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Recent developments in molecular modeling tools and applications related to pharmaceutical and biomedical research

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ABSTRACT

In modern pharmaceutical and biomedical research, molecular modeling represents a useful tool to explore processes and their mechanistic bases at the molecular level. Integrating experimental and virtual analysis is a fruitful approach to study ligand-receptor interaction in chemical, biochemical and biological environments. In these fields, molecular docking and molecular dynamics are considered privileged techniques for modeling (bio) macromolecules and related complexes. This review aims to present the current landscape of molecular modeling in pharmaceutical and biomedical research by examining selected representative applications published in the last years and highlighting current topics and trends of this field. Thus, a systematic compilation of all published literature has not been attempted herein. After a brief overview of the main theoretical and computational tools used to investigate mechanisms at molecular level, recent applications of molecular modeling in drug discovery, ligand binding and for studying protein conformation and function will be discussed. Furthermore, specific sections will be devoted to the application of molecular modeling for unravelling enantioselective mechanisms underlying the enantioseparation of chiral compounds of pharmaceutical and biomedical interest as well as for studying new forms of noncovalent interactivity identified in biochemical and biological environments. The general aim of this review is to provide the reader with a modern overview of the topic, highlighting advancements and outlooks as well as drawbacks and pitfalls still affecting the applicability of theoretical and computational methods in the field of pharmaceutical and biomedical research.

1. Introduction

Molecular modeling tools are classically used in pharmaceutical and biomedical research for facilitating the three-dimensional visualization of ligand-receptor complexes and of (bio)macromolecule dynamics, for determining structures, dynamics and thermodynamics properties of receptors, ligands, and related complexes, for reducing the chemical space to be analysed in drug discovery, and for developing predictive models. Determining how much in silico analysis itself contributed to pharmaceutical and biomedical research so far is not trivial. On one hand, in the frame of the Human Genome Project, bioinformatics and related techniques have catalysed investments by governments and companies active in life sciences. Nowadays, computational biology and molecular modeling techniques allow scientists to explore protein structures and conformations, this knowledge being essential for understanding protein function. Furthermore, several strategies in drug discovery are based on molecular modeling to explore ligand binding modes toward possible "druggable" targets. In silico approaches underlie structure-based and ligand-based drug design focusing on noncovalent interactions to identify and optimize potential drugs and their interactions with biomacromolecules as hosts [1]. On the other hand, we can say that no available drug was discovered by using computational analysis exclusively so far [2,3]. Rather, in all cases, two hybrid approaches were used: *a)* the pharmaceutical target was discovered through computational analysis of available data, with the final development of the therapeutic agent achieved through experimental analysis; *b)* the initial lead compound was discovered experimentally and refined later with computational methods.

Furthermore, in the last few decades, interdisciplinary teamwork at the interface between organic chemistry, chemical and structural biology, and computational chemistry has driven the development of modern drug discovery [4]. The same type of multidisciplinary approaches has characterized recent developments of enantioseparation science [5]. This field is of great interest in pharmaceutical and

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biomedical research given the importance of chirality and chiral pharmaceuticals in life sciences. In the last few decades, the boundaries of a joint field of knowledge at the interface between physical, theoretical, organic, and analytical chemistry, based on integration of multidisciplinary information about chirality and noncovalent interactions have also been profiling with the aim to lay the bases of a new attitude toward enantioseparation science, with plans which are guided by the rational design of experiments. On this basis, molecular modeling approaches may enable analytical scientists to unravel binding and recognition mechanisms occurring in separation and enantioseparation processes of many pharmaceuticals by using conventional or enantioselective chromatography, and electromigration techniques.

In both, chemical and biochemical environments, deciphering mechanisms at molecular level requires the identification of noncovalent interactions occurring between ligand and receptor. Integrating structural and thermodynamic experimental data produced through spectroscopic techniques, isothermal titration calorimetry (ITC), X-ray crystallography, and various other analytical techniques, with computational analysis has provided relevant information on noncovalent interactions underlying mechanisms of fundamental chemical, biochemical, and biological processes. In the frame of a mutual exchange of information, theoretical and computational analysis are used to explain experimental processes, and experimental data, in turn, may be fruitfully exploited to validate theoretical tools and approaches.

In biological systems, hydrogen bonds (HBs), dipole-dipole, π-π, and ionic interactions are considered leading noncovalent interactions regulating drug action at different levels including absorption, transport, and distribution in the living body, metabolism, pharmacokinetics, pharmacodynamics, and excretion [5,6]. More recently, other noncovalent interactions like halogen, chalcogen, spodium, and π-hole bonds were also identified as forces underlying ligand-receptor binding and recognition, these achievements paving the way for new horizons in chemical [7,8] and biological systems [9,10].

In this short review, current topics, and trends in molecular modeling tools for pharmaceutical and biomedical research will be presented by discussing selected new representative applications reported in the last years. After a brief overview on the main theoretical and computation tools used to explore chemical and biochemical processes at molecular level, this review will report representative applications of molecular modeling for *a*) drug discovery, *b*) profiling ligand binding modes, and *c*) studying protein structure and functions, involving biomacromolecules as receptors. Then, a specific section will be devoted to the application of molecular modeling for disclosing mechanisms underlying separation and enantioseparation of compounds of pharmaceutical and biomedical interest by using synthetic and semi-synthetic molecules as receptors. Finally, recent studies focusing on the function of new forms of noncovalent interactivity in pharmaceutical and biomedical research will be also and discussed.

2. Overview of computational methods and techniques for pharmaceutical and biomedical research

A fundamental paradigm in molecular recognition is that structure underlies function. From this, the relationship between the structures of the interacting partners in their (electronically unperturbed) isolated state and their binding affinities emerges. Electrostatic potential (V) analysis provides an interesting view on molecule structures through the evaluation of the electron charge density distribution on molecular regions involved in noncovalent contacts. Given a molecule, the $V(\mathbf{r})$ at each point $\mathbf{r}$ in the surrounding space is generated by each nucleus in a system (first positive term) and by the system's electron distribution (second negative term) according to Eq. 1:

$$V(\mathrm{r}) = \sum_A \frac{Z_A}{R_A - \mathbf{r}} - \int \frac{\rho(\mathbf{r})\mathrm{d}\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \quad (1)$$

where Z_A is the charge on nucleus A located at R_A and $\rho(\mathrm{r})$ is the electron density function [11]. Thus, the sign of $V(\mathbf{r})$ may be positive or negative because of the positive and negative contributions derived from nuclei and electrons, respectively. $V(\mathbf{r})$ may provide information on specific regions of the molecules, such as lone pairs and π-clouds. The concept is that when two molecules approach each other, the tendency will be that the regions of positive $V(\mathbf{r})$ on a molecule (electrophile) are attracted to those of negative $V(\mathbf{r})$ on another molecule (nucleophile), and the molecules will "recognize" that this will lead to energetically favourable interactions [12]. Thus, the $V(\mathbf{r})$ analysis of the interacting partners in their isolated state can be advantageously used to predict and explain noncovalent interaction strength and direction by mapping $V(\mathbf{r})$ on molecular electron density isosurface (V_S) [13]. Very recently, Ciccozzi et al. reported that for the SARS-CoV-2 B.1.617 Indian variants, a major effect of the mutations characterizing this lineage is represented by a marked alteration of the V_S of the receptor-binding domain of the spike protein, this feature conferring a potential increase in the virus transmission [14]. Within a cause–effect view, the electronic properties of molecules and interacting systems can be further investigated by applying the Source Function (SF) analysis that unravels the contribution of each individual atom to the electron density and the $V(\mathbf{r})$ at a point [15]. If such point is the most representative electron density location for a given chemical interaction, the pattern of the atomic SF contributions provides a visible representation of the delocalized nature of the interaction. Recently, Gatti et al. applied this theoretical technique to respond the question whether distant atoms or groups have a significant contribution to the density at the bond critical point of the individual HBs in the Watson–Crick DNA base pairs [16]. Among other results, the study revealed that distant groups and rings have non-negligible effects especially on the weak C–H···O interaction in the adenine-thymine pair. It is worth mentioning that quantum mechanics (QM) calculations are less frequently used in pharmaceutical and biomedical analysis than molecular mechanics (MM)-based modeling. Rather, hybrid QM/MM approach are not uncommon in this field because combining the accuracy of QM and speed of MM allows for treating modeling of large molecules in solution with more reliability.

