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Some remarks about the relationships between the common skeleton concept within the Klopman-Peradejordi-Gómez QSAR method and the weak molecule-site interactions

Juan S. Gómez-Jeria[1,3], Andrés Robles-Navarro[1], Gaston Assongba Kpotin[2], Nicolás Garrido-Sáez[1], Nelson Gatica-Díaz[1]

[1]Quantum Pharmacology Unit, Department of Chemistry, Faculty of Sciences, University of Chile. Las Palmeras 3425, Santiago 7800003, Chile
[2]Department of Chemistry, Faculty of Sciences and Technologies, University of Abomey-Calavi, Abomey-Calavi, Republic of Benin
[3]Glowing Neurons Group, CP 8270745 Santiago, Chile
Corresponding author: facien03@uchile.cl

Abstract The Klopman-Peradejordi-Gómez (KPG) method relates the variation of the numerical values of a biological activity, measured *in vivo* or in *vitro*, with the variation of the numerical values of a set of local atomic reactivity and orientational parameters of the substituents indices belonging to a certain skeleton, defined as a set of atoms common to all the set of molecules under study. The KPG method was developed only for weak molecule-site interactions. The local atomic reactivity indices appearing in the KPG equations allow suggesting the possible nature of the (weak) atom-site interactions. It has been found that an atom/group-site weak interaction table is urgently needed to standardize the physical interpretation of the results. We present here such a Table built from the Discovery Studio Visualizer software. We expect that this table of atom/group-atom/group interactions will also serve as a beacon of light across the path to find the possible relationships between KPG and docking studies.

Keywords Klopman-Peradejordi-Gómez method, QSAR, chemical reactivity, common skeleton, weak molecular interactions, drug-site interaction, atom-atom interaction, quantum pharmacology

Introduction

Molecular interactions (intermolecular and intramolecular) are still studied experimentally and theoretically in different combinations of phases: solid-solid, solid-liquid, liquid-gas, etc [1-9]. Within this research area, the endogenous molecule-site (enzymes, neurotransmitters, etc.), drug-receptor or drug-site interactions are of paramount importance in many biological and pharmacological processes. The research area searching for relationships between the electronic structure and biological activity produces yearly a plethora of linear and nonlinear equations relating both topics. In the case of weak intermolecular interactions we expect that some structure-activity relationships allow us to get an insight on the possible nature of these interactions.

The Klopman-Peradejordi-Gómez method (KPG hereafter) is a member of the class of model-based methods [10]. As a paper presenting its scientific and philosophical foundations was recently published, here we shall present only a very general description [11]. The method is based in solving a system of N linear equations relating a certain

biological activity (originally the KPG method was developed only for experimentally measured drug-receptor affinities)with a set of local atomic reactivity indices (LARIs) belonging to a molecular structure common to a group of N molecules. If we consider that each atom of this common skeleton is described by twenty local atomic reactivity indices and that the smallest common skeleton we have employed has about ten atoms, in this simplest case approximately 200 constants must be found for the system of linear equations (N=200). To this large set of data sometimes we must add the values of the orientational effect of the substituent. As no paper publishes the experimental data for such a large number of molecules, we cannot solve the system of linear equations. This is the only reason why the traditional techniques of Linear Multiple Regression Analysis (LMRA) are employed to find a solution. In this last case the results appear in the form of a linear equation satisfying all required statistical tests. This equation shows a relationship between the *variation* of the value of a biological activity and the *variation* of the numerical values of a set of local atomic reactivity indices. This involves two important facts. The first one is that the equation contains no LARIs having a constant value. The second fact is that the equation does not contain those LARIs the variation of whose numerical values is not statistically significant. Then, this equation displays at most the importance of *some* atoms and *some* substituents. It is important to stress that the KPG model was developed only for weak interactions (i.e., molecular interactions with no formation of covalent bonds) [12-15].

On the other hand, we have carried out some docking studies for a diversity of molecules and receptors [16-23]. Given that docking procedures are less exact than the KPG results, when we have found what at first glance seem to be discrepancies between the results of both methods, we have suggested that it is more likely that the results of the docking procedure are probably not accurate. It should be emphasized that the KPG method works with atom-atom interactions while docking techniques are not restricted to these types of interactions. However, some results of the KPG method suggest that there is a possibility that interactions of different types of a single atom with two different sites are represented through the appearance in the QSAR equation of more than one reactivity index associated with the same atom. This fact deserves more research.

To achieve this goal it seems necessary to create a Table of the different atom/group-site weak interactions. This table will also serve to standardize the interpretation of future KPG-QSAR results.

The common skeleton

The common skeleton is defined as a set of atoms, forming a connected or non-connected structure. These atoms are common to all the molecules analyzed.

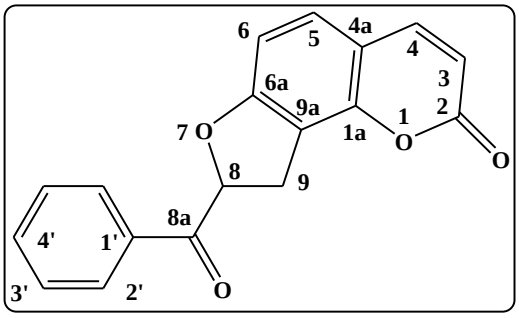

Figure 1: Common skeleton of angelicin derivatives [29]

Let Θ the set of n molecules θ_i considered for a KPG study. Then:

$$\Theta=\{\theta_1,\theta_2,.....\theta_n\}$$

Let Ξ the set of p atoms ε_i forming the common skeleton:

$$\Xi=\{\varepsilon_1,\varepsilon_2,...\varepsilon_p\}$$

Let Ω the set of all elements, τ_i, of the Periodic Table:

$$\Omega=\{\tau_1,\tau_2,....\tau_i\}$$

In the first applications of the KPG method atom ε_i was taken as being of the same nature in all molecules: for a given atom ε_i, $\varepsilon_i = \tau_j \ \forall i$ (for example, the fifth atom of the common skeleton was a carbon atom in all the set of molecules under study) [24-28]. Figure 1 shows an example of this kind of common skeleton [29].

Over time the definition of common skeleton underwent two important changes. The first one was to accept that a particular atom of the common skeleton does not need to have the same nature in all the molecules. Figures 2 and 3 show some examples.

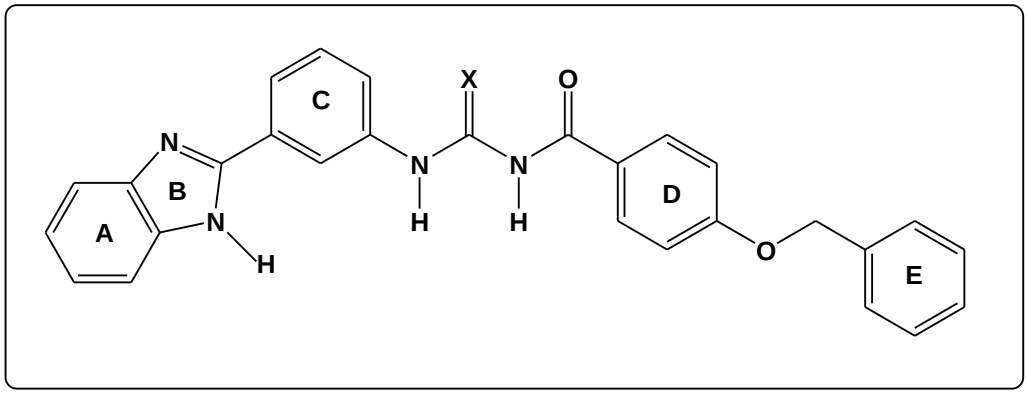

Figure 2: Common skeleton ofN-3-benzimidazolephenylbisamide derivatives [30].

Figure 2 shows an example of common skeleton in which atom 'X' is not the same in all cases (X= S *or* O) [30].

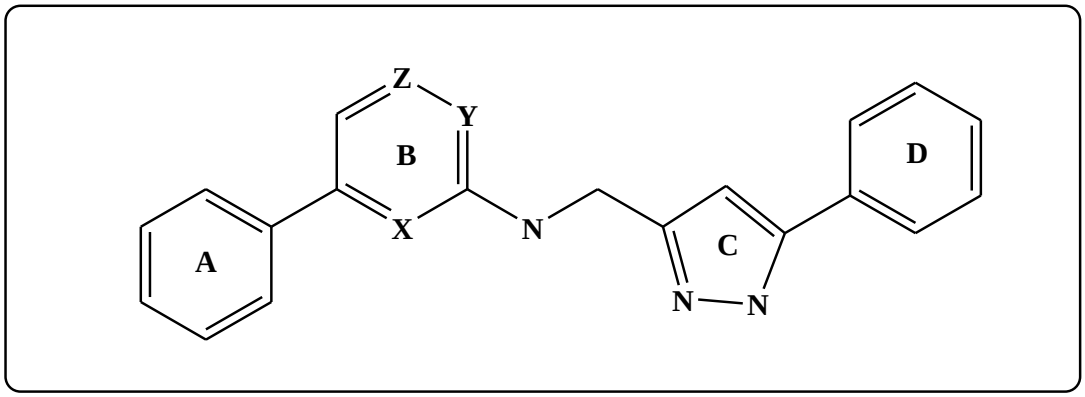

Figure 3: Common skeleton of phenylaminopyridine derivatives [31].

Figure 3 shows another case in which atoms 'X', 'Y' and 'Z' are different (X, Y and Z are C *or* N) [31]. The second change was mainly related to substituents bonded to atoms belonging to aromatic zones of the molecules. In some QSAR studies it was not possible to obtain statistically significant results with the abovementioned definitions of the common skeleton. Good results appeared only when the local atomic reactivity indices from the atom of the substituent directly bonded to the aromatic zone were included (note that if a substituent at a certain position has two or more atoms in *all* the molecules, the common skeleton may be enlarged with these atoms).A recent possibility, that has not been tested yet, considers the case in which a common skeleton has N atoms for all but one molecules, this last one having (N-1) atoms. In this case, *only* the local atomic reactivity indices having numerical values equal or greater than 0.0 should be included for the case of the missing atom.

