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Scientific paper

Application of Hybrid Density Functional Theory in Calculation of Edge-to-Face Interactions of Receptor-Ligand System

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Abstract

Our previously described research on docking analysis of a series of isosteric N4-arylpiperazines on a model of 5-HT_{1A} receptor was used earlier to investigate interactions of different ligands with the receptor binding site. Due to the limitations of molecular mechanics (MM) methods, docking analysis failed to give precise results about interactions that influence binding affinity of the ligands, but we presumed that aromatic-aromatic interactions, or edge-to-face, to be more precise, play an important role in the binding process. In order to further elaborate on this hypothesis, *ab initio* approach was used to calculate possible edge-to-face interactions on a model system and correlate them to ligand affinity. Obtained results indicate that those dispersive interactions can show notable influence on the binding of the ligands to 5-HT_{1A} receptor. Stabilization energies of modeled receptor-ligand complex, calculated using Becke's "half-and-half" hybrid DFT method showed strong correlation with the affinity of investigated ligands towards 5-HT_{1A} receptor.

Keywords: Hybrid DFT; ligand affinity; correlation; 5-HT_{1A}

1. Introduction

If standard covalent bonds are responsible for the basic structure of the molecules, then the weaker, non-covalent interactions maintain the shape, function and properties of numerous physiologically significant compounds.[1] This is not the case only with the well-known hydrogen bonding or ionic interactions, but also with weak, but nevertheless significant, interactions, like aromatic-aromatic interactions (edge-to-face or similar), C–H···π, C–H···Hal interactions, indirect hydrogen bonding and other. Despite lower per bond energy value when compared with, for instance, hydrogen bond, their cumulative effect can be significant.

Development of new 5-HT_{1A} receptor ligands has become a challenging field of research. The main feature of many substances that exhibit 5-HT_{1A} affinity is the presence of an arylpiperazine moiety. To investigate the interactions that are responsible for high activity complex formation, methods of computational chemistry, namely docking analysis and molecular properties calculations (LogP and electrostatic isopotential)[2] were employed. Those results led us to a hypothesis that edge-to-face interactions can have a significant role in the receptor-ligand formation and stabilization.

Observation of all interactions that contribute to the receptor-ligand complex formation is especially important when computer based methods are used to model or explain such assemblies. Neglecting the interactions, e.g. edge-to-face interactions, despite their low absolute strength, may lead to a series of wrong conclusions. But research of structures possessing a large number of atoms, like 5-HT_{1A} receptor-ligand complex, usually limits the calculations to molecular mechanics (MM), because only that kind of calculations can be performed using computer equipment with a reasonable processing power and in a reasonable time. However, MM force fields (even advanced class II, like CFF) cannot guarantee that all of the inf-

luencing forces would be taken in account. Dispersive forces, like edge-to-face interactions fall well beyond computing capabilities of MM force fields. Because of this, aromatic-aromatic interactions cannot be investigated without employing more precise *ab initio* methods.

Several authors worked on calculation of the strength[3,4,5] of aromatic-aromatic interactions and their stabilization effects. These types of interactions were mentioned for the first time in 1958, when their role in crystal structure of benzene was discussed.[6] Idea of edge-to-face interactions as a significant factor of protein stability is more recent[7] and only in the past twenty years its possible influence on tertiary and quaternary structure of peptides and proteins[8,9] was considered. Those interactions are best described on the model of benzene dimer (Figure 1).

kcal/mol (7.5–8.4 kJ/mol) for structure **1**.[5] Structures **3a**–**c** showed minor change in dissociation energies for angle changes up to 30°.[4] Besides benzene dimers, calculation and experimental determination of energies of edge-to-face interactions were made on other model systems. Although by their strength these interactions are counted as weak, their significance lies in the fact that in biological macromolecules they can be very frequent and in sum can contribute noticeably to the entire structure stability. Nonbonding interactions of this type have been intensively studied particularly because of their role in the structure of DNA.[12]

Countless experimental and theoretical methods have been employed to investigate π interactions. [13,14] Electronic structure methods such as Møller–Plesset perturbation and coupled-cluster methods show that, besides elec-