On the other hand, the dynamic nature of biomacromolecules and synthetic receptors like the polysaccharide-based selectors, popular in enantioseparation science, must be accounted for. Indeed, synthetic, and biological receptor are, in general, flexible and deformable, thus, different conformations can affect recognition functions of these molecular platforms. Moreover, recognition mechanisms occur in solvated medium, and in biological environment water may play a relevant energetic role in intermolecular interactions.

Thus, we can say that structure and dynamics are the two components determining binding, recognition, and function between two interacting molecular species. The thermodynamic equation of the free energy defines these features (Fig. 1) [3]. While thermodynamically favourable noncovalent interactions move the equilibrium towards receptor-ligand binding (*entalphy term*), ligand and receptor desolvation as well as reduction in entropy associated with complexation and conformational adjustments of both ligand and receptor may exert a thermodynamically unfavourable contributions to receptor-ligand association (*entropy term*). The balance between the two components determines the strength of receptor-ligand binding in terms of thermodynamics.

An important aspect of modeling intermolecular interaction concerns the concept of molecular potential energy surface which determines shape and dynamic features of the related system. In this regard, the questions are where to locate a ligand, in or around the receptor [17,18], and how many ligand-receptor complexes must be computed (and sample among all the possible reciprocal orientations) to make the calculation representative of the experimental system [19]. As response to these questions, molecular docking and molecular dynamics (MD) are exploited in both chemical and biological contexts with

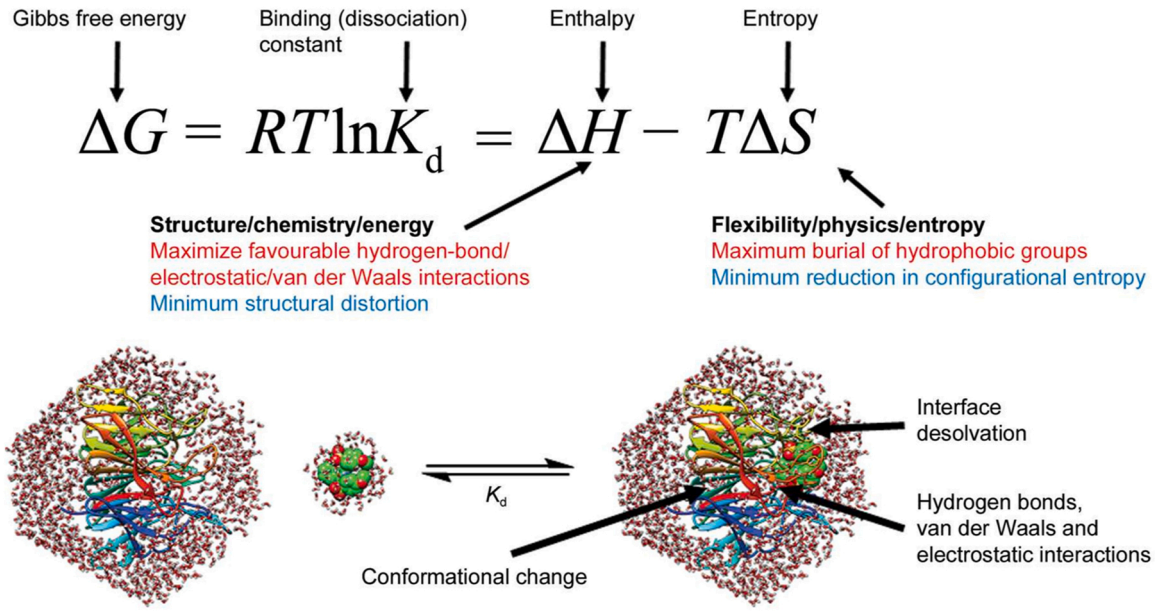

Fig. 1. General scheme of ligand-receptor molecular recognition and related thermodynamic parameters. Reprinted with permission from Ref. [3].

different levels of advancement and reliability that are dependent on the structural features of receptor, on its dynamics, and on boundary conditions. In this context, the word 'simulation' refers to the process of generating states by numerically solving a set of differential equations for the selected degrees of freedom (state variables) of the given model system [20]. In this perspective, the scope of a computational simulation is to describe the experimental molecular system virtually, gaining insight into properties and features of such system. For this purpose, an algorithm generates a series of states for the model system, and various properties of the system can be calculated from the resulting states.

Molecular docking is generally used to simulate the interaction between ligand and the active site of the receptor to predict both energy and geometry of receptor-ligand binding [17]. A docking process consists of two general steps, namely conformational search through various algorithms, and scoring or ranking of the docked 'poses' (receptor-ligand mutual orientations). AutoDock [21,22] and GLIDE [23] are popular programs for docking. In particular, AutoDock employs Lamarckian Genetic Algorithm (LGA) [21] to identify binding conformations of the ligand, as a flexible ligand, to the receptor. Genetic algorithm methods describe the three-dimensional arrangement of the molecules involved in the docking by using geometrical state variables which are receptor-ligand distance, mutual orientation of the interacting species, and the torsional degrees of freedom (number of rotatable bonds) of the ligand. The program uses a simplified form of AMBER (Assisted Model Building with Energy Refinement) force field for the energy calculations, and the free energy of binding is calculated by computing van der Waals and Coulombic energy contributions between all atoms of receptor and ligand. In the biological context, as a target has been identified and its structure determined by X-ray crystallography or released by the Protein Data Bank (PDB) [24], the binding pockets on the target must also be characterized for drug screening. In this field, molecular docking can be used to visualize protein surface and predict which ligands can bind to a certain binding pocket. Molecular docking is frequently used to screen databases for potential ligands (*high-throughput docking* or *virtual screening*).

In pharmaceutical and biomedical research, MD simulations are widely used to address issues concerning (bio)macromolecule folding, function, and dynamics, and drug design. MD is a simulation that shows how molecules move, vibrate, diffuse, and interact over time, inside a sufficiently large simulation box, where their movements are described by classical Newton's laws of motions (Fig. 2) [20]. Basically, forces acting on particles are computed by using an empirical potential energy ('force field'), a function of particle positions, including electrostatic and Lennard-Jones forces as noncovalent interactions, and 'bonded' potentials for assuring structural integrity to the (bio)molecular system under investigation. The MD protocol normally consists of six phases: initial assignment, system minimization, heating, cooling, equilibration, and dynamics production. Based on this sequence, the molecular system is free to run, and the process is iterated for thousands of steps to bring the system to an equilibrium state, saving all the information about the atomic positions, velocities, and other variables as a function of time. The set of data emerging from the MD experiment is called trajectory that profiles positions and velocities of the interacting partners in the system and their variation with time. All the equilibrium and dynamic properties of the system can be calculated from trajectory data set. Several computer programs have been made available, and nowadays commonly used programs for MD simulations include AMBER [25], CHARMM [26], GROMACS [27], and NAMD [28], among others. The first 9.2 picoseconds MD simulation of a biomolecule was achieved by McCammon et al. in 1977 [29]. Today, microsecond timescale can be achieved with relatively small proteins [30], whereas, in general, MD of larger biomolecular systems is limited to hundreds of nanoseconds. It must be stressed that although MD simulation is a powerful tool to study dynamics in complement to experimental techniques, currently available MD simulation techniques are often unable to probe biologically relevant processes that occur beyond millisecond timescale with atomistic resolution, accurately predicting long time-scale dynamics [31]. On the other hand, advanced models have been developed for biological macromolecules that need to dynamically change their shapes and/or conformations to perform their function, for overcoming successfully current weaknesses observed in the application of MD in biological contexts [31].

