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Interaction of arylpiperazine ligands with the hydrophobic part of the 5-HT_{1A} receptor binding site

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Abstract—A flexible docking of a series of arylpiperazine derivatives with structurally different aryl part to the binding site of a model of human 5-HT_{1A} receptor was exercised. The influence of structure and hydrophobic properties of aryl moiety on binding affinities was discussed and a model for ligand binding in the hydrophobic part of the binding site was proposed.

1. Introduction

During recent years, the identification of multiple serotonin receptor subtypes has been accompanied by the development of agents that alter serotonin neurotransmission. Serotonin receptors may be involved in impulsivity and alcoholism,[1,2] and in the different phases of sleep,[3] sexual behavior, appetite control, thermoregulation, and cardiovascular function.[4,5]

Our study focuses on serotonin receptors, especially the 5-HT_{1A} receptor, a major target for research and drug development due to its implication in many physiological processes. The main obstacle in the efficient search for new serotonergic ligands is the lack of knowledge about correct 3D structures of the receptor, so we have to rely on computer-generated models, based on the known 3D structure of bacteriorhodopsin and human rhodopsin.

The main feature of many drugs that exhibit 5-HT_{1A} affinity is the presence of arylpiperazine moiety. Among serotonergic ligands, arylpiperazines are the most commonly used pharmacophore moieties, defined earlier by Hibert et al.[6] N4-Unsubstituted N1-arylpiperazines display moderate affinity for the 5-HT_{1A} receptor, but structure–affinity relationship, so far, is quite limited.[7]

In this work, the influence of the structure of several arylpiperazines (Table 1) on binding affinity to the 5-HT_{1A} receptor is investigated. Starting from a well-known key and lock theory, for ligand–receptor binding we applied computational chemistry tools to study the properties of aryl moiety and its interactions within the binding site. To accomplish this, we used docking analysis to investigate fitting of ligand geometry to the receptor binding site, while electrostatic potential calculation showed complementarity of electrostatic surfaces of the ligands and the receptor.

The binding pocket of 5-HT_{1A} was designed using computer and Insight II software. Amino acid residues that form the binding pocket were selected based on literature data and corresponding results obtained by computer analysis (see Section 2). Special attention has been paid to aromatic–aromatic interactions, principally to the edge-to-face interactions (ETF interactions in further text), playing a significant role in the formation of the receptor–ligand complexes.[11] These attractive interactions occur between aromatic moieties devoid of polar substituents. ETF interactions, though modest in energy terms, can play an important role in diverse areas such as protein folding, host–guest binding in supramolecular assemblies, crystal engineering, drug–receptor interactions, and other molecular recognition processes.[12,13] Energetically, they can stabilize the system by up to 2.5 kcal/mol. ETF interactions between receptors and their ligands should be exclusively dependent on the shape of the ligand molecule and its ability to interact with aromatic residues in the binding pocket of the

Keywords: 5-HT_{1A}; Binding site; Hydrophobic pocket; Arylpiperazine.
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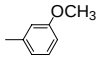
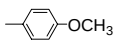
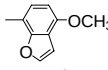
Table 1. Structures, affinities[a] proton charges, and calculated Clog*P* values of 1-arylpiperazines at 5-HT_{1A} receptor

