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# Molecular Docking in Halogen Bonding

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Additional information is available at the end of the chapter

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## Abstract

Molecular modeling applies several computational chemistry tools as molecular docking; this latter has been useful in medicinal chemistry for prediction of interactions between small ligands and biological targets measuring angles, enthalpy and other physical-chemical properties involved in the supramolecular entities. In this chapter, we present molecular docking advances with a perspective to the improvement of parameterization including halogen bonding interactions (XB) and the modification of scoring functions based on halogen sigma-hole polarization. At the same time, we have included the current computational methods to study halogen bonding that increased the accuracy of predicted entities. Finally, we present examples of the main force fields including electronic distribution and modifications for halogen atoms.

**Keywords:** molecular docking, scoring functions, force fields, halogen bonding, molecular modeling,  $\sigma$ -hole

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## 1. Introduction

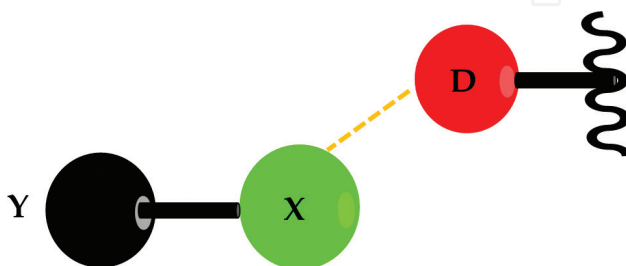
Molecular docking is a powerful computational method to predict the pose and intermolecular interactions between a small ligand and a specific receptor (in most of the cases), using algorithms and scoring functions to obtain numerical scores or thermodynamic properties from the most favorable molecular interactions through predicted supramolecular entities. The molecular docking is a useful tool for the medicinal chemist who wants to know with certain accuracy the outcomes for each project; it involves a low computational cost in the quest of utility for predicted compounds in several ligands, i.e., virtual screening. The accuracy of the molecular docking predictions came up from the algorithm and the scoring function that needs to be adequate for each objective. In recent years, it has been a goal to improve the

analysis and prediction of the halogen bonding interactions (XB) that several halogenated small compounds can perform and have a huge relevance in drug discovery.

The molecular interactions generated from a halogenated compound with a specific receptor could be addressed with molecular docking studies using quantum mechanics/molecular mechanics (QM/MM) approaches, combining a specific force field that could predict the chemical interactions of halogenated ligands based in their electronic distribution when they are close to an electronegative or electropositive atom. Here, we present some of current scoring functions (SF) used in molecular docking and some examples of works starting with the XB potential of mean force (XBPMF) that is a knowledge-based SF, following with the VinaXB, which is an implementation of the halogen bonding scoring function (XBSF) classified into the empirical-based SF. In order to improve molecular docking experiments regarding the XB interaction, in the last years, some force fields presented with high detail in here have been implemented and have been used by numerous researchers with fine performance and high accuracy; these are the optimized potentials for liquid simulations-all atoms (OPLS-AA), which is applied to biological macromolecules and the force field for biological halogen bonds (ffBxB) that implemented the anisotropic effect to investigate the XB between small compounds as ligands and specific receptors in molecular modeling.

### 1.1. Halogen bonding (XB)

The XB is defined as the interaction where a halogen is an electrophilic species and can be described as  $D \cdots X-Y$ , where X is the electrophilic halogen atom (Lewis acid, XB donor), D is the donor of electron density (Lewis base, XB acceptor) and Y is a carbon, nitrogen or halogen atom, and in this context, the X electrophilic halogen atoms are iodine, bromine and chlorine (**Figure 1**), and the fluorine halogen atom is not considered under this description because this atom does not have the capacity to form the  $\sigma$ -hole effect [1]. The ability of halogens to form interactions with electron donor species was reported unequivocal the first time by Guthrie in 1896 [2] where he reported the formation of ammoniac-iodine complex and described the properties and the necessary conditions to obtain this unusual interaction now. In the subsequent years, there are reports about the interactions between amines and the bromine and chlorine halogens. In 1970, Odd Hassel explained the similarities in halogen and hydrogen bonding and remarked the importance of this kind of interactions and the opportunity to understand the atomic arrangements in donor-acceptor complexes [3]. The study of XB interaction has become interesting to be studied in many fields including rational drug design under the basis