Considering that solvent can strongly influence the energy of different complex orientations, in MD simulations solvent can be parametrized by treating it explicitly or implicitly [32]. Explicit-solvent methods introduce solvent molecules by computing interactions involving solvent atoms, whereas implicit-solvent methods reduce simulation time by treating the discrete solvent as a continuum, thus drastically reducing the number of particles in the system.

Comparing docking and MD, although various forms of 'flexible

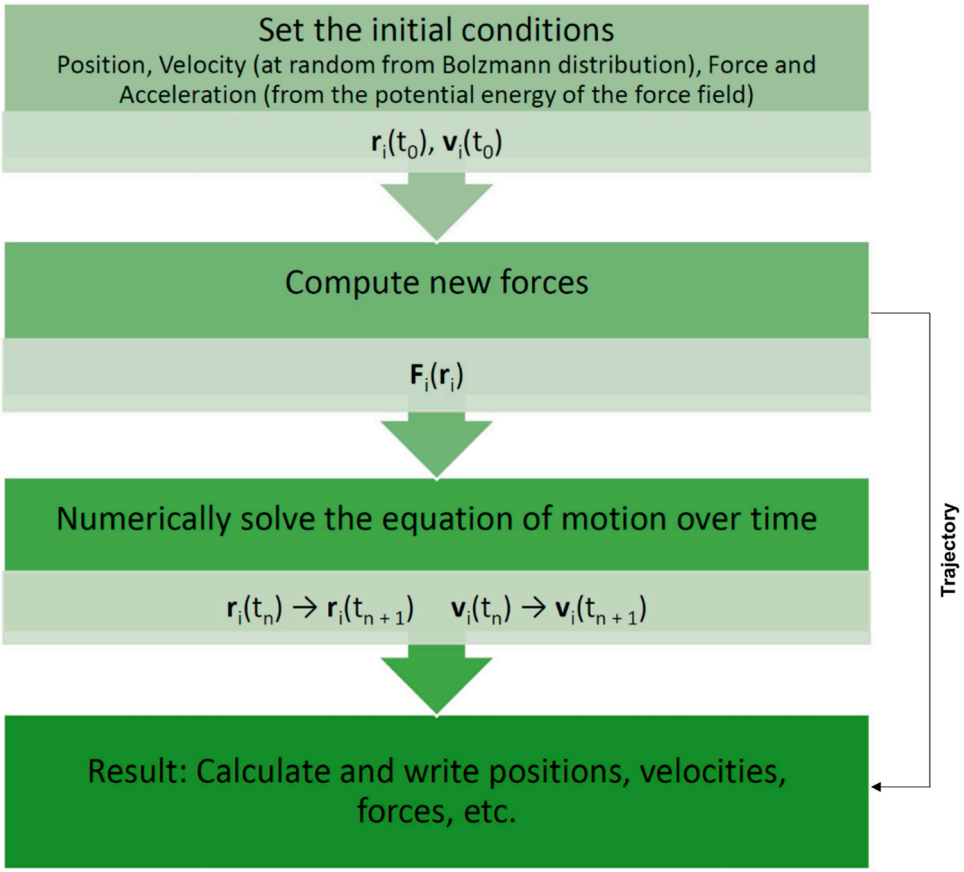

Fig. 2. Basic molecular dynamics simulation algorithm. Each particle moves according to Newton's second law or the equation of motion, $F = ma$, (F = force exerted on the particle, m = particle mass, a = particle acceleration under a potential field), such that the particles in the system are captured in the trajectory (r = position, v = velocity, t = time).
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docking' [33–35] were introduced over time, the lack of the proper description of the dynamics of the molecular system is one of the main flaws of classical docking [36]. Rather, docking studies provide small set of possible complexes, typically ranked according to the used force field. On this basis, a useful approach is to select the highest-ranked complex by docking, and to carry out a MD simulation, exploring the complex in detail, in a dynamic perspective [37].

3. Applications

3.1. Drug discovery

Although water molecules are not considered as part of the modeled system in molecular docking, this technique is likely the most popular for the high-throughput virtual screening of protein ligands derived from literature or database. The model of the target protein is usually prepared starting from the crystallographic structure released by the PDB, after removing water molecules and, often, cofactors from the original PDB file. In most cases, proteins involved in diseases and disorders are considered as drug targets for the high-throughput screening of potential inhibitors of the aberrant protein function. On this basis, a small subset of potential inhibitors is selected for subsequent experimental binding assays. In this field, Halim et al. used molecular docking to perform a small-sized screening, evaluating 43 structures reported in the literature as potential inhibitors of Interleukin-2, a cytokine which is considered a promising drug target for several immunological disorders, to develop and compare 3D-QSAR models derived from different alignment methods and charge calculations [38]. Very recently, Macchiarulo et al. reported a structure-based screening of 5801 small molecules to identify novel hit compounds featuring pH-dependent binding potency and the ability to disrupt the programmed cell death protein-1 (PD-1)/PD-1 complex (PD-L1) protein-protein interaction which was found to interfere in the immune system's response toward multiple cancer types [39]. This study integrated molecular docking and microscale thermophoresis experiments designed to prove the binding activity of the selected compounds to PD-L1, as well as the ability to inhibit the formation of the PD-1/PD-L1 complex.

The inhibition of protein-protein interaction for therapeutic purposes also was at the core of the study of Lammi et al., concerning the activity of the proprotein convertase subtilisin/kexin 9 (PCSK9) which is responsible for the degradation of the hepatic low-density lipoprotein receptor (LDLR), which regulates circulating cholesterol levels [40]. Given that the PCSK9 inhibition represents a valuable therapeutic approach for the treatment of hypercholesterolemia and cardiovascular diseases, the authors reported computational design, synthesis, and biological evaluation of diimidazole analogues reducing the protein-protein interaction between PCSK9 and LDLR. Carrying out biological assays to fully characterize the cholesterol-lowering activity of the new analogues and using both biochemical and cellular techniques, compounds showing relevant PCSK9 inhibitory activity (IC_{50} = 1.6 μM and 0.9 nM) were developed. In this study, a combined docking/MD computational approach integrated the experimental data. The structure of the inhibitors was optimized to better fit the PCSK9 surface through supervised MD, classical MD, cluster analysis, and molecular mechanics-generalized Born surface area (MM-GBSA) calculations [41]. The binding free energy of inhibitor-PCSK9 surface association was estimated by docking calculations, pose selection carried out by metadynamics simulations to improve the accuracy of the binding pose

selection, and MD simulations. Grether et al. also used a combined docking/MD approach to guide probe design and assess the feasibility of first ligand-directed covalent (LDC) labeling of cannabinoid receptor type 2 (CB2R) to understand its expression and downstream signaling in disease- and tissue-specific contexts [42].

Molecular docking has been also reported for small-sized screening of newly synthesized analogues to explore the binding affinity of the new compounds to a target protein. However, the results of this kind of study may be conclusive only if the modeling study is supported by focused experimental data, for instance in vitro binding assays. Very recently, experimental/computational integrated study were reported to develop new antidiabetic agents [43], negative allosteric modulators of the μ-opioid receptor [44], and potential agents for fibrosis cystic therapy [45].

3.1.1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

In the last two years, given the urgency arising from the COVID-19 pandemic, huge efforts were made to understand the molecular basis of SARS-CoV-2 transmission and to develop novel anti-COVID therapeutics. A great number of studies, using a combination of bioinformatics and computational tools, reported the screening of potential inhibitors into the binding pocket of genes or enzyme of SARS-CoV2 to explore their binding affinity toward virus sites [46–49]. The main limitation of these studies is that they were developed on computational basis exclusively, lacking experimental confirmation of the virtual results in most cases.

As highlighted by Wei et al. [50], a tsunami of literature on the molecular modeling, simulations, and predictions of SARS-CoV-2 and related developments of drugs, vaccines, antibodies, and diagnostics were published in the last two years. These studies, published with the aim to tackle the pandemic emergency, showed that the mechanism that governs evolution and transmission of SARS-CoV-2 cannot be revealed from individual experiments and techniques. Rather, useful data and results were gained by integrating biological and structural experimental data and advanced computational analysis [51–55].

