HHS Public Access

Author manuscript

Mini Rev Med Chem. Author manuscript; available in PMC 2018 July 01.

Published in final edited form as:

Mini Rev Med Chem. 2018 ; 18(7): 552–560. doi:10.2174/1389557517666170913111533.

Pharmacophore Comparison and Development of Recently Discovered Long Chain Arylpiperazine and Sulfonamide Based 5-HT$_7$ Ligands

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Abstract

The serotonin system exerts its effects on the CNS and many peripheral systems. Of the 14 serotonin receptors, the 5-HT$_7$ receptor is the most recently discovered. The 5-HT$_7$ receptor has been shown to be involved in stress reduction, depression, and nociceptive control. Despite the 20 years since the discovery of 5-HT$_7$R, there are still few truly selective ligands. Two of the common scaffolds for 5-HT$_7$R ligands are long chain arylpiperazines (LCAPs) and sulfonamide containing compounds. This review focuses on recently developed (2014–2016) 5-HT$_7$R ligands, their selectivity for the receptor, and suggests possible new pharmacophore models for these ligands.

Keywords

5-HT7; Pharmacophore; Serotonin; Drug Design

1. INTRODUCTION

1.1. Serotonin

Serotonin, or 5-hydroxytryptamine (5-HT), is a multifunctional, monoamine neurotransmitter with action in the central and peripheral systems of animals and is present as a secondary metabolite in a number of plants. The serotonergic system is important for the regulation of many processes in the central nervous system (CNS) and many peripheral systems. Serotonin has been linked to regulation of some aspects of the cardiovascular system, including blood pressure regulation, vasodilation or vasoconstriction, and the onset of arrhythmias.[1–3] In the pulmonary system, serotonin affects both breathing and regulating respiratory drive.[4,5] Serotonin has been shown to play a major role in many gastrointestinal disorders such as irritable bowel syndrome, nausea, and diarrhea.[6–8] While nearly 95% of the body's serotonin is localized in the gut, one of the more widely studied roles of serotonin is its function within the central nervous system.[9] Here the neurotransmitter has been shown to play a significant role in modulation of physiological functions. These functions include,

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thermoregulation, sleep, pain, hunger, cognition, emotions, learning, memory, and many others.[10–16]

1.2. Serotonin Receptors

There are 14 serotonin receptors (5-HTR). Each of these is a G-protein coupled receptor (GPCR), except for the 5-HT_3R, which is a ligand-gated ion channel. These receptors are classified into 7 families based on sequence homology. Additionally, these families of receptors are often classified into 3 larger groups based on the GPCR subunit with which they are coupled and consequently, their effect on GPCR-triggered signaling cascades:

1. The G_i-protein coupled receptors group is comprised of the 5-HT_1R family (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}) and the 5-HT_5R family (5-HT_{5A} and 5-HT_{5B}). Being coupled to the inhibitory G-protein, these receptors inhibit the production of cAMP from ATP, which then has effect on downstream pathways.
2. The G_q-protein coupled receptors group is comprised of the 5-HT_2R family (5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}). These receptors work by activating phospholipase C, which through a series of reactions, activates the phosphatidylinositol signaling pathway.
3. The G_s-protein coupled receptors include the 5-HT_4R, 5-HT_6R, and 5-HT_7R. These receptors work by activating cAMP, which in turn activates the cAMP-dependant pathway.

1.3 5-HT_7 Receptors

In 1983, a "5-HT_1-like" receptor was described based on its function in the relaxation of smooth muscle tissue of mammals.[17] Ten years later, in 1993, the 5-HT_7 receptor was discovered independently by three research groups.[18–20] After some time, it became clear that this "5-HT_1-like" receptor was, in fact, 5-HT_7R.[21] Since its discovery over 20 years ago, there has been extensive research into its role in signal transmission; however, because there are few ligands which are selective for 5-HT_7R over other 5-HT_1 receptors, there is still more to be learned about its role.

The 5-HT_7 receptor has been reported in the CNS, as well as in the periphery. Within the CNS, it is found in high concentration in the brainstem, hypothalamus, thalamus, hippocampus, and cortex.[22] Outside of the CNS, the 5-HT_7R can be found in the ileum, spleen, endocrine glands, and arteries.[23] 5-HT_7R antagonists have demonstrated a variety of effects including stress reduction and antidepressant effects.[24,25] On the other hand, 5-HT_7R agonists have been shown to inhibit nociceptive control, which could make them good candidates as analgesic drugs.[26]

One of the issues that has arisen in 5-HT_7 research is that ligands for 5-HT_7R are often also ligands for 5-HT_{1A}, making it difficult to find selective ligands for the 5-HT_7 receptor. 5-HT_{1A}R and 5-HT_7R have both been linked to anxiety, depression, thermoregulation and both may play a role in the drug action of TCAs and SSRIs.[27–37] Despite previous difficulties in

designing selective ligands for the 5-HT_7 receptor, in the past few years, several selective ligands have emerged.

1.4 Current Pharmacophore Models

There are several pharmacophore models that have been constructed for the 5-HT_7 receptor since its discovery in 1993. One of the first published models in 2003, (Fig. 1A), proposed five key features necessary for antagonism: 3 hydrophobic regions (HYD1, HYD2, HYD3), a positively charged center (PI), and a hydrogen bond acceptor (HBA).[38] While the model has been adapted in the years since, these hydrophobic regions and the positively charged center have remained integral to the model. In 2006, the features which were attributed to selectivity and non-selectivity for 5-HT_7 were studied and another pharmacophore model was elucidated (Fig. 1B).[39] In 2004 Vermeulen et al. presented a pharmacophore model for agonist vs. antagonist activity(Fig. 1C).[40] The major differences include the presence of two additional hydrophobic regions to select for antagonism. While the exact mechanism of the receptor is not yet fully understood, these pharmacophore models have led to the development of several classes of 5-HT_7 ligands including long chain arylpiperazines (LCAPs), and sulfonamide containing compounds.

1.5 Pharmacophore Model for LCAPs and Sulfonamide Containing Compounds

Herein, two new pharmacophore models for the LCAP and sulfonamide containing compounds are presented and were generated using MOE software.[41] For each set of compounds, a database was prepared using the ligands referenced in this paper and the Flexible Alignment calculation was performed to align the parts of these ligands with similar features. The Pharmacophore Consensus application was used to calculate a pharmacophore query based on the flexible alignment, and the pharmacophore expressions which were satisfied by the highest percentage of ligands were selected as part of the model. Each ligand was then superimposed with the pharmacophore model and the individual interactions were analyzed. While the pharmacophore models generated in this review are based on recently developed selective ligands, they incorporate the knowledge from previous pharmacophore models. The recently developed selective ligands satisfy the older models and these new modified models.

2. LONG CHAIN ARYLPIPERAZINES

One of the most thoroughly explored classes of 5-HT_7 ligands is the long chain arylpiperazine. Based on the pharmacophore model described in Kołaczkowski et al. (Fig. 1A) the aromatic ring of the arylpiperazine occupies a hydrophobic pocket. Additionally, the tertiary amine can form hydrogen bonds with the nearby Asp residue. The other aromatic ring has pi-pi interactions when it binds in AR1.These three interactions are proposed to lead to selective 5-HT_7R ligands, but, if a carbonyl is present that binds in HBA1, it is less likely that the compound will be selective. Commercially available LCAPs, such as LP-12 and LP-44, (Fig. 2) have demonstrated selectivity over the 5-HT_{1A} receptor, and for this reason, are commonly used as leads for further SAR studies.

2.1 Pharmacophore Model

Using the recently discovered LCAPs described below, a new pharmacophore model for LCAPs which act as 5-HT_7 antagonists was elucidated (Fig. 3).[41] The critical components of this model include 3 hydrophobic/aromatic binding regions (HYD/AR1, HYD/AR2, and HYD/AR3), a large, non-aromatic hydrophobic region (HYD1) and a hydrogen bond donor (HBD) located inside of HYD1. These regions were determined to be critical as they were satisfied by at least 83% of the molecules described below. Moreover, each compound below satisfies at least 4 of the 5 pharmacophoric regions.

