,[116] Thomas and Eckert dilution model,[117] least-squares support vector machine (LSSVM),[118] multivariate stepwise linear regression applied as a linear solvation energy approach[119] and solvent-dependent conformational analysis program (SCAP).[120]

In the present thesis, two computational techniques have been used for modeling the properties of carbon nanostructures: QSPR/QSAR approach and *ab initio* quantum chemistry. The *ab initio* technique was used to generate the database on the polarizability for the fullerenes and PAHs used further for QSPR modeling. The QSPR/QSAR modeling was employed to generate useful models for the solubility of PAH and C_{60} in two solvents: n-heptane and 1-octanol, for the polarizability of PAH and fullerenes, for the HIV protease inhibition by a series of substituted fullerenes and for the β-amyloid peptides aggregation inhibition.

1.3.1. Ab initio calculations

Many carbon nanostructures are rather large compounds, containing sometimes even thousands of atoms, which make the use of *ab initio* calculation for these structures a computationally highly expensive technique.

An alternative to *ab initio* Hartree-Fock theory with many-electron wavefunctions is the use of Density Functional Theory (DFT)[121] which is a simplified quantum chemistry method based on functionals of spatially dependent electron density. In the article (II) DFT techniques with B3LYP functional,[122] 6–31G*[123] and 6–311G(d)[124] basis sets were used to calculate the polarizabilities of PAH and fullerenes included in the training and test sets of compounds. The calculations were carried out with the Gaussian03[125] program and consisted of the optimization of molecular geometries using 6–31G* basis set and calculation of polarizabilities with 6–311G(d) basis set.

1.3.2. QSAR Methodology

The basic idea behind the QSPR/QSAR is that there is a relationship between the chemical structure of an organic compound and its bio-physical-chemical

properties. In what follows we will make a short overview of the QSPR/QSAR flow, with emphasis on the special problems encountered when modeling the properties of carbon nanostructures by this computational technique.

The QSPR/QSAR methodology has three well defined steps, irrespective of the property that is being modeled: data preparation, data analysis and model validation. Each of these main steps can be further subdivided as can be seen in the table bellow:

Main step	Sub steps
Data preparation	Collection of the property data to be modeled
	Preparation of the molecular structures for QSPR/QSAR studies
	Collection of experimental descriptors Calculation of theoretical descriptors
Data analysis	Selection of the QSPR/QSAR statistical analysis and correlation method
	Development of QSPR/QSAR model
	Interpretation of the model
Model validation	Model validation
	Prediction of the property of interest

The physical, chemical or biological property that is modeled should have a suitable database of experimentally measured values of good quality. The quality of experimental data is crucial for obtaining reliable and robust models. For this reason, compounds with known large experimental errors in property values should be discarded from the set of data. Ideally, the experiments for determining the property values should be made by standardized methods in the same laboratory. Often, the property values are logarithmically transformed for QSPR/QSAR modeling purposes. In the case of carbon nanostructures, the experimental data are rather scarce and the property values from different laboratories that used similar experimental methods need to be collected. Thus, a special attention has to be paid to experimental protocols to avoid pitfalls due to poor data.[126]

The 2D or 3D structures of the compounds needed for the calculation of molecular descriptors and in QSAR/QSPR model development can be drawn using software like MDL ISIS Draw,[127] Chem Draw,[128] or in the case of more complicated compounds like fullerenes and carbon nanotubes, structures can be downloaded from internet sites[129] or generated using special programs.[130] For obtaining the values of 3D theoretical descriptors, the structures should be prepared by energy minimization using quantum-chemical programs (e.g. MOPAC[131]). A commonly used molecular geometry optimization methods in QSPR/QSAR are the semi-empirical quantum chemistry methods with different parameterization like AM1[132] and PM3.[133] Based on the molecular structures with

optimized geometrical parameters, the descriptors can be calculated using many different programs (e.g. CODESSA,[134] CODESSA Pro,[135] QSARModel,[136] and DRAGON[137]).

The computational methodologies developed for building the QSPR/QSAR models that relate the theoretical descriptors to the experimental properties, can be classified as linear and nonlinear. Among the linear computational techniques, Multilinear Regression,[138] Partial Least Squares (PLS)[139] and Principal Component Analysis (PCA)[140] are the most widespread. The nonlinear relationship between property and descriptors can be built using techniques such as Artificial Neuronal Networks (ANN)[141] and the Support Vector Machine (SVM).[142] In the present thesis, multilinear regression techniques the Best Multiple Linear Regression (BMLR)[138] and Heuristic[143] implemented in CODESSA[134] and QSARModel[136] were used.