3.2. Ligand binding

Integrating experimental and computational analysis is very useful to probe the interaction mode which underpins the binding of a ligand to a biological receptor. These studies are very important in drug discovery because the knowledge of the function of a specific framework in the receptor-ligand binding may be relevant in drug design, for instance, for the bioisosteric substitution of a group that can lead to enhanced potency, solubility, metabolic stability, and protein binding of the lead drug [56]. The structures of the ligands discussed in this section are reported in Fig. 3. Several studies focused on human serum albumin (HSA) as bioreceptor, this protein being the most abundant serum

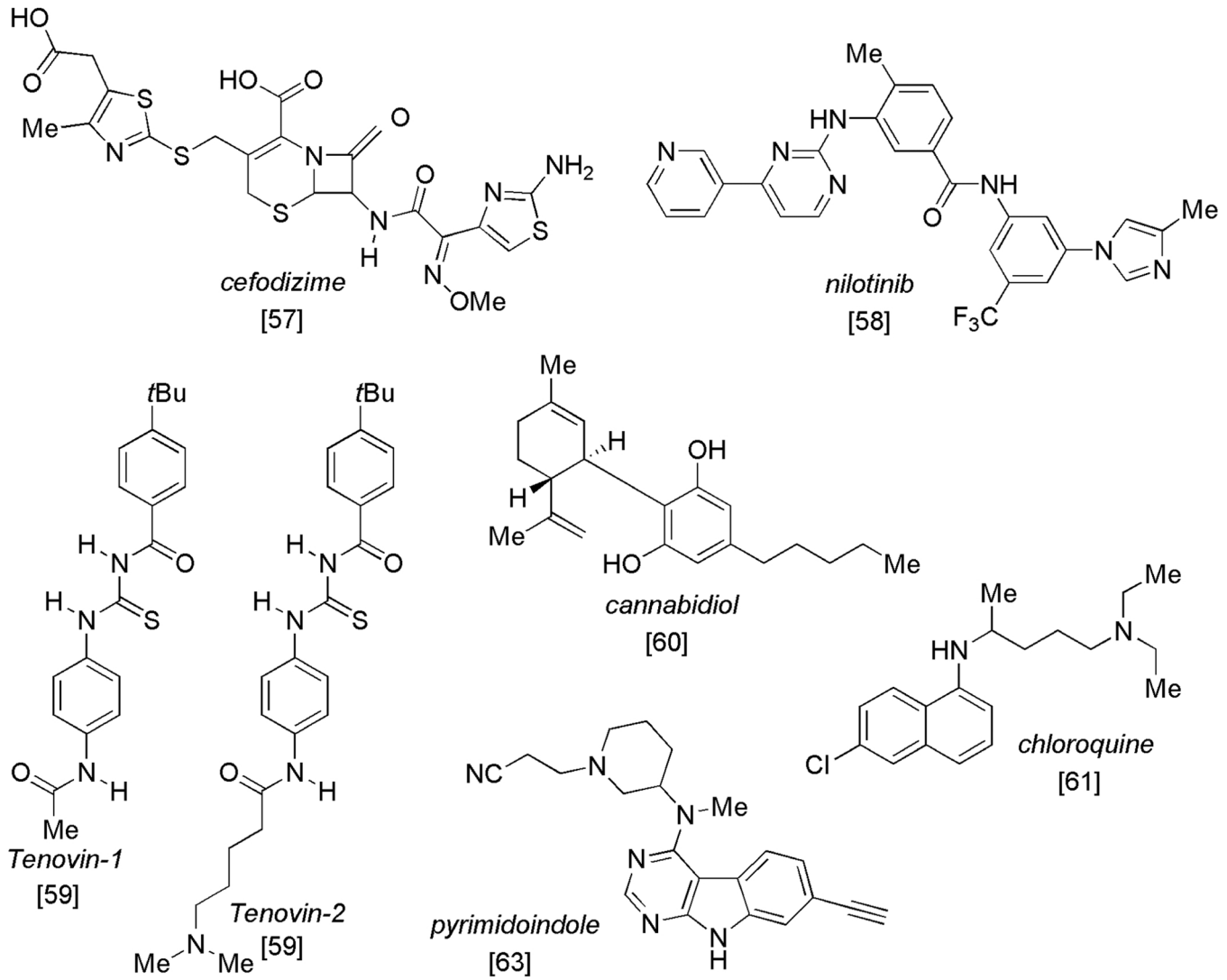

Fig. 3. Structures of the protein ligands discussed in Section 3.2.

protein, serving as a transport vehicle for several endogenous and exogenous compounds, such as fatty acids, dyes, drugs, and steroids. Liu et al. explored the interaction of cefodizime (CEF) with HSA by using spectroscopic techniques and molecular docking [57]. Based on the experimental results, it was considered that CEF was bound to site I (subdomain IIA) of HSA mainly by HBs and van der Waals forces. Molecular docking was applied to profile the interaction pattern of CEF with the amino acidic residues of HSA. Furthermore, three-dimensional fluorescence and circular dichroism results showed that the binding of CEF can cause conformational and some microenvironmental changes of HSA. These results provided reasonable models helping further understand the transportation and distribution of CEF when it spreads into human blood serum. More recently, other studies explored the binding mechanisms of ligand like tyrosine-kinase inhibitor nilotinib [58], sirtuin inhibitors Tenovin-1 and Tenovin-6 [59], and cannabidiol [60] to HSA. In all these cases, the studies were based on integration of molecular docking or MD, as modeling techniques, and experimental analysis like ^{1}H saturation-transfer difference (STD) nuclear magnetic resonance (NMR) spectroscopy, ^{19}F NMR spectroscopy, steady-state fluorescence quenching, CD, Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry, ITC, and surface plasmon resonance (SPR).

Lo Presti et al. combined high-resolution single-crystal X-ray diffraction experiment and density functional theory (DFT) calculations to investigate the intermolecular recognition of the antimalarial drug chloroquine in its bioactive deprotonated form [61]. The context of this study concerns the formation of some kind of heme-drug complex which is at the core of the antimalarial activity of 4-aminoquinoline drugs, including cloroquine. Furthermore, spectroscopic analyses and molecular modeling supported the relevant role of π···π stacking interactions between the quinoline core of the drug and the heme pyrrole subunits as interaction stabilizing the complex. On the other hand, a previous study of the same authors showed that a direct Fe−N (quinoline) coordinative bond might be also established in solution [62], the two recognition modes (π···π stacking or Fe−N) usually believed to be mutually exclusive. On this basis, the new study explored the noncovalent interaction network which determines how the drug interacts with its neighbourhood in the solid state, as a model for the drug-substrate recognition process. Strong charge-assisted HBs and, to a minor extent, π···π interactions were found to cooperate in determining the drug-substrate recognition mode in an acidic chemical environment. Furthermore, the chemical features explaining the heme-binding ability of chloroquine were profiled as follows: a hydrocarbon chain long enough to reach the propionic functions of the protoporphyrin system, a protonable strong basic function at the end of the chain, a less strong Lewis base at the other end of the molecule, able to saturate the axial position of the metal centre, and a flat aromatic system to further stabilize the complex through π···π interactions.

Very recently, the study performed by Koch et al. confirmed that water is not a passive bystander in small molecule binding, but rather takes an active role in the binding site, which may increase the strength of the inhibitor [63]. By integrating experimental analysis and microsecond timescale MD simulations, the authors demonstrated that, in the complex of a pyrimidoindole ligand with Glycogen Synthase Kinase-3β (Fig. 4), the high-energy water was not displaced by the inhibitor, rather only a subtle shift in the location of this water molecule resulted in a dramatic decrease in the energy of this high-energy hydration site.