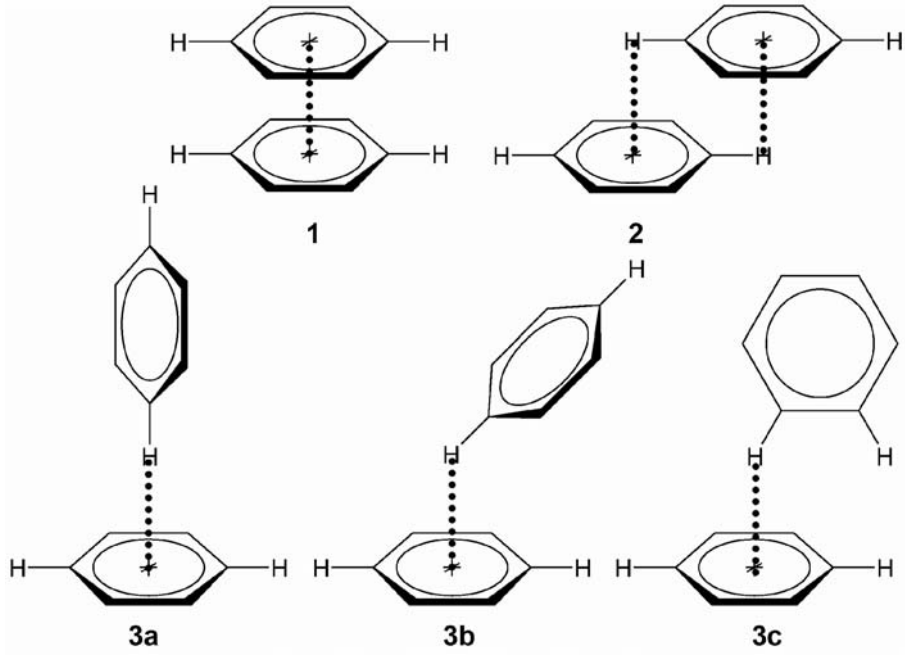


Figure 1. Possible orientations for benzene couple. Structure **1**: π–π *stacking* interaction (parallel, sandwich); structure **2**: between edge-to-face and π–π *stacking*, *parallel displaced*; structures **3a**–**c**: edge-to-face interactions (*T-shaped*).

The combined experimental and theoretical work to date suggests that the most favorable configurations of edge-to-face are T-shaped **3a**–**c** geometries. Those structures are not uncommon among the interacting amino acid residues in proteins, while configuration **1** is rare. [9] In early molecular beam electric resonance (MBER) experiments, as well as in rotation spectra later, for structure **3a** the distance of 4.96 Å between centers of mass of benzene rings was found[10] which corresponds to the distance of 2.48 Å between proton and center of a neighboring benzene ring.[11] Calculated stabilization energies for these structures are: 2.4–2.8 kcal/mol (10.04–11.3 kJ/mol) for **3**, 2.7–2.8 kcal/mol (11.7–11.3 kJ/mol) for **2** and 1.8–2

trostatic and exchange-repulsion forces, dispersive forces play a primary stabilizing role in π-stacking interactions.[5] But the computational resources required for correlated post-self-consistent field (post-SCF) methods increase rapidly with molecular size, and hence are practically limited to relatively small model systems. Density functional theory (DFT) has been widely used to study many intermolecular interactions, including those in C–H···π systems. But, as the dispersion is a result of electron correlation, methods that approximate or ignore electron correlation are deemed unsuitable. A variety of solutions have been proposed to overcome this problem.[15] As the hybrid functionals contain adjustable parameters, they can be sui-

tably adjusted to reproduce the results of higher level calculations, if only due to a cancellation of errors.[12,16] Because hybrid DFT methods require less computational power and can be used on larger systems with reasonable time for calculations, the aim of this work is to investigate whether they can be used with sufficient accuracy for computation of binding energies. We have made extensive use of Becke's "half-and-half" functional, **BH and H**,[17] an *ad hoc* mixture of exact (HF) and local density approximation exchange, coupled with Lee, Yang and Parr's expression for the correlation energy. This method was selected because it can reproduce binding energies of aromatic dimers even using the medium Pople basis set (6-31G) and polarization and diffuse functions.[3]

2. Experimental

2. 1. Docking Analysis

Modeling of 5-HT_{1A} receptor, docking of selected ligands and selection of most favorable docked structure was carried out as described before. Structures were visualized using DS Visualizer v1.7[18] and the obtained images were rendered using PovRay Raytracer v3.6[19] and DS Visualizer. Structures and affinities of the investigated ligands are shown in Table 1.