A good QSPR/QSAR model is interpretable and includes optimal number of descriptors that provide satisfactory explanation for the variance of the experimental data, accompanied with good quality statistical parameters.[144] Another necessary characteristic of a good model is the ability of the descriptors of the model to reflect adequately the mechanism that governs the physical, chemical or biological property that has been modeled.

The usefulness of the model is related to its reliability and predictive power. The reliability of a model is estimated by internal or external validation procedures. The validation with an external test set is more reliable than the internal validation, but is not always applicable. For instance, in the case of carbon nanostructures, it is limited due to the small datasets available for these compounds. The model developed should also have good predictive power,[145] which means that the values of the property obtained with the model based on the structure of the molecule, should be as close as possible to the experimentally measured property of that compound. The QSPR/QSAR models should be associated with a defined domain of applicability which means that they are generally applicable to congeneric compounds and are able to make reliable predictions only within the structural and physicochemical domain that is known from the training set.

1.3.2.1. Descriptors used to calculate the properties of carbon nanostructures

Molecular descriptors are numerical values that characterize properties of molecules and they are used as independent variables in QSPR/QSAR models. The descriptors can be empirical or theoretical. Empirical descriptors are various experimentally measured properties while theoretical descriptors are calculated by some algorithm.

The experimentally measurable properties of carbon nanostructures that can be used as descriptors include: the nanoparticle's size and size distribution, surface area, shape, surface functionalization and surface charge, redox potential, porosity, water solubility and lipophilicity. The water solubility and lipophili-

city are properties that are rather difficult to measure experimentally and often the theoretically calculated water/octanol partition coefficient logP[146] is used as a more accessible alternative.

For the calculation of theoretical descriptors, the only prerequisite is the chemical structure of the compound. The CODESSA[134] and QSARModel[136] programs have been used to calculate the theoretical descriptors used in the present thesis. When a certain part of the molecules is invariable in the data set, which is the case of the substituted fullerenes, theoretical descriptors for variable fragments of the compound can be calculated and used to build QSAR/QSPR models. For the fullerenes, their PAH precursors and the substituted fullerenes the following theoretical descriptors have been calculated: constitutional, topological, geometrical, electrostatic, quantum chemical and thermodynamic.[147] The calculation of constitutional descriptors is based on molecular formula and they describe features like the number of specific atoms and atomic groups in molecule and molecular weight. Topological descriptors are calculated using graph theory and reflect the connectivity and the branching of a molecule. Geometrical descriptors describe characteristics related to the size, volume, surface and shape of a molecule. The electrostatic descriptors reflect the charge distribution in a molecule and include the properties like polarity and polarizability. The quantum chemical descriptors give information about the energy of a molecule and the molecule's ability to participate in chemical reactions, polar or hydrogen bonding interactions. The thermodynamic descriptors are calculated based on the total partition function of the molecule and its electronic, translational, rotational and vibrational components.

Many topological descriptors like the distance matrix, the resistance-distance matrix, the corresponding distance-related and resistance-distance-related descriptors (Wiener index, Balaban indices, Kirchhoff index, Wiener-sum index, Kirchhoff-sum index)[148] and the Cahn-Ingold-Prelog configurational descriptors[149] have been previously calculated for fullerenes. A problem that could appear in calculating topological descriptors for fullerenes is their degeneracy.[150] The quantum chemical descriptors like local softness and hardness have also been previously calculated and served as descriptors determining the regioselectivity of fullerenes towards the nucleophilic attack.[151] The geometrical descriptors calculated for substituted fullerenes like the hydrophilic and hydrophobic areas[51] have been used to evaluate the cytotoxic and hemolytic properties of the water-soluble fullerene C_{60} derivatives. For large structures like carbon nanotubes the computation of descriptors requires extended calculations, even for topological descriptors like the Wiener index.[152,153]

1.3.2.2. Multivariate linear regression models

In building QSPR/QSAR models, the multiparameter linear regression method establishes a correlation between the *dependent* variable which is the property of a series of compounds and the *independent* variables which are the theoretical or experimental descriptors. The quality of the regression is reflected by the numerical values of several statistical parameters including the correla-

tion coefficient of the regression (R), the coefficient of determination (R^2), the standard error of the multiple linear regression (s), the normalized standard error (s_0), Fisher criterion (F), Student's test (t), cross validation coefficient of the determination (R^2_{cv}), prediction sum of squares (PRESS) and root-mean-square prediction error (RMSPE)[147]. In the present thesis, the Heuristic and BMLR regression techniques have been used in building models for the properties of carbon nanostructures.

