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Aryl Biphenyl-3-ylmethylpiperazines as 5-HT$_7$ Receptor Antagonists

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The 5-HT$_7$ receptor (5-HT$_7$R) is a promising therapeutic target for the treatment of depression and neuropathic pain. The 5-HT$_7$R antagonist SB-269970 exhibited antidepressant-like activity, whereas systemic administration of the 5-HT$_7$R agonist AS-19 significantly inhibited mechanical hypersensitivity and thermal hyperalgesia. In our efforts to discover selective 5-HT$_7$R antagonists or agonists, aryl biphenyl-3-ylmethylpiperazines were designed, synthesized, and biologically evaluated against the 5-HT$_7$R. Among the synthesized compounds, 1-([2′-methoxy-(1,1′-biphenyl)-3-yl]methyl)-4-(2-methoxyphenyl)piperazine (**28**) was the best binder to the 5-HT$_7$R (pK_i = 7.83), and its antagonistic property was confirmed by functional assays. The selectivity profile of compound **28** was also recorded for the 5-HT$_7$R over other serotonin receptor subtypes, such as 5-HT$_1$R, 5-HT$_2$R, 5-HT$_3$R, and 5-HT$_6$R. In a molecular modeling study, the 2-methoxyphenyl moiety attached to the piperazine ring of compound **28** was proposed to be essential for the antagonistic function.

Introduction

According to sequence similarity and function, the serotonin receptors are classified into seven families (5-HT$_1$R–5-HT$_7$R). Among these, the 5-HT$_7$ receptor (5-HT$_7$R) was the most recently cloned one.[1] The 5-HT$_7$R belongs to the group of G-protein-coupled receptors (GPCRs) and is coupled to the stimulatory G protein (G$_s$), which activates adenylate cyclase, with a resultant increase of the intracellular level of the secondary messenger cyclic adenosine monophosphate (cAMP).[2–4] The 5-HT$_7$Rs are located in the central nervous system, such as the thalamus, hypothalamus, hippocampus, and cortex, as well as in the peripheral tissues.[2–4] Recently, attention has been given to 5-HT$_7$Rs because of their potential roles in depression, control of circadian rhythms, migraine, epilepsy, and neuropathic pain.[5] In particular, observations such as the down regulation of 5-HT$_7$Rs after chronic antidepressant administration and antidepressant-like behaviors in 5-HT$_7$R-knock-out mice[6] suggested the use of 5-HT$_7$R antagonists as possible antidepressants. Thus, it has been reported that SB-269970 (Figure 1), which had been a well-known selective 5-HT$_7$R antagonist until it was reported to block α2-adrenoreceptors,[7] exhibited antidepressant-like activity in a forced swimming test and showed fast effects in an open field test with olfactory bulbectomized rats (OBX), which is an important indication of the 5-HT$_7$R antagonist being a putative fast-acting antidepressant.[8] On the other hand, there have been several reports that activation of 5-

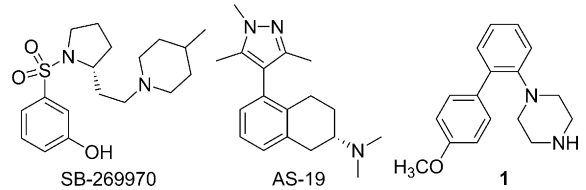

Figure 1. Structures of 5-HT$_7$R modulators.

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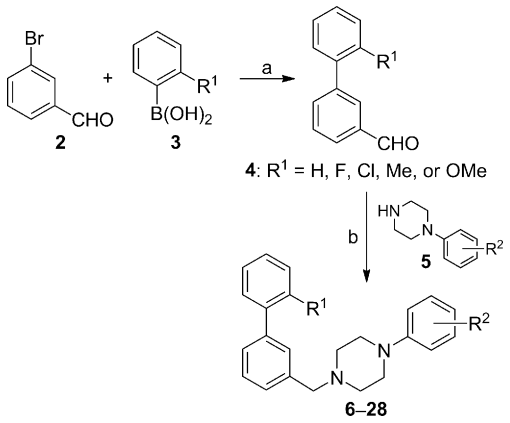
HT_7Rs is involved in pain processing,[9] and both pronociceptive and antinociceptive roles have been proposed to be associated with 5-HT_7Rs; activation of 5-HT_7Rs exerts antinociceptive effects in the central nervous system,[9d–g] whereas 5-HT_7Rs participate in the peripheral pronociceptive effect of serotonin, a neurotransmitter.[9h,i] Systemic administration of the 5-HT_7R agonist AS-19 (Figure 1) significantly inhibited mechanical hypersensitivity and thermal hyperalgesia in the neuropathic-pain animal model. Therefore, the 5-HT_7R is a promising therapeutic target for the treatment of depression and neuropathic pain.

There have been reports of 5-HT_7R ligands with biaryl moieties by several groups.[10] Recently, 1-[2-(4-methoxyphenyl)phenyl]piperazine (**1**; Figure 1) was identified as a high-affinity 5-HT_7R ligand.[10c] We have also been involved in the discovery of novel selective 5-HT_7R modulators and focused on the biaryl moiety for several years.[10d–f] Herein, we report the design, synthesis, binding affinity, and functional in vitro activity at the 5-HT_7R of a series of biphenyl compounds. Based on the pharmacological data, such as selectivity over other subtype serotonin receptors and functional activity, we suggest the most active compound as a lead compound for the treatment of depression. In addition, we address a key structural moiety and determine its antagonistic activity to the 5-HT_7R through a molecular modeling study.

Results and Discussion

Chemistry

The title compounds, aryl biphenyl-3-ylmethylpiperazines **6**–**28**, were synthesized in two steps from commercially available 3-bromobenzaldehyde (**2**) and aryl boronic acid **3** (Scheme 1). Suzuki coupling of 3-bromobenzaldehyde (**2**) with aryl boronic acids **3** (R^1: H, F, Cl, CH_3, or OCH_3) was performed in the presence of a catalytic amount of $Pd(PPh_3)_4$ and Na_2CO_3 in DMF heated at reflux to afford biphenyl-3-carbaldehydes **4** in 37–81% yields.[11] Biphenyl-3-carbaldehydes **4** were treated with various aryl piperazines, **5**, under reductive amination conditions to afford the title compounds **6**–**28** in 15–78% yields.[12] In total, 23 aryl biphenyl-3-ylmethylpiperazines, **6**–**28**, were synthesized.



Scheme 1. Synthesis of aryl biphenyl-3-ylmethylpiperazines **6**–**28**. *Reagents and conditions*: a) $Pd(PPh_3)_4$, Na_2CO_3, *N*,*N*-dimethylformamide (DMF), reflux, 6 h, 37–81%; b) $NaBH(OAc)_3$, MeOH, RT, 8 h, 15–78%.