Ar	K_i (nM)	Point charges (*e*)	Clog*P*
 **1**	380	$H_a = 0.105$ $H_b = 0.082$ $H_d = 0.092$ $H_e = 0.101$	1.58
 **2**	130	$H_a = 0.144$ $H_d = 0.114$ $H_e = 0.109$	2.47
 **3**	175	$H_a = 0.148$ $H_d = 0.105$ $H_e = 0.105$	2.77
 **4**	68	$H_b = 0.125$ $H_d = 0.102$ $H_e = 0.109$	1.61
 **5**	320	$H_a = 0.202$ $H_d = 0.105$ $H_e = 0.131$	1.61
 **6**	20,000	$H_a = 0.121$ $H_b = 0.121$ $H_d = 0.117$ $H_e = 0.124$	1.61
 **7**	1410	$H_b = 0.043$ $H_d = 0.043$	−0.13
 **8**	11	$H_a = 0.098$ $H_b = 0.104$ $H_e = 0.087$ $H_f = 0.091$	2.79
 **9**	40	$H_a = 0.117$ $H_b = 0.114$	1.53
 **10**	12	$H_a = 0.124$ $H_b = 0.111$ $H_e = 0.104$ $H_f = 0.112$	2.59
 **11**	13	$H_a = 0.107$ $H_b = 0.105$ $H_e = 0.132$	2.14
 **12**	9.9	$H_a = 0.117$ $H_b = 0.095$ $H_e = 0.148$	2.70
 **13**	27	$H_a = 0.118$ $H_b = 0.114$ $H_e = 0.057$	1.42
 **14**	18	$H_a = 0.154$ $H_b = 0.165$ $H_e = 0.133$	2.46
 **15**	220	$H_a = 0.131$ $H_b = 0.129$ $H_e = 0.125$	2.64
 **16**	430	$H_a = 0.140$ $H_b = 0.144$ $H_e = 0.131$	2.17

[a] References: **1**–**4**, **7** and **8**,[8] **5**, **6**, **9**–**12**, **14**–**16**,[9] and **13**.[10]

receptor.[11] Complementarities of electrostatic potential (ESP) isosurfaces of the aromatic part of the ligand and aromatic residues of the receptor, as well as a proper orientation of molecular entities forming the complex, are prerequisites for this type of interactions.

2. Experimental

The model of the human serotonine receptor 1A (SWISS-PROT Primary accession number P08908) was built using the crystal structures of bovine rhodopsin (PDB codes 1F88, 1HZX, and 1L9H)[14] as a template. Prediction of the transmembrane helices was done using the HMM-TOP method.[15] Comparative modeling by means of the MODELER program,[16] which is part of the Insight II package from Accelrys, has been used. The full model would include seven transmembrane helices, three extracellular loops, three intracellular loops, and C-terminus. As stated earlier,[17] because of non-existent structure and sequence similarity modeling the N-terminus and *i3* loop were omitted. Furthermore, the modeling of intracellular loops *i1*, *i2* and C-terminus as well as extracellular loops *e1* and *e3* was not our primary goal, because the structure of those parts of the molecule does not interfere directly with binding of the ligands.[18,19] Contrary to that, the *e2* loop is of high importance as it can be in some parts in direct contact with the ligand and thus can present one of the central points in our model, as was already shown in, to some extent in similar receptors.[20] In this manner, we kept the highly conserved disulfide bond between Cys109 (3.25) and Cys187 (*e2*)[21] (the numbering scheme from Ballesteros and Weinstein[22] is given in parentheses). The best models from MODELLER have been chosen upon energetic consideration and meaningful side-chain rotamers as well as side-chain directions.

2.1. Ligand binding site

The binding site of the ligand in the 5-HT_{1A} receptor was determined in the following manner. Starting from the fact that for the ligand activity formation of the salt bridge between protonated piperazine nitrogen and Asp 116 (Asp 3.32) is necessary,[23] active site search procedure from binding site analysis module (Insight II[24]) was used to select all amino acid residues forming the cavity near Asp 116. The binding site defined in the previous step was further refined by manually excluding all amino acid residues that cannot come in direct contact with the inside of the cavity. Amino acids forming the binding site of 5-HT_{1A} model are listed in Table 2. The position of the key amino acids in this binding site can be seen in Figure 1.

This binding site corresponds well to a rather conserved binding domain of rhodopsin-like receptors between helices III, V, VI, and VII of class A transmembrane receptors.[25] Some of the listed amino acids were earlier identified by point mutations, to have key interactions with different ligand types.[18,19,26–29] In conclusion, the proposed binding site includes well-defined, conserved amino acid residues and amino acid residues included by computer analysis of 5-HT_{1A} receptor model.

