Abstract

In recent decades, functionalized organic chemicals play a crucial role for industrial applications, in addition to organic compounds combined with nanoforms of the substance, leading to reliable development of new, safe, and sustainable chemicals for various applications, such as antibacterial activity and efficient drug delivery. The development of new advanced chemicals requires an understanding of the relationship between their structure, physicochemical properties, and the potential hazards that newly developed chemicals may pose to humans and the environment. Unfortunately, experimental studies using various complex methods are time consuming and costly. Several strategies have been proposed in the literature to reduce the number of experiments and increase the efficiency of selecting an 'optimal candidate'. One of the most promising approaches for the development of new functional chemicals is based on a computational framework combined with experimental validation. In this context, I have developed four case studies based on industry needs. In my first case study **[A]**, an integrated approach based on molecular dynamics (MD) and experimental validation was proposed to investigate the interaction and stability of BSA with newly synthesized potent pyrene derivatives (PS1 and PS2) and the free energies of the BSA-PS1 and BSA-PS2 binding complexes with MMPBSA tools useful for improving antibacterial properties. And the second case study **[B]** describes the MD, to investigate the influence of the selected physicochemical properties of the anticancer drug methotrexate (MTX) grafted with hydrophilic-γ-polyglutamic acid (MTX-SS-γ-PGA) on its cellular uptake at different pH values. In the third case study **[C]**, a set of complex descriptors describing the quantitative relationship between the value of the zeta potential (ζ), the core, the coating of the NPs and their PC fingerprints (the so-called nano-QSPR model) was developed. The nano-QSPR model was developed by partial least squares regression using a genetic algorithm (GA-PLS) and is characterized by a high external predictive power (Q^2_{EXT} = 0.89). The fourth case study **[D]** describes the combination of TD-DFT calculations with experimental data and uses an additional molecular electrostatic potential (MESP) map to understand the mechanism of charge variation in the nucleophilic addition of cyanide ions inside and outside the surface with functionalized DMN probe.

Based on my research, I could draw four lessons related to the computational design process of safe, sustainable, and targeted chemicals and nanoforms of substances. First, the project is aimed at nanoinformaticians. Second, the project is aimed at the nanosafety community. Third,

the charge, geometry, and energetics of NP, which affect the mechanism of cellular uptake, should be studied using molecular models that describe different and real environments that can be expressed by different pH values. Fourth, the same newly developed substances that open new opportunities for industry may pose a serious risk to humans and the natural environment.