Pharmacology

The pharmacological profiles of compounds **6**–**28** were determined for 5-HT_7R by [^{3}H]D-lysergic acid diethylamide ([^{3}H]LSD) radioligand binding assays in transfected CHO-K1 cells.[13] SB-269970 and AS-19 were used as reference compounds. The selectivity profile of compound **28** for other subtype serotonin receptors was also obtained by radioligand binding assays with the corresponding radioligands, namely [^{3}H]8-hydroxy-2-(dipropylamino)tetralin ([^{3}H]8-OH-DPAT) for the 5-HT_{1A} receptor, [^{3}H]GR125743 for the 5-HT_{1B} and 5-HT_{1D} receptors, [^{3}H]ketanserin for the 5-HT_{2A} receptor, [^{3}H]LSD for the 5-$HT_{2B}$and 5-HT_6 receptors, [^{3}H]mesulergine for the 5-HT_{2C} receptor, and [^{3}H]LY278584 for the 5-HT_3 receptor.[13c] Selectivity indexes (SIs) were preliminarily calculated by comparing other subtype serotonin receptor binding affinities (expressed as inhibition constant (K_i) values) with that for 5-HT_7R (expressed as a K_i value). Functional characterization of compound **28** was carried out by measuring cAMP levels from HEK293 cells transiently transfected with human cloned 5-HT_7R, with 5-carboxamidotryptamine (5-CT) or SB-269970 as reference compounds.[4]

Structure–activity relationship analysis

The binding affinity of the designed compound **6** with no substituents on the biphenyl and piperazinylphenyl moieties was evaluated, and the pK_i value was determined as 6.35 (Table 1). We then fixed the biphenyl substituent R^1 as H to understand the role of the piperazinylphenyl substituent R^2 for the binding affinity. Compounds **7**–**24**, with the unsubstituted biphenyl moiety (R^1: H) and various aryl piperazines (R^2: F, Cl, Me, OMe, and so on), were tested for 5-HT_7R binding affinities (Table 1). Compounds **7**–**9**, with the R^2 group as a fluorine, showed moderate binding affinities to 5-HT_7R; compound **7**, with the 2-fluoro substituent, had better binding affinity (pK_i = 6.48) than the unsubstituted compound **6**. When a chorine atom was attached to the piperazinylphenyl ring, the overall binding affinities of compounds **10**–**12** were lower than that of the original compound **6**. Compounds **13**–**15**, with methyl substituents, showed binding affinities with pK_i values of 6.01, 6.32, and 5.42, respectively. Compounds **16**–**19**, with two methyl substituents, showed only marginal binding affinities against 5-HT_7R. Among compounds **20**–**22**, with methoxy substituents, only the 2-methoxy-substituted compound **20** showed good binding affinity, with a pK_i value of 7.10. Compound **23**, with a 3,4-dimethoxy substituent, showed only marginal binding affinity (pK_i = 5.68). Compound **24**, with a 3-CF_3 substituent, showed lower binding affinity (pK_i = 6.15) than the unsubstituted compound **6**. Taken together, the compounds with the *ortho* substituents 2-F, 2-Cl, and 2-OCH_3 showed better binding affinities than the equivalent compounds with *meta* or *para*

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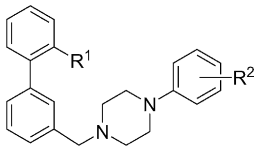
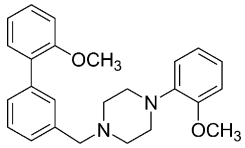
Table 1. Binding affinities to the 5-HT_7R.



Compd	R^1	R^2	pK_i[a]	K_i [nM]
6	H	H	6.35 ± 0.08	422
7	H	2-F	6.48 ± 0.06	332
8	H	3-F	5.85 ± 0.07	1420
9	H	4-F	6.03 ± 0.06	930
10	H	2-Cl	5.83 ± 0.06	1480
11	H	3-Cl	5.24 ± 0.08	5770
12	H	4-Cl	< 5	> 10000
13	H	2-CH_3	6.01 ± 0.07	981
14	H	3-CH_3	6.32 ± 0.09	479
15	H	4-CH_3	5.42 ± 0.07	3760
16	H	2,3-diCH_3	5.90 ± 0.06	1250
17	H	2,4-diCH_3	5.47 ± 0.08	3390
18	H	2,5-diCH_3	5.64 ± 0.07	2310
19	H	3,5-diCH_3	6.03 ± 0.08	932
20	H	2-OCH_3	7.10 ± 0.06	79.0
21	H	3-OCH_3	6.16 ± 0.08	694
22	H	4-OCH_3	6.34 ± 0.07	458
23	H	3,4-diOCH_3	5.68 ± 0.07	2080
24	H	3-CF_3	6.15 ± 0.07	711
25	2-F	2-OCH_3	7.3 ± 0.1	54
26	2-Cl	2-OCH_3	7.48 ± 0.08	33.0
27	2-CH_3	2-OCH_3	7.29 ± 0.07	51.0
28	2-OCH_3	2-OCH_3	7.83 ± 0.06	15.0
SB-269970			9.47 ± 0.05	0.34
AS-19			9.09 ± 0.05	0.81

[a] Values are the mean ± SEM of triplicate binding experiments.

Table 2. Selectivity profile of compound **28** over other serotonin receptor subtypes.



28

Receptor	pK_i[a]	K_i [nM]
5-HT_7	7.83 ± 0.06	15.0
5-HT_{1A}	7.00 ± 0.09	100
5-HT_{1B}	6.17 ± 0.04	679
5-HT_{1D}	6.65 ± 0.03	225
5-HT_{2A}	7.16 ± 0.06	70.0
5-HT_{2B}	7.37 ± 0.07	43.0
5-HT_{2C}	6.63 ± 0.08	233
5-HT_3	6.5 ± 0.1	295
5-HT_6	< 5	> 10000

[a] Values are the mean ± SEM of triplicate binding experiments.

substituents, whereas in the case of methyl substituents, compound **14**, with a 3-CH_3 group, was the better binder to 5-HT_7R. Monosubstituted compounds showed better binding affinities than disubstituted compounds (**16**–**19** and **23**). Among compounds **7**–**24**, compound **20**, with the 2-methoxy substituent, was the most active.

To further improve the binding affinity to the 5-HT_7R, we fixed the piperazinylphenyl moiety R^2 as the 2-OCH_3 group and modified the biphenyl substituent R^1 with 2-F, 2-Cl, 2-CH_3, or 2-OCH_3 groups. The binding affinities of the substituted compounds **25**–**28** against 5-HT_7R were improved relative to the original compound, with pK_i values between 7.29 and 7.83, with the bismethoxy-substituted compound **28** being the most potent (pK_i = 7.83). Even though **28** showed 28-fold increased binding affinity over that of the original compound **6**, it is still a relatively weaker binder to the 5-HT_7R compared with the well-known 5-HT_7R antagonist SB-269970 (pK_i = 9.47) and the agonist AS-19 (pK_i = 9.09).

For compound **28**, which had the best binding affinity in this series, the selectivity profile over other subtype serotonin receptors was examined, and the results are summarized in Table 2. Each subtype serotonin receptor is a therapeutic target for the treatment of central nervous system disorders such as schizophrenia, anxiety, depression, and cognition.[14–18] Still, to decrease the side effects caused by action on other serotonin receptors, as well as other GPCRs, the selectivity profile is very important in drug discovery. Compound **28** was not binding effectively to the 5-HT_6R and was moderately selective for the 5-HT_1R, 5-HT_{2C}R, and 5-HT_3R. However, compound **28** was less selective for the 5-HT_{2A}R and 5-HT_{2B}R, with pK_i values of 7.16 and 7.37, respectively.

In a functional characterization test against the 5-HT_7R, compound **28** was evaluated for adenylate cyclase activity by using HEK293 cells transiently transfected with human 5-HT_7R.[4] For the agonist test, in which the nonselective 5-HT_7R agonist 5-CT was used as positive control, compound **28** showed only a 20% cAMP level, compared with the 100% cAMP level with 5-CT at 12.5 μM (Figure 2a). On the other hand, compound **28** blocked the cAMP level increase by 5-HT (serotonin), with 70% inhibition at 10 μM, compared with 100% inhibition by SB-269970. According to these functional assays, compound **28** could be defined as a 5-HT_7R antagonist. Overall, compound **28** is a novel 5-HT_7R antagonist.