An additional problem is represented in the following figures. Figure 4 shows an aromatic ring of a molecule interacting simultaneously with two amino acids of the binding site through π-alkyl and π-sigma interactions (see below). It is not clear the number of atoms participating in the interaction thorough their π electrons.

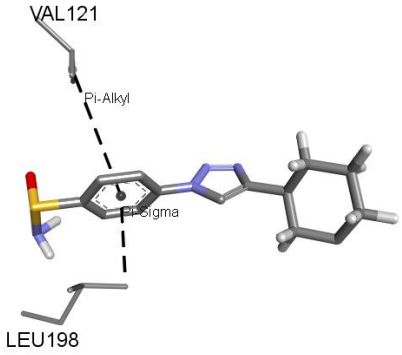

Figure 4: Example of a simultaneous interaction of a molecule with two sites

Figure 5 shows an aromatic ring of a molecule interacting simultaneously with three sites through one π-donor, one π-cation, π-donor and two π-π T-shaped interactions (see below).

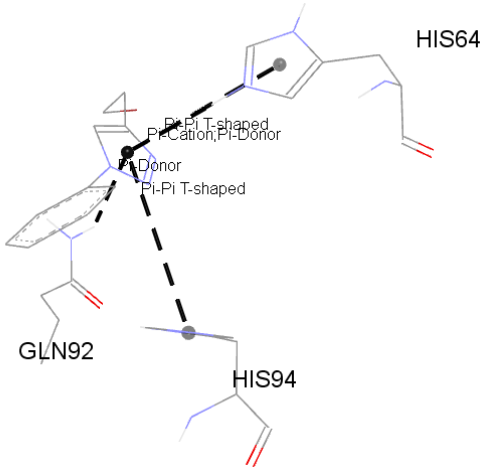

Figure 5: Example of a simultaneous interaction with four sites

The conceptual approach as a tool to use before any quantum chemical calculation

It is possible to employ the common skeleton to generate *previous* and detailed information about *possible* drug-site interactions before carrying out the electronic structure calculations or any QSAR study. For this task we need a pen, a paper, the structure of the proposed common skeleton and a list of non-bond interactions. With these elements we may create and analyze our set of molecules searching for similitudes and differences.

A Weak Molecular Interactions List

To build a preliminary list of non-bond molecular interactions, we have used the list of Discovery Studio Visualizer, v. 17.2.0.16340 from Dassault Systèmes Biovia Corporation [32] for the corresponding definitions and requirements. The definitions and requirements were copied directly from the Help section of the software. For almost all interactions we provided examples taken from our previous docking [16-23] or metallic surface-molecule interactions studies [33-37]. This Table was cited in a previous work as being an interesting starting point for future developments [11]. There are previous lists of molecular interactions [38] but we selected this one because it seems that if more complete and well ordered.

A. Hydrogen bonds

Within this category the following types are included: classical hydrogen bond, non-classical carbon hydrogen bonds (weaker hydrogen bonds), non-classical π-donor hydrogen bonds and salt bridges [32].

a1. Conventional hydrogen bonds [38-46]

Conventional hydrogen bond interactions can exist between a hydrogen bond donor atom (D) and an acceptor atom (A). Atoms N, O, P and S are considered to be classical hydrogen bond donor atoms, and hydrogen atoms are considered as hydrogen bond donors if connected to such atoms. Atoms of element types N, O, P and S are also hydrogen bond acceptor atoms if at least one electron lone pair is present.[32]Atoms of elements F, Cl, Br and I are also considered hydrogen bond acceptor atoms.If both atoms are N or O, the distance between the heavy donor and acceptor atoms is about 3.4 Å. Otherwise the distance is 3.8 Å (weak H-bond) [47]. Figures 6 and 7 show examples of conventional H-bonds.

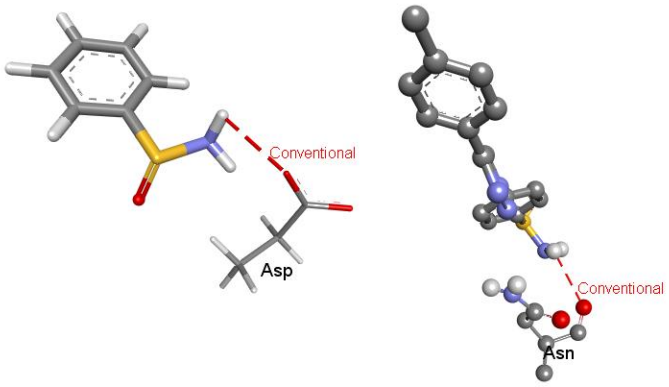

Figure 6: Conventional hydrogen bond between molecules and amino acids (red = O, blue = N, white = H)

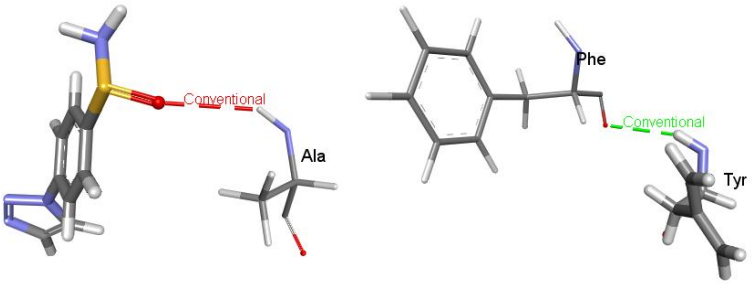

Figure 7. Conventional hydrogen bond between molecule and amino acid (left) and between amino acids (right) (red = O, blue = N, white = H)

a2. Salt bridge [48-58]

Salt bridge interactions are relatively strong non-bonded interactions between pairs of oppositely charged groups where hydrogen bonding also occurs. Interactions are classified as salt bridges for pairs of atoms where one atom is positively charged, one is negatively charged, *and there is a hydrogen bond between them*[32]. Figures 8 and 9 show some examples of this kind of interaction.

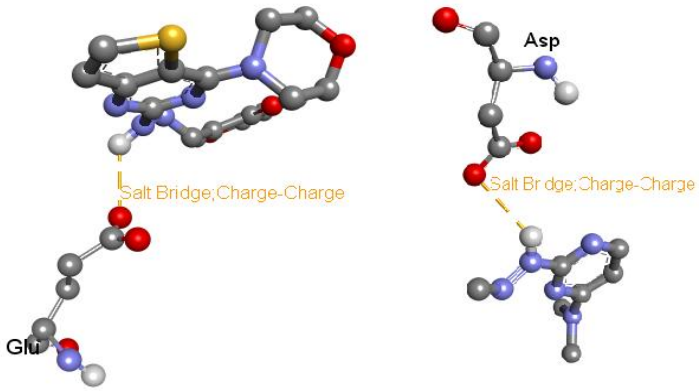

Figure 8: Examples of salt bridge interaction

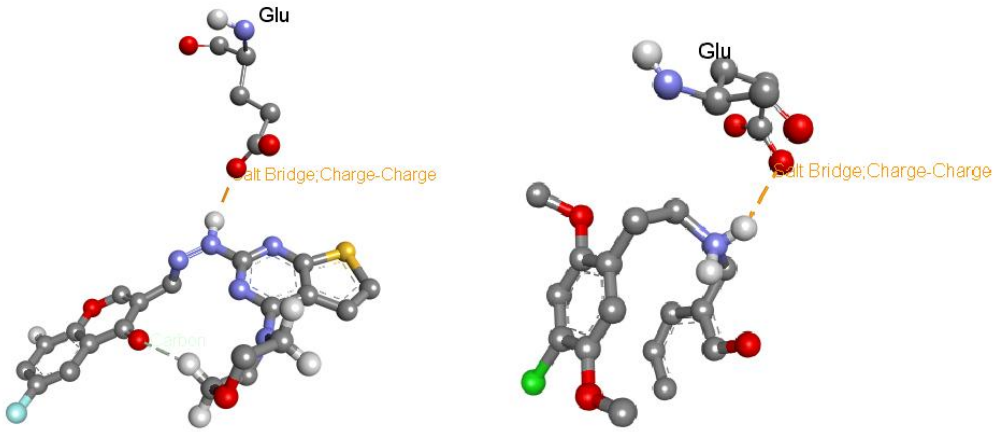

Figure 9: Examples of salt bridge interaction

a3. Non-classical carbon hydrogen bonds (weaker hydrogen bonds) [59-65]

Carbon hydrogen bond interactions are considered weaker hydrogen bonds where the donor is a polarized carbon atom. A carbon atom is considered to be a donor if it is *either in an acetylene group or if it is adjacent to an oxygen or nitrogen atom* [32]. Figures 10 and 11 show some examples.

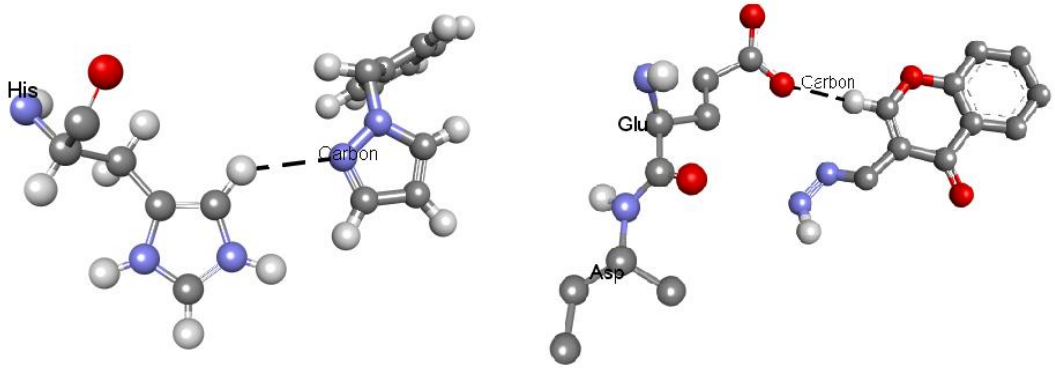

Figure 10: Examples of carbon hydrogen bond interaction.