The Heuristic method consists of several steps: i) selection of the descriptors with available values and good variability of the values; ii) building of one-descriptor equations with previously selected descriptors and selection of the best equations accordingly to F, R^2_{min}, t and descriptor intercorrelation criteria; iii) arranging of the selected one-descriptor equations in increasing order of the correlation coefficient and building of two-descriptor equations by adding descriptors that are not already in the equation, meanwhile taking into account that the descriptors in the model should have a low inter- correlation; iv) selection of the best two-descriptors models and further addition of descriptors that have low correlation with descriptors already present in the equation until the resulting correlation has a F value above the F value of previous equation and the number of the descriptors in the equation is under an acceptable established limit.

The BMLR method includes the following steps: i) finding all orthogonal pairs of descriptors in a given dataset; ii) building two-descriptor models with the orthogonal pairs of descriptors previously found and selecting those equations that have high correlation coefficient; iii) to the previously developed two-descriptors equations non-colinear descriptors are added, as long as it leads to an improvement of F otherwise the procedure is stopped and the best equations according to the coefficient of determination are obtained; iv) additional descriptors are added to the previously obtained three-descriptor equations until the additional descriptors cease to bring an improvement of F. Thereafter the procedure is stopped and the best equations according to R^2, R^2_{cv} and F are obtained.

1.3.2.3. Model validation for nanostructures

The reliability and statistical relevance of the QSPR/QSAR models developed should be examined by validation procedures. The QSPR/QSAR methodology makes use of two validation methods, called external and internal validation.[154,155]

The external validation can be applied as an assessment of the quality of the QSPR/QSAR models when the dataset of the property is large enough to be divided into training and test sets. The QSPR/QSAR model is built based on the training set, while the test set is used to compare the results predicted with the developed QSPR/QSAR model and the experimental values. Unfortunately, in the case of carbon nanostructures the datasets have relatively few experimental values and thus it is not always possible to apply the external validation method.

In the case of smaller datasets, dividing the compounds in training and test datasets reduces the structural diversity of compounds in the training set and makes the model more biased and with lower predictive power.

The internal validation is more suitable for validating the datasets with a small number of experimental values. For maximizing the structural motifs of such small datasets all the molecules can be used to build the model and the validation can be made by procedures like Leave One Out (LOO) and Leave Many Out (LMO). In the case of LMO the training set is divided into equal-sized groups containing *m* elements. Each group is omitted in turn from the data and the model is fitted with the remaining groups that together contain *n* elements. The omitted property values $\hat{y}_i$ are calculated with the fitted model and the quality of the model is given by the R^2 of the correlation between the initial property values y_i and those predicted with the model $\hat{y}_i$. The predicted property values $\hat{y}_i$ can also be used for calculating two other validation criteria, the prediction sum of squares (*PRESS*) and the standardized prediction sum of squares (*sPRESS*)(see eq. (2) and (3)).[156]

$$PRESS = \sum_{i=n+1}^{n+m} (\hat{y}_i - y_i)^2 \tag{2}$$

$$sPRESS = \frac{PRESS}{\sum_{i=n+1}^{n+m} (y_i - \bar{y}_i)^2}, \text{ where } \bar{y} = \frac{1}{m} \sum_{n=1}^{n+m} y_i \tag{3}$$

LOO is a special case of LMO in which each of the training subsets contain all the available values but one. However even if LOO is one of the most popular internal validation criteria, a high value for R^2_{LOO} is not always a proof of the high predictive ability of the model,[157] and additional statistical criteria like *PRESS*, *sPRESS* should be used for assessing the quality of the model.