2. 2. *Ab Initio* Calculations

Gaussian 03W[20] was used to carry on calculation of energy contribution of the chosen ligand-receptor assembly. All structures were subjected to prior geometry optimization, using HF method and 6-31+G* basis set, until energy minima were reached. Mutual orientation of interacting groups were taken from docking analysis results and later adjusted as needed. The stabilization energies of the paired structures were calculated as a difference between trimer and separate molecular entities using BH&H DFT method and MP2 procedure for one geometry, with 6-31+G* basis set. All binding energies reported have been corrected for basis set superposition error using the counterpoise method of Boys and Bernardi.[21]

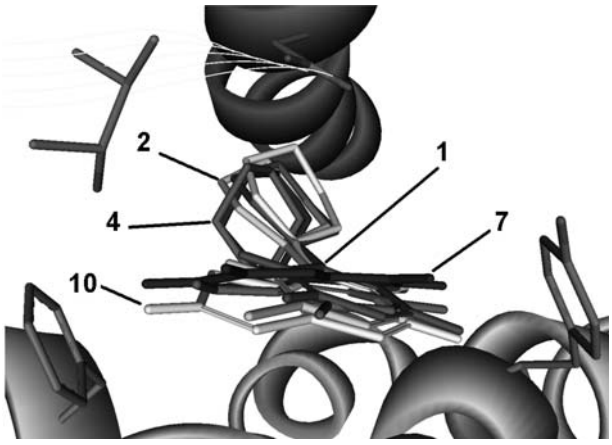
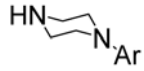
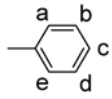
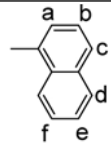
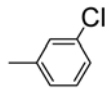
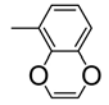
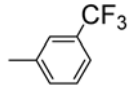
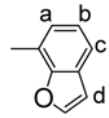
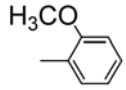
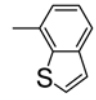
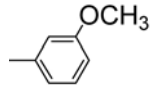


Figure 2. Docking structures for some ligands (**1**,**2**,**4**,**7**,**10**).

Table 1. Structures and affinities* of 1-arylpiperazines at 5-HT_{1A} receptor.



Ar		pK_i	Ar		pK_i
1		6.4202	**7**		7.9586
2		6.8861	**8**		7.9208
3		6.7570	**9**		7.8861
4		7.1675	**10**		8.0044
5		6.4949	**11**		7.5686
6		5.8508			

* references: **1**–**4**,**6**,**7**,[22] **5**,**8**–**10**,[23] and **11**.[24]

Docking analysis failed to give a precise answer regarding ligand orientation in receptor binding site (Figure 2). In order to establish exact docking geometry as close as possible, every possible receptor-ligand orientation has to be considered. Based on docking analysis data we already have the general idea about ligand placement inside the binding site, so the more narrow approach is possible.

In all docked structures, ligand was positioned in such a manner that it can easily establish at least one aromatic-aromatic interaction, edge-to-face type in this case. Interactions are possible between the aromatic part of the ligand and phenylalanine 361 (6.51) from transmembrane helix VI and tyrosine 390 (7.43) on transmembrane helix VII. In our earlier work, it was stated that those interactions play a significant role in the stabilization of the receptor-ligand complex, but the evidence was incomplete.[2]

Edge-to-face interactions were often used as some kind of "miracle remedy", whenever some complex stability, structure or even reaction had to be explained. For that reason, in order to find confirmation that will support our hypothesis, we searched for some correlation between stabilization energies and affinities of ligands, thus providing evidence for influence of edge-to-face interactions on receptor-ligand complex formation.