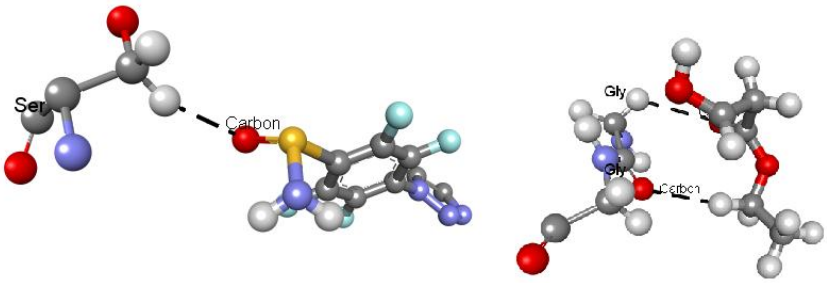

Figure 11: Examples of carbon hydrogen bond interaction

a4. Non-classical π-donor hydrogen bond

π-donor hydrogen bond interactions are hydrogen bonds that occur between hydrogen bond donor atoms and a π ring that functions as a hydrogen bond acceptor [32]. Figures 12 and 13 show two examples of this interaction. The question of the participation of the entire π ring or part of it in this kind of interaction is not yet solved.

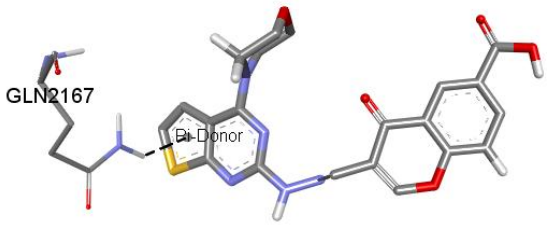

Figure 12: Example of π-donor hydrogen bond interaction

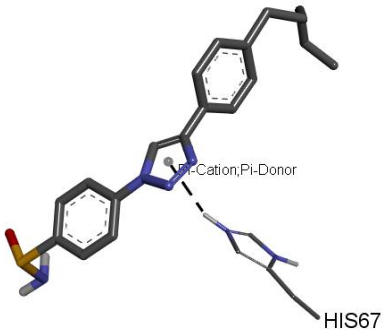

Figure 13: Example of π-donor hydrogen bond interaction

B. Electrostatic interactions

Within this category we include attractive charges interactions, salt bridges without hydrogen bond, π-cation and π-anion interactions [32].

b1. Attractive charge-charge interaction [66-69]

Attractive charge interactions exist between atoms bearing opposite whole or fractional formal charges that are within the charge-charge maximal distance of 5.6 Å (by default in the software) [32]. Figure 14 shows two examples of such kind of interaction.

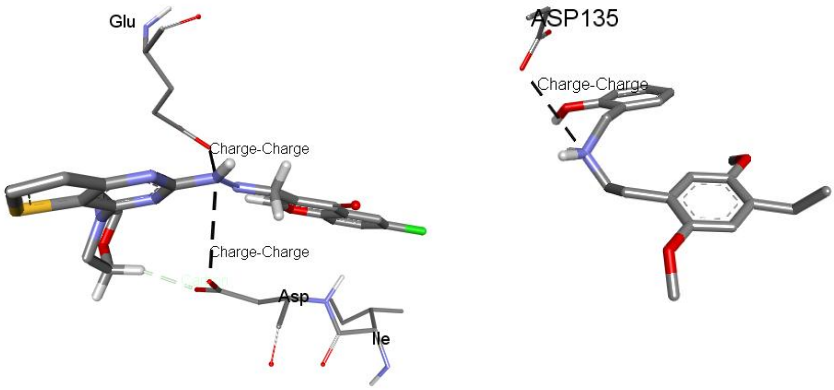

Figure 14: Examples of attractive charge-charge interactions

b2. Salt bridge (see a2)

Salt bridge interactions are also recorded in the electrostatic category as well as in the hydrogen bonds category because they can be considered members of both [32].

b3. π-cation interactions[70-78]

π-cation interactions can exist between a positively charged atom and the electrons of a delocalized pi system [32]. Cations are considered to be atoms that have a net charge of at least +0.5. This permits the inclusion of delocalized

cationic species such as lysine and arginine side chains [32]. Figure 15 shows two examples of this kind of interactions. The question of the participation of the entire π ring or part of it in this kind of interaction is not yet solved.

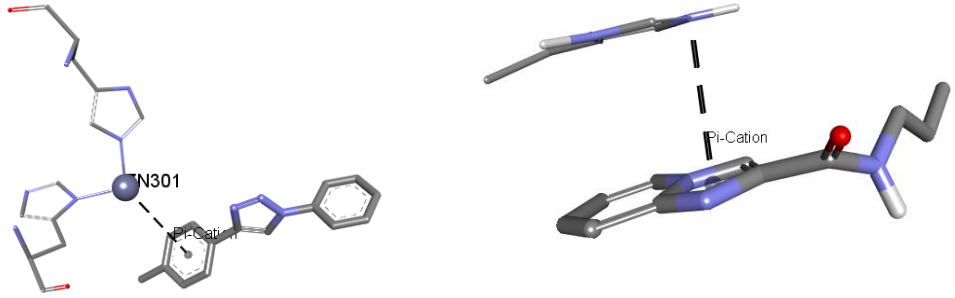

Figure 15: Examples of π-cation interactions

b4. π-anion interactions[79-85]

π-anion interactions are calculated in the same manner as π-cation interactions, but only atoms with net charges of -0.5 or less are considered[32]. Figure 16 shows two examples. The question of the participation of the entire π ring or part of it in this kind of interaction is not yet solved.

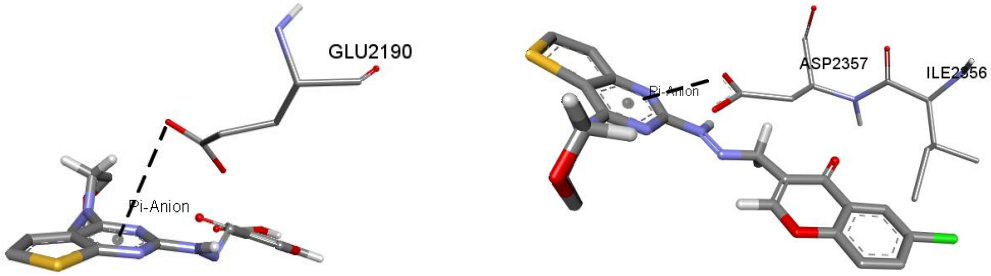

Figure 16: Examples of π-anion interactions

C. Hydrophobic interactions

They include π-π stacked, π-π T-shaped, amide-π stacked, alkyl, π-σ and π-alkyl interactions.

c1. π-π stacked interactions[86, 87]

π rings are defined as planar ring systems composed of sp^2 hybridized atoms. They include (but are not confined to) aromatic rings [32]. The conditions to define this interaction are those of McGaughey et al. [88]. Figure 17 shows two examples. The question of the participation of the entire π ring or part of it in this kind of interaction is not yet solved.

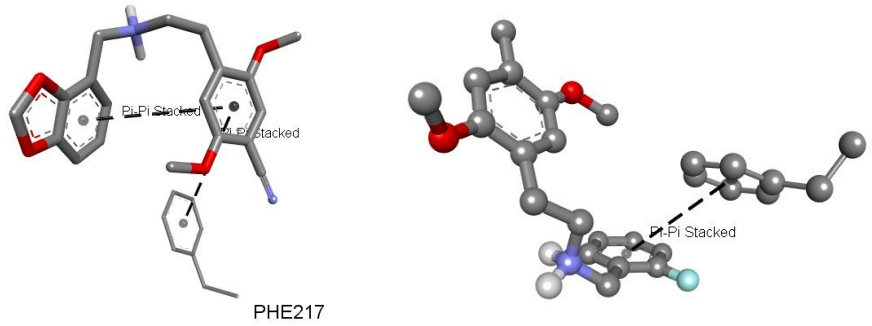

Figure 17: Examples of π-π stacked interactions

c2. π-π T-shaped interactions[89, 90]

π-π T-shaped interactions happen if the following conditions are met [32]: (1). The distance between the centroid of each pair of π rings is determined to find those which fall within the π-π centroid (max. distance) cutoff distance (6

Å by default), and (2). An atom from each ring should be within the π-π closest atom (max. distance) cutoff (4.5 Å by default) [32]. Figure 18 shows a couple of examples. The question of the participation of the entire π ring or part of it in this kind of interaction is not yet solved.

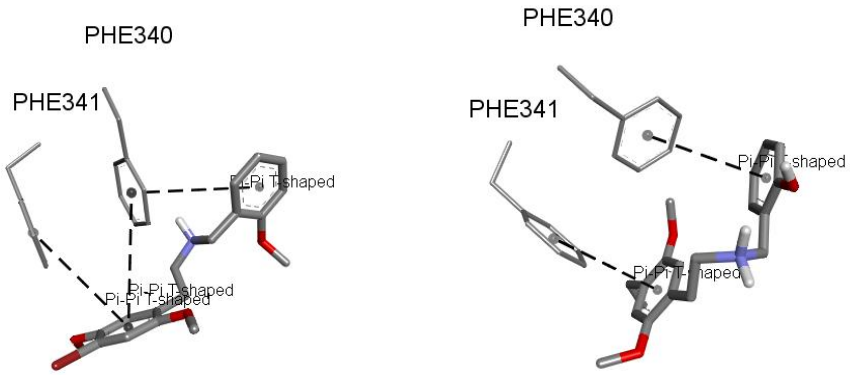

Figure 18: Examples of π-π T-shaped interactions

c3. Amide-π stacked interactions

Amide-π stacked interactions occur between an amide group and a π ring [32]. Regarding the π systems the following criteria must be met: (1). The distance between the centroid of the amide group and the π rings falls within the π-π centroid (max. distance) (6 Å by default) [32] and (2). An atom from each group should be within the π-π closest atom (max. distance) (4.5 Å by default) [32]. Figure 19 shows an example. The question of the participation of the entire π ring or part of it in this kind of interaction is not yet solved.