**Figure 1.** Schematic representation of a XB interaction, X = Lewis acid donor, halogen (I, Br, Cl); D = Lewis base acceptor; Y = carbon, nitrogen.

of medicinal chemistry and theoretical chemistry calculations using *ab initio* approaches [4]. Here, we describe the XB and their importance in biological systems, the theoretical and chemical bases, the computational methods that have been used to study this interaction to improve the drug design process and the recent applications in the computer drug design research.

### 1.2. Halogen bonding in drug design: an emerged non-covalent interaction

The importance of XB in drug design research has emerged from the past decade with the discovery of its importance in biological systems as potent stabilizing non-covalent interaction between ligand and receptor complexes. Although the first successful application of the XB concept was in 1996 by the optimization of an inhibitor of clotting factor Xa stressing, the importance of this kind of interaction started since the past decade with the discovery of a four-stranded DNA and aldose reductase complexes with halogens [5, 6]. As an example, one of the first applications of the XB interaction was the development of a compound that contains iodine atom in a pyridinone derivative identified as R221239 as inhibitor of reverse transcriptase in human immunodeficiency virus 1 [7] where the authors compare the reported angles between  $C-X\cdots O$  and their findings in the complex interaction between this inhibitor and the reverse transcriptase receptor. For 2009, around 25% was reported that the brand name drugs possess halogen atoms in their chemical structure becoming this type of atoms in important molecular scaffold fragments in drug design [8]. The insights about the XB concept have led to its implementation into the principal approaches of drug design process being the computational methods of the most useful approaches to predict this kind of interactions to improve the predictions through the computer calculations to generate accurate results that can help for the best design of compounds as drug candidates for many diseases [4]. The importance of XB in drug design has been compared with the hydrogen bonding (XB) interactions but with the difference that the first ones have some chemical properties in the strength and short distances between the atoms that form them [9].

### 1.3. Importance of halogen bonding in biological systems

Biological systems are composed of few elements from the periodic table, being based on carbon, oxygen, nitrogen, hydrogen, phosphorus and sulfur, but at the same time, few biological compounds contain halogens as iodine in the thyroid hormones functions [10], fluorine in bone-specific structures as teeth [11] and the chloride that has an anionic effect [12]. This type of elements is very important because they are not abundant in the cellular or subcellular structures, which means that they have specific interactions. In the human body, the presence of some biological compounds and ions that are halogenated starting with the thyroid hormones, the fluoride and chloride ions and its effect as anions playing an important role keeping the homeostasis of some important physiological mechanisms is well known. The beginning of the importance about the XB in biological systems started in 2003 with the discovery of a four-stranded DNA Holliday Junction that contains a bromine atom that played an important role in this type of macromolecular interaction [5] and the discovery of the complex aldolase reductase and a halogenated inhibitor at high resolution [6] where a bromine interaction was found as unusual showing short bromine-oxygen contact around 12% less

than their van der Waals radii of both atoms. These findings attracted the attention of medicinal chemists and theoretical chemists to search deeply the characteristics of these interactions. The thyroid hormones are the most studied and understood halogen compounds in biological systems where the iodine atom forms a halogen bonding with the oxygen atom in the binding site for the thyroxine with short I—O interactions that play essential roles for the highly recognition of these types of hormones. Also, the thyroxine hormone binds to RNA sequences through halogen bonds [13]. Although the fluoride is not considered as a halogen bond, its molecular mechanisms are the more studied in the aspect of the toxicity of this halogen that explains the high negative effect of this halogen in the cellular respiration, generation of reactive oxygen species, necrosis and apoptosis between others [14]. The halogen bonding has the effect of stabilizing inter- and intramolecular interactions that can stabilize ligand interactions and can affect molecular folding [15]. In drug design, the pharmacological research has included many halogenated molecules that are inhibitors (some of them approved), but only few times, this interaction is considered as important for the rational drug design process. There are many X-ray crystal structures in the PDB that contain halogen bonding interactions.