2.2 Recently Discovered LCAP Ligands for 5-HT_7

In 2014, Kim et al. developed a series of 20 methoxyphenyl-LCAPs. When the length of the carbon linker was varied, it was found that a 4-carbon chain resulted in the highest affinity for the 5-HT_7 receptor.[42] The substitution of the biphenyl group was then examined. The chlorophenyl substitution lead to the greatest increase in affinity. The 2'-Cl substituted compound **1**, (Fig. 4), had the highest affinity for 5-HT_7 (K_i = 8.69 ± 0.77 nM), while the 3'-Cl and 4'-Cl had much lower affinities. The arylpiperazine moiety satisfies both the HYD/AR2 and HYD/AR3. HYD1 is filled with the carbon linker and the amide, and the amide also satisfies the HBD, which may explain why the 4-carbon linker resulted in increased activity, as a longer or shorter chain would result in a molecule that no longer can satisfy both the HYD/AR regions and the HBD. HYD/AR1 is filled with the aryl ring adjacent to the amide, and interestingly, in 3D space, the chlorophenyl ring can extend back into the HYD1 region. Additionally, the 2-chloro substituent can rotate away from the hydrophobic region, while the 3- and 4-chloro derivatives would be closer to this region. Because of its affinity for the 5-HT_7 receptor, compound **1** was subjected to a panel of radioligand binding assays to determine its affinity for other receptors (K_i 5-HT_7 =8.69 nM, K_i 5-HT_{1A} =20.0 nM, K_i 5-HT_{1B} =131.0 nM, K_i 5-HT_{1D} =418.0 nM, K_i 5-HT_{2A} =478.0 nM, K_i 5-HT_{2C} =26.0 nM, K_i 5-HT_3 = >10,000 nM, K_i 5-HT_{5A} =1178.0 nM, K_i 5-HT_6 =1517.0 nM). It was determined that **1** is selective over all the other 5-HT receptors tested, including 5-HT_{1A}, and acted as a 5-HT_7 antagonist. This compound was then tested in vivo and demonstrated antidepressant effects at 25 mg/kg in the forced swimming test in mice.

In 2015, Pytka et al. synthesized two LCAP derivatives, **2** and **3** (Fig. 5), which showed high affinity for the 5-HT_7 receptor (K_i = 156 nM, K_i = 34 nM, respectively) but with poor selectivity over the 5-HT_{1A} receptor (K_i = 41 nM, K_i <1 nM, respectively), with antagonist activity at 5-HT_7.[25] However, because both of these receptors are known to play a role in depression and anxiety, the compounds were tested in vivo. In the forced swim test, **2** (5.0 mg/kg) decreased immobility time by 38% compared to the vehicle and increased swimming behavior by 185%. **3** (2.5 mg/kg) decreased immobility time by 38% and increased swimming time by 191%. Additionally, **2** and **3** both showed mild anxiolytic activity, but less than diazepam. These compounds both align with four of the five components of the pharmacophore model. HYD/AR1 and HYD/AR2 are satisfied by the two terminal aromatic rings. The piperazine ring and carbon linker fill the HYD region, although the ether could be the cause of lower affinity in this region. HYD/AR3 is not filled because the molecule does not extend far enough in that space. For these compounds, the piperazine amine, which is protonated at physiological pH, provides the proton to be a hydrogen bond donor, rather than

an amide nitrogen. The methoxy-substituent on the phenyl ring does not interact with any of the key parts of the pharmacophore model, but is able to rotate back into the hydrophobic region (HYD1). Additionally, while substituting a phenyl with a chlorine shows no difference in interaction with the pharmacophore, it does however improve 5-HT_7 activity, so it could be useful to explore chlorination of the HYD/AR2 moieties in other LCAPS.

In 2015, Canale et al. investigated the use of the cyclic amino acids Pro-amide and Tic-amide as modifications to the LCAP scaffold.[43] Upon biological testing of a 26- membered library of LCAPs with cyclic amino acid moieties, compounds **4** and **5**, (Fig. 6) emerged as a 5-HT_{1A} partial agonist and 5-HT_7 = 12 ± 22 nM and K_i 5-HT_{1A} = 66 ± 22 nM, demonstrating a 6-fold preference for the 5-HT_7R. When comparing the molecule to the pharmacophore model presented above, both 4 and 5 satisfy all 5 components of the molecule. HBD is satisfied by the piperazine nitrogen, much like **2** and **3** (Fig. 5). The HYD1 region is filled with carbon linker and amide, and all three of the HYD/AR regions are satisfied with either aromatic rings or the conjugated amide bond. It should be noted that although **4** has a longer carbon linker, the molecule could bend in space so that the HYD/AR2 and HYD/AR3 regions are satisfied. The substituents on the HYD/AR3 phenyl ring are the major differences between these compounds. The large hydrophobic benzyl ring provides more selectivity than the methylsulfide, which suggests that there is another hydrophobic pocket that is being filled. 5 was tested in vivo using the forced swim test and it was shown to reduce the immobility time of the mice by 24%, but did not affect the spontaneous locomotor activity.

Current studies have developed more selective 5-HT_7 ligands with the LCAP structure. In 2016, Intagliata et al. synthesized a series of twenty 4-arylpiperazine containing compounds, six of which demonstrated high affinity for the 5-HT_7 receptor and no measureable affinity for the 5-HT_{1A}R.[44] Compound **6,** (Fig. 7, K_i 5-HT_7 = 52.0 ± 15 nM), utilizes a phenyl group and benzyl group to fill the HYD/AR1 and HYD/AR3 (Fig. 7). It had been determined that the 2 carbon polylinker yielded higher affinity for the 5-HT_7 receptors, so each of the subsequent compounds contained linkers of the same length as well as the benzyl moiety to fill the aromatic pocket. Several analogues of **6** with different substitutions on the HYD/AR3 pocket were synthesized. Compounds **7** (K_i 5-HT_7 = 36.6 ± 2.92 nM), **8** (K_i 5-HT_7 = 50.2 ± 12.3 nM), and **9** (K_i 5-HT_7 = 24.2 ± 4.34 nM) utilized 4-chloro, 2-chloro, and 2-methoxyphenyl groups, respectively (Fig. 7). Compounds **10** (K_i 5-HT_7 = 29.5 ± 8.21 nM), and **11** (K_i 5-HT_7 = 23.5 ± 2.32 nM) utilized the nitrogen containing 2-pyridyl and 2-pyrimidyl groups, respectively, with the pyrimidyl group showing increased affinity compared to the pyridyl as well as the chloro and methoxy substituted derivatives. This series of analogues is different from the previously discussed compounds because it contains two piperazine rings which are able to satisfy both the HBD1 and the HYD/AR2 pockets. These are the most selective 5-HT_7 ligands, so it is possible that the two-piperazine scaffold is important for increased selectivity. While the substitution of the benzyl ring was not explored in this study, increases in activity have been seen by introducing hydrophobic substituents to the 2 position of the aromatic ring in HYD/AR1, which can extend back to the HYD1 region, and this could be an area for further exploration.

Finally, in 2016, Kucwaj-Brysz et al. synthesized fifteen 5-HT_7 antagonists based on the lead compound **MF-8** (K_i 5-HT_7 = 3 nM, K_i 5-HT_{1A} = 121 nM, K_i D_2 = 715 nM), with compounds **12** and **13** showing at least 10-fold affinity over both 5-HT_{1A} and D_2 (Fig. 8).[45] This scaffold is unique in that the HYD/AR2 is filled by the hydantoin ring rather than a phenyl or piperazine. This is much more hydrophilic than a benzyl group and there is much more of an opportunity for hydrogen bonding. Compound **12** (K_i 5-HT_7 = 89 nM, K_i 5-HT_{1A} = 2969 nM, K_i D_2 = 5187 nM) introduced a 3-methoxy group to the HYD/AR1 phenyl moiety, and while it showed a higher affinity for 5-HT_7R over 5-HT_{1A}R and D_2R, its affinity for the 5-HT_7 receptor was almost 30 times less than the lead compound. Compound **13** (K_i 5-HT_7 = 56 nM, K_i 5-HT_{1A} = 1304 nM, K_i D2 = 1814 nM), utilized 2,5-dimethyl substitutions which increased the affinity for the 5-HT_7 receptor while maintaining significant selectivity over the 5-HT_{1A} receptor.

2.3 Important Binding Elements

Within the LCAP group of 5-HT_7 ligands, there is still room for improvement in selectivity. It seems that the use of bis- arylpiperazine scaffolds to satisfy both HBD1 and HYD/AR2 may increase selectivity for the 5-HT_7 receptor. Additionally, the use of phenyl rings with hydrophobic 2-substituents to fill the HYD/AR1 pocket may increase activity by allowing the hydrophobic group to reach back into the HYD1 pocket. Moreover, exploration of the substitution of the HYD/AR3 pocket may lead to more potent ligands. Halogens, methoxy, and methyl substituents have all resulted in increased activity in different compounds, however, it would be useful to determine whether it is merely the space-filling that is important, or if activity can be increased with hydrogen bonding in that region. Finally, exploration of the use of hydrogen bond acceptors in the HYD/AR2 region like **13**, could lead to increases in activity for already active compounds.