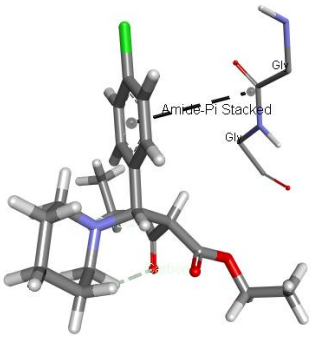

Figure 19: Example of amide-π stacked interactions

c4. Alkyl interactions [91-96]

Alkyl groups are defined as the following non-polarized, non-π systems [32]: Mainly aliphatic amino acid side-chains. These include alanine, valine, leucine, isoleucine, methionine, selenomethionine, cysteine, proline, atoms CB, CG, and CD of lysine and atoms CB and CG of arginine [32].

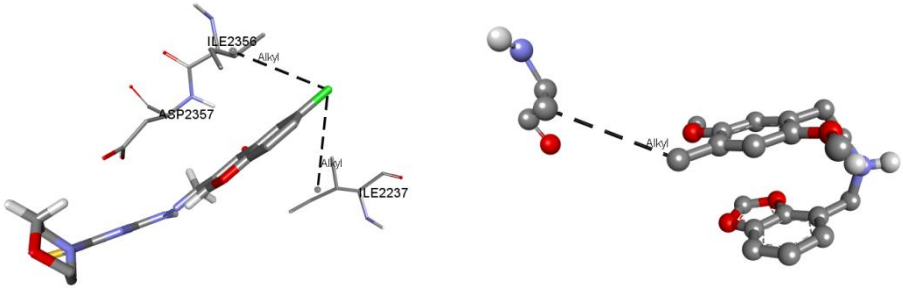

Figure 20: Examples of alkyl interactions

Hydrophobic groups on ligands are contiguous sets of atoms that are not adjacent to concentrations of charge (charged atoms or electronegative atoms). A group of atoms is considered hydrophobic if their surface area is equal

or greater than the area of a methyl group multiplied by the surface area scale factor (default 0.65), which corresponds to the surface area of a chlorine atom [32]. Figure 20 shows two examples.The σ-σ stacking interaction of the cyclohexane dimer is another good example [97]. In the case of the drug-receptor interactions the σ-σ interaction should occur between occupied and empty MOs. We guess that evolution excluded interactions between occupied orbitals (four electron) or between empty orbitals (zero-electron) which are generally repulsive [98].

c5. π-σ interactions [97, 99-101]

π-σ interactions (sometimes referred to as CH-π interactions) are weak interactions between a hydrogen and a π ring system [32]. Besides the requirements of distance and relative position, the hydrogen acting as the donor can be implicit or explicit hydrogen and they must be connected to a non-aromatic carbon atom [32]. Figure 21 shows two examples. The question of the participation of the entire π ring or part of it in this kind of interaction is not yet solved.

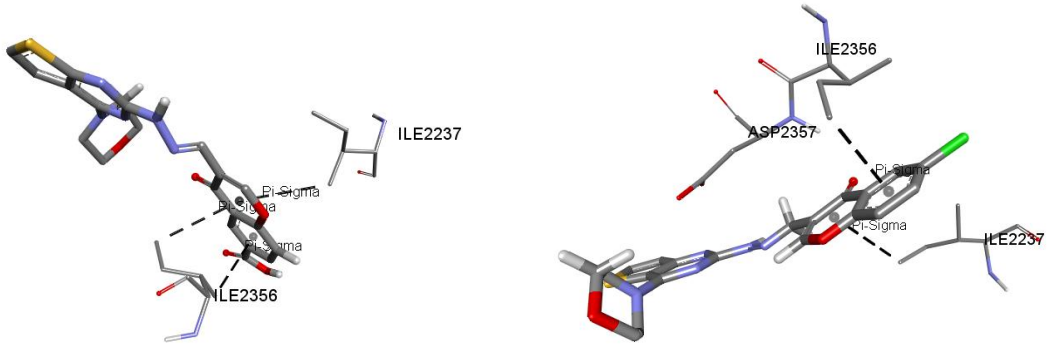

Figure 21: π-σ interactions

c6. π-alkyl interactions

π-alkyl interactions exist where the centroids of a π ring and an alkyl group are within the alkyl centroid (max. distance) cutoff (5.5 Å by default) and they have at least one pair of atoms within the same π-π closest atom (max. dist.) cutoff as used for π-π interactions[32]. Figure 22 shows two examples. One of them has multiple π-alkyl interactions. The question of the participation of the entire π ring or part of it in this kind of interaction is not yet solved.

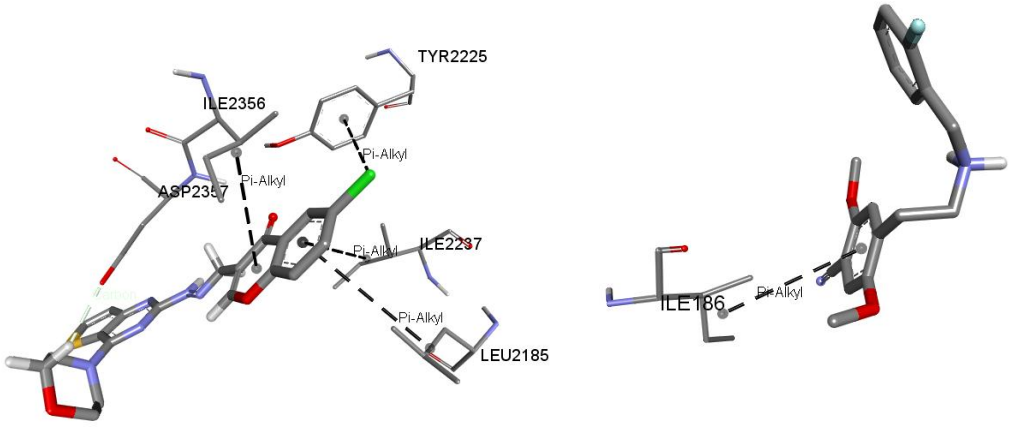

Figure 22: π-alkyl interactions

D. Halogen interactions [102-106]

d1. Halogen (Fluorine) interactions

Halogen (Fluorine) interactions are carbon-bound halogen interactions (C-X...B-Y) that have similar structural significance to weak hydrogen bonds [32]. Fluorine interactions (C-F...B-Y) are identified and monitored with all hydrogen donors and the specific case where B is carbon, nitrogen, and oxygen. In all cases, a maximum distance

criterion (Fluorine non-bond (max. dist.) is 3.7 Å by default) is used. When the interaction is with a hydrogen donor, the hydrogen bond angle criteria are used and the interaction is identified as both a fluorine and a hydrogen bond interaction [32]. Fluorine interactions with carbon and oxygen are limited to C=O moieties. Nitrogen interactions are limited to nucleophile nitrogen. These interactions are also limited by the same maximum distance criterion (3.7 Å by default) [32]. Figure 23 shows two examples.

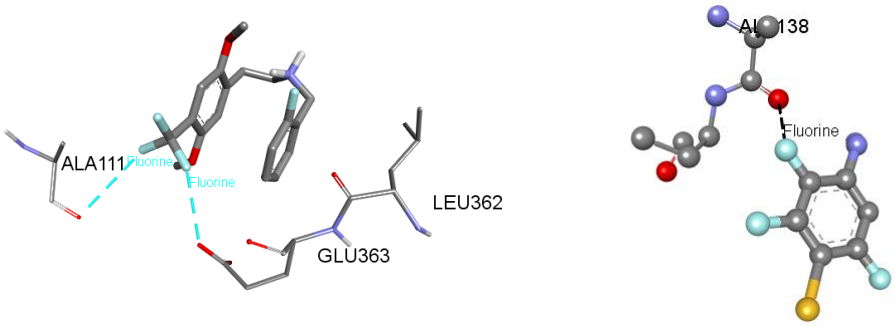

Figure 23: Examples of halogen (Fluorine) interactions

d2. Halogen (Cl, Br, I) interactions

Halogen (Cl, Br, I) interactions have distance criteria defined as a fraction of the sum of the atoms' van der Waals radii (controlled by Halogen (Cl, Br, I) VDW fraction (max.)). The default fraction is 1, using the full van der Waals distance as the cutoff [32]. Non-fluorine halogen interactions to carbon and oxygen are also limited to C=O moieties. Additionally, interactions with (B-Y) N-C, N-S, N-P, S-C, S-S and S-P are considered [32]. Figures 24 and 25 show some examples.