Molecular modeling study

The high binding affinity and antagonistic property of compound **28** to 5-HT_7R was then tackled by a molecular docking study. The geometry-optimized structure of **28** was docked to the modeled structure of the 5-HT_7R by Glide 4.0 software implemented in Maestro 7.5 (Schrödinger Inc.).[10b] In accordance with the previously reported binding models,[19–23] an ionic interaction between the protonated amino group of compound **28** and Asp162 in the 5-HT_7R was shown to constitute a main essential binding interaction (Figure 3a). Also, the 2-methoxyphenyl and 2′-methoxybiphenyl-3-ylmethyl functionalities attached at both ends of the piperazine moiety of compound **28** were found in the two hydrophobic pockets HPP1 (yellow dotted half-circle in Figure 3b) and HPP2 (red dotted half-circle in Figure 3b). It is of particular interest that the two aromatic methoxy substituents on the piperazinylphenyl and the bi-

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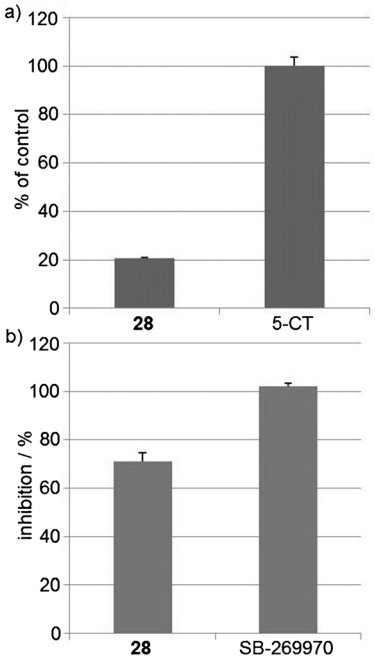

Figure 2. Functional assays against 5-HT$_7$R.

phenyl functionalities of compound **28** were snugly fitted into the small hydrophobic pockets HPP1 (Val163/Thr214/Phe344, Figure 3b) and HPP2 (Leu232/Ile233/Arg367, Figure 3b), respectively (Figure 3c), and the resulting hydrophobic interaction must be responsible for the high binding affinity of compound **28** to the 5-HT$_7$R. Taken together, the binding interactions of the aryl piperazine ligand **28** with the 5-HT$_7$R can be characterized as bidirectional hydrophobic interactions anchored at the salt bridge, the binding interaction of which is significantly enhanced by additional hydrophobic interactions around the two aromatic methoxy substituents.

Based on the understanding of the binding mode of compound **28**, we then attempted to explain its antagonistic property through comparison with the binding modes of SB-269970 and AS-19, the representative 5-HT$_7$R antagonist and agonist, respectively. Thus, the geometry-optimized structures of both SB-269970 and AS-19 were docked to the ligand binding site of the 5-HT$_7$R by using the same docking protocol, and their binding modes were compared with that of compound **28** (Figure 4). The three 5-HT$_7$R ligands commonly occupied one of the two hydrophobic pockets (HPP1; yellow dotted half-circles in Figure 4), and the 2′-methoxybiphenyl moiety of compound **28** (Figure 4a), 2-hydroxybenzenesulfonyl moiety of SB-269970 (Figure 4b), and trimethylpyrazole moiety of AS-19 (Figure 4c) were observed in this pocket. However, the binding interactions of these ligands to the other hydrophobic pocket (HPP2; red dotted half-circles in Figure 4) were strikingly different. Whereas compound **28** (Figure 4a) and SB-269970 (Fig-

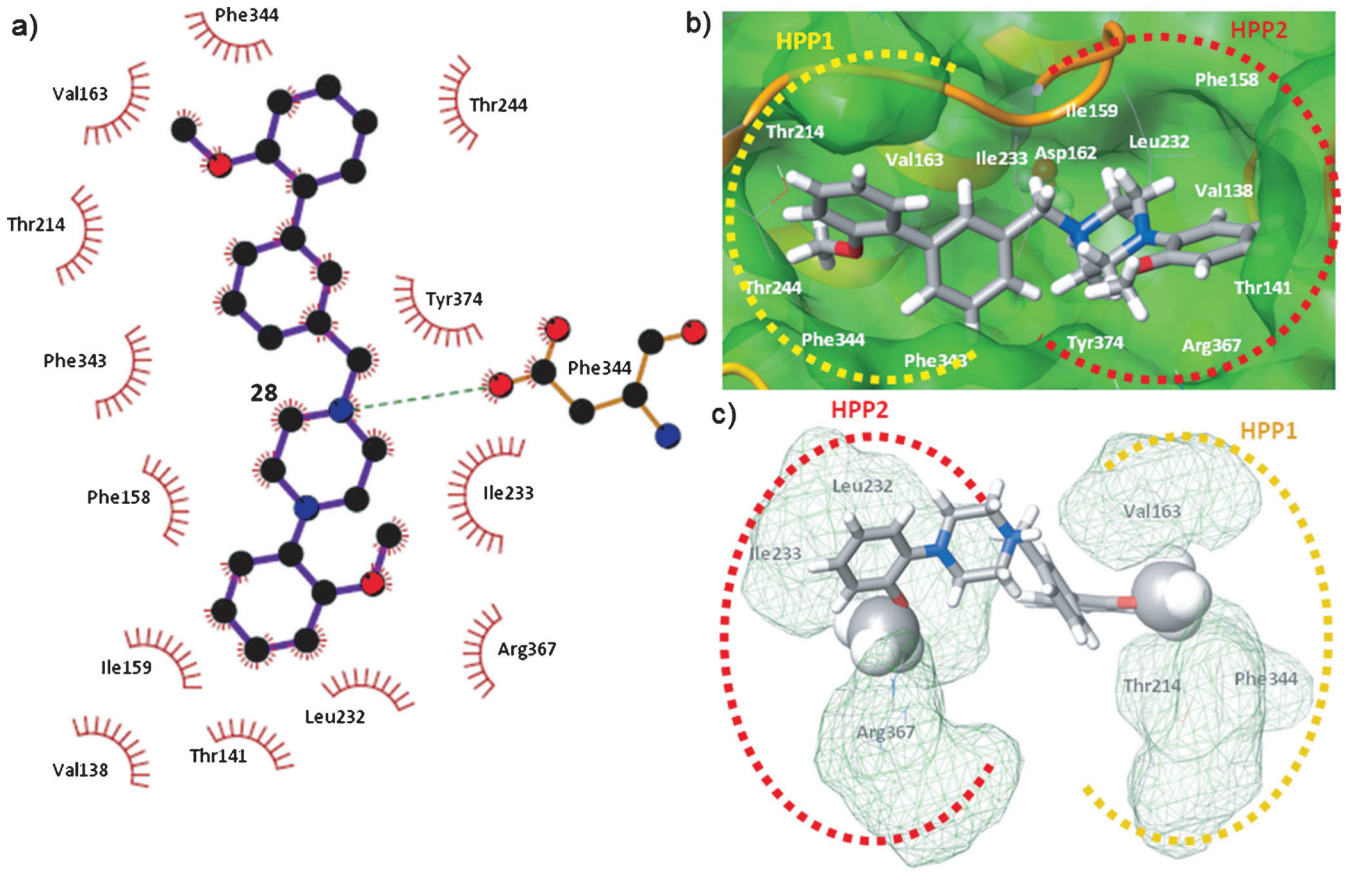

Figure 3. Docking mode of compound **28** in the ligand binding site of modeled 5-HT$_7$R: a) 2D schematic plot created with the program LIGPLOT; b) molecular surface representation of the binding pockets HPP1 (yellow dotted half-circle) and HPP2 (red dotted half-circle); c) the two hydrophobic sites, HPP1 and HPP2, around the aromatic methoxy substituents.