2. SUMMARY OF ORIGINAL PUBLICATIONS

2.1. QSPR Modeling of Solubility of Polyaromatic Hydrocarbons and Fullerene in 1-Octanol and n-Heptane

Many polyaromatic hydrocarbons (PAH) are useful technical compounds and precursors in the fabrication of carbon nanostructures (fullerenes and carbon nanotubes); as a side effect, they also appear as byproducts in combustion processes. Most chemical syntheses and separation processes involving PAH and nanostructures take place in liquid media, rendering the solubility of these compounds in different solvents a very important technical problem. Both PAH and nanostructures have significant toxicity and carcinogenic potential, which makes their impact upon the environment and health a reason of concern, thus justifying studies of solubility in water and solvents similar to tissue fluids. Most of the PAH and carbon nanostructures solubility studies express the solubility of a single solute in a series of solvents as being correlated to the structural properties of the solvents. To our knowledge, to the date of publication of the present article there were no models made for a series of PAH and carbon nanostructures in the same solvent, maybe because of the difficulties of finding solubility data for many PAH and carbon nanostructures made at the same temperature in the same solvent. The present study aims to define the solubility of a series of PAH and carbon nanostructure in the same solvent, as a (multi)linear relationship between the solubility and the structural descriptors of the solutes.

Two QSPR models are reported in article (I) that describe the solubility of PAHs and carbon nanostructures (C_{60}) in two different condensed media (n-heptane and 1-octanol).

The experimental solubility data for PAH and fullerene were collected from the IUPAC-NIST database. The 2D-QSAR models were obtained with Heuristic and best multiple linear regression (BMLR) descriptor selection modules implemented in the CODESSA program[134]. For both the solubility in n-heptane (eq. 4) and 1-octanol (eq. 5) three descriptor models were generated:

(4)

$$\log S = 3.49(\pm 3.46) + 76.98(\pm 8.11) \cdot RNCG - 9.56(\pm 2.25) \cdot {}^{2}ASIC - 1.18(\pm 0.45) \cdot E_{ee}^{\min}(C-C)$$

$$R^2 = 0.9047, R_{cv}^2 = 0.8378, s^2 = 0.1816, R_{50}^2 = 0.8232, s_{50}^2 = 0.3503, F = 34.79, N = 15, n = 3$$

(5)

$$\log S = 10.45(\pm 1.30) - 8.40 \cdot 10^{-2}(\pm 7.71 \cdot 10^{-3}) \cdot {}^{1}IC - 1.57(\pm 0.16) \cdot E_{ee}^{\min}(C-C) + 0.88(\pm 0.15) \cdot RPCS$$

$$R^2 = 0.9637, R_{cv}^2 = 0.9346, s^2 = 0.0782, R_{50}^2 = 0.9554, s_{50}^2 = 0.1008, F = 97.28, N = 15, n = 3$$

The model describing the solubility in n-heptane (eq. (4)) involves three descriptors: Relative negative charge (Zefirov's PC) (*RNCG*), Average structural information content (order 2) (^2ASIC) and Min exchange energy for a C-C bond ($E_{ee}^{\min}(C-C)$). The descriptor *RNCG* is defined as the charge of the most negative atom divided by the sum of negative charges and its presence in eq. (4) indicates that compounds with higher localization of the negative partial charges have better solubility in n-heptane. The descriptor ^2ASIC is a topological descriptor and shows the influence of the size and compactness of a molecule on its solubility in n-heptane. The descriptor $E_{ee}^{\min}(C-C)$ can be related to the short-range contribution to the interaction energy between solute and solvent molecules and reflects the rather trivial observation that compounds with nonaromatic carbon-carbon bonds in molecule have better solubility in n-heptane.

The descriptors that appear in eq.(5) are: Information content of order 1(^1IC), Min exchange energy for a C-C bond ($E_{ee}^{\min}(C-C)$) and Relative positive charged surface area (*RPCS*). The solubility in 1-octanol decreases with the increasing of the dimension of the molecule and its extension along one axis; this size effect is described by the descriptor ^1IC. The descriptor *RPCS* is defined as the most positive surface area in a molecule. Compounds that have higher values for *RPCS* descriptor have higher density of positive partial charges interacting more efficiently with the partial negative charge of the –OH group of the solvent thus making the compound more soluble in 1-octanol. The descriptor $E_{ee}^{\min}(C-C)$ features the same solute solvent interaction as in equation (4).

The models made for PAH and fullerene in n-heptane and 1-octanol indicate that the solubility depends on the compound's spatial structure, of the electron distribution in the compounds and the interaction energy between the solute and solvent molecules. Importantly, the solubility of fullerenes in both n-heptane and 1-octanol was robustly predicted by the QSPR models developed for simpler organics.