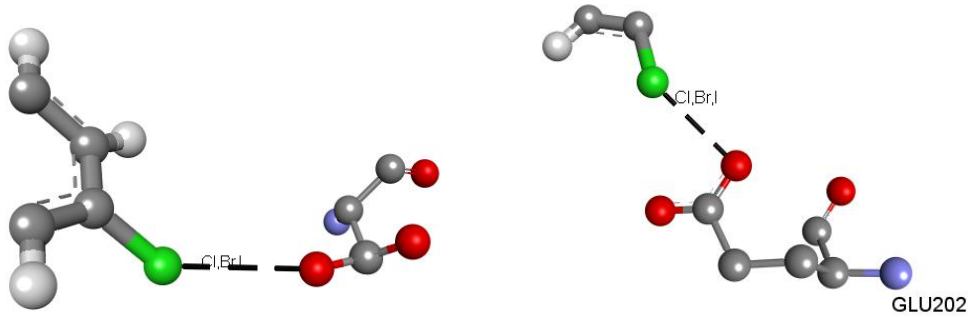

Figure 24: Examples of halogen (Cl, Br, I) interactions

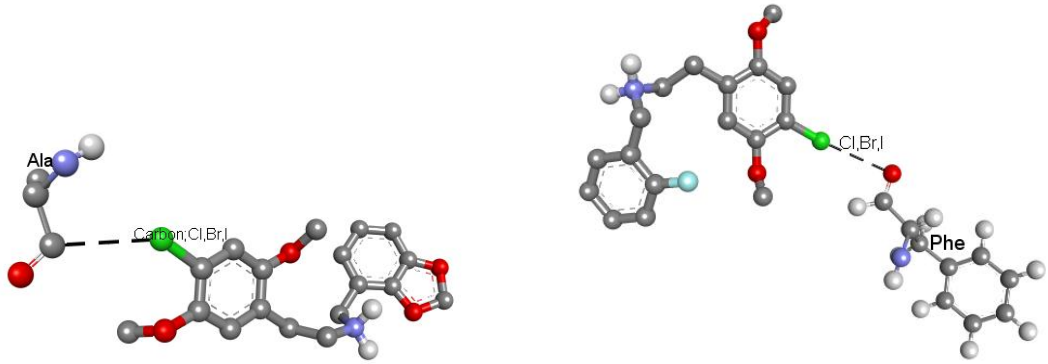

Figure 25: Examples of halogen (Cl, Br, I) interactions

E. Miscellaneous interactions

e1. Metal-acceptor interactions

Metal-acceptor interactions are analogous to hydrogen bonds and can exist between metal cations and hydrogen bond acceptors. The geometric parameters are the same as for hydrogen bonds, with the metal in place of the heavy atom hydrogen donor [32]. Figures 26-29 show some examples of this kind of interaction.

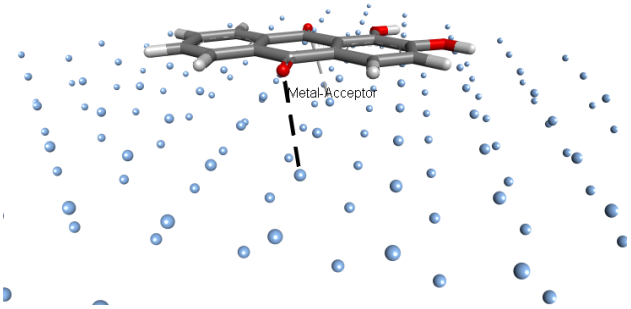

Figure 26: Metal-acceptor interaction between alizarin and a silver layer

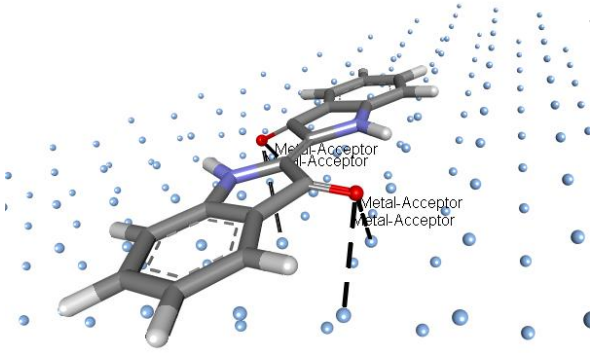

Figure 27: Metal-acceptor interactions between indigo and a silver surface [33]

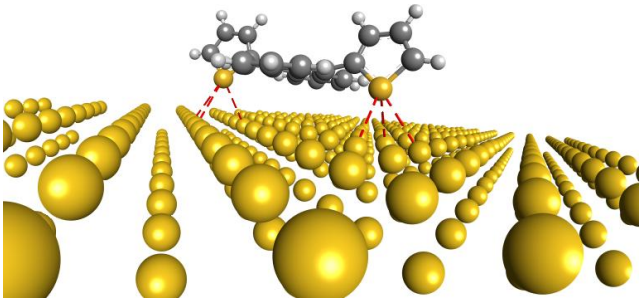

Figure 28: Metal-acceptor interactions between 9,10-di(thiophen-2-yl)anthracene and a gold surface [107]

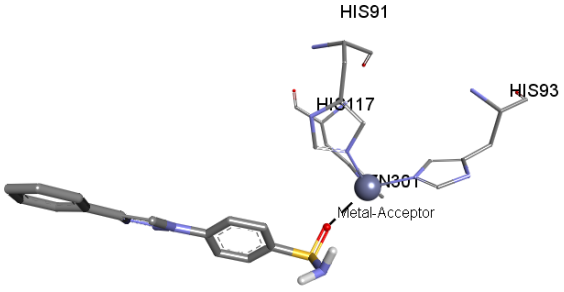

Figure 29: Example of metal-acceptor interaction

e2. π-sulfur interactions

π-sulfur interactions can adopt two distinct configurations: face on and edge on [32]. Figure 29 shows two examples. The question of the participation of the entire π ring or part of it in this kind of interaction is not yet solved.

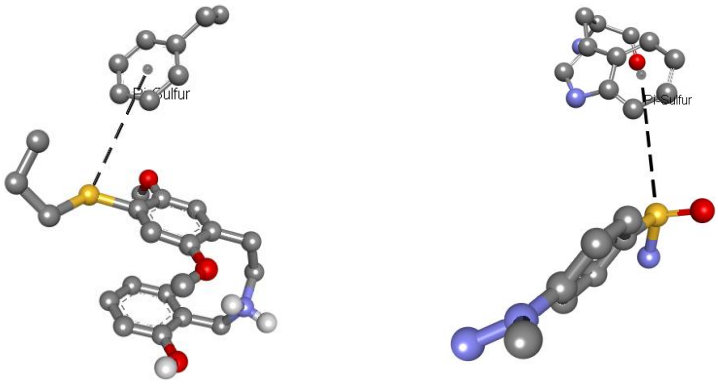

Figure 29: Examples of π-sulfur interactions

e3. Sulfur-X interactions

Sulfur-X interactions are found between divalent sulfur and N, O, or S atoms [32]. No examples were found in our studies.

e4. π-lone pair interactions[108-111]

A lone pair can form a favorable interaction with positively polarized π rings [32]: Hydrogen bond acceptor atoms are considered provided they do not already participate in other atom-π ring interactions. The distance between the acceptor and the ring centroid is within the π-lone pair (max. dist.) cutoff (3.0 Å by default).The angle between the acceptor-centroid vector and the normal to the ring plane is less than the π-lone pair angle (45° by default). No examples were found in our studies. The question of the participation of the entire π ring or part of it in this kind of interaction is not yet solved.

F. Unfavorable interactions

Steric bumps (they occur when the atom-atom distance is less than or equal to a threshold expressed as a fraction of the sum of the atoms' van der Waals radii),repulsive charge interactions (they occur between atoms bearing the same-signed whole or fractional formal charge, with a charge-charge max. distance is 5.6 Å by default), acceptor-acceptor clashes (when two acceptor atoms are within the acceptor-acceptor cutoff distance of 3.0 Å by default), donor-donor clashes (they occur between two donor atoms within hydrogen bonding distance) and metal repulsion (is a close interaction between a metal ion and a donor) are within this class[32].Figures 30 and 31 show some examples.

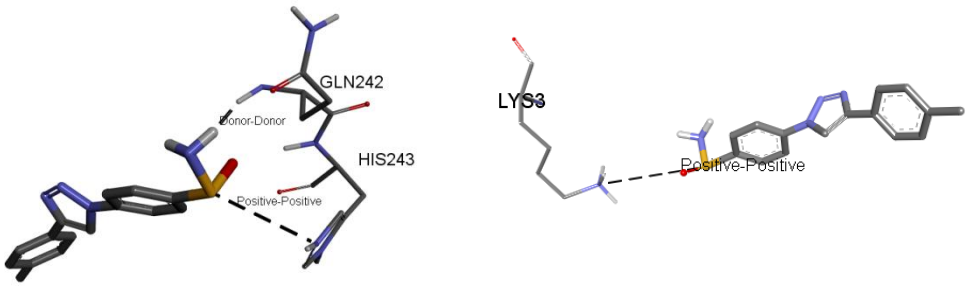

Figure 30: Examples of unfavorable interactions

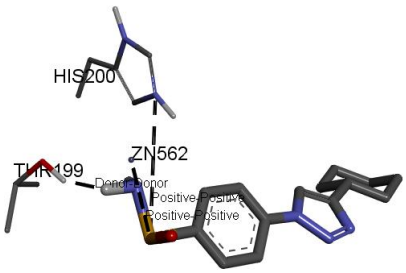

Figure 31: Examples of unfavorable interactions

It is conceptually clear that these unfavorable interactions must appear together with favorable ones.

The relationship between non-bond interactions and receptor model

In a paper devoted to the 45 years of the KPG model one of us presented a partial Table of non-bonded interactions built from the Discovery Studio Visualizer [11, 32]. Here we present a more complete Table containing also the approximate distance between the partners.

Table 1: Non-bond interactions

Category	Type	Distance (Å)
Hydrogen Bonds	Conventional H-bond	3.4, 3.8
Hydrogen Bonds	Carbon H-bond	3.8
Hydrogen Bonds	π donor H-bond	4.2
Hydrogen Bonds	Salt bridge	4.1
Electrostatic	Attractive charges	5.6
Electrostatic	π-cation	5.0
Electrostatic	π-anion	5.0
Hydrophobic	π-π stacked	6.0
Hydrophobic	π-π T-shaped	6.0
Hydrophobic	Amide-π stacked	6.0
Hydrophobic	Alkyl	5.5
Hydrophobic	π-σ	4.1
Hydrophobic	π-alkyl	5.5
Halogen	Halogen (F)	3.7
Halogen	Halogen (Cl, Br, I)	3.7
Miscellaneous	π-sulfur	4.5
Miscellaneous	Sulfur-X	4.5, 6.0
Miscellaneous	π-lone pair	3.0

On the other hand, and based on the work of Ariëns, one of us suggested a simple model of the space around the binding site[11, 112]. We present a modification of that model in Figure 32.