Table 2. Amino acids forming the binding site of the 5-HT_{1A} model

Amino acids in				
TM3	*e2*	TM5	TM6	TM7
Phe 112 (3.28)	Asp 185 (*e2*)	Tyr 195 (5.38)	Cys 357 (6.47)	Ile 385 (7.38)
Ile 113 (3.29)	Ala 186 (*e2*)	Thr 196 (5.39)	Trp 358 (6.48)	Asn 386 (7.39)
Ala 114 (3.30)	Cys 187 (*e2*)	Ser 199 (5.42)	Leu 359 (6.49)	Trp 387 (7.40)
Asp 116 (3.32)	Thr 188 (*e2*)	Thr 200 (5.43)	Pro 360 (6.50)	Leu 388 (7.41)
Val 117 (3.33)	Ile 189 (*e2*)	Gly 202 (5.45)	Phe 361 (6.51)	Gly 389 (7.42)
Leu 118 (3.34)		Ala 203 (5.46)	Phe 362 (6.52)	Tyr 390 (7.43)
Cys 119 (3.35)		Phe 204 (5.47)		Ser 391 (7.44)
Cys 120 (3.36)				Asn 392 (7.45)
Thr 121 (3.37)				

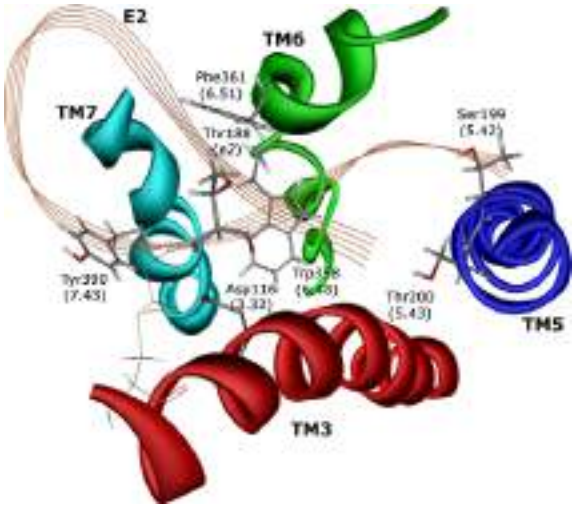


Figure 1. Key amino acids in the binding site of the 5-HT_{1A} receptor model.

2.2. ESP calculations

Ligand models, designed as previously described, were further optimized in Gaussian 03W software,[30] using the DFT B3LYP method, with 6-31g* basis set. Used key words were: fopt b3lyp 6-31g* pop=chelpg test. Geometry optimized in this way was used for calculation of ESP and atom charges. Although the ligands bind 5-HT_{1A} in a protonated form, all ESP calculations were carried out on neutral molecules, since the ESP of the aryl functional group does not significantly change upon protonation of the molecules.[11] The obtained results are given in Table 1. Charge values for H_c for ligands **1** to **7**, and H_c and H_d for ligands **8** to **16** were not listed in the table because no kind of interaction with these protons was observed. Results are visualized in gOpenMol,[31] calculated ESP values were mapped on the ligand electron density and are given in Figure 2.