3. SULFONAMIDE CONTAINING COMPOUNDS

Another common feature of selective 5-HT_7R ligands is the presence of a sulfonamide to satisfy a hydrogen bond acceptor region of a pharmacophore model. Kołaczkowski et al. proposed that a selective ligand could be characterized by satisfying HBA1, AR1 and PI in their pharmacophore model, and this is the case for several of the recently developed ligands for the 5-HT_7 receptor. Currently several commercially available sulfonamides are classified as 5-HT_7R ligands such as SB-258719 and SB-269970 (Fig. 9).

3.1 Pharmacophore Model

It is likely that these sulfonamide-containing compounds bind to the receptor with the sulfonamide group in the same region. For this reason, a separate pharmacophore model for 5-HT_7 antagonism was elucidated using the sulfonamide containing compounds described below (Fig. 10).[41] In this model, there are three regions where a hydrogen bond acceptor is necessary (HBA1, HBA2, and HBA3). These regions are all surrounding a large hydrophobic region on one side (HYD1). There are two hydrophobic/aromatic regions (HYD/AR1 and HYD/AR2) on each side of HYD1. Finally, within HYD1 there is a hydrogen bond donor (HBD) that is usually satisfied by a tertiary amine.

3.2 Recently Discovered Sulfonamide-containing Ligands for 5-HT$_7$

In 2015, Canale et al. synthesized a library of N-Alkylated arylsulfonamides of (aryloxy)ethyl piperidines in order to study the effects of various N-alkylations on the affinity and selectivity towards the 5-HT$_7$ receptor.[46] Two compounds, **14** and **15** were found to be highly selective 5-HT$_7$R antagonists (Fig. 11). Compound **14**, (K_i 5-HT$_7$ = 58 nM, K_i 5-HT$_{1A}$ = 9625 nM, K_i 5-HT$_{2A}$ = 557 nM, K_i D$_2$ = 280 nM) showed very high selectivity over the $_{1A}$ receptor and utilized the N-methyl substitution on the sulfonamide moiety. Additionally, compound **15**, (K_i 5-HT$_7$ = 49 nM, K_i 5-HT$_{1A}$ = 17,770 nM, K_i 5-HT$_{2A}$ = 1479 nM, K_i D$_2$ = 230 nM), which possessed a N-cyclopropylmethyl substitution, showed very high selectivity over the 5-HT$_{1A}$ receptor. Both **14** and **15** satisfy the pharmacophore model presented earlier. The pyrazole ring fills HYD/AR2 and the oxygens of the sulfonamide fit within HBA2 and HBA3. The hydrophobic region (HYD1) is filled with the piperadine, carbon linker, and the substituted nitrogen. The difference between these two compounds is the cyclopropylmethyl group in **15** and the N-methyl in **14**. This cyclopropylmethyl is larger and extends to the edge of the hydrophobic pocket, filling it without causing too much steric bulk outside of this region. The tert-butyl group may be effective because it is able to extend back into the large hydrophobic region as well. Because of their high affinity and selectivity for 5-HT$_7$R, **14** and **15** were also tested *in vivo* using the forced swim test and **15** was also tested in the novel object recognition test. Both compounds showed the greatest decrease in immobility at a 1.25 mg/kg dose (between 70–80% of the control), with a U-shaped response curve in the FST. In the novel object recognition test, **15** also demonstrated pro-cognitive abilities at a 1mg/kg dose.

In 2016, the same group published the evaluation of another set of 39 arylsulfonamide compounds. Two compounds, **16** (K_i 5-HT$_7$ = 19 nM, K_i 5-HT$_{1A}$ = 545 nM) and **17** (K_i 5-HT$_7$ = 1 nM, K_i 5-HT$_{1A}$ = 98 nM) were identified as selective 5-HT$_7$R antagonists (Fig. 12).[47] While compounds **16** contained a piperidine ring, **17** has an azabicyclooctane ring system. For **16** and **17**, there are several differences in the substitution, but the core structure remains the same. For these compounds, a fluorophenyl group fills the HYD/AR2 pocket. The sulfonamide oxygens still lie in HBA2 and HBA3, and a piperazine fills the large hydrophobic pocket. In **17**, the addition of a carbon bridge on the piperazine helps to fill the hydrophobic pocket even more, increasing the affinity for 5-HT$_7$R. Another difference between **16** and **17** is the cyclopentyl and isopropyl substituents on the benzyl ring that fills HYD/AR1. Compound **17** utilizes the isopropyl group which adds to the hydrophobicity ion this region, without increasing the bulk of the compounds as much as the cyclopentyl. This group however does not extend fully into the hydrophobic region, so it is possible that these substituents are extending into hydrophobic regions on the other side of the phenyl ring. Both compounds were subjected to three functional tests: the forced swim test, tail suspension test, and the four-plate test. The FST confirmed the antidepressant activity of **16** and **17** compared to known 5-HT$_7$R antagonist SB-269970. Additionally, the antidepressant activity was also confirmed with the tail suspension test. In addition, the compounds both showed anxiolytic activity with the four-plate test.

3.3 Important Binding Elements

In general, the sulfonamide containing compounds presented have higher affinities for the 5-HT_7R than those without, therefore, it is possible that the HBA2 and HBA3 regions of the pharmacophore are the reason for this increased selectivity. One of the more interesting strategies was the introduction of the bicyclic ring system to fill the HYD1 region for compound **17**.

4. COMPARISON OF LCAP AND SULFONAMIDE PHARMACOPHORES

The pharmacophore for the sulfonamide compounds is very similar to the LCAP scaffold, and there are several regions in which overlap occurs. Both of the pharmacophore models were overlaid (Fig. 13a) in order to see which regions were essential in both, or just one of the pharmacophore models. The regions which overlapped in both models (Fig. 13b) were the HYD/AR1 and HYD/AR2 regions, the hydrogen bond donor, and the large hydrophobic region. For the molecules that did not fit the pharmacophore completely, the regions that were satisfied were the regions that overlap.

When overlaying the two pharmacophores, it is interesting to see which areas do not overlap. First, the HYD/AR3 region for LCAPs is not in the pharmacophore model for sulfonamides. Looking at the compounds presented, none of the compounds presented extended into this region either. It would be interesting to explore compounds which contain a sulfonamide and extend out into this HYD/AR3 region. Additionally, the bicyclic ring system in **17** could be applied to LCAPs as well to fill the HYD1 region and possibly increase selectivity. Finally, the hydantoin ring used to fill HYD/AR2 in **MF-8**, **12**, and **13**, or other aromatic yet hydrophilic ring systems could be used (1) explore whether it is the aromaticity or the hydrophobicity that is more important in this region for both LCAPs and sulfonamides, then (2) potentially develop sulfonamides that combine this polar ring with the sulfonamide so satisfy the HBA2 and HBA3 regions.

5. CONCLUSIONS

In recent years, there have been several novel compounds developed which bind to the 5-HT_7 receptor. While many strategies have been developed to create selective compounds, there is still much to be explored. This review discussed some of the most potent ligands for the 5-HT_7 receptor, their selectivity profiles, and their effects in functional assays. Three pharmacophore models were elucidated, one for LCAPS, another for sulfonamide containing compounds, and a third for the combined LCAP and sulfonamide models. From these models, several areas for exploration were determined.

5-HT_7 receptors are widespread throughout the brains, which suggest that it may have multiple roles in the CNS. There is still a need for novel, potent 5-HT_7R agonist and antagonists in order to elucidate all of the roles that 5-HT_7R serves in the CNS and periphery.

LIST OF ABBREVIATIONS

5-HT	Serotonin, 5-Hydroxytriptamine
5-HTR	Serotonin receptor
ATP	Adenosine triphosphate
cAMP	Cyclic adenosine monophosphate
CNS	Central nervous system
FST	Forced swim test
GPCR	G-protein coupled receptor
LCAP	Long chain arylpiperazine
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressants