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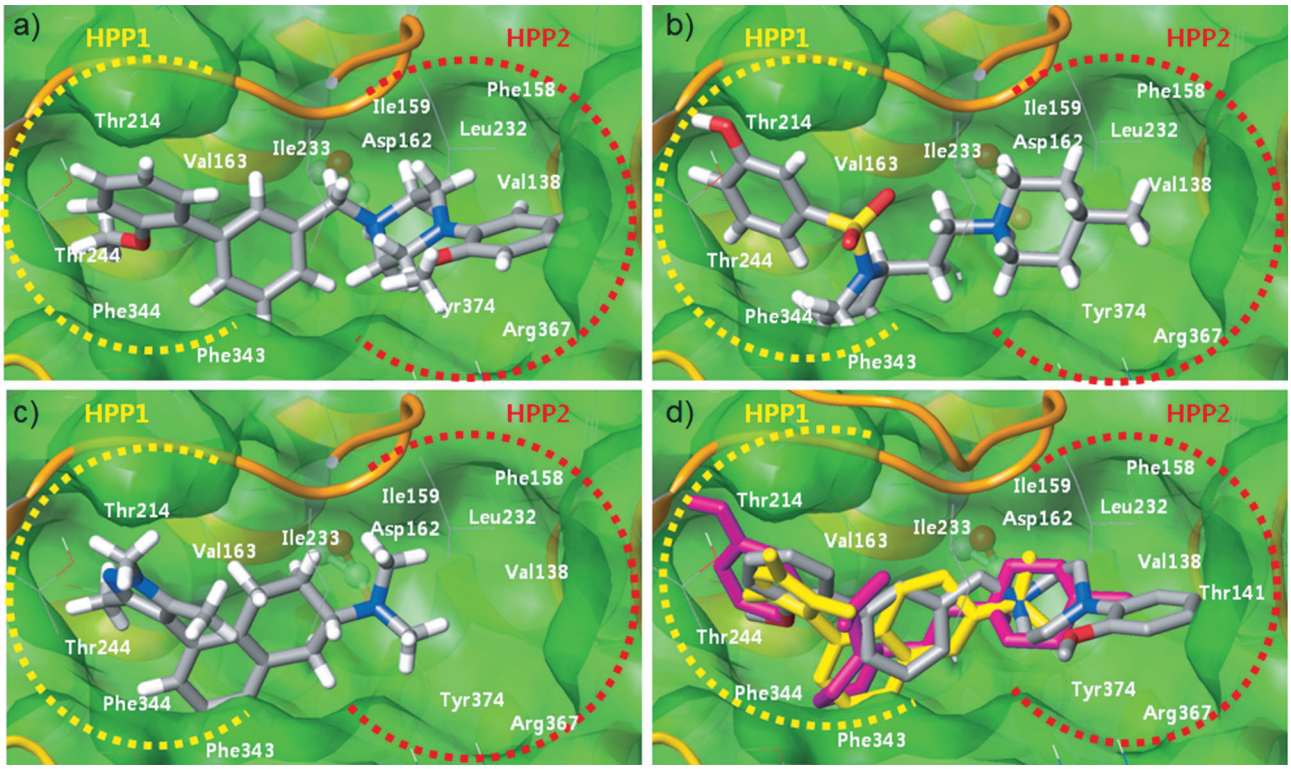

Figure 4. Docking modes of a) compound **28**, b) SB-269970, and c) AS-19 in the ligand binding site of the 5-HT$_7$R and d) their superimposed structures, with **28**, SB-269970, and AS-19 shown in gray, magenta, and yellow, respectively. The two hydrophobic pockets HPP1 and HPP2 are shown in molecular surface representation, respectively highlighted with yellow and red dotted half-circles.

ure 4b) were shown to cover this pocket with their 2-methoxyphenyl and 4-methylpiperidine functionalities, respectively, the short dimethylamino moiety of AS-19 leaves this pocket almost unoccupied (Figure 4c). It could be assumed that the resulting flexibility conferred to the hydrophobic pocket HPP2 of the 5-HT$_7$R upon binding to AS-19 might allow conformational change to the receptor that would result in agonism of AS-19, which is not feasible in the binding events with the antagonists, such as compound **28** and SB-269970.

Conclusions

Aryl biphenyl-3-ylmethylpiperazines were designed, synthesized, and biologically evaluated against the 5-HT$_7$R. Among the synthesized compounds, compound **28** was the best binder to the 5-HT$_7$R, with a pK_i value of 7.83, and it was confirmed as an antagonist according to the functional assays. Also, the selectivity profile of compound **28** was reported over other serotonin receptor subtypes such as the 5-HT$_1$R, 5-HT$_2$R, 5-HT$_3$R, and 5-HT$_6$R. A molecular modeling study was performed in comparison with the known 5-HT$_7$R modulators SB-269970 and AS-19 to show that the 2-methoxyphenyl moiety attached to the piperazine ring of compound **28** may be essential to the antagonistic function. Further structure–activity relationship studies on these biphenyl compounds are in progress and will be reported in due course.

Experimental Section

Chemistry

General: All reactions were carried out under dry nitrogen or argon unless otherwise indicated. Commercially available reagents were used without further purification. Solvents and gases were dried according to standard procedures. Organic solvents were evaporated with reduced pressure by using a rotary evaporator. Analytical thin layer chromatography (TLC) was performed by using glass plates pre-coated with silica gel (0.25 mm). TLC plates were developed by exposure to UV light (UV) and then were visualized with a $KMnO_4$ stain followed by brief heating on hot plate. Flash column chromatography was performed by using silica gel 60 (230–400 mesh, Merck) with the indicated solvents. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 300, Bruker 400, or Varian 300 NMR spectrometers. ^{1}H NMR spectra are represented as follows: chemical shift, multiplicity (s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet; dd: doublet of doublet; td: triplet of doublet; brs: broad singlet; brt: broad triplet), integration, and coupling constant (J) in Hertz (Hz). ^{1}H NMR chemical shifts are reported relative to $CDCl_3$ ($\delta = 7.26$ ppm). ^{13}C NMR chemical shifts were recorded relative to the central line of $CDCl_3$ ($\delta = 77.0$ ppm). LC–MS analyses were performed on either a Micromass QUATTRO micro or an Agilent 6410 Triple Quad system. Purity was checked on a Waters HPLC e2695 instrument equipped with a UV/Vis 2489 detector and a SunFire C_{18} (4.6×150 mm, 5 μm) reversed-phase column. Standard conditions were as follows: eluents: system A (CH_3CN), system B (H_2O/0.1 M NH_4OAc); a flow rate of 1 mL min^{-1}; a gradient of 30–100% A over 20 min; detection at λ 254 and 280 nm.

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(1,1′-Biphenyl)-3-carbaldehyde (4a): Phenylboronic acid (**3a**; 395 mg, 3.24 mmol), tetrakis(triphenylphosphine)palladium (31 mg, 0.027 mmol), and Na_2CO_3 (430 mg, 4.05 mmol) were added to a solution of 3-bromobenzaldehyde (**2**; 315 μL, 2.70 mmol) in DMF (20 mL). The resulting solution was stirred and heated at reflux for 6 h. After termination of this reaction, the solution was allowed to cool to room temperature, partitioned between saturated $NaHCO_3$ solution and EtOAc, and extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/Et_2O, 8:1) to afford the product **4a** (380 mg, 2.09 mmol, 77% yield): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 10.10 (s, 1H), 8.08 (s, 1H), 7.84 (d, $J=7.2$ Hz, 2H), 7.62–7.56 (m, 3H), 7.48–7.35 ppm (m, 3H).