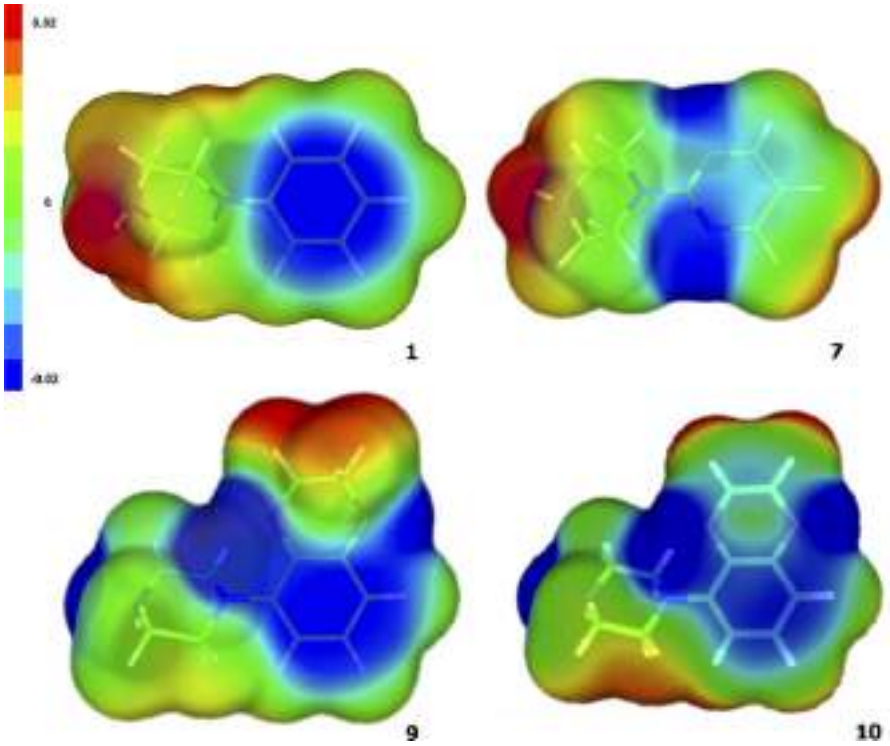


Figure 2. **ESP** isosurfaces of selected ligands. Areas of positive ESP are colored in red, while negative ESP is displayed in blue color.

Ligand docking to the binding site of the 5-HT_{1A} receptor was done using the Affinity module from Insight II,[24] on SGI Octane2 workstation.[32] All ligands from Table 1 were docked as protonated molecules using the CFF91 force field. Every run generated up to 100 docked structures that were finally optimized to remove steric interaction, until reaching 0.001 kcal/mol gradient limit or 4000 optimization steps. The obtained results were analyzed using the following criteria: among the structures with the lowest total energy, we selected the ones with the shortest salt bridge between Asp 116 and protonated nitrogen. Further decisive factors were the conformation of the piperazine ring, and the number and strength of the other observed ligand–protein interactions. After that, structures were rendered using PowRay raytracer v3.6[33] and some of them are shown in Figure 3.

3. Results

Docking analysis of the ligands from Table 1 showed that all arylpiperazine ligands bind to 5-HT_{1A} in a similar way. In Figure 3, common properties of all receptor–ligand complexes, for example, formation of the salt bridge between Asp 116 and protonated nitrogen with less than 3 Å distance and formation of one or more interactions of ligand aryl moiety with aromatic amino acid residues that form hydrophobic pocket of