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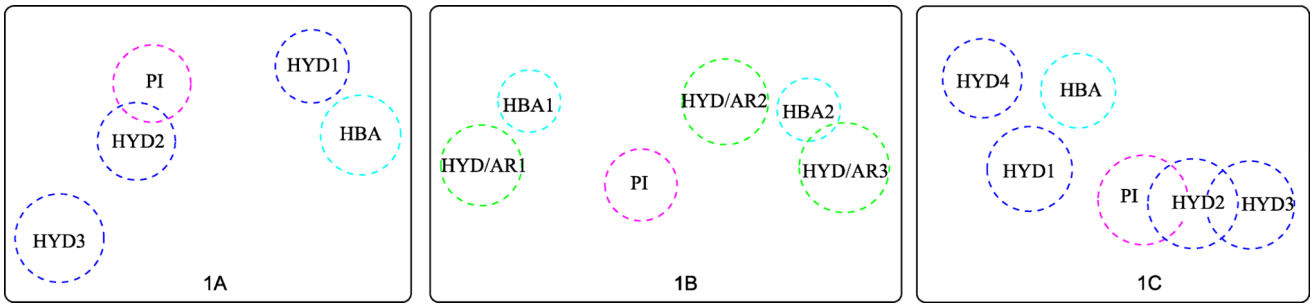
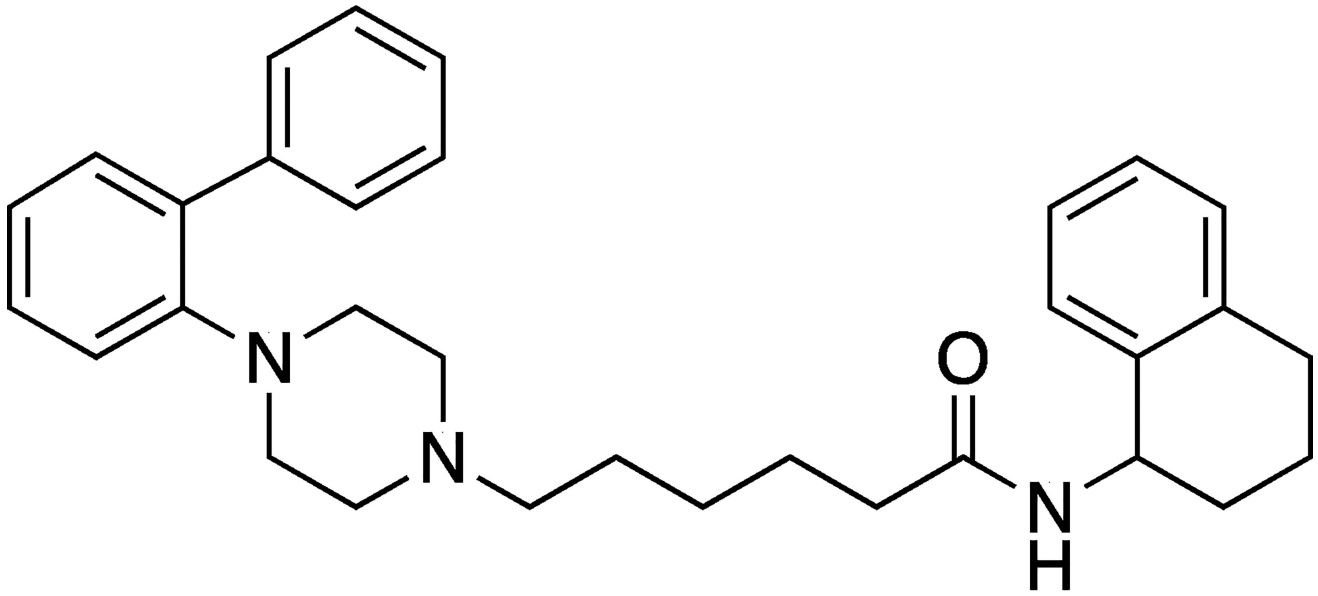
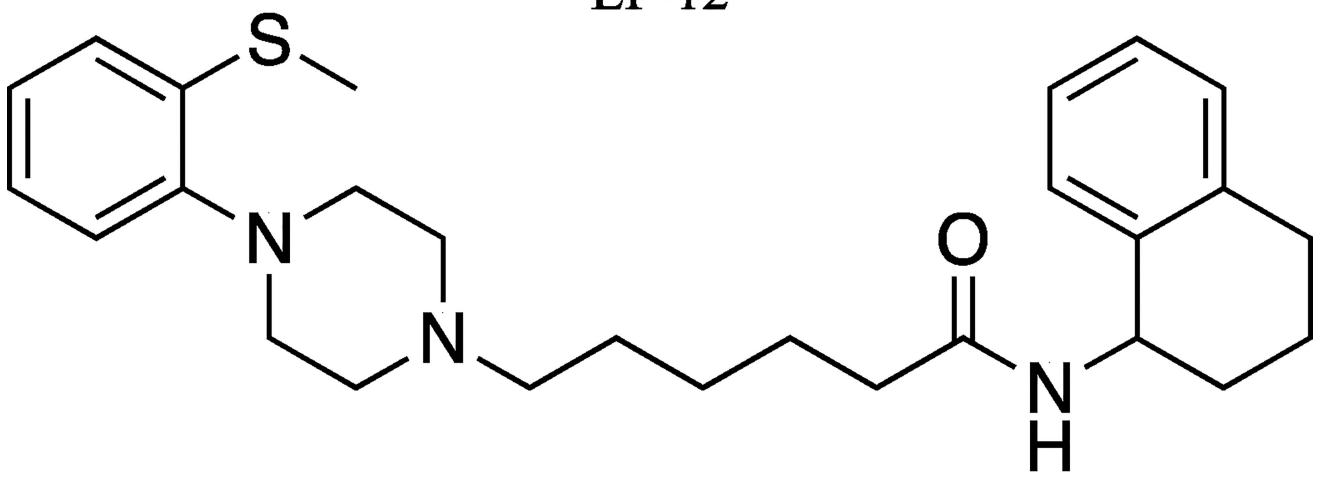


Fig. 1.

Published pharmocaphore models by (A) López-Rodríguez et al., (B) Kołaczkowski et al., and (C) Vermeulen et al



LP-12



LP-44

Fig. 2.
Chemical structures of commercially available 5-HT_7 ligands LP-12 and LP-44