2′-Fluoro-(1,1′-biphenyl)-3-carbaldehyde (4b): Following the same procedure as that used for the synthesis of **4a**, the reaction of 3-bromobenzaldehyde (**2**; 315 μL, 2.70 mmol), 2-fluorophenylboronic acid (**3b**; 454 mg, 3.24 mmol), tetrakis(triphenylphosphine)palladium (31 mg, 0.027 mmol), and Na_2CO_3 (430 mg, 4.05 mmol) in DMF (20 mL) gave the title compound **4b** (440 mg, 2.20 mmol, 81% yield): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 10.09 (s, 1H), 8.07 (d, $J=1.5$ Hz, 1H), 7.90 (dt, $J=7.6$, 1.3 Hz, 1H), 7.85–7.82 (m, 1H), 7.62 (t, $J=7.8$, Hz, 1H), 7.48 (td, $J=7.9$, 2.0 Hz, 1H), 7.39–7.35 (m, 1H), 7.28–7.16 ppm (m, 3H).

2′-Chloro-(1,1′-biphenyl)-3-carbaldehyde (4c): Following the same procedure as that used for the synthesis of **4a**, the reaction of 3-bromobenzaldehyde (**2**; 277 μL, 2.37 mmol), 2-chlorophenylboronic acid (**3c**; 446 mg, 2.85 mmol), tetrakis(triphenylphosphine)-palladium (27 mg, 0.024 mmol), and Na_2CO_3 (377 mg, 3.56 mmol) in DMF (20 mL) gave the title compound **4c** (189 mg, 0.87 mmol, 37% yield): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 10.01 (s, 1H), 8.06–7.68 (m, 1H), 7.58–7.50 (m, 2H), 7.43–7.33 ppm (m, 4H).

2′-Methyl-(1,1′-biphenyl)-3-carbaldehyde (4d): Following the same procedure as that used for the synthesis of **4a**, the reaction of 3-bromobenzaldehyde (**2**; 315 μL, 2.70 mmol), 2-methylphenylboronic acid (**3d**; 439 mg, 3.24 mmol), tetrakis(triphenylphosphine)palladium (31 mg, 0.027 mmol), and Na_2CO_3 (430 mg, 4.05 mmol) in DMF (20 mL) gave the title compound **4d** (402 mg, 2.05 mmol, 76% yield): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 10.08 (s, 1H), 7.89–7.84 (m, 2H), 7.61–7.58 (m, 2H), 7.32–7.23 (m, 4H), 2.27 ppm (s, 3H).

2′-Methoxy-(1,1′-biphenyl)-3-carbaldehyde (4e): Following the same procedure as that used for the synthesis of **4a**, the reaction of 3-bromobenzaldehyde (**2**; 315 μL, 2.70 mmol), 2-methoxyphenylboronic acid (**3e**; 492 mg, 3.24 mmol), tetrakis(triphenylphosphine)palladium (31 mg, 0.027 mmol), and Na_2CO_3 (430 mg, 4.05 mmol) in DMF (20 mL) gave the title compound **4e** (447 mg, 2.11 mmol, 78% yield): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 10.07 (s, 1H), 8.04 (brt, $J=1.5$ Hz, 1H), 7.86–7.79 (m, 2H), 7.57 (t, $J=7.6$ Hz, 1H), 7.39–7.33 (m, 2H), 7.08–7.00 (m, 2H), 3.83 ppm (s, 3H).

1-([1,1′-Biphenyl]-3-ylmethyl)-4-phenylpiperazine (6): (1,1′-Biphenyl)-3-carbaldehyde (**4a**; 150 mg, 0.82 mmol) was added to a solution of 1-phenylpiperazine (**5a**; 266 mg, 1.64 mmol) in MeOH (10 mL). The reaction mixture was stirred at room temperature for 2 h, then $NaBH(OAc)_3$ (529 mg, 2.46 mmol) was added, and the resulting mixture was stirred for 8 h. After termination of the reaction, the solution was partitioned between saturated $NaHCO_3$ solution and CH_2Cl_2 and was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/Et_2O, 8:1) to afford product **6** (49 mg, 0.15 mmol, 18% yield): HPLC: purity 99%, $t_R=16.9$ min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.61–7.18 (m, 11H), 6.93–6.81 (m, 3H), 3.63 (s, 2H), 3.20 (brt, $J=5.1$ Hz, 4H), 2.64 ppm (brt, $J=5.1$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 151.4, 141.3, 141.2, 138.5, 129.2, 128.8, 128.3, 128.1, 127.4, 127.3, 126.1, 119.7, 116.1, 115.6, 63.2, 53.2, 49.2 ppm; LC–MS (ESI): *m/z* calcd for $C_{23}H_{24}N_2$: 329.20 $[M+H]^+$; found: 329.4.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(2-fluorophenyl)piperazine (7): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(2-fluorophenyl)piperazine (**5b**; 296 mg, 1.64 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in MeOH (10 mL) gave the title compound **7** (191 mg, 0.55 mmol, 67% yield): HPLC: purity 96%, $t_R=16.7$ min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.63–7.32 (m, 9H), 6.98–6.84 (m, 4H), 3.64 (s, 2H), 3.13 (brt, $J=5.1$ Hz, 4H), 2.65 ppm (brt, $J=5.1$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 157.2 (d, $J=237$ Hz), 148.1 (d, $J=1.5$ Hz), 141.3 (d, $J=8.25$ Hz), 138.6, 132.0, 130.4, 128.8, 128.2, 128.0, 127.7, 127.4, 127.3, 126.1, 117.8 (d, $J=7.5$ Hz), 115.7, 115.4, 63.1, 53.2, 50.2 ppm; LC–MS (ESI): *m/z* calcd for $C_{23}H_{23}FN_2$: 347.19 $[M+H]^+$; found: 347.4.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(3-fluorophenyl)piperazine (8): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(3-fluorophenyl)piperazine (**5c**; 198 mg, 1.10 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 100 mg, 0.55 mmol), and $NaBH(OAc)_3$ (355 mg, 1.65 mmol) in MeOH (10 mL) gave the title compound **8** (113 mg, 0.33 mmol, 59% yield): HPLC: purity 99%, $t_R=17.1$ min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.67–7.37 (m, 9H), 7.22 (q, $J=7.2$ Hz, 1H), 6.72–6.55 (m, 3H), 3.67 (s, 2H), 3.26 (brt, $J=5.1$ Hz, 4H), 2.67 ppm (brt, $J=4.8$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 164.0 (d, $J=241.5$ Hz), 153.1 (d, $J=9.75$ Hz), 141.4, 141.2, 138.7, 130.3, 130.1, 128.9, 128.2, 128.0, 127.5, 127.3, 126.1, 111.2, 105.8 (d, $J=21$ Hz), 102.7 (d, $J=24.75$ Hz), 63.1, 53.0, 48.7 ppm; LC–MS (ESI): *m/z* calcd for $C_{23}H_{23}FN_2$: 347.19 $[M+H]^+$; found: 347.4.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(4-fluorophenyl)piperazine (9): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(4-fluorophenyl)piperazine (**5d**; 296 mg, 1.64 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in MeOH (10 mL) gave the title compound **9** (75 mg, 0.22 mmol, 27% yield): HPLC: purity 96%, $t_R=17.2$ min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.64–7.33 (m, 9H), 7.05–6.89 (m, 4H), 3.65 (s, 2H), 3.13 (brt, $J=4.8$ Hz, 4H), 2.68 ppm (brt, $J=4.8$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 155.9 (d, $J=244.5$ Hz), 141.3 (d, $J=6$ Hz), 140.4 (d, $J=8.25$ Hz), 138.7, 128.9, 128.3, 128.1, 127.4, 127.3, 126.1, 124.6 (d, $J=3$ Hz), 119.0 (d, $J=3$ Hz), 116.2 (d, $J=20.25$ Hz), 63.2, 53.3, 50.7 ppm; LC–MS (ESI): *m/z* calcd for $C_{23}H_{23}FN_2$: 347.19 $[M+H]^+$; found: 347.4.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(2-chlorophenyl)piperazine (10): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(2-chlorophenyl)piperazine (**5e**; 382 mg, 1.64 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in MeOH (10 mL) gave the title compound **10** (200 mg, 0.55 mmol, 67% yield): HPLC: purity 99%, $t_R=18.3$ min; ^{1}H NMR (300 MHz, $CDCl_3$) 7.59–7.62 (m, 3H), 7.30–7.50 (m, 7H), 7.15–7.20 (m, 1H), 7.01 (dd, $J=8.0$, 1.3 Hz, 1H), 6.92 (td, $J=7.6$, 1.3 Hz, 1H), 3.63 (s, 2H), 3.07 (brs, 4H), 2.66 ppm (brs, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 149.5, 141.3, 141.3, 138.8, 130.7, 128.8, 128.8, 128.3, 128.1, 127.7, 127.4, 127.3, 126.0, 123.7, 120.5, 63.3, 53.4, 51.3 ppm; LC–MS (ESI): *m/z* calcd for $C_{23}H_{23}ClN_2$: 363.16 $[M+H]^+$; found: 363.4.