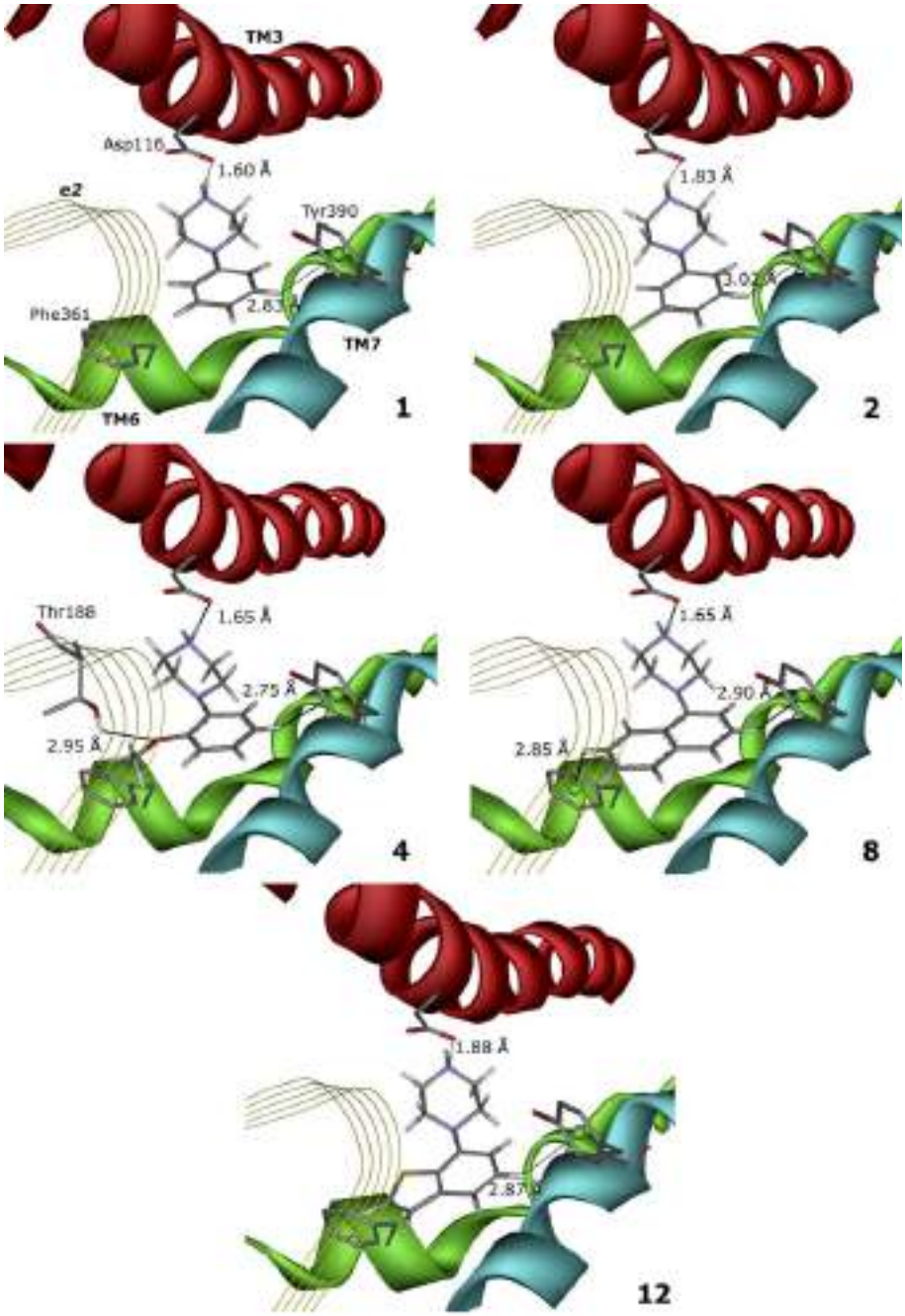


Figure 3. Ligands **1**, **2**, **4**, **8**, and **12** docked to the binding site of 5-HT_{1A} receptor.

receptor binding site can be seen. The hydrophobic pocket consists of aromatic amino acids Trp 358 (6.48), Phe 361 (6.51), and Tyr 390 (7.43), in close proximity to Asp 116 (3.32). The existence of such a hydrophobic part of the binding site already has been suggested by Bondensgaard et al.[25] They postulated that in class A of GPCR proteins there are some highly conserved preserved residues in binding sites that form a hydrophobic pocket, recognizable by many different ligands, having the same aromatic structure—so-called privileged structure by the authors. The binding site designed in this work shows high agreement with their results.

The interactions of the ligands with the residues in the hydrophobic pocket are mainly ETF in their nature.

Apart from the formation of the salt bridge, which is a common feature of all investigated ligands, ligands **1**–**3** interact with Phe 361 or Tyr 390 via protons H_a or H_b and H_d or H_e (the distances between aryl moiety of ligand and those residues being less than 3 Å). Ligand **1**, using its protons—edge—interacts with negative ESP of listed amino acid residues—face. Ligand **2**, with position 3 in aromatic part of the molecule substituted with Cl, has almost three times stronger affinity toward the receptor. This can be explained to some extent by significant increase of positive charge on H_a, and to a lesser extent on H_d,in comparison to ligand **1**, because of introducing an electron-withdrawing substituent. Protons with higher charge are more likely to be involved in ETF interactions. Another factor that influences higher binding affinity can be C–H···Hal interaction, between Cl atom and the corresponding amino acid residue (Phe 361). Such interactions are observed in proteins and their models earlier,[34] but so far, they could not be clearly distinguished from ETF interactions. There is a possibility that an increase in binding affinity is in direct dependence on either one, or both, of these interactions.

Similar behavior can be found in the case of ligand **3**, the affinity of which is almost identical to that of ligand **2**. Size and ESP distribution of ligand **3** are similar to those found in ligand **2**. We believe that the same ETF interaction between a proton on aryl moiety of the ligand and Phe 361 residue of the receptor is involved together with C–H···Hal interactions.