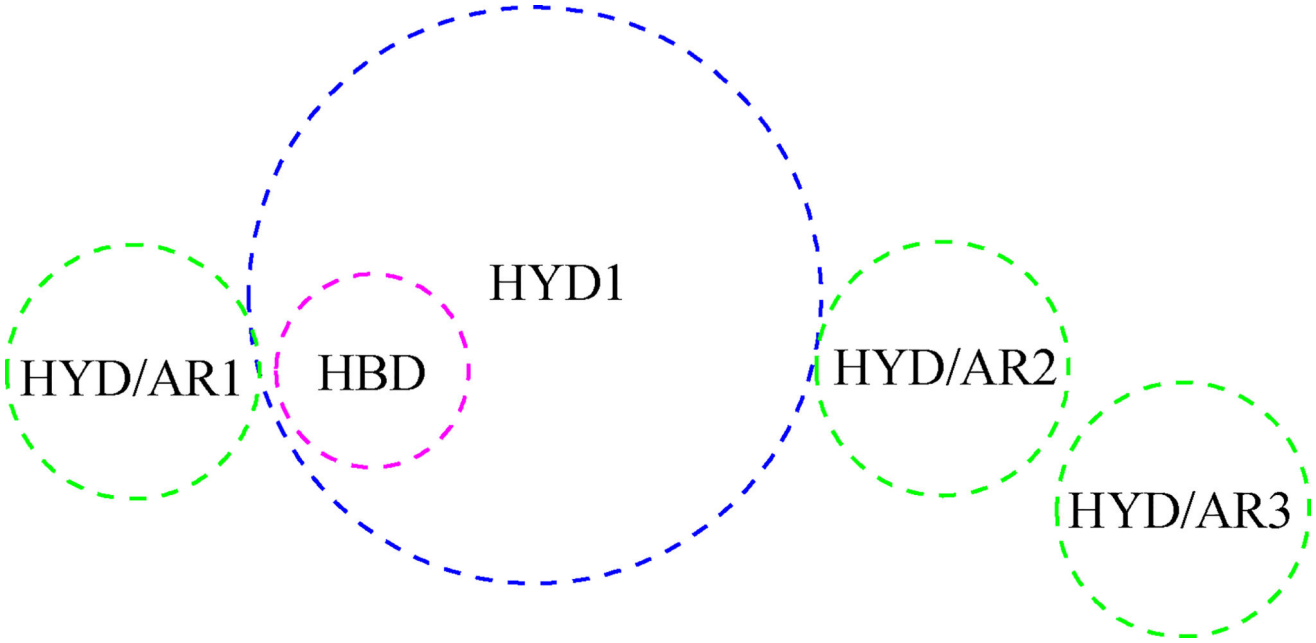


Fig. 3.
Pharmacophore model for LCAPS

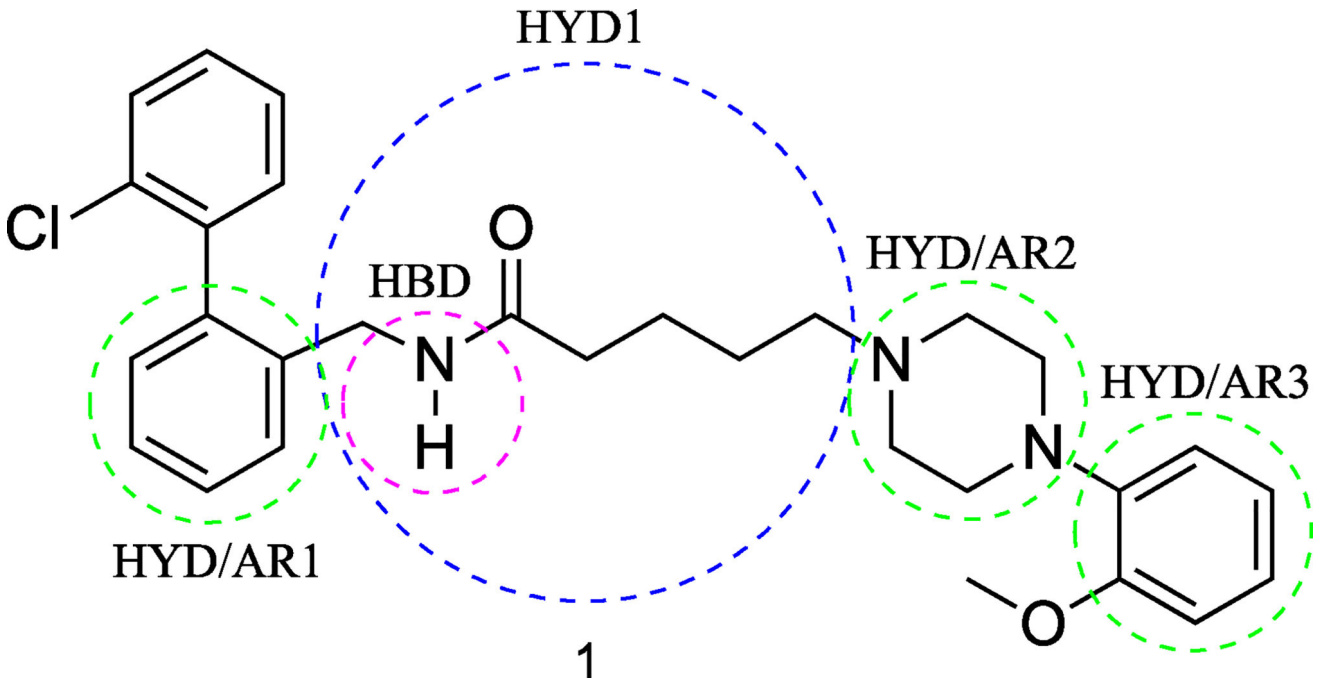


Fig. 4.
Chemical structure of 5-HT_7 ligand **1**

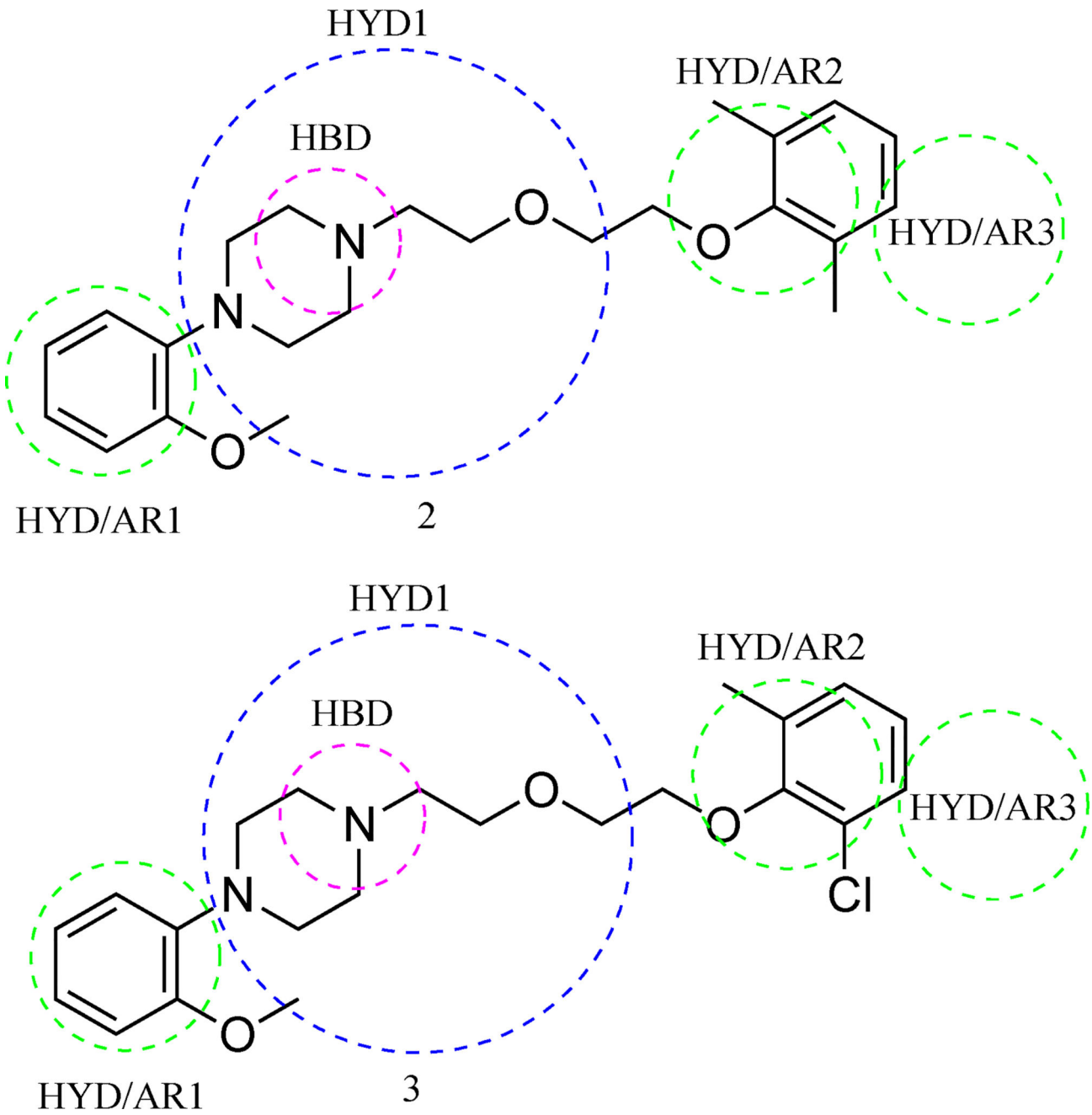


Fig. 5.