3.3. Studies of biomacromolecule conformation, features, and function

In the last few years, classical and advanced MD simulations gave a significant contribution to probe the conformational dynamics of biomacromolecules, when the modeling approach was combined with experimental analysis to confirm the reliability of the theoretical data. Combined approaches were used to study, among others, structure and function of transaminase enzymes [64], of the actin homologue bacteria

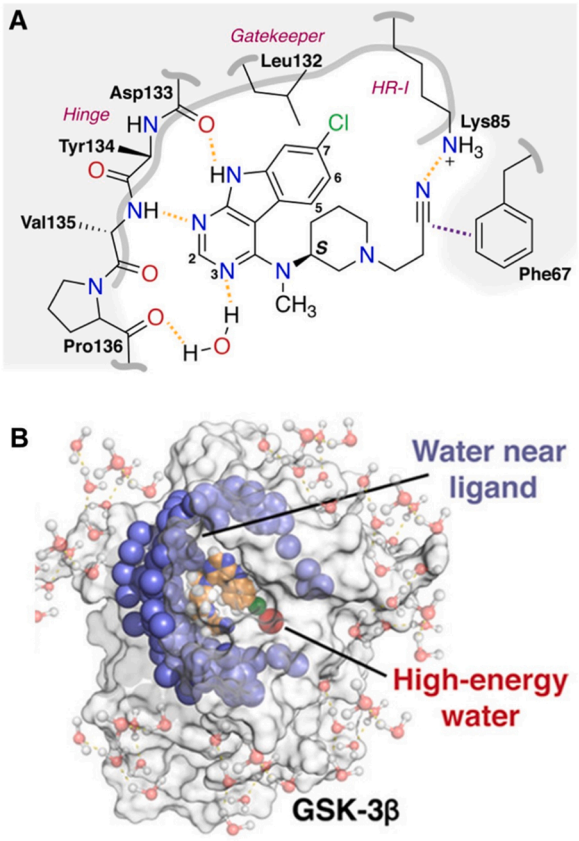

Fig. 4. Binding mode in the complex of pyrimidoindole ligand with GSK-3β: 2D depiction of the binding mode observed in the co-crystal structure of the complex (A); scheme of water role in the ligand-protein binding mode (B). Reprinted with permission from Ref. [63].

protein MreB [65], and of insulin [66]. This peptide hormone exists in the pancreatic β-cells as hexameric structure, while its biologically active form is monomeric. Given that insulin showed a series of conformational variations during the transition from the hexamer form to its biologically-active monomer form, MD greatly contributed to elucidate the conformational dynamics of insulin at molecular level.

In cellular processes like protein transport and degradation, signal transduction, gene regulation, and metabolism, protein-protein interactions are essential, promoting the formation of stable complexes of multiple proteins, rapid and transient hetero-oligomerizations, and dynamic polymers. Aberrant protein-protein interactions have been exploited as markers to trace human diseases, and the entry of pathogens into host cells. In this field, several studies highlighted the importance of 'molecular glues' action to stabilize endogenous protein-protein interactions or induces non-native interactions with clinically relevant effects [67]. Although no molecular glues were developed based on computational analysis so far, in silico interaction detection methods have been paving the way to new possibilities in this field. For instance, knowing the crystal structure of the protein-protein system, molecular docking allowed to screen molecules as potential 'glues', exploring their interaction modes. In several cases, this approach contributed to identify likely binders, significantly reducing the chemical space under investigation. In this field, Nemetski et al. performed docking to discover a protein-protein interaction stabilizer, confirming in silico results by crystallizing the compound in complex with both protein partners. The aim of the study was to stabilize *Plasmodium falciparum* aldolase with thrombospondin-related anonymous protein to lock these necessarily dynamic proteins in a single conformation for preventing malaria infection. By docking, the authors virtually screened a huge number of candidates, selecting sixty compounds for biological evaluation, and

thirteen with appreciable activity [68]. More recently, Lin et al. used docking to computationally identify molecular glue inhibiting Middle East respiratory syndrome coronavirus (MERS-CoV) replication (Fig. 5) [69]. First, the authors crystallized the N-terminal domain of the MERS-CoV nucleocapsid protein. Then, a set of three small-molecule databases were docked and, after multiple rounds of docking and filtering, three compounds were selected for further study. One of the compounds inhibited MERS-CoV by promoting oligomerization of nucleocapsid proteins within cells, and the crystallization of this compound with full length nucleocapsid protein revealed that it induced eight-membered nucleocapsid ring formation that inhibited the protein's active interface.

It is worth stressing that, the efficacy of in silico analysis in this field is strictly related to the availability of the crystal structure of the protein-protein complex under investigation, whereas it is low if only individual structures are known. Furthermore, application of docking may be ineffective when information on protein structure is missing. On the other hand, the structure of proteins which cannot be crystallized may be deduced from the crystal structure of analogous proteins in some cases. Moreover, new algorithms for designing protein folds and protein–protein interfaces have been used to engineer novel high-order assemblies and to design proteins with novel or enhanced properties, as well as signalling proteins with therapeutic potential [70].

3.3.1. *Simulations of biological membranes and their functions*

The primary function of biological membranes is their selective permeability that separates internal and outer regions of the cell. In computational simulations of membranes and their biological environment, one of the main issues is that the shape of biological membranes is continuously adapted to develop different functions. On this basis, membrane re-modeling processes involve multiple phenomena taking place at a different time and length scale [71]. For this reason, although several studies focused on the set-up of specific methodologies to tackle modeling of membrane structures and dynamics, currently methods are optimized on a case-to-case basis and at a specific scale [71–73].

Lipid bilayers are essential structural elements of living cells and are

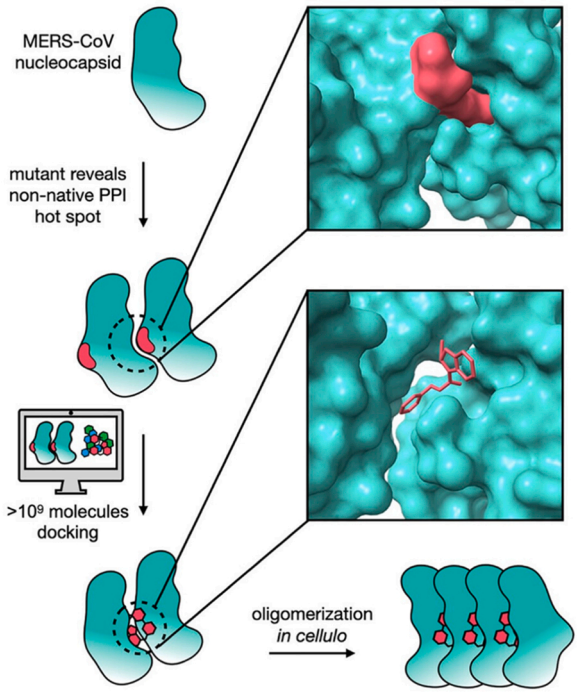

Fig. 5. Methodological scheme of computationally identification of a molecular glue inhibiting MERS-CoV replication.
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important for various cellular functions. In several studies developed on computational bases exclusively, MD simulations also were fruitfully applied to the study of lipid structure and function in cell membranes. In this field, de Groot et al. conducted MD simulations to investigate how different membrane environments affect protein structure and function, focusing on the case of MthK, a potassium channel. The results of this study showed how lipid-protein interactions affect the conformational equilibrium of a membrane protein. MD simulations were conducted using the GROMACS software package and the CHARMM36m force field. Interestingly, to test the robustness of their conclusions and its possible dependence on the choice of force field, the authors repeated some of the simulations using the AMBER14 force field for the protein and the Slipids force field for the lipids, confirming the first results and simulation reliability [74].

Very recently, other advanced MD simulations were conducted to study structure and dynamics of biomacromolecules involved in membrane processes like lipid scramblases of the TMEM16 (anoctamin), a family of membrane proteins that facilitate the passive transport of lipids across the membrane in response to an increase in intracellular Ca^{2+} concentration [75], and prestin, a high-density motor protein in the outer hair cells, whose conformational response to acoustic signals alters the shape of the cell, thereby playing a major role in sound amplification by the cochlea [76]. In the latter study, the results of course-grained MD simulations demonstrated a clear case of protein-protein cooperative communication in membrane, purely mediated by interactions with lipids.