In order to investigate our theory further, we calculated the partition coefficient C log *P*, using the ALOGSP 2.1 web service at http://vcclab.org/lab/alogps.[35,36] Calculated C log *P* values for ligands **1**–**3**, **5**, **7**, **8**, and **10**–**12**, showing modest to high affinity toward 5-HT_{1A}, but not capable of forming hydrogen bond with Thr 188, have good correlation with K_i values calculated from experimental data ($r^2 = 0.90$). Affinity of this group of ligands depends primarily on aromatic–aromatic interactions.

Ligand **4**, with the methoxy group in position 2, shows an increase in affinity toward the 5-HT_{1A} receptor. This ligand has a higher positive charge on aromatic protons, especially H_b, because of the presence of an electron-withdrawing methoxy group on the aromatic ring. But, this increase in affinity can not be explained only on the basis of the ETF interactions. In our analysis of docked structures, we found that this ligand is capable of forming an H-bond with Thr 188 in the *e2* loop. Although it is a well-known fact that Thr 200 residue plays an important role in the binding of some 5-HT_{1A} ligands and we consider it a part of our binding site, none of the obtained docking structures shows formation of hydrogen bonding between tested ligands and Thr 200. Arylpiperazines tested with this 5-HT_{1A} model are relatively small molecules and, as such, cannot span the distance between Thr 200 and Asp 116. If the arylpiperazine moiety is introduced as part of the larger molecule, capable of forming hydrogen bonding with Thr 200, it will be docked inside the hydrophobic pocket.[37]

On the contrary, ligand **5**, with methoxy group in position 3 of the aromatic ring, shows lower affinity toward the 5-HT_{1A} receptor. Methoxy group in position 3 is too far from Thr 188 for an effective H-bond formation. Stabilization of this ligand–receptor complex is done via ETF interactions. Calculated C log *P* values for ligands **4** and **5** are similar to the C log *P* values of ligand **1**. This shows that ETF interactions alone cannot be account for the affinity of ligand **4**. While ligand **4**, due to its hydrogen bond formation, shows the highest affinity in the phenyl-like series, ligand **5**, having the log *P* alike, but lacking the hydrogen bond, shows affinity closer to ligand **1**.

Ligand **6**, with a methoxy group in position 4 of the aromatic ring, forms the weakest complex with the 5-HT_{1A} receptor. The large substituent in position 4 of the aromatic ring is not tolerated by the binding site, because of steric interactions with Trp 358 and in part with the backbone of TM6.

Ligand **7** lacks the protons in positions a and e, and possesses negatively charged nitrogen atoms instead. Moreover, the H_b and H_d protons are mildly positively charged (H_b and H_d charge is 0.043 compared to 0.105 of ligand **1** and 0.144 of ligand **2**), which makes them unsuitable for establishing ETF interactions. Thus, this ligand shows the lowest affinity for the receptor ($K_i > 1000$ nM, Table 1). C log *P* value for this ligand is lowest in the whole series, showing that ligand **7** is the least hydrophobic of all. Low hydrophobicity as well as absence of properly charged protons can explain its weak binding to the 5-HT_{1A} receptor.

Naphthyl-like arylpiperazine ligands **8** to **16** show affinities generally higher than those of ligands **1** to **7**. Being similar in shape and size (they possess two fused rings, one 6-membered aromatic and one 5- or 6-membered ring), their overall 3D structure results in their increased activities, enabling them to establish two ETF interactions, both with Tyr 390 as well as with Phe 361 at the same time. Observed docking structures show shorter distances between groups involved in this type of interaction. All naphthyl-like ligands bind to 5-HT_{1A} with their second ring oriented toward Phe 361, showing that the receptor binding site can accommodate larger

substituents in the vicinity of Phe 361 than Tyr 390. ESP calculations confirm that facing negative aromatic and positive proton charges exist, except in the case of ligand **9** which has no aromatic protons in positions e and f.