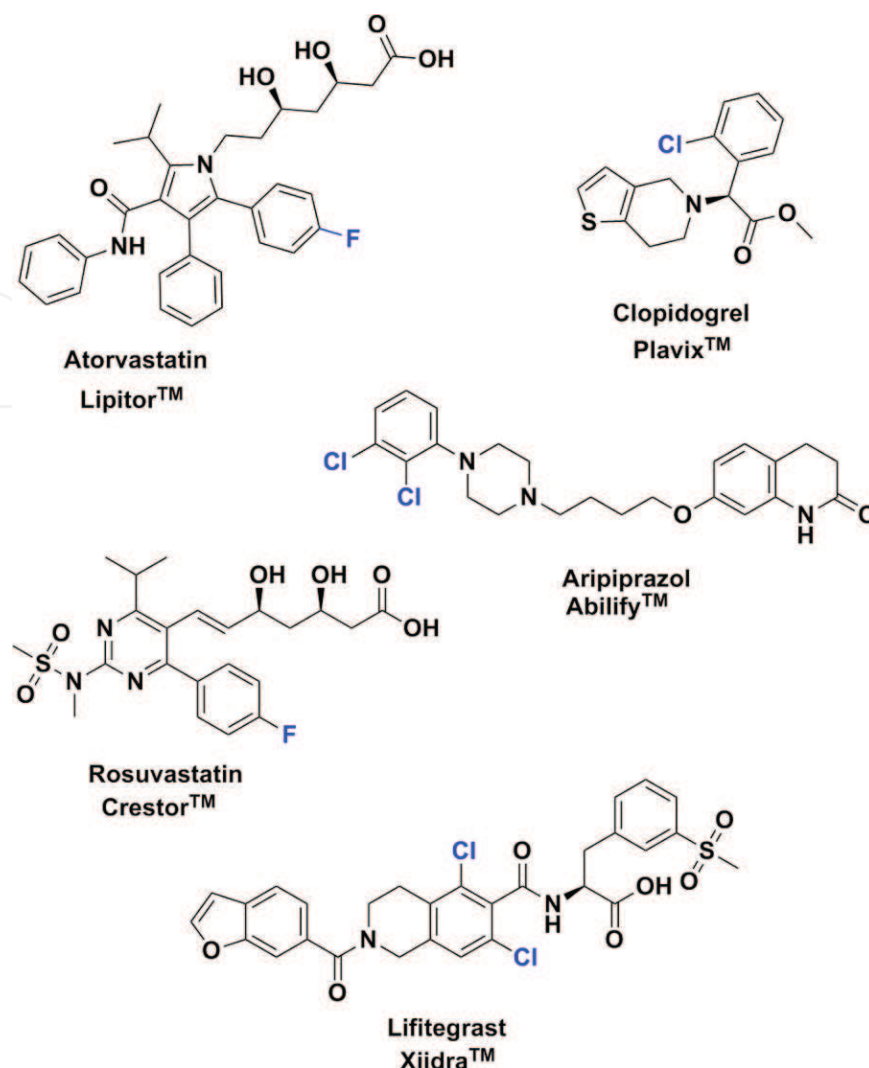
## 2. Halogenated drugs in medicinal chemistry

At present, the insertion of halogen atoms to improve the biological profile of a candidate compound has become an important strategy in drug development, and it is quite common in analogue-based drug discovery [16, 17]. Consequently, in medicinal chemistry the halogenation benefits include (a) increased membrane permeability, facilitating the blood-brain barrier crossing; (b) lower metabolic degradation, prolonging the lifetime of the drug; and (c) the addition of specific effects that enhance its binding to target macromolecules [18–20]. However, it was only recently that heavy halogen atoms are recognized to play an important role in the pharmacological activity through an interaction now defined as the halogen bond [21]. For this reason, it should not be surprising to find a greater presence of halogenated compounds at all stages of drug development.