2.2. QSPR Modeling of the Polarizability of Polyaromatic Hydrocarbons and Fullerenes

Carbon nanostructures like fullerenes, carbon nanotubes (CNT) and their precursors – the polyaromatic hydrocarbons (PAH), exhibit extended π electron systems that make them suitable compounds for nonlinear optical (NLO) applications. The linear polarizability α_{ij} controls the refraction index (n) and the spatial modulation of the refractive index, which is responsible for the photorefractive effect, phenomenon on which NLO devices are based.

The experimental polarizability of fullerenes can be measured for bulk fullerenes by indirect optical and conductivity measurements or for isolated molecules using beam deflection techniques. The techniques used for polarizability

measurements in the case of CNT involve laser beams and optical Kerr effect. The polarizability of PAHs is measured by dielectric measurements, optical Kerr effect and NMR studies in solution.

A quick tool for assessing the NLO behavior of compounds is the theoretical calculation of the polarizability. *Ab initio* methods give good results for polarizability calculations but are rather slow for the case of large molecular systems like carbon nanostructures. A more time efficient method for polarizability calculation is based on the finite field approach with PM3 parametrization and MNDO Hamiltonian. Other methods used for the estimation of polarizabilities in the case of fullerenes and PAH are: the ”bond polarizability” model, the “charge dipole” model, the “point dipole interaction” model, the “dipole interaction” model and the linear correlation of polarizability with the surface area, effective molecular radius or number of C atoms.

In publication (II), a QSPR model describing the polarizability of PAH and fullerenes is presented. The polarizability of 18 PAH and 30 fullerenes molecules was calculated at *ab initio* DFT level using the B3LYP functional and the 6–311G(d) basis set. The compounds were separated into training and test set. The training set contained compounds for which only theoretical *ab initio* calculated polarizability was available and the test set contained compounds for which the experimental determined polarizability was also available. The 2D-QSPR model for the *ab initio* calculated polarizability was obtained with the Heuristic descriptor selection module implemented in the CODESSA program. The high power predictive model contains only one descriptor *‘total molecular two-center exchange energy’* ($E_{exc}(tot)$).

$$\begin{aligned} p &= 0.8715(\pm 1.3618) - 0.1290(\pm 0.0024) E_{exc}(tot) \\ R^2 &= 0.9863, R^2_{cv} = 0.9845, s^2 = 16.2579, F = 2797.67, N = 40, n = 1 \end{aligned} \quad (6)$$

The good predictive power of the model with only one descriptor indicates that the $E_{exc}(tot)$ descriptor accounts for both the isotropic and anisotropic factors that influence the molecular polarizability. While the isotropic factor influencing the polarizability is an additive property and depends on the molecular size, the anisotropic part is largely determined by intramolecular interatomic interactions.

The QSPR model thus obtained was used to predict the polarizability values for the test set. The predicted polarizability values for the test set, with the above model, are in good agreement with the experimental values (R^2=0.985). The developed QSAR model is a quick tool for estimating the polarizability of PAHs and fullerenes.

2.3. QSAR for Predicting HIV Protease Inhibition by Substituted Fullerenes

The inhibition of the HIV virus by different drugs in different stages of virus development is part of the antiviral treatment that is the main anti HIV therapy nowadays. The HIV aspartyl protease is one of the main targets of this treatment being inhibited by both peptidic and non peptidic drugs. QSAR and 3D QSAR have proved useful tools in developing models for the prediction of the activity of numerous HIV protease inhibition drugs.

Both C_{60} and the inside channel of HIV protease have similar dimensions. This observation induced the idea that substituted fullerenes could be useful drugs in inhibiting HIV protease. The activity of substituted fullerenes against HIV protease has been measured experimentally and estimated by computational techniques like docking, CoMFA and CoMSIA.

The article (III) reports QSAR models to predict the inhibitory power against HIV protease of substituted fullerenes. The models were developed using experimental data EC50 (half maximum effective concentration) and K_i (binding affinity) of 20 substituted fullerenes tested for PBMC cells infected with the HIV-1(LAI) strain. Two approaches were employed in QSAR model development. First the descriptors were calculated for the whole molecule of the substituted fullerenes and BMLR descriptor selection module implemented in the QSARModel[136] was applied to obtain the best QSAR equations. Within another approach, the descriptors were calculated for fragments of the substituted fullerenes (like fullerene core or substituent arms) and the BMLR and Heuristic descriptors selection modules implemented in CODESSA were used to get the best models.