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1-([1,1′-Biphenyl]-3-ylmethyl)-4-(3-chlorophenyl)piperazine (11): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(3-chlorophenyl)piperazine (**5f**; 382 mg, 1.64 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in MeOH (10 mL) gave the title compound **11** (159 mg, 0.44 mmol, 53% yield): HPLC: purity 99%, $t_R = 18.6$ min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.41–7.44 (m, 1H), 7.13–7.30 (m, 8H), 6.98 (t, $J = 8.1$ Hz, 1H), 6.58–6.72 (m, 3H), 3.33 (s, 2H), 2.97 (brt, $J = 4.9$ Hz, 4H), 2.34 ppm (brt, $J = 5.0$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 152.6$, 142.9, 141.6, 135.6, 135.0, 130.3, 130.1, 129.7, 128.0, 127.3, 127.1, 127.1, 119.2, 115.7, 113.9, 59.9, 52.7, 48.8 ppm; LC–MS (ESI): *m/z* calcd for $C_{23}H_{23}ClN_2$: 363.16 $[M+H]^+$; found: 363.1.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(4-chlorophenyl)piperazine (12): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(4-chlorophenyl)piperazine (**5g**; 382 mg, 1.64 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in MeOH (10 mL) gave the title compound **12** (192 mg, 0.53 mmol, 64% yield): HPLC: purity 99%, $t_R = 18.4$ min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.40–7.43 (m, 1H), 7.12–7.29 (m, 8H), 6.99–7.04 (m, 2H), 6.60–6.64 (m, 2H), 3.32 (s, 2H), 2.92 (brt, $J = 4.8$ Hz, 4H), 2.34 ppm (brt, $J =$ 4.9 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.2$, 143.0, 141.6, 135.6, 130.4, 130.2, 129.7, 128.1, 127.4, 127.2, 127.1, 124.4, 117.3, 60.0, 52.8, 49.3 ppm; LC–MS (ESI): *m/z* calcd for $C_{23}H_{23}ClN_2$: 363.16 $[M+H]^+$; found: 363.4.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(2-methylphenyl)piperazine (13): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(2-methylphenyl)piperazine (**5h**; 289 mg, 1.64 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in MeOH (10 mL) gave the title compound **13** (41 mg, 0.12 mmol, 15% yield): HPLC: purity 99%, $t_R = 18.5$ min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.73–7.70 (m, 3H), 7.61–7.43 (m, 6H), 7.30–7.03 (m, 4H), 3.74 (s, 2H), 3.04 (brt, $J = 4.5$ Hz, 4H), 2.75 (brs, 4H), 2.40 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 151.7$, 141.3, 138.8, 132.7, 131.1, 128.8, 128.8, 128.3, 128.1, 127.4, 127.3, 126.7, 126.0, 123.1, 119.1, 63.4, 53.8, 51.8, 18.0 ppm; LC–MS (ESI): *m/z* calcd for $C_{24}H_{26}N_2$: 343.22 $[M+H]^+$; found: 343.4.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(3-methylphenyl)piperazine (14): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(3-methylphenyl)piperazine (**5i**; 289 mg, 1.64 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in MeOH (10 mL) gave the title compound **14** (119 mg, 0.35 mmol, 42% yield): HPLC: purity 98%, $t_R = 17.6$ min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.80–7.77 (m, 3H), 7.69–7.47 (m, 6H), 7.31 (t, $J = 7.8$ Hz, 1H), 6.91–6.83 (m, 3H), 3.78 (s, 2H), 3.36 (brt, $J = 4.8$ Hz, 4H), 2.79 (brt, $J =$ 4.8 Hz, 4H), 2.48 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 151.7$, 141.4, 141.3, 138.9, 138.8, 129.2, 129.0, 128.4, 128.1, 127.5, 127.4, 126.2, 120.7, 117.1, 113.4, 63.3, 49.4, 22.1 ppm; LC–MS (ESI): *m/z* calcd for $C_{24}H_{26}N_2$: 343.22 $[M+H]^+$; found: 343.2.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(4-methylphenyl)piperazine (15): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(4-methylphenyl)piperazine (**5j**; 155 mg, 0.88 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 80 mg, 0.44 mmol), and $NaBH(OAc)_3$ (284 mg, 1.32 mmol) in MeOH (10 mL) gave the title compound **15** (54 mg, 0.16 mmol, 36% yield): HPLC: purity 99%, $t_R = 18.3$ min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.71$–7.69 (m, 1H), 7.58–7.40 (m, 8H), 7.19 (d, $J = 8.1$ Hz, 2H), 6.95 (d, $J = 8.4$ Hz, 2H), 3.61 (s, 2H), 3.22 (brt, $J = 5.1$ Hz, 4H), 2.65 (brt, $J = 5.1$ Hz, 4H), 2.40 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.3$, 149.4, 142.9, 141.5, 135.7, 130.3, 130.1, 129.7, 129.7, 129.1, 128.0, 127.2, 127.0, 116.4, 59.9, 52.9, 49.9, 20.5 ppm; LC–MS (ESI): *m/z* calcd for $C_{24}H_{26}N_2$: 343.22 $[M+H]^+$; found: 343.2.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(2,3-dimethylphenyl)piperazine (16): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(2,3-dimethylphenyl)piperazine (**5k**; 312 mg, 1.64 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in MeOH (10 mL) gave the title compound **16** (58 mg, 0.16 mmol, 20% yield): HPLC: purity 99%, $t_R = 19.2$ min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.63–7.34 (m, 9H), 7.09–6.88 (m, 3H), 3.65 (s, 2H), 2.92 (brt, $J = 4.8$ Hz, 4H), 2.66 (brs, 4H), 2.26 (s, 3H), 2.21 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 151.8$, 141.3, 138.9, 138.0, 131.3, 128.8, 128.8, 128.4, 128.2, 127.4, 127.3, 126.0, 125.9, 125.0, 116.8, 63.4, 53.9, 52.3, 20.7, 14.1 ppm; LC–MS (ESI): *m/z* calcd for $C_{25}H_{28}N_2$: 357.23 $[M+H]^+$; found: 357.4.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(2,4-dimethylphenyl)piperazine (17): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(2,4-dimethylphenyl)piperazine (**5l**; 312 mg, 1.64 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in MeOH (10 mL) gave the title compound **17** (156 mg, 0.44 mmol, 54% yield): HPLC: purity 98%, $t_R = 19.5$ min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.87–7.53 (m, 9H), 7.22–7.16 (m, 3H), 3.85 (s, 2H), 3.14 (brt, $J =$ 4.8 Hz, 4H), 2.86 (brs, 4H), 2.51 (s, 3H), 2.50 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 149.4$, 141.4, 139.0, 132.7, 132.6, 132.0, 129.0, 128.9, 128.4, 128.2, 127.5, 127.4, 127.2, 126.1, 119.2, 63.5, 54.0, 52.2, 20.9, 18.0 ppm; LC–MS (ESI): *m/z* calcd for $C_{25}H_{28}N_2$: 357.23 $[M+H]^+$; found: 357.4.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(2,5-dimethylphenyl)piperazine (18): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(2,5-dimethylphenyl)piperazine (**5m**; 312 mg, 1.64 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in MeOH (10 mL) gave the title compound **18** (62 mg, 0.17 mmol, 21% yield): HPLC: purity 98%, $t_R = 19.6$ min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.62–7.30 (m, 9H), 7.07 (d, $J = 7.5$ Hz, 1H), 6.89–6.80 (m, 2H), 3.51 (s, 2H), 2.90 (brt, $J = 4.5$ Hz, 4H), 2.56 (brs, 4H), 2.33 (s, 3H), 2.25 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 141.4$, 139.1, 138.0, 136.2, 131.4, 131.1, 129.5, 128.9, 128.4, 128.2, 127.4, 126.1, 125.1, 123.9, 120.0, 116.9, 63.5, 54.0, 52.0, 21.5, 17.7 ppm; LC–MS (ESI): *m/z* calcd for $C_{25}H_{28}N_2$: 357.23 $[M+H]^+$; found: 357.4.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(3,5-dimethylphenyl)piperazine (19): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(3,5-dimethylphenyl)piperazine (**5n**; 312 mg, 1.64 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in MeOH (10 mL) gave the title compound **19** (139 mg, 0.39 mmol, 48% yield): HPLC: purity 97%, $t_R = 18.4$ min; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.81–7.78 (m, 3H), 7.70–7.48 (m, 6H), 6.74–6.70 (m, 3H), 3.79 (s, 2H), 3.36 (brt, $J = 4.8$ Hz, 4H), 2.79 (brs, 4H), 2.45 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 151.7$, 141.4, 141.3, 138.8, 138.7, 128.9, 128.9, 128.3, 128.1, 127.5, 127.4, 126.1, 121.8, 114.3, 63.3, 53.4, 49.5, 21.9 ppm; LC–MS (ESI): *m/z* calcd for $C_{25}H_{28}N_2$: 357.23 $[M+H]^+$; found: 357.4.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(2-methoxyphenyl)piperazine (20): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(2-methoxyphenyl)piperazine (**5o**; 209 mg, 1.09 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 100 mg, 0.55 mmol), and $NaBH(OAc)_3$ (355 mg, 1.65 mmol) in MeOH (10 mL)