In this context, the FDA has approved over 1582 new molecular entities (NME), of which approximately 20% are halogenated [22, 23]. On the other hand, 35% of the top 15 best-selling drugs between 2010 and 2016 were halogenated [24–26]. What is more interesting is that the pharmaceuticals called “blockbuster drugs” are mostly halogenated compounds (some examples are shown in **Figure 2**) [27, 28]. Additionally, a detailed analysis about the halogen atoms and statistical analysis of organohalogens and halogen bonds in medicinal chemistry were performed by Njardarson et al. [29], Hernandez et al. [18] and Zhu et al. [30], respectively.

### 2.1. Optimization of the halogenated drugs

The objectives to optimizing a drug are to increase their oral bioability and pharmacological pharmacodynamics and improve its metabolism. In the case of halogenated drugs, the influence of a halogen atom or substituents improves the thermodynamic parameters of the system (ligand-receptor pair), and the dissociation constant ( $K_d$ ) is positively modified [18].



**Figure 2.** Some halogenated drugs considered as “blockbuster” drugs.

The XB is an important approach in lead optimization of drug development and increases the binding affinity and binding selectivity [31].

### 3. Theory and concepts of halogen bonding

Considered as the first event in a chemical process, molecular recognition is a fundamental but complex step in the building of supramolecular entities [32]. Molecular recognition involves the synergy of a vast number of weak interactions, such as hydrogen bonding, and electrostatic, hydrophobic and other nonconventional interactions [33]. In this context, we can mention anion- $\pi$  stacking, hyper-coordination of carbon atoms and the  $\sigma$ -hole deformation that originates from the halogen bonding interactions [34–36].

Halogen bonding (XB) is a non-covalent interaction classified into Lewis acid-base bonding, where particularly in this species, halogen acts as the Lewis acid in front of neutral or anionic



Lewis base entities. This interaction was first reported by Guthrie in the middle of the nineteenth century; nonetheless, it has attracted attention after its “rediscovery” in the 1990s as a strong interaction even compared with hydrogen bonding [37].

The halogen bonding interaction is defined as pre-reactive complexes formed between species with a type  $Y-X\cdots D$ , where X is a halogen atom that can behave as an electron acceptor, D is a neutral or anionic nucleophile and Y could be nitrogen, oxygen, carbon, halogen, etc. Also,  $n$  and  $\pi$  electron pairs can form interactions as XB acceptors. It is well known that alkenes and arenes can form complexes with dihalogen molecules prior to formation of addition or substitution products [15].

Theoretical and experimental data about this phenomenon prove that the four halogens can act as XB formers marking a tendency in strength from the strongest  $I > Br > Cl > F$  to the weakest interaction. Charge transfer, polarization, concentration, temperature, solvent properties and the nature of A play an important role in the ability of halogen.

The XB interaction energy spans from 5 to 180 KJ/mol, giving stability to formed complexes and a typical interaction angle of  $\sim 180^\circ$ , leading to linear or slightly bended architectures in crystallographic data of available complexes, which correlates with the calculations that propose a deformation in the halogen  $\sigma^*$  molecular orbital. This phenomenon is called “the sigma hole” [15, 38].

Applications of XB properties are wide, covering crystal engineering design, improvement of conductor materials and the design of drugs.

The employment of halogen bonding in biomedical tasks is a new and interesting trend as the halogen can afford a short-range interaction (smaller to van der Waals interaction length) with electron-rich atoms involved in biological receptors and enzyme’s active sites [38].