Chemical structure of 5-HT_7 ligands **2** and **3**

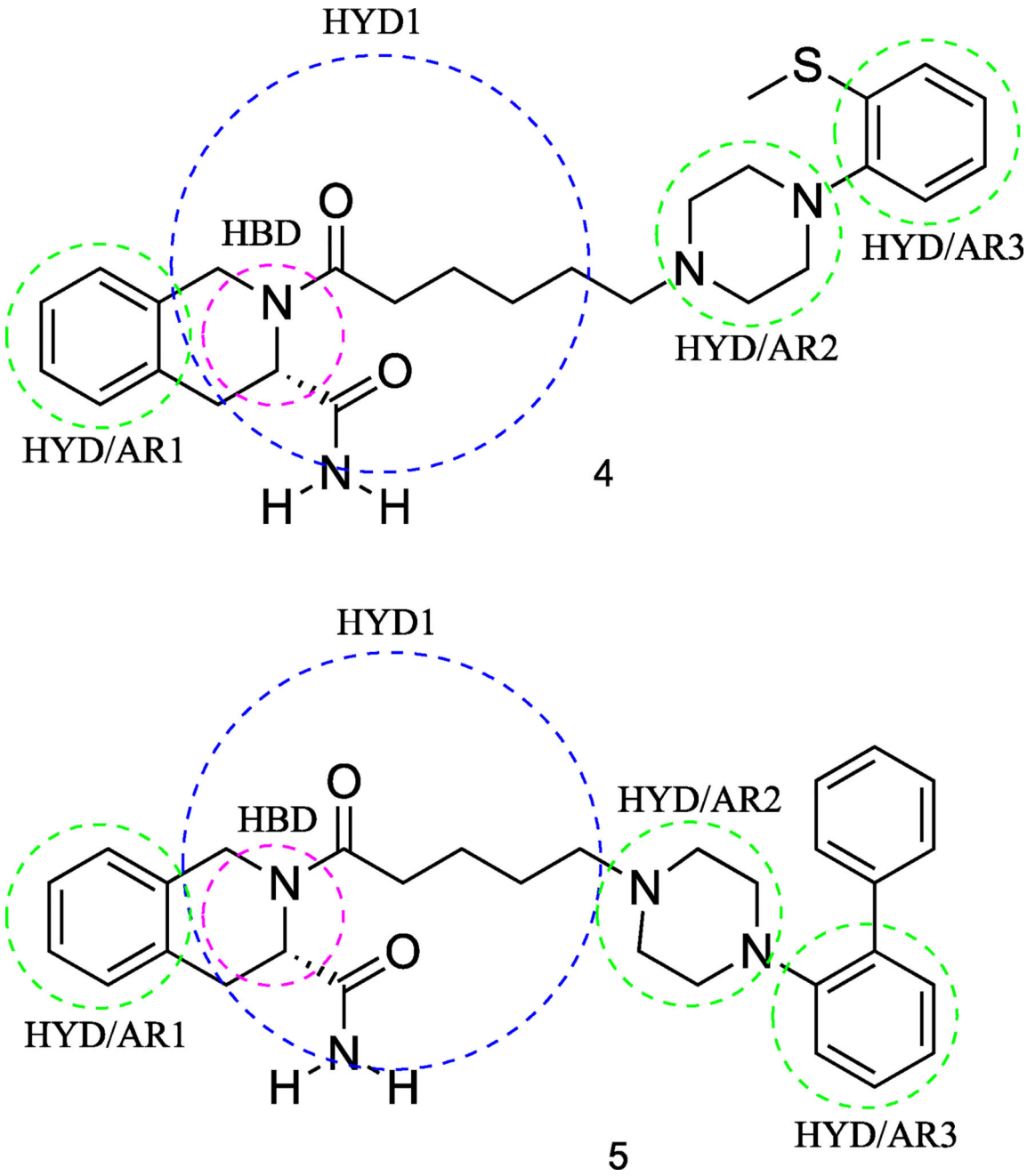


Fig. 6.
Chemical structure of 5-HT_7 ligands **4** and **5**

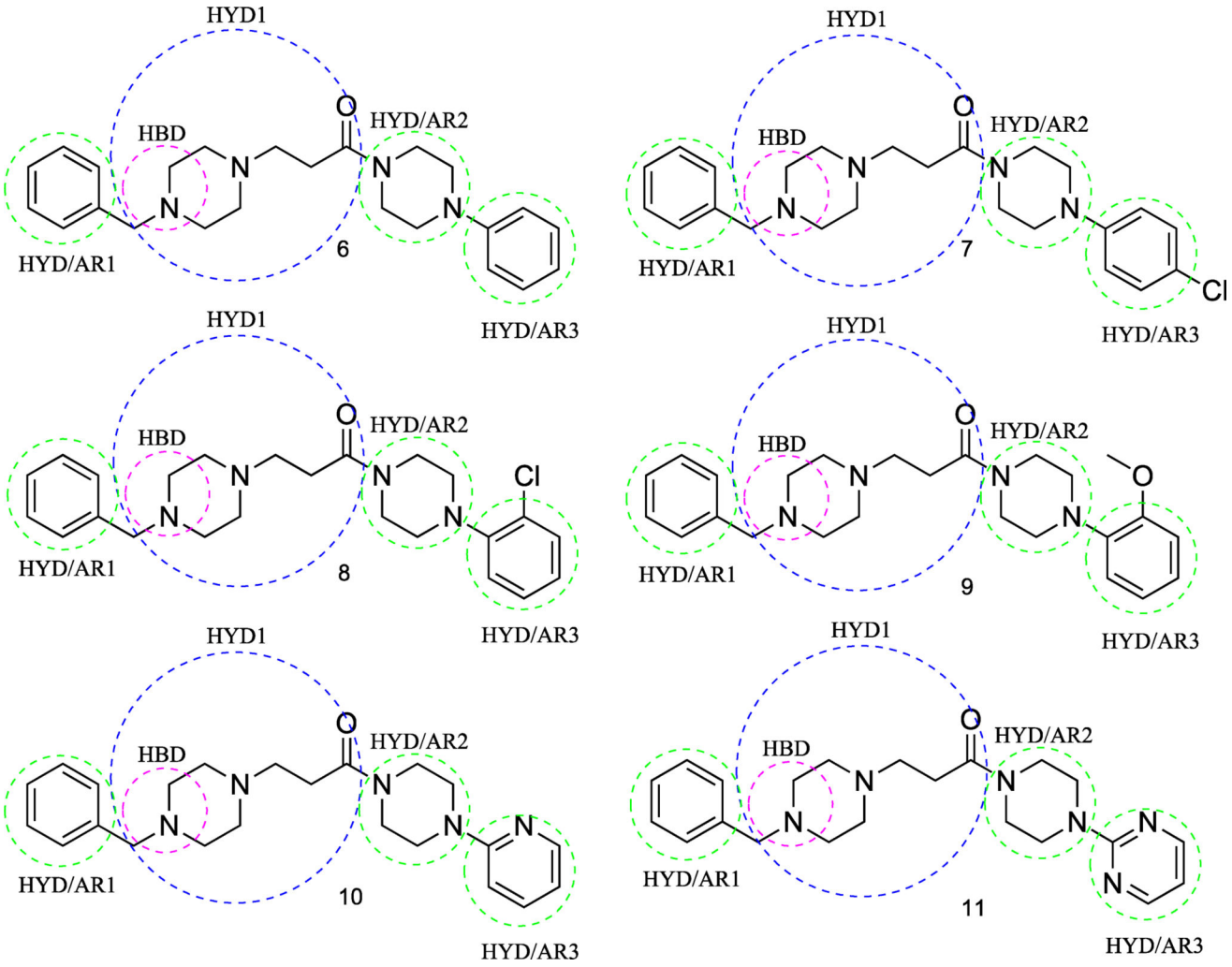


Fig. 7.
Chemical structure of 5-HT_7 ligands **6–11**