To utilize *ab initio* methods in the research of receptor-ligand interactions, few approximations had to be applied, taking into account given computer resources and available (or reasonable) time. Thus our system had to be made smaller and the calculations more efficient. To simplify the system, we concentrated our effort on the key amino acid residues and the part of the ligand responsible for edge-to-face interactions. Ethylbenzene was used instead of phenylalanine and 4-ethylphenol instead of tyrosine. This kind of simplifications did not influence properties of aromatic moiety and gave a more compact model system to work on. In a similar way, piperazinyl group of the ligand was replaced by *N*,*N*-dimethylamino group (Figure 3).

2. 3. Horizontal Positioning of the Ligand

Since three different sizes of the ligand need to be considered, horizontal placement of the ligand, regarding the obtained docking results was performed as follows. We presumed that both the small and both types of the large (naphthyl-like and benzimidazole-like) ligands can fit in the proposed binding pocket lying perpendicularly to amino acid residues. Small ligands will form a loose fit in which one edge-to-face interaction with a nearby amino acid residue will be possible due to the optimal distance for this kind of interaction, while larger ligands will form a tight fit that would facilitate two edge-to-face interactions, with optimal distances for both amino acid residues. A loose fit will favor one or create another edge-to-face interaction, similar in strength with phenylalanine aromatic residue. However, positioning the aromatic moiety of a ligand at a distance suitable for establishing a dispersive interaction with phenylalanine aromatic residue would require that the whole ligand is moved towards the other side of the binding site, which would unavoidably lead to an increase in the distance between Asp 3.32 and protonated

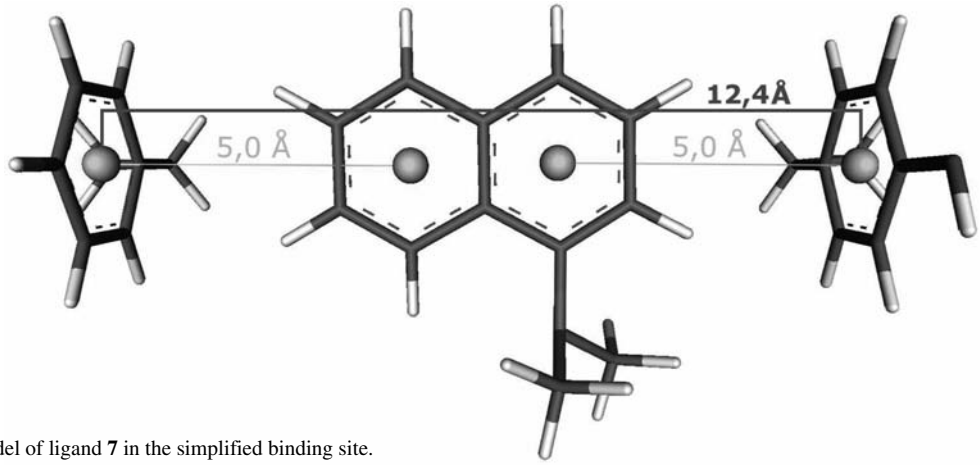


Figure 3. Model of ligand **7** in the simplified binding site.

In all favorable docked structures, centers of aromatic rings of phenylalanine and tyrosine were separated between 12 and 13 Å. This distance is large enough to accommodate ligands with two condensed aromatic rings, for instance ligand **7**. Thus, putting *N*,*N*-dimethyl-1-naphtylamine between aromatic rings in the shape of the letter H, in such a manner that the "edge" protons from the aromatic group from the ligand "target" the "face" of aromatic rings, with plane perpendicular to the planes of both aromatic rings and the distance between centers of the rings and center of the neighboring aromatic moiety is 5 Å, will put the surrounding aromatic rings to a distance of 12.4 Å (Figure 3). This distance is in good concordance with the values obtained during docking analysis, so this conformation was chosen for the starting point of our calculations.

nitrogen of the piperazine ring, and to a decrease in the most significant interaction for this kind of ligands.[25] To test this model where the distance from the center of the