The best QSAR model (eq. 7) made with descriptors calculated for the full molecule of the substituted fullerenes has good statistical quality.

$$pEC50 = -78.07 + 11.44 \cdot (\varepsilon_{HOMO} - \varepsilon_{LIUMO}) - 52.55 \cdot (HDCA - 2/SQRT) - 31.23 \cdot q_{\min} \quad (7)$$

$$R^2 = 0.82, R^2_{cv} = 0.75, s^2 = 0.20, F = 23.50, N = 20, n = 3, sPRESS = 0.33$$

The positive sign of the term involving descriptor *HOMO-LUMO energy gap(AM1)*($\varepsilon_{HOMO} - \varepsilon_{LUMO}$) in this model (7) indicates that the inhibitory power of the substituted fullerenes towards the HIV protease increases with the increased stability of the molecules. The descriptor *HA dependent HDCA-2/SQRT(TMSA) (Zefirov)* (*HDCA-2/SQRT)* can be related to the ability of the substituted fullerenes to form hydrogen bonds and to participate in polar interactions. The descriptor *Min net atomic charge (Zefirov) for any atom type* (q_{min}) represents the charge, calculated based on electron density allocated to atoms. Both descriptors *HDCA-2/SQRT* and q_{min} appear in the QSAR model with the negative sign which indicates that the potency of the substituted fullerenes to inhibit the HIV protease increases with the decreasing ability to form polar interactions and with the increased hydrophobicity of the compound. For assessing how

much the hydrophobicity of the substituted fullerenes influences their activity, *logP* was calculated and introduced as an additional descriptor for compounds. The inclusion of this descriptor slightly improved the statistical quality of the model (eq. 8).

$$pEC50 = -12.13 + 9.65 \cdot Max\sigma - \sigma + 4.88 \cdot RNCG + 0.38 \cdot \log P \qquad (8)$$
$$R^2 = 0.84, R^2_{cv} = 0.79, s^2 = 0.17, F = 28.77, N = 20, n = 3, sPRESS = 0.22$$

In addition to the descriptor *logP*, this QSAR model contains two additional descriptors, i.e. *Relative negative charge (Zefirov's PC) (RNCG)* and *Max sigma-sigma bond order (AM1) (Max σ-σ).* The potency of the substituted fullerenes increases with the increasing in values of both descriptors *RNCG* and *Max σ-σ.* The low values for the descriptor *RNCG* correspond to multiple centers with negative charge which render the compound incompatible with the hydrophobic channel of the protease. The descriptor *Max σ-σ* is related to the stability of the molecule.

The models obtained with descriptors calculated for fragments of the substituted fullerenes like the C_{60} core or substituent arms are significantly poorer. These results imply the conclusion that both fullerene core and substituent fragments are important for the antiviral activity of the fullerenes.

2.4. QSAR for Describing the Inhibition of β Amyloid Fibril Formation

Alzhaimer's disease that mostly appears in the old age population, is an incurable, degenerative disease characterized by brain damage often due to the deposition of β amyloid neuritic extracelular plaque and to the formation of Tau protein intraneuronal filamentous inclusions. The amyloid plaque appears due to overproduction of amyloid peptides (Aβs) and is formed in several stages that include the conformational change of Aβ monomer from α helical to β structure and aggregation in oligomers, the oligomers aggregation in protofibrils and finally protofibril maturation into fibrils.

A potential treatment for Alzheimer's disease is to block the enzymes that cleave the amyloid precursor protein (APP) thus preventing the over flooding of the brain with Aβs. Another strategy of treatment is to disrupt amyloid plaque formation by preventing the aggregation of Aβs with different compounds such as Zn/Cu chelating molecules, surfactants, dyes, phenothiazines, polyphenols, porphyrines, antiinflamatory drugs, small peptides, dendrimers and nanostructures.