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gave the title compound **20** (47 mg, 0.13 mmol, 24% yield): HPLC: purity 98%, t_R = 16.2 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 3H), 7.56–7.37 (m, 6H), 7.03–6.84 (m, 4H), 3.88 (s, 3H), 3.69 (s, 2H), 3.14 (brs, 4H), 2.74 ppm (brs, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 141.5, 141.3, 141.2, 138.7, 128.8, 128.8, 128.3, 128.2, 127.3, 126.0, 122.9, 121.0, 118.3, 111.2, 63.3, 55.4, 53.4, 50.8 ppm; LC–MS (ESI): *m/z* calcd for $C_{24}H_{26}N_2O$: 359.21 $[M+H]^+$; found: 359.4.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(3-methoxyphenyl)piperazine (21): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(3-methoxyphenyl)piperazine (**5p**; 315 mg, 1.64 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in MeOH (10 mL) gave the title compound **21** (126 mg, 0.35 mmol, 43% yield): HPLC: purity 96%, t_R = 16.5 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78–7.45 (m, 8H), 7.33–7.27 (m, 1H), 6.69–6.53 (m, 3H), 3.90 (s, 3H), 3.75 (s, 2H), 3.34 (brs, 4H), 2.76 ppm (brs, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 153.0, 141.4, 141.3, 138.8, 129.9, 128.9, 128.9, 128.3, 128.1, 127.5, 127.3, 126.1, 109.0, 104.5, 102.6, 63.2, 55.3, 53.3, 49.2 ppm; LC–MS (ESI): *m/z* calcd for $C_{24}H_{26}N_2O$: 359.21 $[M+H]^+$; found: 359.4.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(4-methoxyphenyl)piperazine (22): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(4-methoxyphenyl)piperazine (**5q**; 212 mg, 1.10 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 100 mg, 0.55 mmol), and $NaBH(OAc)_3$ (355 mg, 1.65 mmol) in MeOH (5 mL) gave the title compound **22** (128 mg, 0.36 mmol, 65% yield): HPLC: purity 99%, t_R = 16.0 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 3H), 7.56–7.37 (m, 6H), 6.96–6.87 (m, 4H), 3.80 (s, 3H), 3.68 (s, 2H), 3.15 (brt, J = 4.5 Hz, 4H), 2.70 ppm (brt, J = 4.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.9, 145.9, 141.3, 141.2, 138.7, 129.0, 128.9, 128.4, 128.1, 127.5, 127.3, 126.1, 118.3, 114.5, 63.2, 55.6, 53.4, 50.7 ppm; LC–MS (ESI): *m/z* calcd for $C_{24}H_{26}N_2O$: 359.21 $[M+H]^+$; found: 359.4.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(3,4-dimethoxyphenyl)piperazine (23): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(3,4-dimethoxyphenyl)piperazine (**5r**; 245 mg, 1.10 mmol), (1,1′-biphenyl)-3-carbaldehyde (**4a**; 100 mg, 0.55 mmol), and $NaBH(OAc)_3$ (355 mg, 1.65 mmol) in MeOH (5 mL) gave the title compound **23** (167 mg, 0.43 mmol, 78% yield): HPLC: purity 99%, t_R = 16.0 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.61 (m, 1H), 7.45–7.30 (m, 9H), 6.83–6.80 (m, 1H), 6.59–6.58 (m, 1H), 6.46 (dd, J = 8.7, 2.7 Hz, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 3.54 (s, 2H), 3.10 (brs, 4H), 2.58 ppm (brs, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3, 149.5, 146.5, 143.4, 142.9, 141.5, 135.6, 130.2, 130.1, 129.7, 128.0, 127.2, 127.0, 112.0, 107.9, 102.9, 59.9, 56.3, 55.9, 53.0, 50.9 ppm; LC–MS (ESI): *m/z* calcd for $C_{25}H_{28}N_2O_2$: 389.22 $[M+H]^+$; found: 389.3.