The electron acceptor stage of a halogen atom is a fashion research topic due to its outstanding properties. The preferred complexes that are subject of study are those where B is a tertiary amine. For example, García-Garibay’s group recently reported the dynamics of a supramolecular rotor where the axle is based on this interaction between DABCO as an acceptor and 1,4-diiodotetrafluorobenzene as the halogen donor [39].

Applications of XB properties are wide, covering crystal engineering design, development of drugs and improvement of conductor materials.

Computational calculations help to explain, correlate and predict behavior of halogen donors and acceptors. The most accurate methods involve the use of quantum mechanics (QM) to calculate geometry and architecture of halogen bonding, but most of them are just available for small molecules. The development of different algorithms and methods is a useful tool to generate indirect experimental measurements of halogen bonding involving biological targets [38–40].

Interactions between proteins and drugs can be predicted by molecular docking; this method analyzes two crystallographic structures: one about biological target and the other about drug’s molecule. This computational experiment uses classic mechanic’s collisions, potential energy surfaces and some electrostatic and geometrical descriptors to correlate assemblies and enthalpy of the supramolecular complexes; the best methods will be treated further in this chapter.

## 4. Current computational methods to study the halogen bonding

As we have described so far in this chapter, the XB is relevant in drug design, and it requires to be studied and implemented by the current auxiliary computational tools and methods for drug design, and for this propose, the simulations of the  $\sigma$ -hole effect is a challenging task because not all the computational methods can achieve the accuracy to predict the distance, angle and strength of the interaction. There are references addressing algorithms to describe this phenomenon [41, 42], and the main parameters employed have been the charge-transfer (CT) complex, the electrostatic interactions (EI) and the polarization of the halogen atoms when they are in an environment where their behavior is as a Lewis acid. The XB interactions arise from a combination of EI, CT and dispersion interactions. Other important considerations are the net attractive Coulomb interactions that play a key role in the  $\sigma$ -hole interactions. One of the deepest methods to simulate the XB came from the coupled clusters with single and double (CCSD) substitution method which came from the Hartree-Fock determinant, and the CCSD (T) provides better results in the type of interaction; the lighter Moller-Plesset truncated at the second order (MP2) is valid for XB interactions [43].

It is important to consider that to apply computational methods in drug design, it is necessary to consider the use of those that are accessible and reliable for simulating. The docking experiments can help us to process a big amount of information through virtual screening where many compounds are halogenated, and in this sense, this calculation is more efficient to know how the halogenated ligand can bind in some specific target, but almost all the docking scoring functions are not capable to model the XB in a correct way, leading to some errors that we can interpret as false positives or vice versa. To address this point, there are some methods and approaches that allow us to model, search and know the best rank poses into a binding site, and this type of calculations is based on ab initio calculations and, in some cases, is modified as scoring functions into the docking algorithms with the software that are well known. The ab initio calculations can be performed with the evaluation of quantum mechanics/molecular mechanics (QM/MM) approaches. Therefore, some accurate methods play a key role in the prediction of binding free energy that rescores the best docking poses; the most useful method to do that is the molecular mechanics/generalized-born/surface area (MM/GBSA) [44]. Molecular docking is in some cases improved by this type of calculations, but now we described the molecular docking scoring functions as improved tools to get accurate predicted results in XB.

## 5. Molecular docking and halogen bonding

Molecular docking is classified into the structure-based drug design methods and is a good and extensively medicinal chemistry tool to predict the pose of a ligand in a specific region of the receptor structure. As is well known, molecular docking has two main components: scoring functions and search algorithms. The scoring functions can predict the affinity energy between the ligand and the receptor by calculations of the all possible interactions being the best ranked those that have the minimum energy ( $\Delta G$ ). One of the most used applications of molecular docking is virtual screening to find probable lead compounds against some specific receptor, because this method has the capability to do this and presents a less consuming time



of the calculations during the process, but we may say that not all of the scoring functions have the capacity to identify and predict the best XB interactions, and for this task, many scoring functions have emerged in molecular docking to improve and try to solve this problem.