Ligand **8** possesses a similar charge on all the 4 protons capable of forming ETF-type interactions (H_a, H_b, H_e, and H_f). Its size enables it to interact both with Phe 361 and Tyr 390 at the same time (Fig. 3), ensuring best fitting in the hydrophobic pocket. Ligand **9**, although slightly larger than **8**, shows a lower activity because of a non-aromatic system in the second fused ring and distorted planar orientation of that part of the ligand, resulting in one ETF interaction less. Both $H_a$and H_b protons are free to form ETF interaction with Tyr 390 (calculated charge 0.140 and 0.114). On the other side, protons that belong to the non-aromatic system show mild positive charge, unsuitable to form ETF interactions with Phe 361 (results not shown). The ligand **9** can compensate for the lack of ETF interaction by forming the H-bond with Thr 188, but its affinity toward receptor is reduced in comparison to structurally similar ligands **8** and **10**.

Ligand **10**, although similar to ligand **9**, shows increased activity toward 5-HT_{1A}. This can be explained by the fact that ligand **10** retains the aromatic nature of both the rings, in contrast to ligand **9**, and as such is capable of forming multiple ETF interactions via its protons H_a, H_b, H_e, and H_f.

Ligands **11** and **12** are similar in affinity and in charge distribution. Ligand **12** having a sulfur atom is somewhat larger than ligand **11**, resulting in slightly increased affinity due to shorter ETF interactions. In both ligands, the rings preserve aromatic nature and planar conformation, which enable protons H_a, H_b, and H_e to form ETF interactions with the receptor.

Ligand **13** shows reduced charge on H_e proton, which influences its affinity. Mild positive charge (0.057) is less likely to form an effective ETF interaction with Phe 361, thus we presume that ligand **13** is capable of forming only one ETF interaction with Tyr 390 via H_a and/or H_b proton. This ligand can also make H-bond with the oxygen atom on Thr 188 and in that way compensate for the loss of ETF interaction. Its measured affinity is closer to ligand **9**, which exhibits similar behavior, than to ligand **11** or **12** that can form two effective ETF interactions. Calculated C$\log P$ values for ligands **8**–**13** show that ligands forming only ETF interactions, **8** and **10**–**12**, have both high C$\log P$ and affinity.

Ligands **14**–**16** were included in this study in order to investigate the influence of size of the substituent in position 4 on the ligand affinity. If affinities of ligands **11** and **14**–**16** are compared, a clear trend between ligand affinity and substituent size in position 4 can be seen. Ligand **11**, having a hydrogen atom in position 4, forms the strongest complex with 5-HT_{1A} receptor, while ligands **15** and **16** that have larger methyl and methoxy substituents form weaker complexes with the receptor, because of steric interactions between the substituent in position 4 and Trp 358, and/or the backbone of TM6. Ligand **14**, with fluorine atom in position 4, shows a similar affinity as ligand **11**. Strong electron withdrawing effect of fluorine atom favors ETF interactions with Phe 361 and Tyr 390. On the other hand, the van der Waals radius of fluorine atom is slightly larger then that of hydrogen atom, which causes mild repulsive interactions compensated in part with ETF interactions.

4. Discussion

In this research, it was found that binding of ligands with arylpiperazine moiety to 5-HT_{1A} receptor depends on several types of interactions. First, the salt bridge is formed between the charged nitrogen of the ligand and Asp 116 of the receptor. This is the main interaction, stabilizing the receptor–ligand complex. After the salt bridge formation, the ligand can engage its aromatic moiety in various interactions with the hydrophobic pocket of the binding site. These interactions can be ETF in nature, between protons of the aromatic part of the ligand and Phe 361 or Tyr 390 of the receptor, or the hydrogen bond between Thr 188 and the corresponding atoms of the ligand. Number, nature, and strength of these interactions depend mostly on the ligand structure, more precisely on its shape and charge.

Highly conserved disulfide bond between Cys 109 and Cys 187 places the Thr 188 in the position suitable for hydrogen bonding with ligands.