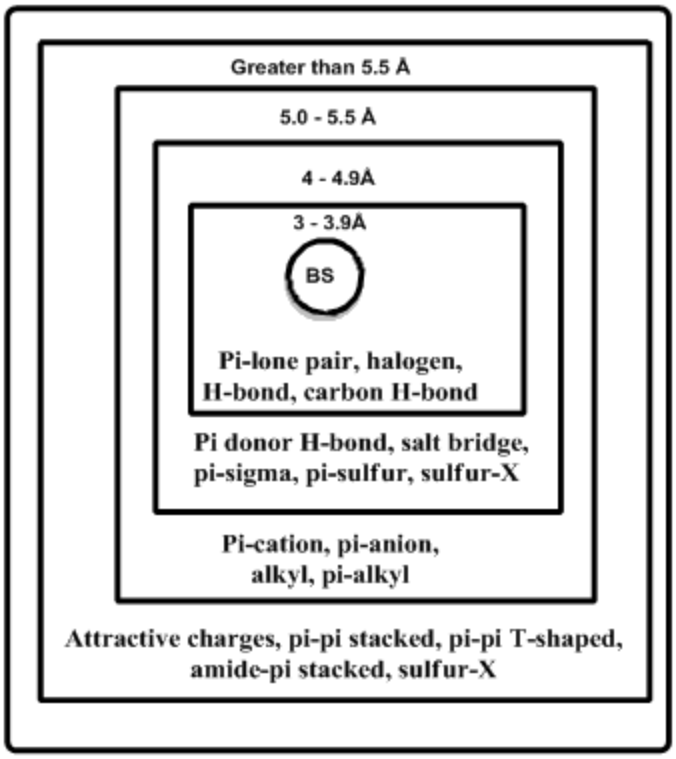

Figure 32: A simple 2D model of the 3D volume around the binding site

We must not forget that the real situation occurs in a three-dimensional space and that many binding sites are inside complex structures formed by amino acids. We expect that thermal agitation 'pushes' the molecule toward a point where long-range electrostatic interactions begin to guide and orientate it until the place to engage in the final interaction with the site. This suggests that, despite their difference in biological activity, the molecules able to interact with a given biding site must have a very similar molecular electrostatic potential structure at about 6-6.5 Å. Figure 32 highlights the importance of π systems in several kinds of weak molecule-site interactions. We must distinguish between two processes. The first one involved the guiding of the molecule toward the binding site. The second one is the action of those short-range interactions that start a certain process leading ultimately to the manifestation of a biological activity.

In summary, we have proposed a Table of atom-atom weak interactions to be employed for the analysis of the KPG-QSAR results and for the study of the possible connections between these results and the ones coming from the field of docking studies.

References

[1]. Baev, A. K. *Specific intermolecular interactions of element-organic compounds*. Springer International Publishing: Heidelberg, 2015.

[2]. Hobza, P.; Zahradník, R. *Weak intermolecular interactions in chemistry and biology*. Elsevier Scientific Pub. Co ; Distribution for the U.S.A. and Canada, Elsevier/North-Holland: Amsterdam; New York; New York, 1980.

[3]. Meghea, A. *Molecular interactions*. InTech: Rijeka, 2012.

[4]. Cooksy, A. *Physical chemistry : quantum chemistry and molecular interactions*. Pearson: Boston, 2014.

[5]. Karabencheva-Christova, T. *Combined quantum mechanical and molecular mechanical modelling of biomolecular interactions*. Elsevier : Academic Press: Amsterdam; Boston; Paris, 2015.

[6]. Kleinschmidt, J. *Lipid-protein interactions: methods and protocols*. Humana Press: Totowa, NJ, 2019.

[7]. Canzar, S.; Ringeling, F. R. *Protein-Protein Interaction Networks Methods and Protocols*. 2020.
[8]. Israelachvili, J. N. *Intermolecular and Surface Forces: Revised Third Edition*. Elsevier Science: Burlington, 2011.
[9]. Rowlinson, J. S. *Cohesion : a scientific history of intermolecular forces*. Cambridge University Press: Cambridge; New York, 2005.
[10]. Martin, Y. C. *Quantitative drug design: a critical introduction*. M. Dekker: New York, 1978; p x, 425 p.
[11]. Gómez-Jeria, J. S. 45 Years of the KPG Method: A Tribute to Federico Peradejordi. *Journal of Computational Methods in Molecular Design* 2017, 7, 17-37.
[12]. Gómez-Jeria, J. S. On some problems in quantum pharmacology I. The partition functions. *International Journal of Quantum Chemistry* 1983, 23, 1969-1972.
[13]. Gómez-Jeria, J. S. Modeling the Drug-Receptor Interaction in Quantum Pharmacology. In *Molecules in Physics, Chemistry, and Biology*, Maruani, J., Ed. Springer Netherlands: 1989; Vol. 4, pp 215-231.
[14]. Gómez-Jeria, J. S. *Elements of Molecular Electronic Pharmacology (in Spanish)*. 1st ed.; Ediciones Sokar: Santiago de Chile, 2013; p 104.
[15]. Gómez-Jeria, J. S. A New Set of Local Reactivity Indices within the Hartree-Fock-Roothaan and Density Functional Theory Frameworks. *Canadian Chemical Transactions* 2013, 1, 25-55.
[16]. Gómez-Jeria, J. S.; Reyes-Díaz, I.; Valdebenito-Gamboa, J. Quantum-Chemical and Docking Studies of 8-Hydroxy-Quinolines as Inhibitors of the Botulinum Neurotoxin A Light Chain (BoNT/A LC). *Journal of Computational Methods in Molecular Design* 2015, 5, 25-56.
[17]. Gómez-Jeria, J. S.; Robles-Navarro, A. A Density Functional Theory and Docking study of the Relationships between Electronic Structure and 5-HT_{2B} Receptor Binding Affinity in N-Benzyl Phenethylamines. *Der Pharma Chemica* 2015, 7, 243-269.
[18]. Gómez-Jeria, J. S.; Robles-Navarro, A. A Note on the Docking of some Hallucinogens to the 5-HT_{2A} Receptor. *Journal of Computational Methods in Molecular Design* 2015, 5, 45-57.
[19]. Gómez-Jeria, J. S.; Robles-Navarro, A. DFT and Docking Studies of the Relationships between Electronic Structure and 5-HT_{2A} Receptor Binding Affinity in N-Benzylphenethylamines. *Research Journal of Pharmaceutical, Biological and Chemical Sciences* 2015, 6, 1811-1841.
[20]. Gómez-Jeria, J. S.; Robles-Navarro, A. The different modes of docking of a series of benzenesulfonamides and tetrafluorobenzenesulfonamides to the carbonic anhydrase isoform II. *Der Pharma Chemica* 2015, 7, 230-241.
[21]. Gómez-Jeria, J. S.; Robles-Navarro, A.; Valdebenito-Gamboa, J. A Predictive Docking study of the interaction of some Benzenesulfinamides and Tetrafluorobenzenesulfinamides with Human Carbonic Anhydrase Isoforms I, IX and XII. *Research Journal of Pharmaceutical, Biological and Chemical Sciences* 2015, 6, 1606-1638.
[22]. Gómez-Jeria, J. S.; Valdebenito-Gamboa, J. A Quantum-chemical and Docking study of the inhibitory activity of a family of Thienopyrimidine derivatives bearing a chromone moiety against mTOR Kinase. *Der Pharmacia Lettre* 2015, 7, 211-219.
[23]. Gómez-Jeria, J. S.; Valdebenito-Gamboa, J. Electronic structure and docking studies of the Dopamine D_3 receptor binding affinity of a series of [4-(4-Carboxamidobutyl)]-1-arylpiperazines. *Der Pharma Chemica* 2015, 7, 323-347.
[24]. Peradejordi, F.; Martin, A. N.; Cammarata, A. Quantum chemical approach to structure-activity relationships of tetracycline antibiotics. *Journal of Pharmaceutical Sciences* 1971, 60, 576-582.
[25]. Tomas, F.; Aulló, J. M. Monoamine oxidase inhibition by β-carbolines: A quantum chemical approach. *Journal of Pharmaceutical Sciences* 1979, 68, 772-776.
[26]. Gómez-Jeria, J. S.; Morales-Lagos, D. The mode of binding of phenylalkylamines to the Serotonergic Receptor. In *QSAR in design of Bioactive Drugs*, Kuchar, M., Ed. Prous, J.R.: Barcelona, Spain, 1984; pp 145-173.