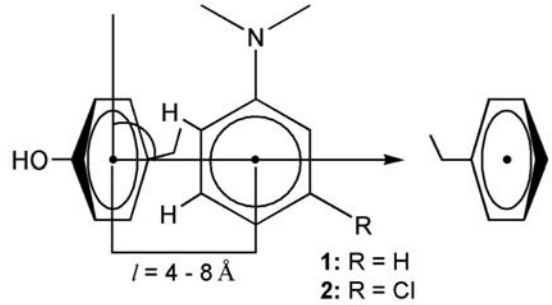


Figure 4. Positioning of the ligands **1** and **2** for calculating the dependence of energies on distance.

ligand aromatic ring to the center of the aromatic ring on 4-ethylphenol was varied from 4 to 8 Å, while structures were held perpendicular (Figure 4), was constructed. Stabilization energy was calculated as described, using BH&H method and the obtained stabilization energies are shown on Figure 5. It can be easily seen that maximal stabilization energy for both ligands lies when centers of the two systems are about 5 Å apart. Again, this is in concordance with the previously published results for the T-shaped benzene dimer. [5,10]

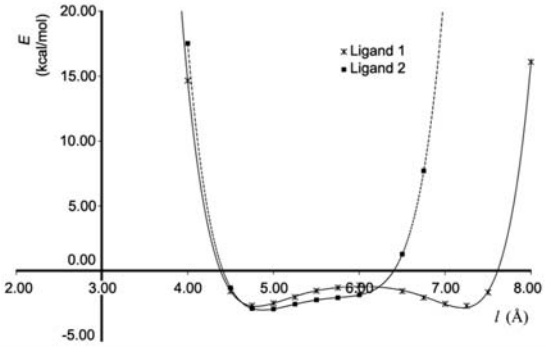


Figure 5. Dependence of energy on distance between aromatic rings.

2. 4. Vertical Positioning of the Ligand

Rather than calculating all possible vertical receptor-ligand orientations, we decided to employ bubble-sort-like procedure, concentrating our effort on the three possible boundary ligand orientations (Figure 6, A, B and C) and compare the obtained results with their respective affinity.

Ligand positions **A** and **C** are designed so that a proton on the ligand aryl part, representing the edge, is facing the center of the aromatic ring of the amino acid residue, representing the face. This orientation is known to be the most favorable in benzene dimer edge-to-face orientation,[5,7–9] and thus we assume that it will be the same in this case. Since the aryl part has two protons that can face an amino acid residue, two boundary orientations named **A** and **C** are possible, according to the orientation of the corresponding proton (*ortho* or *meta*). Orientation **B** will be one in which the center of the aryl ring matches the center of the aryl ring of the amino acid residue. In this orientation neither of protons lies directly in front of the center of the aryl ring of the amino acid residue, but nevertheless, both can form edge-to-face interactions with it.

Considering the results from docking analysis, we excluded orientation **A** from further research, given that this orientation is not favorable due to a bump between the ligand and the backbone of the transmembrane helix VI.[2] That leaves us with two possible vertical ligand orientations to focus on. In this way many calculations were avoided, because optimal orientation would be similar to either **B** or **C** orientation.

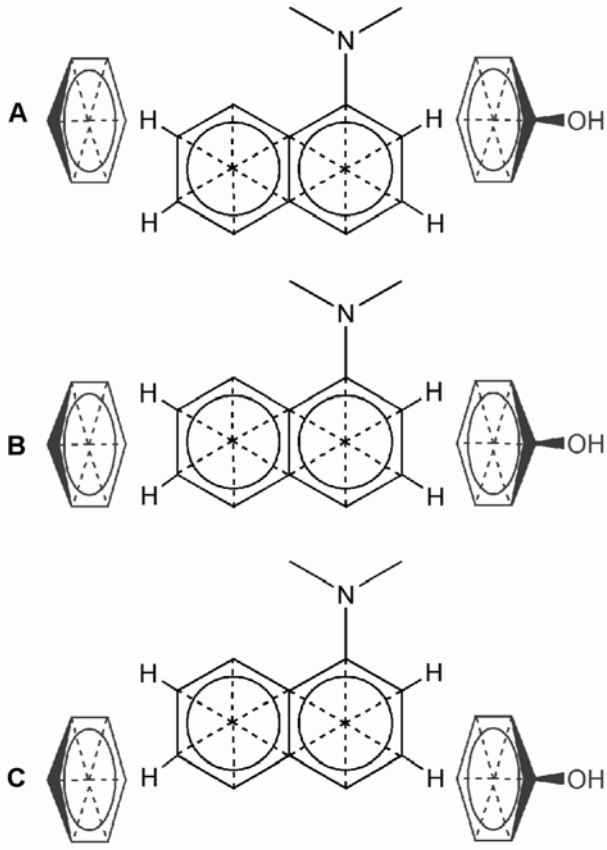


Figure 6. Three ligand orientations. Aromatic residues representing amino acids are drawn without any substituents.