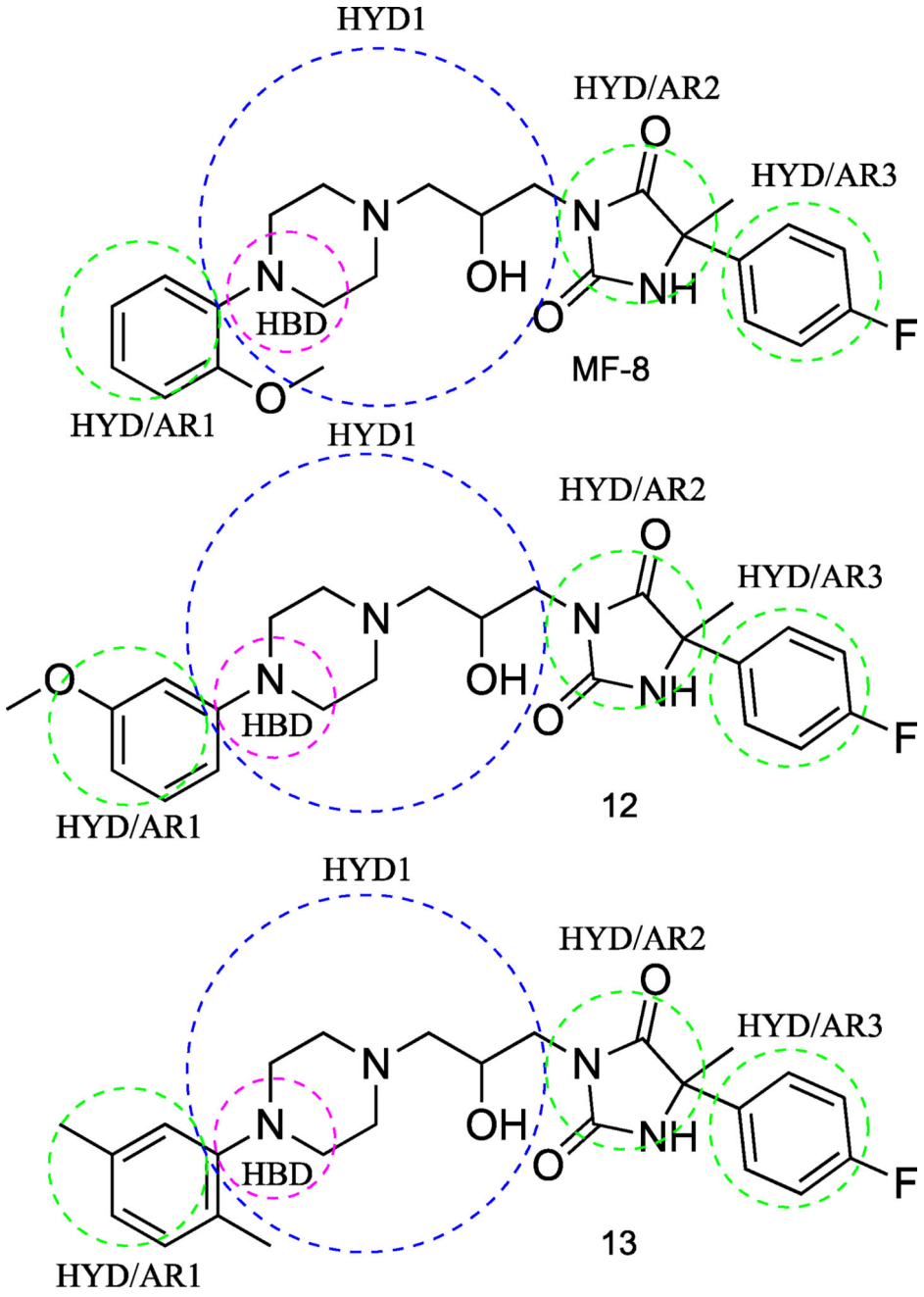


Fig. 8.
Chemical structure of 5-HT$_7$ ligands MF-8, **13** and **14**

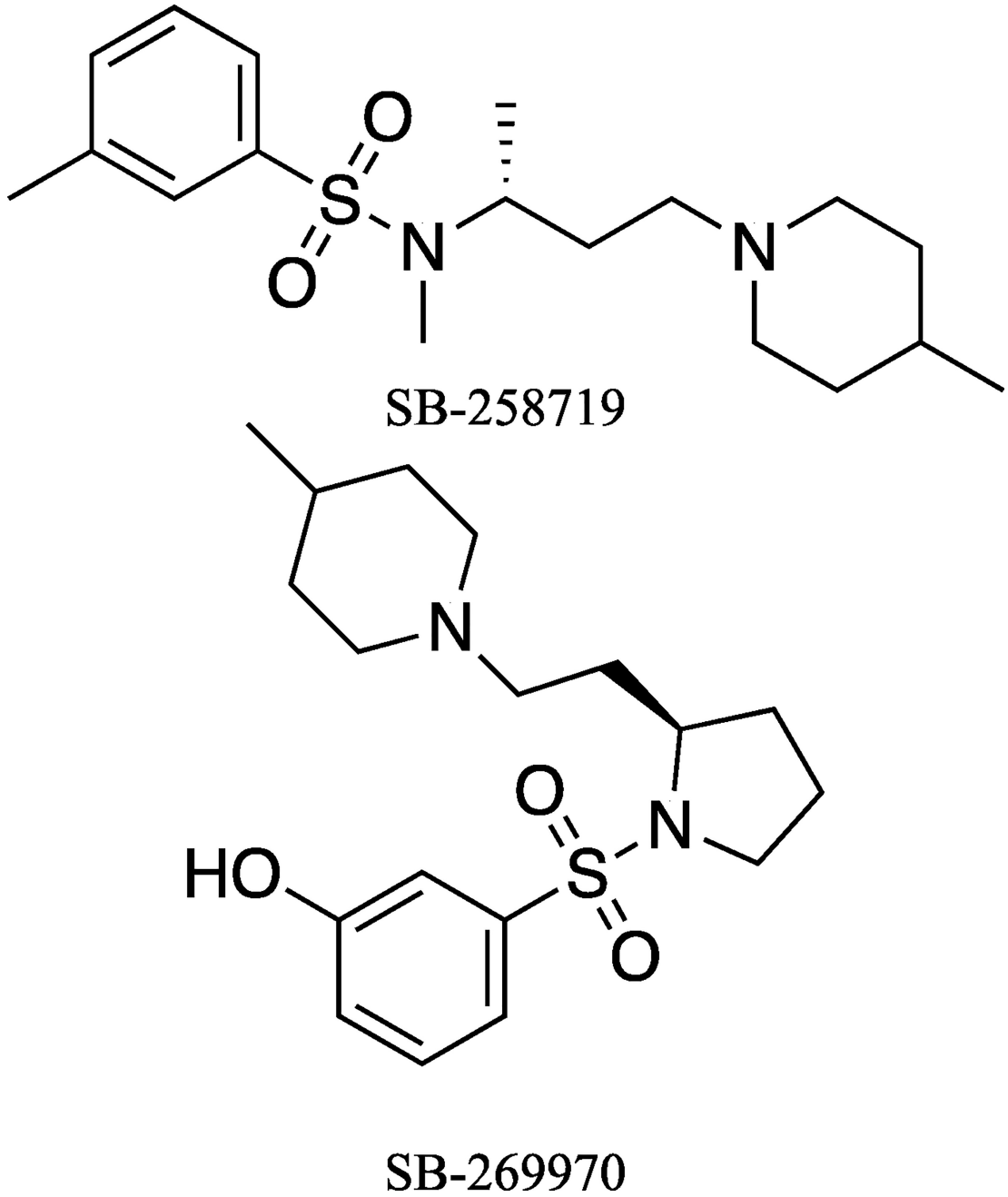


Fig. 9.
Chemical structure of commercially available 5-HT_7 ligands SB-258717 and SB-269970