[27]. Gómez-Jeria, J. S.; Morales-Lagos, D. R. Quantum chemical approach to the relationship between molecular structure and serotonin receptor binding affinity. *Journal of Pharmaceutical Sciences* 1984, 73, 1725-1728.
[28]. Gómez-Jeria, J. S.; Morales-Lagos, D.; Rodriguez-Gatica, J. I.; Saavedra-Aguilar, J. C. Quantum-chemical study of the relation between electronic structure and pA2 in a series of 5-substituted tryptamines. *International Journal of Quantum Chemistry* 1985, 28, 421-428.
[29]. Alarcón, D. A.; Gatica-Díaz, F.; Gómez-Jeria, J. S. Modeling the relationships between molecular structure and inhibition of virus-induced cytopathic efects. Anti-HIV and anti-H1N1 (Influenza) activities as examples. *Journal of the Chilean Chemical Society* 2013, 58, 1651-1659.
[30]. Gómez-Jeria, J. S.; Valdebenito-Gamboa, J. A quantum-chemical analysis of the antiproliferative activity of N-3-benzimidazolephenylbisamide derivatives against MGC803, HT29, MKN45 and SW620 cancer cell lines. *Der Pharma Chemica* 2015, 7, 103-121.
[31]. Gómez-Jeria, J. S.; Flores-Catalán, M. Quantum-chemical modeling of the relationships between molecular structure and in vitro multi-step, multimechanistic drug effects. HIV-1 replication inhibition and inhibition of cell proliferation as examples. *Canadian Chemical Transactions* 2013, 1, 215-237.
[32]. *Dassault Systèmes Biovia Corp. Discovery Studio Visualizer v. 17.2.0.16349*, San Diego, USA, 2016.
[33]. Corales, G.; Celis, F.; Gómez-Jeria, J. S.; Campos, M.; Cárcamo-Vega, J. J. Raman of Indigo on a Silver Surface. Raman and Theoretical Characterization of Indigo Deposited on a Silicon Dioxide-Coated and Uncoated Silver Nanoparticles. *Spectroscopy Letters* 2017.
[34]. Vera, A. M.; Cárcamo, J. J.; Aliaga, A. E.; Gómez-Jeria, J. S.; Kogan, M. J.; Campos-Vallette, M. M. Interaction of the CLPFFD peptide with gold nanospheres. A raman, surface enhanced raman scattering and theoretical study. *Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy* 2015, 134, 251-256.
[35]. Garrido, C.; Aliaga, A. E.; Gómez-Jeria, J. S.; Cárcamo, J. J.; Clavijo, E.; Campos-Vallette, M. M. Interaction of the C-terminal peptide from pigeon cytochrome C with silver nanoparticles. A Raman, SERS and theoretical study. *Vibrational Spectroscopy* 2012, 61, 94-98.
[36]. Cárcamo, J. J.; Aliaga, A. E.; Clavijo, E.; Garrido, C.; Gómez-Jeria, J. S.; Campos-Vallette, M. M. Proline and hydroxyproline deposited on silver nanoparticles. A Raman, SERS and theoretical study. *Journal of Raman Spectroscopy* 2012, 43, 750-755.
[37]. Aliaga, A. E.; Ahumada, H.; Sepúlveda, K.; Gómez-Jeria, J. S.; Garrido, C.; Weiss-López, B. E.; Campos-Vallette, M. M. SERS, Molecular Dynamics and Molecular Orbital Studies of the MRKDV Peptide on Silver and Membrane Surfaces. *The Journal of Physical Chemistry C* 2011, 115, 3982-3989.
[38]. Bissantz, C.; Kuhn, B.; Stahl, M. A Medicinal Chemist's Guide to Molecular Interactions. *Journal of Medicinal Chemistry* 2010, 53, 5061-5084.
[39]. Baker, E. N.; Hubbard, R. E. Hydrogen bonding in globular proteins. *Progress in Biophysics and Molecular Biology* 1984, 44, 97-179.
[40]. Chen, D.; Zhao, M.; Tan, W.; Li, Y.; Li, X.; Li, Y.; Fan, X. Effects of intramolecular hydrogen bonds on lipophilicity. *European Journal of Pharmaceutical Sciences* 2019, 130, 100-106.
[41]. Gilli, G.; Gilli, P. *The nature of the hydrogen bond : outline of a comprehensive hydrogen bond theory*. 2013.
[42]. Mingos, D. M. P. *Supramolecular assembly via hydrogen bonds II*. Springer: Berlin, 2004.
[43]. Mingos, D. M. P.; Alajarin, M. *Supramolecular assembly via hydrogen bonds I*. Springer: Berlin, 2004.
[44]. Pimentel, G. C.; McClellan, A. L. *The Hydrogen bond*. W.H. Freeman: San Francisco, 1960.
[45]. Saá, J. M.; Lillo, V. J.; Mansilla, J.; Mahmudov, M.; MFCG da Silva, A. Catalysis by Networks of Cooperative Hydrogen Bonds. *Noncovalent Interactions in Catalysis* 2019, 36, 66.
[46]. Schuster, P.; Beyer, A.; Dyke, T. R.; Karpfen, A.; Sandorfy, C. *Hydrogen Bonds*. Springer Berlin: Berlin, 2013.

[47]. Contreras, R.; Gómez-Jeria, J. S. Proton transfer in water polymers as a model for intime and solvent-separated ion pairs. *Journal of Physical Chemistry* 1984, 88, 1905-1908.
[48]. Mason, P. E.; Jungwirth, P.; Duboué-Dijon, E. Quantifying the strength of a salt bridge by neutron scattering and molecular dynamics. *The journal of physical chemistry letters* 2019.
[49]. Kurczab, R.; Śliwa, P.; Rataj, K.; Kafel, R.; Bojarski, A. J. Salt bridge in ligand–protein complexes—systematic theoretical and statistical investigations. *Journal of Chemical Information and Modeling* 2018, 58, 2224-2238.
[50]. Ghosh, S.; Bierig, T.; Lee, S.; Jana, S.; Löhle, A.; Schnapp, G.; Tautermann, C. S.; Vaidehi, N. Engineering Salt Bridge Networks between Transmembrane Helices Confers Thermostability in G-Protein-Coupled Receptors. *Journal of chemical theory and computation* 2018, 14, 6574-6585.
[51]. Donald, J. E.; Kulp, D. W.; DeGrado, W. F. Salt bridges: Geometrically specific, designable interactions. *Proteins: Structure, Function, and Bioinformatics* 2011, 79, 898-915.
[52]. Kiehna, S. E.; Waters, M. L. Sequence dependence of β-hairpin structure: comparison of a salt bridge and an aromatic interaction. *Protein science* 2003, 12, 2657-2667.
[53]. Aliste, M. P.; MacCallum, J. L.; Tieleman, D. P. Molecular dynamics simulations of pentapeptides at interfaces: salt bridge and cation− π interactions. *Biochemistry* 2003, 42, 8976-8987.
[54]. Julian, R. R.; Beauchamp, J.; Goddard, W. A. Cooperative salt bridge stabilization of gas-phase zwitterions in neutral arginine clusters. *The Journal of Physical Chemistry A* 2002, 106, 32-34.
[55]. Kumar, S.; Nussinov, R. Salt bridge stability in monomeric proteins. *Journal of molecular biology* 1999, 293, 1241-1255.
[56]. Barril, X.; Aleman, C.; Orozco, M.; Luque, F. Salt bridge interactions: stability of the ionic and neutral complexes in the gas phase, in solution, and in proteins. *Proteins: Structure, Function, and Bioinformatics* 1998, 32, 67-79.
[57]. Ardalan, A.; Uwumarenogie, S.; Fish, M.; Sowlati-Hashjin, S.; Karttunen, M.; Smith, M. D.; Jelokhani-Niaraki, M. Regulation of Proton Transport in Tetrameric UCP2 by an Intramolecular Salt-Bridge Network. *Biophysical Journal* 2019, 116, 54a.
[58]. Wimley, W. C.; Gawrisch, K.; Creamer, T. P.; White, S. H. Direct measurement of salt-bridge solvation energies using a peptide model system: implications for protein stability. *Proceedings of the National Academy of Sciences* 1996, 93, 2985-2990.
[59]. Jones, W. D. On the Nature of Carbon−Hydrogen Bond Activation at Rhodium and Related Reactions. *Inorganic Chemistry* 2005, 44, 4475-4484.
[60]. Vastine, B. A.; Hall, M. B. Carbon−Hydrogen Bond Activation: Two, Three, or More Mechanisms? *Journal of the American Chemical Society* 2007, 129, 12068-12069.
[61]. Nanda, V.; Schmiedekamp, A. Are aromatic carbon donor hydrogen bonds linear in proteins? *Proteins: Structure, Function, and Bioinformatics* 2008, 70, 489-497.
[62]. Frey, R.; Hayashi, T.; Buller, R. M. Directed evolution of carbon–hydrogen bond activating enzymes. *Current Opinion in Biotechnology* 2019, 60, 29-38.
[63]. Vastine, B. A.; Hall, M. B. The molecular and electronic structure of carbon–hydrogen bond activation and transition metal assisted hydrogen transfer. *Coordination Chemistry Reviews* 2009, 253, 1202-1218.
[64]. Sharp, T. R. Calculated carbon–hydrogen bond dissociation enthalpies for predicting oxidative susceptibility of drug substance molecules. *International Journal of Pharmaceutics* 2011, 418, 304-317.
[65]. Guan, J.; Zarić, S. D.; Brothers, E. N.; Hall, M. B. Recent computational studies on transition-metal carbon–hydrogen bond activation of alkanes. *International Journal of Quantum Chemistry* 2018, 118, e25605.
[66]. Nick Pace, C.; Alston, R. W.; Shaw, K. L. Charge–charge interactions influence the denatured state ensemble and contribute to protein stability. *Protein science* 2000, 9, 1395-1398.
[67]. Kundrotas, P. J.; Karshikoff, A. Effects of charge–charge interactions on dimensions of unfolded proteins: A Monte Carlo study. *The Journal of Chemical Physics* 2003, 119, 3574-3581.