In order to make sure that results obtained via two different methods (MP2 *vs.* BH&H) do not differ, a "test run" using selected ligands and both methods mentioned to calculate and compare stabilization energies was done (Table 2).

Although there were some small differences, our prime interest was to try to correlate energies of the system and the affinities and not to calculate absolute energies, so those relatively small deviations from results achieved by higher level calculations were not considered important for this purpose. As can be clearly seen, calculated energies of stabilization showed high values for squared regression coefficient, indicating possible strong linear dependence $pK_i = f(E)$.

3. Results and Discussion

3. 1. Horizontal Placement of the Ligand

Calculations of different horizontal ligand positions calculated for two different ligands (**1** and **2**) are shown in Figure 5. The optimal distance between the ring centers is 5 Å. In the case of both ligands, energy shows sharp rise when the distance is shorter than 4.5 Å to 4-ethylphenol. On the other side of the pocket, ligand **1** has a sharp ener-

Table 2. Calculated stabilization energies of the ligand models in the hypothetic binding site in two different positions.

ligand	position B *E* (kcal/mol) BH&H	position B *E* (kcal/mol) MP2	position C *E* (kcal/mol) BH&H	pK_i
8	–5.66	–5.04	–5.18	7.9208
7	–5.41	–4.85	–5.17	7.9586
10	–5.31	–5.24	–4.74	8.0044
9	–4.56	–4.54	–4.55	7.8861
11	–4.48	–4.50	–4.55	7.5686
2	–2.89	–2.66	–2.80	6.8861
3	–2.87	–3.12	–2.17	6.7570
4	–2.86	–2.72	–2.24	7.1675
1	–2.47	–2.62	–2.12	6.4202
5	–2.20	–2.47	–2.10	6.4949
6	–1.49	–1.76	–2.68	5.8508
r^2 for p*K*i = *f*(E)	**93.05%**	**90.82%**	**74.94%**	

gy rise at distances over 7.5 Å from 4-ethylphenol (4.5 Å from ethylbenzene), while ligand **2**, having Cl in position 3, cannot come closer than 6 Å to 4-ethylphenole without a significant loss of stabilization. Ligand **1**, being symmetrical can form edge-to-face interaction either with ethylbenzene or 4-ethylphenol, while ligand **2** can form only one edge-to-face interaction with 4-ethylphenol. Although ligands can form edge-to-face interactions with tyrosine, this will lead to ligand rotation inside the binding site and increased distances to Asp 3.32. Since the shortest distance to Asp 3.32 is crucial for salt bridge formation and early ligand positioning,[25] it can be concluded that this is not the case. Because all obtained docking results place ligands **1**–**6** in the vicinity of 4-ethylphenol, it is confirmed that optimal binding distance for small ligands is at 5 Å from phenylalanine. This result is in agreement with a presumption made before, that the binding pocket is approximately 12.5 Å wide, since that distance will put both ring centers of ligand **7** at the optimal 5 Å from amino acid residues that form the pocket. Having all this in mind, all vertical placement ligand conformations were calculated at distances of 5 Å between centers of the aromatic ring of the ligand and 4-ethylphenol.

3. 2. Vertical Placement of the Ligand

Stabilization energy, obtained through BH&H calculations, was correlated with ligand affinity and the results obtained are shown in Table 2. Correlation varies with different ligand orientation, and the highest correlation, $r^2 = 93.05\%$ is obtained when the ligand is in the position **B** (Figure 6). For the ligand orientation **C**, calculated energies show significantly lower correlation than the previous orientation ($r^2 = 74.94\%$).