3.4. *Liquid-phase separation of pharmaceuticals*

Although the weakness of molecular docking in terms of solvent and dynamics modeling, the use of this technique to understand the molecular bases of the binding affinity of analyte and separation matrix is very popular in separation science. However, given that the separation process of pharmaceuticals and drugs occurs in liquid-phase in most cases, MD sounds more reliable as simulation technique than docking. On the other hand, the application of MD in the field of liquid-phase separation may be not easy due to the following reasons: *a)* MD techniques were developed for modeling molecular species and processes occurring in biological environment. Thus, using MD software and methods in non-biological environment requires adaptation of MD parameters and algorithms; *b)* the construction of the virtual model of a synthetic or semi-synthetic matrix inducing separation or enantioseparation may be challenging given that crystallographic structures of this kind of materials are missing in some cases.

By parametrizing explicitly solvent, MD may be very useful to explore solvent-related effects. Phuong et al. used MD simulation to complement their experimental study on the green extraction of apigenin and luteolin from celery seed using combined betaine hydrochloride and propylene glycol as deep eutectic solvent (DES) containing 40% water [77]. Antisolvent (water) combined with distillation was proposed as an efficient method to recover apigenin and luteolin from the DES extract. A 500 ps MD revealed that betaine hydrochloride and propylene glycol could interact with each other by the formation of two types of HBs. Moreover, water molecules might play an important role in the interaction between the HB acceptor and donor components of DES.

Recently, Bagadi et al. reported the RP-HPLC separation of interconvertible rotamers of the sodium-2-(tert-butoxy)− 2-(5-(2-(2-chloro-6-methylbenzyl)− 1,2,3,4-tetrahydroisoquinolin-6-yl)- 4-(4,4-dimethylpiperidin-1-yl)− 2,6-dimethylpyridin-3-yl) acetate (SCMTDDA), designed and prepared as a HIV-1 integrase inhibitor, on a C18 column [78]. The chromatographic observations were complemented with variable-temperature NMR and energy barrier calculations of rotamers of SCMTDDA. For this purpose, a relaxed coordinate scan of the C5-C6-C21-C26 dihedral angle was performed using DFT calculations (Fig. 6). Two pronounced minima were identified around dihedral angles of 83.5° and - 97.5°. There was one pronounced maximum at

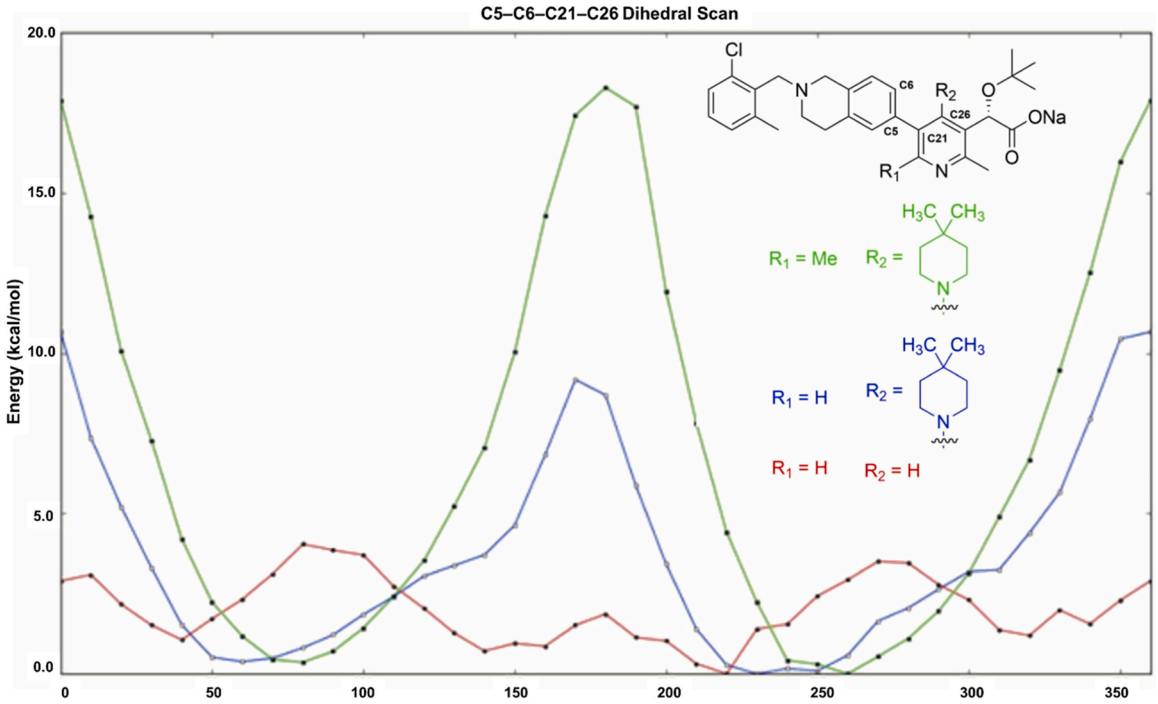

Fig. 6. Relative energy conformer for SCMTDDA in kcal/mol (green line) and related derivatives.
Adapted with permission from Ref. [78].

around 0° (or 180°) that was approximately 19 kcal/mol higher than the global minimum energy; thus, the transition of the molecule from one global minimum to another required overcoming an energy barrier of ~19 kcal/mol. Furthermore, variable temperature ^{1}H NMR studies confirmed the presence of restricted rotation around the C5-C21 bond. DFT calculation performed on analogues containing less hindered *ortho*-substituted on the pyridine ring, showing lower energy barrier compared to SCMTDDA, confirmed the presence of two conformational isomers generated by the restricted rotation around the C5-C21 bond.

3.4.1. *Liquid-phase enantioseparations of pharmaceuticals*

In the 1990s, drug-regulatory authorities recognized the importance of molecular chirality in drug action. In 2020, almost 60% of the pharmaceuticals approved by the Food and Drugs Administration were single stereoisomer [79]. This data confirms the importance of enantioseparation science in pharmaceutical and biomedical research. To develop enantioseparation methods based on the rational design of experiments and new innovative chiral selectors, understanding the molecular bases underlying the enantioseparation process is essential. In this field molecular modeling may play a relevant role. In the last few years, several reviews focused on molecular modeling of liquid-phase enantioseparations, or reporting applications in this field, were published [5,17,80–85], witnessing the interest of the scientific community in this topic. For this reason, in this section some comments about this topic as well as most recent applications in this field will be only pointed out.

Despite the urgency of understanding the molecular bases of the enantioseparations processes, while the application of molecular modeling is in advanced stage in fields like drug discovery, computational biology, and medicinal chemistry, further efforts are needed in the field of enantioseparation science. The reasons of this situation are multiple: *a)* enantioselective recognition processes are characterized by very low values of free energy differences between two competitive pathways ranging from 0.1 to few kcal/mol, and currently available theoretical tools may be still inadequate to describe properly such fine mechanisms; *b)* the inherent multistep feature of chromatographic and electromigration processes makes it difficult to deconvolute them at molecular level, compared to one-step enantioselective processes; *c)* prudence of scientists working in enantioseparation science toward first principle-based approaches to enantiorecognition; *d)* computational treatment of large multi-phase non-biological real-life systems is still in its infancy; *e)* theoretical and computational tools and software ecosystem are in constant growth, but this also leads to the lack of algorithmic interoperability between codes resulting in the publication of a series of non-confrontable and not homogeneous results; *f)* crystallographic structures are missing for some chiral selectors available in the market, and modeling this system is often approached on heuristic bases that still need proper validation.

In liquid-phase enantioseparation, molecular modeling is generally applied to determine structure and conformational properties of analytes and selectors, for studying the dynamics of the enantioseparation process, and for the stereochemical characterization of the chiral analytes. In this regard, it is worth stressing that determination of the elution order of the enantiomers is very important in enantioseparation science. When the absolute configuration of the eluted enantiomers is unknown, for instance in case of new chiral analytes, the stereochemical characterization can be performed by separating the enantiomers by HPLC, and assigning their absolute configuration based on X-ray diffraction [86] or electronic circular dichroism analyses coupled with time-dependent DFT calculations [87–89].