### 5.1. Scoring functions to study the halogen bonding

There are some scoring functions to predict and model the XB in molecular docking and now are well known and designed knowledge- and empirical-based methods.

#### 5.1.1. Knowledge-based method

This type of scoring functions is based in pairwise interactions that came from experimental properties of molecular interactions of high-resolution X-ray crystal structures and most of the times came from the Protein Data Bank (PDB). The particularity of this type of scoring functions is that it improves the computational efficiency but lacks enough accuracy. In the case of XB scoring functions of this type, we can cite to Zhu et al. [45] who developed a scoring function named XBPMF (halogen bonding potential of mean force) that was developed from two high-quality training datasets of protein-ligand complexes. The XB and the hydrogen binding (HB) were characterized by two-dimensional potentials for taking the energetic and geometric preferences for ligand-receptor interactions. The authors establish that this scoring function was evaluated to have moderate power of predicting ligand-receptor interactions in terms of docking power that shows the ability of the scoring function to identify the original ligand conformation from a set of decoys and is reflected in the root-mean-square deviation (RMSD) of the best conformation of the ligand with the minimum free energy. At the same time, ranking power that is the ability to rank a set of ligands against a receptor by affinity, was obtained and is described as scoring power being good scoring function for high-throughput virtual screening.

#### 5.1.2. Empirical-based method

This type of scoring functions has been designed to estimate the free energy between ligand and its receptor when it is possible to know the structure information or it can be approximated [46]. This scoring function uses some parameterized functions based in physical or chemical properties, and the most important consideration is that this method is parameterized against training sets derived from experimental data [47]. One of the first empirical-based scoring functions was described by Watts et al., which considers local cooperative effects from the interaction between ligand and receptor [48] using a “small network” approach to describe how the environment affects to the non-covalent interactions as XB. The capability to predict with accuracy the binding affinities is when occurred small local changes in a ligand configuration, leading to obtaining the best affinity values.

More recently, Koebel et al. developed a new empirical-based scoring function that has been added to the most widely free used docking tool as AutoDock Vina (AutoDock VinaXB) that is an implementation of the halogen bonding score function (XBSF) [49]. This scoring function is derived on the  $X \cdots A$  distance and  $C-X \cdots A$  angle; other important parameters that are considered are the size and the anisotropic charge of the halogen atoms; and to define the halogen bonding term, an angle term was included to account for the varying positive charge on the atom (Eq. (1)):

$$E = W\phi D \quad (1)$$

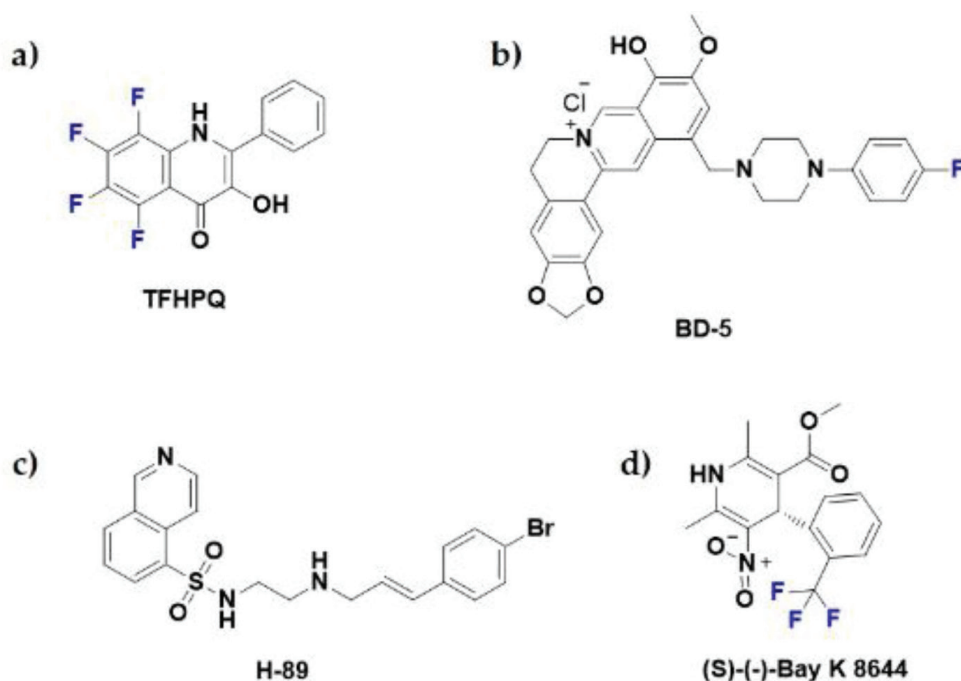
where  $W$  is the weight,  $\phi$  is the angle factor and  $D$  is the distance factor.