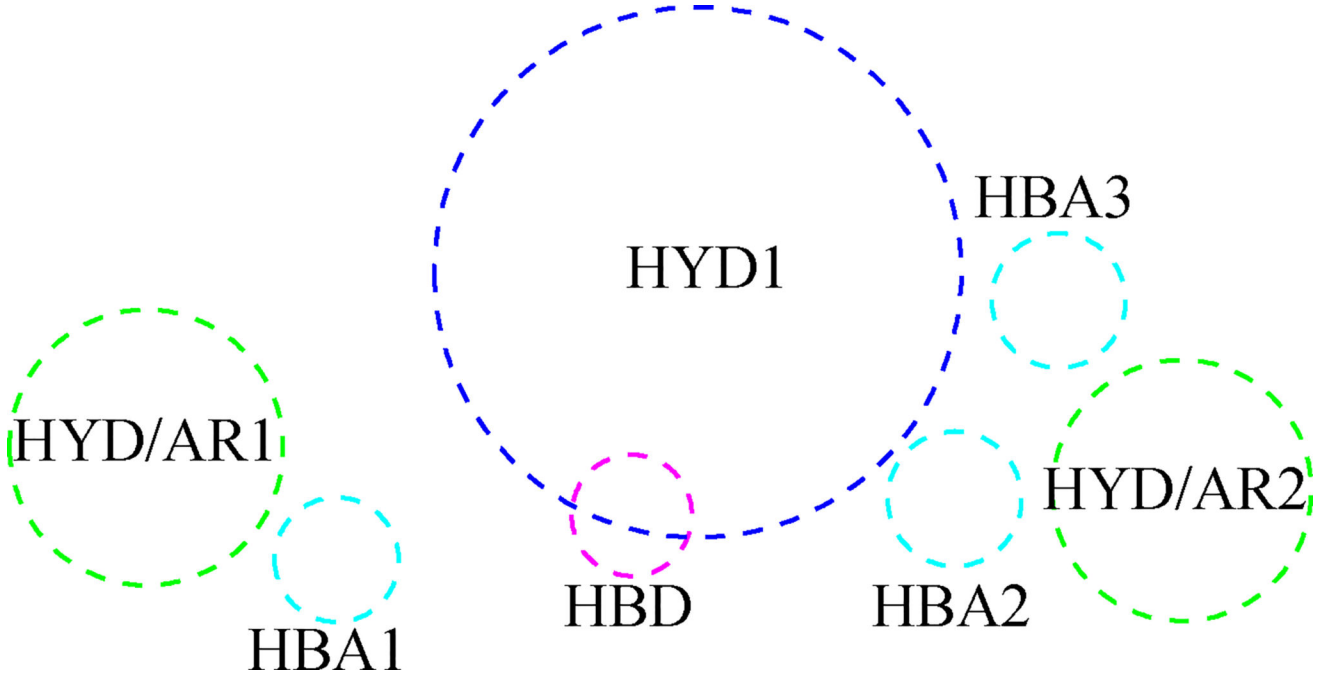


Fig. 10.
Pharmacophore model for sulfonamide containing compounds

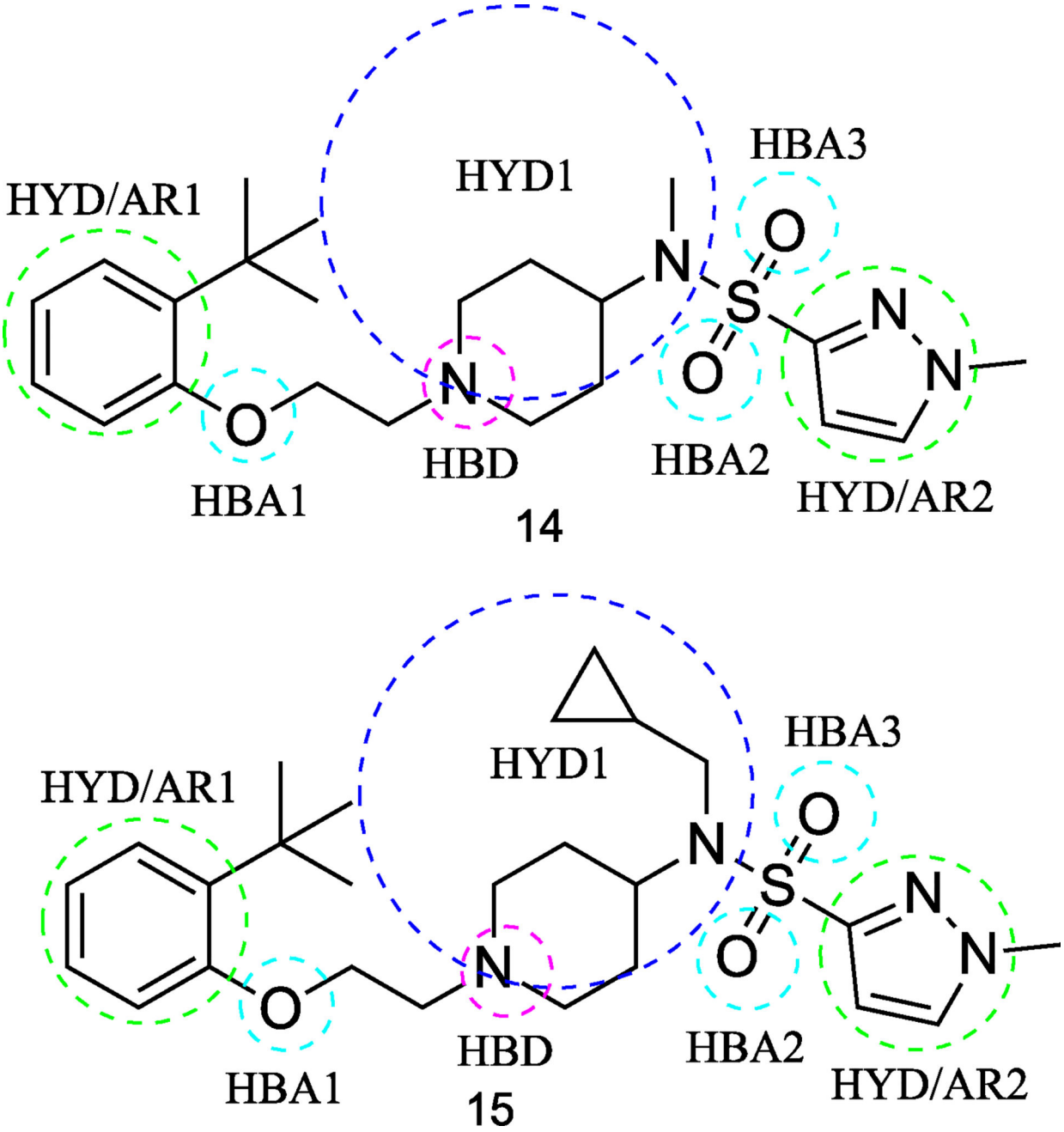


Fig. 11.
Chemical structure of 5-HT$_7$ ligands **14** and **15**

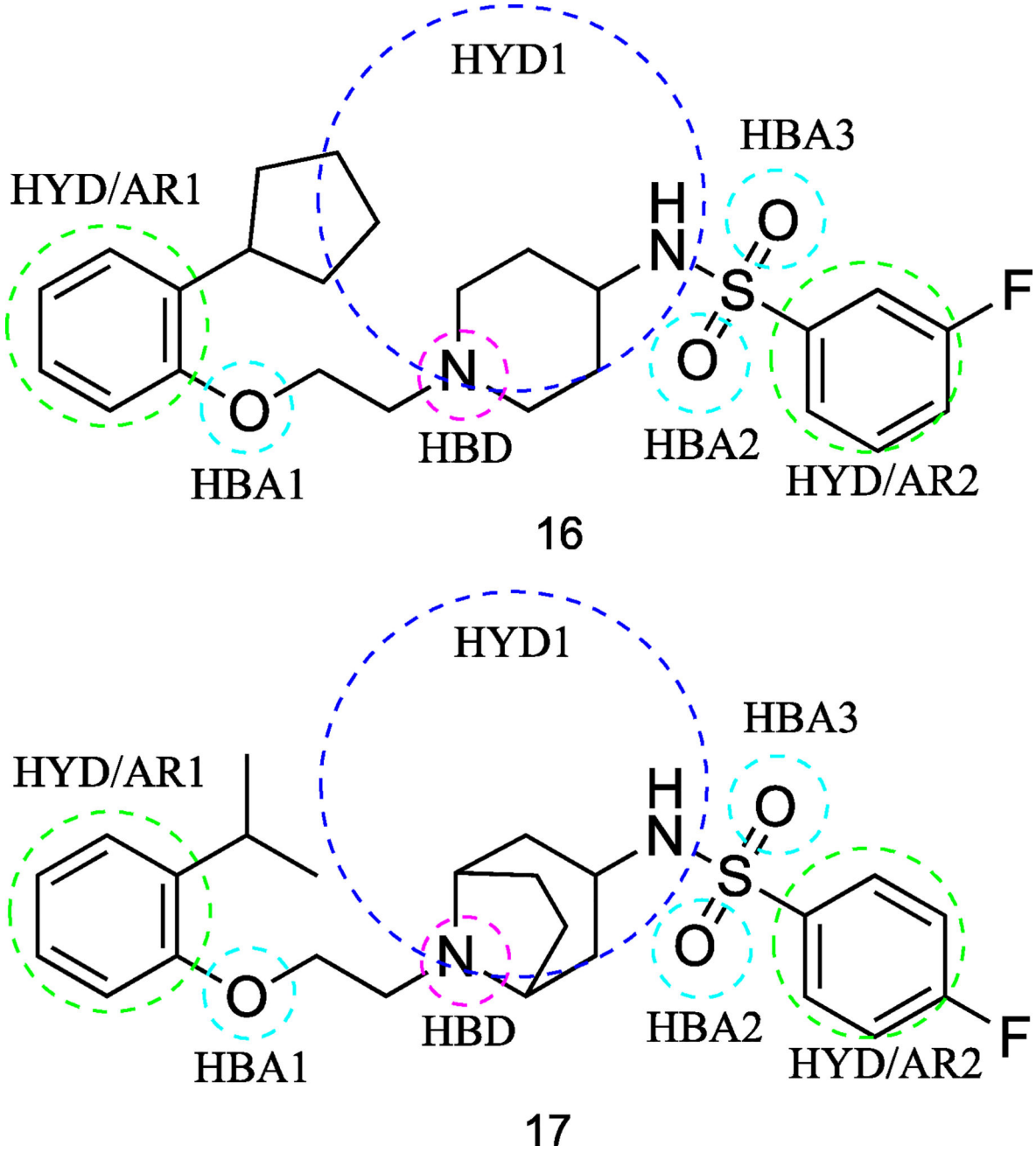


Fig. 12.
Chemical structure of 5-HT$_7$ ligands **16** and **17**

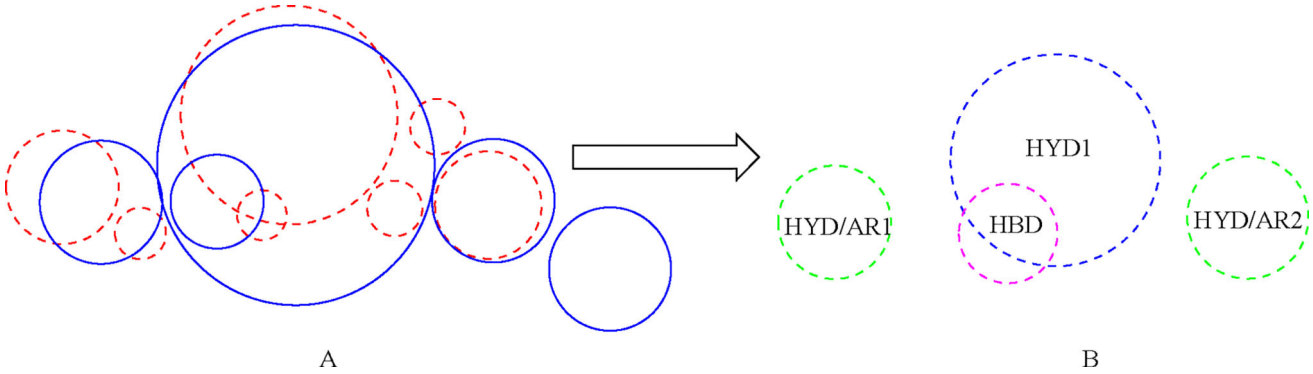


Fig. 13.

(A) Superimposed pharmacophore models for LCAPS (blue) and sulfonamides (red). (B) Combined pharmacophore model for LCAPs and sulfonamides