Two QSAR models are presented in article (IV) for the inhibition of amyloid fibrils (fAβ(1-40) and fAβ(1-42)) formation, based on EC50 for 24 compounds. The QSAR models were obtained with BMLR descriptor selection module implemented in CODESSA and are presented in eq. (9) and (10).

$$pEC50_{AB(1-40)} = 3.007(\pm 0.486) + 0.011(\pm 0.001) \cdot (HASA - 1) + 2107.1(\pm 459.85) \cdot N_C^{\min} -$$
$$- 10.423(\pm 1.402) \cdot (FNSA - 1) - 0.033(\pm 0.005) \cdot {}^2SIC$$
$$R^2 = 0.856, R_{cv}^2 = 0.773, s^2 = 0.123, F = 28.23, N = 24, n = 4, sPRESS = 0.144 \quad (9)$$

$$pEC50_{AB(1-42)} = 1.225(\pm 0.465) + 0.051(\pm 0.006) \cdot (HACA - 1) + 2266.300(\pm 471.24) \cdot N_C^{\min} -$$
$$- 6.166(\pm 1.273) \cdot (FNSA - 1) - 0.019(\pm 0.005) \cdot {}^2SIC$$
$$R^2 = 0.828, R_{cv}^2 = 0.764, s^2 = 0.129, F = 22.83, N = 24, n = 4, sPRESS = 0.364 \quad (10)$$

The two models contain three identical descriptors: Minimum nucleophilic reactivity index for a C atom ($N_C^{\min}$), Fractional Charge Negative Surface Area (*FNSA-1*) and Structural Information Content (order 2) (^2SIC) and one descriptor that is slightly different in the two models, that is the Hydrogen Acceptor Surface Area (*HASA-1*) in eq. (9) or Hydrogen Acceptor Charged Area (*HACA-1*) in eq. (10).

The presence of the *HASA-1* and *HACA-1* descriptors in the models with positive sign indicates that the capacity of the molecules to inhibit fAβs formation increases with their increasing H bonding ability. The importance of H bonding in preventing Aβs aggregation was also confirmed by the experimental observations which showed that small peptides that interact with Aβs by both hydrogen bonding and side chain interactions are better inhibitors and that the replacement in peptides of the amide bonds, which is a H bonding site, with ester bonds, cancel their Aβs inhibition activity. Experimental tests also showed that the compounds which contain more hydroxyl groups in the molecule are more able to inhibit fAβs formation.

The *FNSA-1* descriptor is calculated based on partial negative surface area and its presence in the models with negative sign indicates that the polar interactions between Aβs and inhibitors are not favorable in preventing fAβs formation. The favoring of rather aromatic, hydrophobic, nonpolar interaction between Aβs and inhibitors is mostly due to the presence of hydrophobic regions in the Aβs peptides and it was experimentally confirmed by observations as the interaction between Aβs and cyclodextrins or between the Aβs and rifampicin lipophilic ansa chains. The experimental tests also confirmed the fact that hydrophobic molecules like curcumin, retinol and retinal are better inhibitors than polar molecules like retinoic acid.

The topological descriptor ^2SIC is related to the size and compactness of a molecule, and its presence with a negative sign in the models shows that molecules with rather compact shape are better inhibitors of Aβs. This increased activity with decreasing in molecular size was also experimentally observed in the case of the interaction of gangliosite with Aβs and is due to the fact that large gangliosides do not accommodate well between the hydrophobic regions of Aβs.

The $N_C^{\min}$ descriptor is a measure of the reactivity of the atoms in the molecule. Its appearance with a positive sign in both models indicates that molecules with higher reactivity interact better with Aβs preventing thus their aggregation.

The EC50 for inhibiting fAβ(1-40) formation with 1,2-dimethoxymethano)-fullerene was calculated using the model described by eq. (9). The three order of magnitude difference between the calculated and experimental property appear because the compounds that were used to develop the model (9) have a different mechanism of inhibiting fAβ(1-40) formation and different structures comparing with the substituted fullerene.

3. CONCLUSIONS

The QSPR/QSAR methodology was successfully applied for predicting the physico-chemical and biological properties of carbon nanostructures. The results have been presented in the articles included in the present thesis. The first article presents QSPR models for predicting the solubility of PAH and C60 fullerene in n-heptane and 1-octanol. The second article describes a QSPR model for making predictions of the polarizability of PAH and fullerenes. In the third article, a model for the inhibition of HIV protease by substituted fullerenes is reported. The fourth article involves QSAR models for the inhibition of β-amyloid fibril formation.