To validate the implementation of this scoring function, 106 halogenated ligand-protein complexes were evaluated with Vina and VinaXB finding that XB scoring function was closer to the original poses below 2 Å deviation twice than Vina.

## 6. Achievements and advances in the study of halogen bonding with modified and improved docking scoring functions

Derived from the development and implementation of scoring functions in XB in the past early years, there are few researches that apply this new scoring function. More relevant, we describe the most useful empirical-based scoring function VinaXB so far. As is well known, AutoDock Vina is a free docking tool, and the addition of the XB can be added to it. One of the first researches reported that the empirical-based scoring functions were used in the work developed by Pal et al. [50] where they reported the application of VinaXB scoring function in molecular docking experiments with an aberrant expression of Notch-1 in aldehyde dehydrogenase (ALDH) in cancer stem cells in breast cancer. The aim of using molecular docking was to search for the binding ability of psoralidin with gamma secretase where the best pose ranked with a value of free energy of  $-8.5$  kcal/mol was found suggesting that psoralidin binds to nicastrin in the micromolar concentrations. The docking studies let them know the main chain residues in the binding pocket with accuracy. Šeflová et al. [51] reported the effect of halogenated phenylquinolines specifically 5,6,7,8-tetrafluoro-3-hydroxy-2-phenylquinolin-4(1H)-one (**TFHPQ**) (**Figure 3a**) on  $\text{Na}^+/\text{K}^+$ -ATPase (NKA) where the experimental observations with the results from molecular docking using the VinaXB scoring function correlated. An important observation for these studies is that the compounds investigated firstly were optimized using density functional theory at the B3P86/631 + G (dp) level (289 K and 1 atm) and then were submitted to docking experiments to the open and closed NKA enzyme. The docking was performed in two steps: first, in a general screening with the whole protein, exhaustiveness was set to 400, and the number of modes was 9999; afterwards, they carried out redocking in the most favorable regions using the AutoDock VinaXB extension. The finding in this study that came from molecular docking was that the results provided a clue to the question why only **TFHPQ** inhibited in the in vitro studies to NKA, while other analogues can bind in the **TFHPQ** binding pose but were less active despite that all of molecules have similar chemical structure because the free energies were different by 1–3 kcal/mol, and in addition, they can bind in several sites of the NKA enzyme being different for **TFHPQ**.

Another well application of VinaXB scoring function is in the work developed by Enkhtaivan et al. [52] where they researched the ability of berberine-based derivatives (**BDs**) as anti-influenza agents against the neuraminidase using the VinaXB scoring function finding that **BD-5** (**Figure 3b**) has better affinity energies than oseltamivir that was used as a control in the utilized neuraminidase receptor.



**Figure 3.** Compounds analyzed in recent drug design projects using molecular docking with XB scoring functions.

The other most representative studies are the use of VinaXB scoring function by Fusi et al. [53] where they investigated the block of the vascular  $\text{Ca}_{2+}$  channel by the PKA inhibitor **H-89** (N-[2-[[3-(4-bromophenyl)-2-propen-1-yl] amino] ethyl]-5-isoquinolinesulfonamide) (**Figure 3c**) and the compound named **(S)-(-)-Bay K 8644** ((S)-(-)-methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl) pyridine-5-carboxylate) (**Figure 3d**) in rat artery myocytes. These docking experiments were carried out with a flexible docking in AutoDock with the VinaXB. The findings in this research established the differences between the poses of the analyzed compounds where the compounds positioned at the same binding region but in different binding pockets.