Up to this date, several authors investigated and calculated the possible influence of second extracellular loop on ligand–receptor complex formation.[20,39] Unfortunately, since the position of these residues is uncertain, all investigations are based on hypothetical receptor models. Using site-directed mutagenesis and construction of chimeric opioid receptors it has been proved that one or more amino acid residues in the extracellular loop of opioid receptors plays a key role in the binding of some ligand types.[40] Similar results were obtained in the cholecystokinin B receptor, where it was proved that mutation of His 207 to Phe decreases significantly affinity of the ligand[41] and with human EP2 and EP receptors, where a conserved Thr, required for ligand binding, was found in the second extracellular loop.[42]

Hydrophobic part of the binding site in the 5-HT_{1A} receptor, formed by Trp 358, Phe 361, and Tyr 390, is significant for stabilization of the ligand–receptor complex. The dimension of this cavity is such that it can host ligands of different sizes and shapes. During our research it was found that the introduction of substituents in positions 2 and 3 can increase affinity of the ligand, but substitution in position 4 leads to a decrease of activity.[43,44] Ligands with a noticeably larger aromatic part, like **8**–**16**, possess higher affinity because of the decrease of distances between interacting atoms (Fig. 3).

Interactions that lead to the ligand–receptor complex stabilization are ETF-type interactions; ligand acting as an edge (see Table 1) and aromatic amino acids in the binding site of the receptor as a face (Phe 361 and/

or Tyr 390). The distribution of charge in ligands can be seen in Figure 2. Greater positive charge on protons involved in ETF interactions enhances their strength.

With this in mind it is not difficult to explain variations in affinity of the examined ligands. Ligand **7** shows the lowest affinity because the protons on aromatic ring are less positive (Table 1) compared to all other ligands. Ligand **1** binds stronger than ligand **7** but weaker than **2**–**4**. In ligands **2** and **3** ETF interactions are intensified because of the presence of halogen atom(s), as can be seen from increased potential on H_a (Table 1). The increase in binding affinity with introduction of halogen atom is the result of stronger ETF interactions and/or C–H···Hal interaction. Introducing the halogen atom in systems similar to this one can increase non-covalent interactions for up to 1.5 kcal/mol.[34,38] In case of ligand **4**, besides ETF interaction, additional stabilization is possible by formation of a potential H-bond with Thr 188 in the receptor. Ligand **5** can form only ETF interactions, and its affinity is similar to ligand **1**.

Ligands with aryl part consisting of two rings show increase in binding due to their shape and size, which enables them to make shorter and stronger ETF interactions. Ligands **8**, **10**–**12**, and **14**–**16** can form multiple ETF interactions with the hydrophobic pocket of the receptor. The ligands **9** and **13** are, to some extent, an exception. Ligand **9** is not planar and its second ring is not aromatic, while H_e proton on the imidazole system of ligand **13** has a low positive charge unsuitable for forming ETF interactions.

To compensate for the lack of these interactions, ligands **9** and **13** are capable of forming a H-bond with Thr 188. Their affinity is not as high as can be expected, probably due to utilization of some amount of energy from this bond for the stabilization of the part of the extracellular loop containing the interacting amino acid Thr 188. Single point energy calculations (Gaussian single point b3lyp/6-311g* calculation with the corresponding groups at a distance of 2.74 Å) of systems consisted of ligands **9**–**11** and 2-propanol in the position simulating Thr 188 shows that ligands **10** and **11** are not capable of forming a hydrogen bond of significant energy.

Again, introduction of large substituent in position 4 of the ligand is not tolerated because of steric interactions with the receptor binding site. Ligands **15** and **16** show a sharp drop in affinity in comparison to ligands **11** and **14**, proportional to the size of the substituent group.

The size and shape, together with charge distribution (ESP) and the presence of groups capable for H-bond formation, are vital factors for ligand affinity, but, interactions between a ligand and the hydrophobic part of the binding site are decisive for the binding affinity of arylpiperazine ligands.

In the ligands, where only aromatic–aromatic interactions play a crucial role in complex stabilization, calculated Clog*P* value shows good correlation with experimental results. The more hydrophobic aryl part of the ligand is, the stronger complex with the receptor will be formed, and a stronger affinity observed.

Interactions described here are also observed in docking studies of different ligands having structural similarity in arylpiperazine part of the molecule[44] with the ligands in this study. We have reasons to believe that their receptor affinity is in part defined by interactions of the arylpiperazine part, although the interactions of the other parts of molecules must not be ignored.

These data can be used as a starting point in the synthesis of new serotonergic ligands with increased affinity toward 5-HT_{1A}.

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