(1) The solubility of PAH and C_{60} fullerene in two condensed media i.e. n-heptane and 1-octanol was successfully described with two models, each having three descriptors. The models show that the solubility of PAH and C_{60} depends on descriptors which give information about the size and the shape of the molecule, the charges that appear in molecules and the interactions between the solute and solvent molecules.

(2) A QSPR model was developed for the prediction of polarizability of PAHs and fullerenes. The *ab initio* calculated polarizabilities served as a training dataset for developing a QSPR model with only one descriptor the *'total molecular two-center exchange energy'* ($E_{exc}(tot)$). This one descriptor model has a good predictive power due to the capacity of the descriptor to account for both the isotropic and anisotropic part of the polarizability. The QSAR model was externally validated with a test set containing PAHs and fullerenes for which experimental polarizabily was also available. The predicted polarizability values were within the range of the experimental errors.

(3) Experimental EC50 and K_i for 20 substituted fullerenes were used to develop models for HIV protease inhibition by these structures. The models were developed with descriptors calculated for the full molecule of the substituted fullerenes or for fragments of the molecule (fullerene core and substituent arms). The best model with good statistical quality and predictive power was obtained with descriptors calculated for the full molecules that account for the hydrophobicity and stability of the substituted fullerenes.

(4) Two models for the inhibition of amyloid fibril formation (fAβ(1–40) and fAβ(1–42)) were developed starting from the EC50 of 24 compounds. Both models include almost identical descriptor which suggests a very similar mechanism of inhibition. The descriptors involved in the models reflect the importance of hydrogen bonding, hydrophobic interaction, steric effects and nucleophilic reactivity in the process of inhibiting fAβ formation by different compounds. The model for inhibiting fAβ(1–40) formation is not able to reproduce experimental EC50 for a substituted fullerene because this compound has different inhibition mechanism and structure comparing with the compounds that were used to develop the model.

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SUMMARY IN ESTONIAN

QSPR/QSAR lähenemine süsiniknanoosakeste omaduste ennustamiseks

Peale süsiniknanoosakeste avastamist on selgunud, et nende süntees, analüüs ja omaduste määramine on päris keeruline. Selleks, et vähendada eksperimentaalse töö mahtu, on kasutatud mitmeid arvutustehnikaid nende ühendite omaduste ennustamiseks. Käesolevas doktoritöös on testitud QSPR/QSAR meetodite rakendatavust süsiniknanoosakeste füüsikaliste ja keemiliste omaduste ja bioloogiliste aktiivsuste ennustamiseks.

Sissejuhatus ja kirjanduse ülevaade annavad lühikese kokkuvõtte süsiniknanoosakestest, nende olulisematest ja huvitavamatest tehnilistest ja bioloogilistest omadustest, arvutustehnikatest ja molekulaardeskriptoritest nende omaduste modelleerimiseks ning nende mõjust keskkonnale ja inimeste tervisele.

Doktoritöö kirjeldab järgmiste omaduste modelleerimist: polüaromaatsete süsivesinike ja C_{60} fullereeni lahustuvus n-heptaanis ja 1-oktanoolis, polüaromaatsete süsivesinike ja fullereenide polariseeritavus, HIV-1 proteaasi inhibeerimine asendatud C_{60} fullereeni derivaatide poolt, ning fibrillaarse amüloidi tekkimise inhibeerimine. Kõikide nende omaduste jaoks loodi hea ennustusvõimega mudelid. Need mudelid võivad olla kasulikud tuntud ühendite omaduste ennustamiseks, mille kohta puuduvad veel eksperimentaalsed andmed või isegi rakendada ühenditele mida pole kunagi sünteesitud, kuid mis võivad omada kasulike ja huvipakkuvaid omadusi või aktiivsusi.

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PUBLICATIONS

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Professional Experience

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2007–2010	Research scientist, Molcode Ltd.
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Publications

1. Martin, D.; Karelson, M. Quantitative Structure Activity Relationships for Describing the Inhibition of the β Amyloid Fibril Formation, *Lett. Drug Des. Discov.* **2011**, submitted.
2. Martin, D.; Karelson, M. The Quantitative Structure Activity for Predicting HIV Protease Inhibition by Substituted Fullerenes, *Lett. Drug Des.Discov.* **2010**, *7*, 587–595.
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1. Martin, D.; Karelson, M. Quantitative Structure Activity Relationships for Describing the Inhibition of the β Amyloid Fibril Formation, *Lett. Drug Des. Discov.* **2011**, submitted.
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