[68]. Dogan, J.; Gianni, S.; Jemth, P. The binding mechanisms of intrinsically disordered proteins. *Physical Chemistry Chemical Physics* 2014, 16, 6323-6331.
[69]. Cohen, R. D.; Pielak, G. J. Electrostatic Contributions to Protein Quinary Structure. *Journal of the American Chemical Society* 2016, 138, 13139-13142.
[70]. Pinheiro, S.; Soteras, I.; Gelpí, J. L.; Dehez, F.; Chipot, C.; Luque, F. J.; Curutchet, C. Structural and energetic study of cation–π–cation interactions in proteins. *Physical Chemistry Chemical Physics* 2017, 19, 9849-9861.
[71]. Liang, Z.; Li, Q. X. π–Cation Interactions in Molecular Recognition: Perspectives on Pharmaceuticals and Pesticides. *Journal of Agricultural and Food Chemistry* 2018, 66, 3315-3323.
[72]. Kumar, K.; Woo, S. M.; Siu, T.; Cortopassi, W. A.; Duarte, F.; Paton, R. S. Cation–π interactions in protein–ligand binding: Theory and data-mining reveal different roles for lysine and arginine. *Chemical science* 2018, 9, 2655-2665.
[73]. Craven, T. W.; Cho, M.-K.; Traaseth, N. J.; Bonneau, R.; Kirshenbaum, K. A Miniature Protein Stabilized by a Cation−π Interaction Network. *Journal of the American Chemical Society* 2016, 138, 1543-1550.
[74]. Schmitt, J. D.; Sharples, C. G. V.; Caldwell, W. S. Molecular Recognition in Nicotinic Acetylcholine Receptors: The Importance of π−Cation Interactions. *Journal of Medicinal Chemistry* 1999, 42, 3066-3074.
[75]. Dougherty, D. A. The cation− π interaction. *Accounts of chemical research* 2012, 46, 885-893.
[76]. Rao, J. S.; Zipse, H.; Sastry, G. N. Explicit Solvent Effect on Cation−π Interactions: A First Principle Investigation. *The Journal of Physical Chemistry B* 2009, 113, 7225-7236.
[77]. Aschi, M.; Mazza, F.; Di Nola, A. Cation–π interactions between ammonium ion and aromatic rings: an energy decomposition study. *Journal of Molecular Structure: THEOCHEM* 2002, 587, 177-188.
[78]. Mahadevi, A. S.; Sastry, G. N. Cation− π interaction: Its role and relevance in chemistry, biology, and material science. *Chemical reviews* 2013, 113, 2100-2138.
[79]. Schottel, B. L.; Chifotides, H. T.; Dunbar, K. R. Anion-π interactions. *Chemical Society Reviews* 2008, 37, 68-83.
[80]. Mazzone, G.; Alberto, M. E.; Ponte, F.; Russo, N.; Toscano, M. Anion-π weak interactions in a heteroaromatic calixarene receptor. A theoretical investigation. *Inorganica Chimica Acta* 2018, 470, 379-384.
[81]. Oranskaia, A.; Schwingenschlögl, U. Suppressing X-Migrations and Enhancing the Phase Stability of Cubic FAPbX3 (X = Br, I). *Advanced Energy Materials* 2019, 9, 1901411.
[82]. Gomila, R. M.; Frontera, A. CHAPTER 5 Anion–π Catalysis. In *Noncovalent Interactions in Catalysis*, The Royal Society of Chemistry: 2019; pp 122-136.
[83]. Wang, D.X. Application of Anion-π Interaction on Supramolecular Self-Assembly. In *Handbook of Macrocyclic Supramolecular Assembly*, Liu, Y.; Chen, Y.; Zhang, H.-Y., Eds. Springer Singapore: Singapore, 2019; pp 1-23.
[84]. Saha, B.; Bhattacharyya, P. K. Anion···π interaction in oxoanion-graphene complex using coronene as model system: A DFT study. *Computational and Theoretical Chemistry* 2019, 1147, 62-71.
[85]. Kan, X.; Liu, H.; Pan, Q.; Li, Z.; Zhao, Y. Anion-π interactions: From concept to application. *Chinese Chemical Letters* 2018, 29, 261-266.
[86]. Thakuria, R.; Nath, N. K.; Saha, B. K. The Nature and Applications of π–π Interactions: A Perspective. *Crystal Growth & Design* 2019, 19, 523-528.
[87]. Wilson, K. A.; Wells, R. A.; Abendong, M. N.; Anderson, C. B.; Kung, R. W.; Wetmore, S. D. Landscape of π–π and sugar–π contacts in DNA–protein interactions. *Journal of Biomolecular Structure and Dynamics* 2016, 34, 184-200.
[88]. McGaughey, G. B.; Gagné, M.; Rappé, A. K. π-Stacking interactions alive and well in proteins. *Journal of Biological Chemistry* 1998, 273, 15458-15463.

[89]. Rutledge, L. R.; Churchill, C. D. M.; Wetmore, S. D. A Preliminary Investigation of the Additivity of π−π or π+−π Stacking and T-Shaped Interactions between Natural or Damaged DNA Nucleobases and Histidine. *The Journal of Physical Chemistry B* 2010, 114, 3355-3367.
[90]. Hussain, H. B.; Wilson, K. A.; Wetmore, S. D. Serine and Cysteine π-Interactions in Nature: A Comparison of the Frequency, Structure, and Stability of Contacts Involving Oxygen and Sulfur. *Australian Journal of Chemistry* 2015, 68, 385-395.
[91]. Shimizu, K. D. Intermolecular forces: A solution to dispersion interactions. *Nature chemistry* 2013, 5, 989.
[92]. Kulikov, O. V.; Incarvito, C.; Hamilton, A. D. Hydrophobic side-chain interactions in a family of dimeric amide foldamers-potential alpha-helix mimetics. *Tetrahedron Letters* 2011, 52, 3705-3709.
[93]. Ito, M. M.; Kato, J.; Takagi, S.; Nakashiro, E.; Sato, T.; Yamada, Y.; Saito, H.; Namiki, T.; Takamura, I. Shape-specific weak interactions related to a phenyl group: Determination of their enthalpies by gas-liquid partition chromatography. *Journal of the American Chemical Society* 1988, 110, 5147-5152.
[94]. Yang, L.; Adam, C.; Nichol, G. S.; Cockroft, S. L. How much do van der Waals dispersion forces contribute to molecular recognition in solution? *Nature chemistry* 2013, 5, 1006.
[95]. Strauss, M. A.; Wegner, H. A. Molecular Systems for the Quantification of London Dispersion Interactions. *European Journal of Organic Chemistry* 2019, 2019, 295-302.
[96]. Strauss, M.; Wegner, H. A. Exploring London dispersion and solvent interactions at alkyl-alkyl interfaces using azobenzene switches. *Angewandte Chemie* 2019.
[97]. Alonso, M.; Woller, T.; Martín-Martínez, F. J.; Contreras-García, J.; Geerlings, P.; De Proft, F. Understanding the Fundamental Role of π/π, σ/σ, and σ/π Dispersion Interactions in Shaping Carbon-Based Materials. *Chemistry–A European Journal* 2014, 20, 4931-4941.
[98]. Joselevich, E. Electronic structure and chemical reactivity of carbon nanotubes: a chemist's view. *ChemPhysChem* 2004, 5, 619-624.
[99]. Gleiter, R.; Lange, H.; Borzyk, O. Photoelectron spectra, ab initio scf mo, and natural bond orbital studies on stellenes. Long-range π/σ interactions. *Journal of the American Chemical Society* 1996, 118, 4889-4895.
[100]. Albert, I. D. L.; Ramasesha, S. Role of σ-π interactions on linear and nonlinear susceptibilities in polyenes. *Chemical Physics Letters* 1991, 182, 351-356.
[101]. Cabaleiro-Lago, E. M.; Rodríguez-Otero, J. On the Nature of σ–σ, σ–π, and π–π Stacking in Extended Systems. *ACS Omega* 2018, 3, 9348-9359.
[102]. Sirimulla, S.; Bailey, J. B.; Vegesna, R.; Narayan, M. Halogen interactions in protein–ligand complexes: implications of halogen bonding for rational drug design. *Journal of Chemical Information and Modeling* 2013, 53, 2781-2791.
[103]. Fourmigué, M. Halogen bonding: recent advances. *Current Opinion in Solid State and Materials Science* 2009, 13, 36-45.
[104]. Hardegger, L. A.; Kuhn, B.; Spinnler, B.; Anselm, L.; Ecabert, R.; Stihle, M.; Gsell, B.; Thoma, R.; Diez, J.; Benz, J. Systematic investigation of halogen bonding in protein–ligand interactions. *Angewandte Chemie International Edition* 2011, 50, 314-318.
[105]. Riley, K. E.; Hobza, P. Strength and character of halogen bonds in protein–ligand complexes. *Crystal Growth & Design* 2011, 11, 4272-4278.
[106]. Scholfield, M. R.; Ford, M. C.; Carlsson, A.-C. C.; Butta, H.; Mehl, R. A.; Ho, P. S. Structure–Energy Relationships of Halogen Bonds in Proteins. *Biochemistry* 2017, 56, 2794-2802.
[107]. Muñoz-Pérez, J.; Leyton, P.; Paipa, C.; Soto, J. P.; Brunet, J.; Gómez-Jeria, J. S.; Campos-Vallette, M. M. Raman and surface enhanced Raman scattering study of the orientation of cruciform 9,10-anthracene thiophene and furan derivatives deposited on a gold colloidal surface. *Journal of Molecular Structure* 2016, 1122, 198-204.
[108]. Kozelka, J. Lone pair–π interactions in biological systems: occurrence, function, and physical origin. *European Biophysics Journal* 2017, 46, 729-737.

[109]. Montoro, T.; Tardajos, G.; Guerrero, A.; Torres, M. d. R.; Salgado, C.; Fernández, I.; Osío Barcina, J. σ-Hole···π and lone pair···π interactions in benzylic halides. *Organic & Biomolecular Chemistry* 2015, 13, 6194-6202.

[110]. Egli, M.; Sarkhel, S. Lone pair− aromatic interactions: To stabilize or not to stabilize. *Accounts of chemical research* 2007, 40, 197-205.

[111]. Chawla, M.; Chermak, E.; Zhang, Q.; Bujnicki, J. M.; Oliva, R.; Cavallo, L. Occurrence and stability of lone pair–π stacking interactions between ribose and nucleobases in functional RNAs. *Nucleic acids research* 2017, 45, 11019-11032.

[112]. Ariens, E. J. *Molecular Pharmacology: the mode of action of biologically active compounds*. Academic Press: New York, 1964.