## 7. Quantum mechanics-derived scoring functions

In a normal docking experiment, the atoms are described by an atom type and a partial charge that fails when we want to describe the characteristic of anisotropic electron distribution in XB. In 2012, Jorgensen and Schyman described the additional positive charge in the  $\sigma$ -hole region using their optimized potentials for liquid simulations-all atom (OPLS-AA) that is a force field applied to biological macromolecules [54]. This force field has the ability to predict thermodynamic and physical-chemical properties of biomolecules in aqueous phase with high accuracy for organic liquid compounds and for 20 neutral peptide residues that were investigated first by Monte Carlo simulations where intramolecular terms for bond stretches, angle bending and torsions, as well as the intermolecular and intramolecular nonbonded interactions were taken for the final calculations similar to AMBER or CHARMM force fields, for example, that represent electrostatic interactions with a single partial charge on each atom.

To study the XB interactions with this useful force field at the quantum calculation level, one of the key modifications to the original force field was the inclusion of the X-site term to refer the XC, XB and XI for chlorine-, bromine- and iodine-halogenated compounds being a OPLS-AAx as the new term for the general force field where this X-sites have a stretching bond bringing constants for angle bending except for the fluorine atom. On the other hand, in 2015 as well, Rappé et al. reported the creation of force field named force field for biological halogen bonds (*ffBXB*) that implemented the anisotropic effect of the  $\sigma$ -hole in the bromine atom [55]. In this force field, the calculations are performed based on the anisotropic structure-energy relationships, calorimetric data and ab initio calculations specifically in bromine; in addition, the result was consistent with a charge-dipole electrostatic potential that could calculate and predict properly the XB interaction. Finally, Zimmerman et al. reported in 2015 a development of a scoring function named XB scoring function (XBscore) that includes the force fields described above and the next parameters based in the study of each XB property:  $\sigma$ -hole score that includes the angle, interaction geometry, tuning effects, the interaction partner and the type of halogen [56]. The spherical score comes from the MP2/TZVPP theory level. At least, Zimmerman et al. concluded that using a quantum mechanics calculation they could predict energies with high accuracy and that based in their scoring function quantum mechanics derived, it is possible to apply this term to improve the docking experiments.

## 8. Conclusions

One of the main objectives in computational medicinal chemistry is to generate useful predictions employing different tools that could be achieved through molecular modeling using computational approaches. This fact is very important during the implementation of strategies in the projects or protocols for drug development due to the different tasks and challenges in the quest of hit compounds. Molecular docking is an important part of this area bringing consistent advantages. It is a nice tool that decreases consuming time by allowing calculations with several compounds simultaneously, with the use of an appropriated scoring function, and including a suitable force field, the researcher could obtain positive results in many cases. Nevertheless, it is important to recognize that the halogenated compounds have no chemical behavior that is studied in most of docking programs; thus, it is necessary to take in account the scoring functions or force fields showed here if it is a need to carry out molecular docking with halogenated ligands. The concepts and fundamental aspects of XB are well known, their importance in the drug design and discovery processes, thereby, the non-covalent interactions involving halogens as Lewis acid donors and the Lewis base acceptors have become in an important issue during pharmacophore design suiting halogenated ligand or drugs using computational approaches and methods. Here, we have described the main aspects about the computational considerations, specifically in molecular docking because it remains the tool to investigate the type of ligand-receptor interactions, and the XB represents a challenge due to its electronic anisotropic effects that we need to define and select for the best scoring function to achieve accurate results and to predict good results about the interactions in the supra-macromolecular chemistry leading to the improvement of some techniques and methods in the computer-aided drug discovery field.

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