There is great interest in the application of molecular modeling for studying structure and function of polymeric selectors and the dynamics of related enantioseparation processes. Protein [90], macrocyclic antibiotics [85], and polysaccharide derivatives [83,91], as chiral selectors, are characterized by multiple binding sites able to exert various types of noncovalent interactions, this feature enabling their great versatility for the enantioseparation of various chiral drugs and pharmaceuticals in normal phase, polar organic, and reversed phase (RP) mode. On the other hand, this structural complexity limits the understanding of their enantioselective recognition mechanisms. Therefore, several studies combining experimental and computational analysis are focused on polymeric selectors. In this field, based on the chromatographic properties of native and W26-modified chicken alpha 1-acid glycoprotein (cAGP) columns and docking simulations of benzoin, chlorpheniramine

and propranolol, as chiral analytes, into the generated model structure of cAGP, Haginaka et al. profiled the chiral binding sites within the cAGP for the first time [92]. For this protein-based selector, in addition to hydrophobic interactions, ionic interactions between amino groups of chlorpheniramine enantiomers and a carboxyl group of the protein derivative were shown to play an important role in the enantioselective recognition, while hydrophobic interactions and HBs contributed to the enantioselective recognition of benzoin and propranolol enantiomers. Very recently, Carotti et al. profiled the retention mechanism of dipeptides on a ristocetin A-based CSP by combining chromatographic and molecular simulation techniques [93].

In enantioselective chromatography, HBs play a key role as leading noncovalent interaction, stabilizing the high-ordered structure of polysaccharide-based selectors (intramolecular HBs within the selector) [83,94], and contributing to the enantioselective recognition of chiral analytes (selector-selectand intermolecular HBs), as confirmed by recent MD simulation studies on the enantioseparation of atropisomeric 4, 4′-bipyridines of pharmacological interest with polysaccharide-based selectors [95,96]. Very recently, it was demonstrated by electrostatic potential analysis that an intramolecular HB within the analyte contributed to the large enantioseparation ($\alpha > 100$) observed for benzylsulfinylbenzamide with a dichlorinated cellulose-based selector [97]. Enantioselective intramolecular noncovalent interactions within the analyte are not frequent, but not unusual. For instance, a stereoselective HB within the analyte was also observed by Carotti et al. in the enantioseparation mechanism of carnosine with Teicoplanine based selector by MD simulations [98]. Later, again by MD, the same authors found that an intramolecular π-π stacking contributed to the enantiodifferentiation of the enantiomers of a tetrahydroindazole derivative with a brush-type selector [99].

Cyclodextrin (CD)-based selectors are widely used in capillary electrophoresis enantioseparations of pharmaceuticals. Both molecular docking and MD were used to model native and derivatized cyclodextrin and related processes. Also in this field, multidisciplinary approaches based on capillary electrophoresis, NMR spectroscopy, X-ray crystallography, microcalorimetry, and molecular modeling have shed light on some aspects of recognition mechanisms underlying enantiodifferentiation. Furthermore, modeling is helpful to explore the shape of derivatized CDs and its impact on the enantioselective recognition [84]. Very recently, by molecular modeling Chankvetadze et al. explored the affinity of β-CD and two charged derivatives toward tetrahydrozoline (THZ) enantiomers which were enantioseparated by capillary electrophoresis using these CDs as chiral selectors [100]. *V* analysis showed the impact of the charged substituents on the overall electron charge density of the selector system. Moreover, for the heptakis(2,3-di-O--acetyl-6-O-sulfo)-β-CD (HDAS-β-CD), a bowl-shaped structure was determined by calculation, with the secondary rim of the selector completely closed by the self-inclusion of acetyl groups. This could explain why the inclusion of aromatic moiety of THZ into the cavity of the macrocycle occurred through the narrower primary rim in this case.

Through MD, the geometry of the CD in complexed and non-complexed forms can be explored and compared in terms of degree of ellipticity, tilting of each glucopyranose unit with respect to the CD plane, and distribution of the possible conformations of the glucopyranose unit observable over the MD production time. Moreover, water content into the CD cavity can be quantified to evaluate the impact of the high energy water on the stabilization energy of the complex. From the methodological point of view, it is worth mentioning a recent study by Gilson et al. about the evaluation of force field performance in the thermodynamic calculations of CD host-guest binding by MD simulations, focusing on water models, partial charges, and host force field parameters [101], and comparing the results derived on computational bases to ITC experimental results.

Very recently, some aspects of the mechanisms underlying the complexation of the antiviral Daclatasvir (DCV) with γ-CD, studied in capillary electrophoresis, were investigated by Scriba et al. through MD, and the spontaneous formation of the DCV dimer in water was confirmed in accordance with the results of NMR and ITC experiments (Fig. 7) [102]. In this process, the first contact between the two DCV units occurred through HBs between the polar termini of each monomer, favouring the molecular embrace of the two units stabilized by π-π interactions involving the biphenyl moieties. Moreover, modeling results showed that in the DCV-CD complexation process, an intermolecular HB underlying the dimer weakens at the first stages of the inclusion process, evolving in new intermolecular DCV-CD HBs driving the inclusion into the macrocycle cavity.

3.5. Unravelling noncovalent interactions

As mentioned above, HB, dipole-dipole, π-π interactions, and coulombic forces are considered the most frequent noncovalent interactions acting to promote and regulate molecular binding, recognition, and function in chemical and biological environments. However, advancements in theoretical and experimental analysis contributed to deeply revise the scenario of noncovalent interactions, making this field very crowded with the identification of a huge number of new interactions, among them σ-hole interactions like halogen [7–9,103], chalcogen bond [10,104], and spodium bond [105], and π-hole bond [106].

Boeckler et al. targeted the gatekeeper MET146 of c-Jun N-terminal kinase 3 (JNK3) to exemplify the applicability of halogen···S halogen bonds in molecular design using QM calculations, synthetic, structural, and biophysical techniques [107]. In a designed series of halogenated aminopyrimidine-based inhibitors, by comparing QM calculated interaction energies, a plateau of affinity was observed as the halogen substituent changed. Otherwise, mutation of the gatekeeper residue into leucine, alanine, or threonine reveals that the heavier halides could significantly influence selectivity in the human kinome. Furthermore, determining the crystal structure of an iodine derivative in complex with JNK3 revealed an unusual bivalent halogen/chalcogen bond donated by the ligand and the back-pocket residue MET115. More recently, the same group used QM calculations and *V* analysis, integrating them with NMR analysis, and other biophysical techniques, to screen the diversity-optimized halogen-enriched fragment library against T-p53C-Y220C, the Y220C mutation of the thermally stabilized cellular tumor antigen p53, to identify hits and halogen bonds contribution to the ligand binding [108].

Recently, atropisomeric 4,4′-bipyridyl derivatives were evaluated as potential TTR stabilizers [109]. Some iodinated analogues of the series proved to significantly reduce enantioselectively fibril formation of wild type-TTR, the (*M*)-enantiomers showing slightly better inhibition activity against fibril formation compared to the (*P*)-enantiomers. Both experimental and docking results contributed to indicating the capability of iodine as halogen bond donor, halogen bond contributing to enhance ligand−protein binding.