Besides the significant correlation results, evidence that the ligands bind in the position **B** is the stabilization energy of ligand **6**. This ligand shows rather low affinity towards 5-HT_{1A} receptor. When calculated stabilization energy for this ligand is compared to its affinity, it can be concluded that the only reasonable position for the ligand placement is position **B**. In this position the ligand cannot form strong edge-to-face interaction because of a lack of compatible protons. In the other investigated position, **C**, possible edge-to-face interactions between protons on aromatic moiety of the ligand and aromatic residues of amino acids in the binding site would inevitably lead to higher affinity. We can see that this is not the case, and thus it can be concluded that **B** is the most probable vertical ligand orientation.

The calculated results show that stabilization energy of receptor-ligand model is directly proportional to the number and strength of edge-to-face interactions the ligand can form. The ligands forming stronger and more numerous edge-to-face interactions tend to have higher stabilization energies and affinities compared to ligand **6** that cannot form any edge-to-face interaction.

Some small ligands, like **2** and **3**, have more intensive edge-to-face interactions, because of the presence of halogen atom(s). This can be seen from increased calculated stabilization energy and affinity when compared to ligand **1**. Introduction of the halogen atom in systems similar to this one can increase non-covalent interactions for up to 1 kcal/mol.[26,27] In the case of ligand **4**, besides edge-to-face interaction, formation of a H-bond with Thr 188 in the receptor can lead to additional stabilization. Stabilization energies calculated in this manner did not include possible additional H-bond interactions, so the calculated stabilization energy of this ligand is to some extent lower than one could expect. Ligand **5** can form only edge-to-face interaction and has the affinity similar to the affinity of ligand **1**.

Large ligands show the same behavior as the small ones, the only difference being an increase in affinity due to their shape and size, which enables them to make shor-

ter and stronger edge-to-face interactions. Ligands **7–11** can form multiple edge-to-face interactions with the Phe 361 (6.51) from TMVI and Tyr 390 (7.43) on TMVII of the receptor. The ligand **11** is, to some extent, an exception, since the proton on the benzimidazole system has a low positive charge unsuitable for formation of edge-to-face interactions.[2]

4. Conclusion

It can be stated with a large degree of confidence that investigated ligands and their isosteres tend to bind to 5-HT_{1A} in orientation labeled as **B** on Figure 6. Some of the ligands diverge slightly from the trend, with too low or too high calculated energies. Their binding energies can be dependent not only on edge-to-face interactions calculated in this investigation, but also on hydrogen bond with Thr 188 as well, or some other interactions this procedure failed to take into account (ligands **4** and **8** can form hydrogen bond with Thr 188 and would be more stabilized than ligands capable of forming only edge-to-face interactions). All those results quite strongly indicate that our statement that edge-to-face interactions represent a key factor for binding of ligands of this type is valid. Methods like this, hybrid DFT BH&H could be used in investigations of larger systems even with moderate computer equipment, increasing the quality and accuracy of theoretical research in biomolecules.

6. Acknowledgements

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Povzetek

Naše raziskovanje analize sidranja serije izosterov N4-arilpiperazinov na model receptorja 5-HT_{1A} smo že objavili in ga uporabili za preučevanje interakcij med različnimi ligandi z vezavnim mestom receptorja. Glede na omejitve molekulsko mehanskih (MM) metod, analizi sidranja ni uspelo natančno napovedati interakcij, ki vplivajo na vezavno afiniteto ligandov; predpostavljamo, da namreč interakcije aromat-aromat oz. rob-površje, če smo bolj natančni, igrajo pomembno vlogo pri vezavnem procesu. Da bi izpilili hipotezo, smo za izračun možnih interakcij rob-površje v modelnem sistemu uporabili ab initio pristop ter te interakcije korelirali z afinitetami ligandov. Dobljeni rezultati nakazujejo, da disperzivne interakcije kažejo opazen vpliv na vezavo liganda na receptor 5-HT_{1A}. Stabilizacijske energije modeliranih kompleksov receptor-ligand, izračunane s pomočjo Beckejeve »pol-in-pol« hibridne DFT metode, kažejo močno korelacijo z afinitetami preučevanih ligandov do receptorja 5-HT_{1A}.