In separation and enantioseparation science, σ- and π-hole interactions were identified in processes related to non-pharmaceutical analytes in most cases [8]. Recently, Haginaka et al. reported the preparation of monodisperse molecularly imprinted polymers (MIPs) by using methacrylic acid as a functional monomer and ethylene glycol dimethacrylate as a crosslinker by multi-step swelling and polymerization [110]. The separation of promazine derivatives with these MIPs was studied under hydrophilic interaction chromatography (HILIC) and RPLC conditions. The authors studied the intermolecular interaction modes and complex energies between promazine derivatives and methacrylic acid at the Hartree-Fock (HF)/6–311 G(d,p) level. On this basis, in addition to the shape recognition, ionic and hydrophobic interactions, halogen bonding and HB were found to work for the retention and molecular recognition of promazine and derivatives on the MIPs in RP mode. More recently, to develop a method for determination of warfarin and its metabolites in human serum, Haginaka et al. also exploited the same methodological approaches for preparation and use

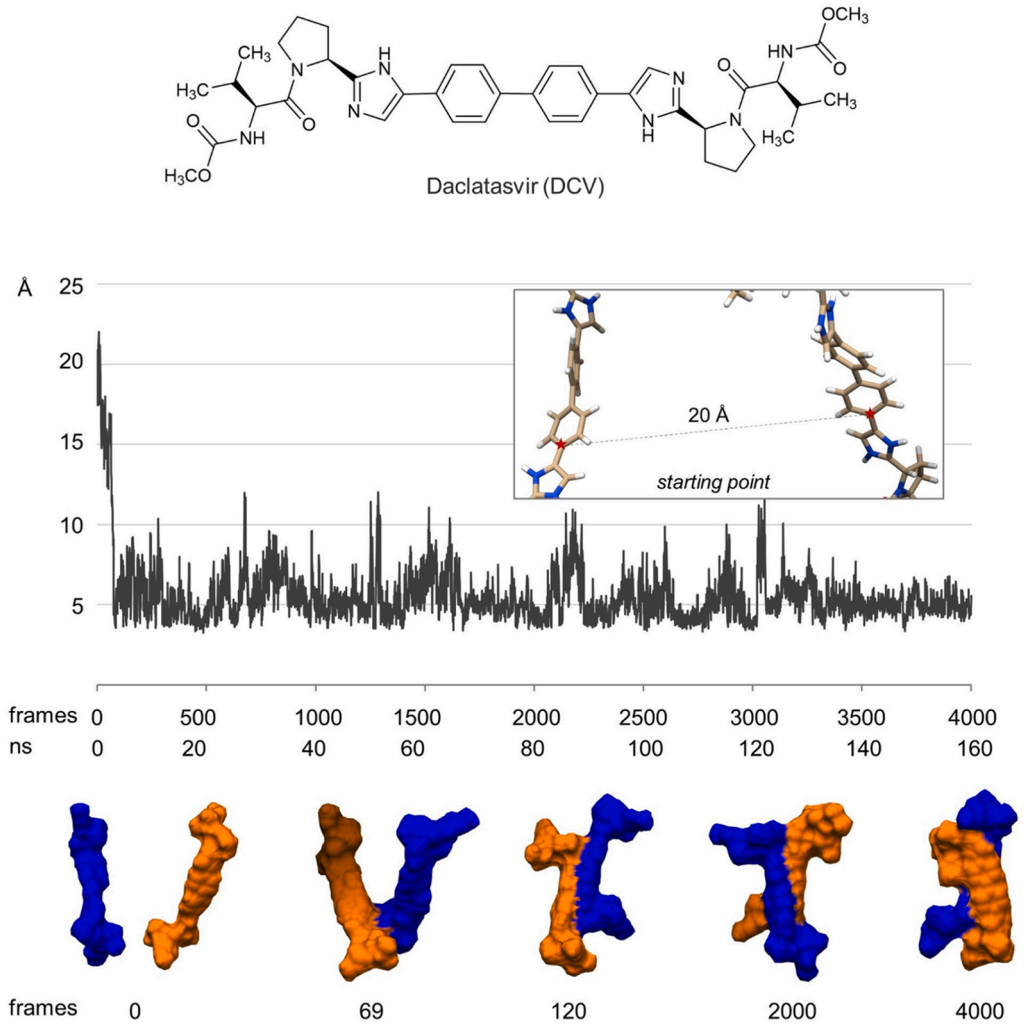

Fig. 7. Structure of DCV, and DCV-DCV dimer formation and distribution of the distances between the two aromatic carbons of two interacting DCV molecules (highlighted with the red stars in the insert) over 160 ns MD (4000 frames), initial distance = 20 Å.
Adapted with permission from Ref. [102].

of monodisperse MIPs for warfarin and derivatives starting from 4-vinylpyridine and ethylene glycol dimethacrylate as a functional monomer and crosslinker, respectively, by multi-step swelling and polymerization [111]. By using a combined approach based on ^{1}H NMR and HF calculations, three HB interactions were found to play important roles in retention and recognition of the warfarin derivatives on MIPs in HILIC and normal-phase modes, whereas HB, ionic and hydrophobic interactions in RP. It is worth mentioning that, in the last decade, computational design has become a routine procedure in the production of MIPs and has led to major advances in functional monomer screening, selection of cross-linker and solvent, optimisation of monomer (s)-template ratio and selectivity analysis [112].

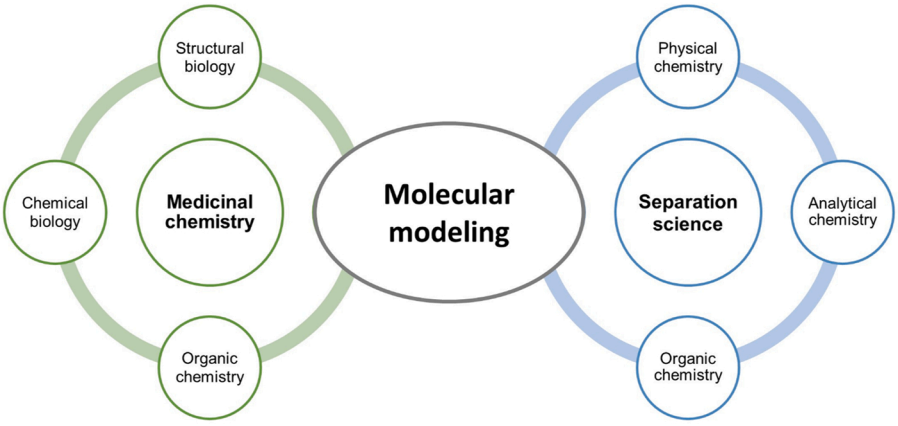

Fig. 8. Multidisciplinary approach to pharmaceutical and biomedical research.

4. Conclusion and future perspectives

Based on a modern and rational approach to scientific research, molecular modeling represents the *fil rouge* which goes across the main fields featuring pharmaceutical and biomedical research, medicinal chemistry and (enantio)separation science (Fig. 8). Modern approaches to medicinal chemistry to develop new drugs and targeting proteins, defining their structure and dynamics are based on multidisciplinary approaches integrating advanced techniques of chemical and structural biology, organic chemistry, and molecular modeling. In this field, investments and interests attracted in the frame of the Human Genoma Project allowed great advancements in bioinformatic and molecular modeling techniques. Furthermore, the availability of the crystallographic structures of a huge number of proteins and related complexes in the Protein Data Bank helped scientists build reliable virtual models of biomacromolecules using them as virtual platforms for advanced modeling studies. Despite that, while molecular modeling techniques are reliable enough concerning visualization and chemical space screening efficiency, the predictive power of the main models developed in the context of medicinal chemistry remains still insufficient. It is not positive to say that, until now, the only strategy to evaluate the efficacy of a prediction method developed on computational bases is to compare the prediction with the experimental results. On the other hand, for biological models, computational analysis provides better results with already known protein structures, whereas in real-life cases related to protein of unknown structures computational analysis may be not very effective. In this field, the main challenges for the future can be summarized in the following points: *a)* better scoring of binding to yield better predictions of free energy, and *b)* exploiting and accurately translating available structural information to new proteins that are difficult to work with experimentally. In (enantio)separation science, further improvements are needed, the main issue being the lack of crystallographic structures for certain selectors as benchmark molecular platforms for building reliable virtual structures and models of the separation process. The main challenges for the future in this field concerns: *a)* development of models able to account for small energy differences, in particular in enantioseparation science; *b)* better representation of long-scale time event; *c)* proper parametrization accounting for water (or other solvents used as mobile phase experimentally) which is often neglected; *d)* proper treatment of ionizable groups, this aspect is sometimes also neglected in virtual screening and structure-based drug design.

CRediT authorship contribution statement

Paola Peluso: Conceptualization, Writing – original draft. **Bezhan Chankvetadze**: Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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