1-([1,1′-Biphenyl]-3-ylmethyl)-4-(3-trifluoromethylphenyl)piperazine (24): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(3-trifluoromethylphenyl)piperazine (**5s**; 252.7 mg, 1.01 mmol), (1,1′-biphenyl)-2-carbaldehyde (**4a**; 100 mg, 0.55 mmol), and $NaBH(OAc)_3$ (353.9 mg, 1.65 mmol) in MeOH (10 mL) gave the title compound **24** (132.1 mg, 0.33 mmol, 60% yield): HPLC: purity 98%, t_R = 17.7 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.30 (m, 10H), 7.10–7.02 (m, 3H), 3.64 (s, 2H), 3.25 (brt, J = 4.8 Hz, 4H), 2.64 ppm (brt, J = 4.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3, 151.5, 141.2 (d, J = 12.75 Hz), 138.5, 129.5, 128.8, 128.1, 127.9, 127.3, 127.2, 126.1, 118.7, 115.7, 115.7, 112.2, 112.1, 63.0, 52.9, 48.7 ppm; LC–MS (ESI): *m/z* calcd for $C_{24}H_{23}F_3N_2$: 397.19 $[M+H]^+$; found: 396.9.

1-([2′-Fluoro-(1,1′-biphenyl)-3-yl]methyl)-4-(2-methoxyphenyl)piperazine (25): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(2-methoxyphenyl)piperazine (**5o**; 192 mg, 1.00 mmol), 2′-fluoro-(1,1′-biphenyl)-3-carbaldehyde (**4b**; 100 mg, 0.50 mmol), and $NaBH(OAc)_3$ (322 mg, 1.50 mmol) in MeOH (10 mL) gave the title compound **25** (164 mg, 0.44 mmol, 87% yield): HPLC: purity 98%, t_R = 16.2 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (brs, 1H), 7.52–7.41 (m, 4H), 7.36–7.30 (m, 1H), 7.26–7.15 (m, 2H), 7.06–6.95 (m, 3H), 6.91 (dd, J = 8.1, 1.2 Hz, 1H), 3.88 (s, 3H), 3.70 (s, 2H), 3.16 (brs, 4H), 2.75 ppm (brs, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.9 (d, J = 246.8 Hz), 152.4, 141.5, 138.4, 135.8, 130.9 (d, J = 3.75 Hz), 130.0 (d, J = 3.0 Hz), 129.3, 129.0 (d, J = 8.25 Hz), 128.7, 128.4, 127.9 (d, J = 3 Hz), 124.4 (d, J = 3.75 Hz), 122.9, 121.1, 118.3, 116.2 (d, J = 22.5 Hz), 111.3, 63.2, 55.4, 53.4, 50.8 ppm; LC–MS (ESI): *m/z* calcd for $C_{24}H_{25}FN_2O$: 377.2 $[M+H]^+$; found: 377.1.

1-([2′-Chloro-(1,1′-biphenyl)-3-yl]methyl)-4-(2-methoxyphenyl)piperazine (26): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(2-methoxyphenyl)piperazine (**5o**; 177 mg, 0.92 mmol), 2′-chloro-(1,1′-biphenyl)-3-carbaldehyde (**4c**; 100 mg, 0.46 mmol), and $NaBH(OAc)_3$ (297 mg, 1.38 mmol) in MeOH (10 mL) gave the title compound **26** (61 mg, 0.16 mmol, 34% yield): HPLC: purity 98%, t_R = 16.9 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.44 (m, 2H), 7.42–7.23 (m, 6H), 7.00–6.87 (m, 3H), 6.84 (d, J = 7.8 Hz, 1H), 3.83 (s, 3H), 3.65 (s, 2H), 3.10 (brs, 4H), 2.70 ppm (brs, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 141.5, 140.6, 139.4, 137.8, 132.6, 131.5, 130.4, 130.0, 128.6, 128.6, 128.2, 128.0, 126.9, 122.9, 121.0, 118.3, 111.2, 63.1, 55.3, 53.3, 50.7 ppm; LC–MS (ESI): *m/z* calcd for $C_{24}H_{25}ClN_2O$: 393.17 $[M+H]^+$; found: 393.9.

1-([2′-Methyl-(1,1′-biphenyl)-3-yl]methyl)-4-(2-methoxyphenyl)-piperazine (27): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(2-methoxyphenyl)piperazine (**5o**; 196 mg, 1.02 mmol), 2′-methyl-(1,1′-biphenyl)-3-carbaldehyde (**4d**; 100 mg, 0.51 mmol), and $NaBH(OAc)_3$ (329 mg, 1.53 mmol) in MeOH (50 mL) gave the title compound **27** (77 mg, 0.21 mmol, 41% yield): HPLC: purity 99%, t_R = 17.1 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 3H), 7.26–7.19 (m, 5H), 6.99–6.81 (m, 4H), 3.82 (s, 3H), 3.62 (s, 2H), 3.09 (brs, 4H), 2.69 (brs, 4H), 2.27 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.4, 142.0, 141.9, 141.6, 138.0, 135.4, 130.4, 130.2, 129.9, 128.1, 128.0, 127.8, 127.3, 125.8, 122.9, 121.1, 118.3, 111.3, 63.2, 55.4, 53.4, 50.8, 20.6 ppm; LC–MS (ESI): *m/z* calcd for $C_{25}H_{28}N_2O$: 373.23 $[M+H]^+$; found: 373.4.

1-([2′-Methoxy-(1,1′-biphenyl)-3-yl]methyl)-4-(2-methoxyphenyl)-piperazine (28): Following the same procedure as that used for the synthesis of **6**, the reaction of 1-(2-methoxyphenyl)piperazine (**5o**; 181 mg, 0.94 mmol), 2′-methoxy-(1,1′-biphenyl)-3-carbaldehyde (**4e**; 100 mg, 0.47 mmol), and $NaBH(OAc)_3$ (303 mg, 1.41 mmol) in MeOH (10 mL) gave the title compound **28** (103 mg, 0.27 mmol, 56% yield): HPLC: purity 99%, t_R = 15.5 min; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (brs, 1H), 7.45–7.27 (m, 5H), 7.04–6.87 (m, 5H), 6.83 (dd, J = 7.8, 0.9 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.63 (s, 2H), 3.09 (brs, 4H), 2.69 ppm (brs, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 152.4, 141.6, 138.5, 137.7, 131.0, 130.8, 130.6, 128.7, 128.4, 128.0, 128.0, 122.9, 121.1, 120.9, 118.3, 111.3, 111.2, 63.3, 55.6, 55.4, 53.4, 50.8 ppm; LC–MS (ESI): *m/z* calcd for $C_{25}H_{28}N_2O_2$: 389.22 $[M+H]^+$; found: 389.1.

Biology

Serotonin receptor binding affinity assay:[13c] Eleven dilutions (5× assay concentration) of the test and reference compounds were

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prepared in standard binding buffer (50 mM tris(hydroxymethyl)-aminomethane–HCl (Tris-HCl), 10 mM $MgCl_2$, 1 mM ethylenediaminetetraacetate (EDTA), pH 7.4) by serial dilution: 0.05 nM, 0.5 nM, 1.5 nM, 5 nM, 15 nM, 50 nM, 150 nM, 500 nM, 1.5 μM, 5 μM, and 50 μM. The radioligand, which was mentioned in the text and was properly chosen for each serotonin subtype receptor, was diluted to five times the assay concentration in standard binding buffer. Aliquots (50 μL) of the appropriate radioligand were dispensed into the wells of a 96-well plate containing standard binding buffer (100 μL). Triplicate aliquots (50 μL) of the test and reference compound dilutions were added. Finally, crude membrane fractions (50 μL) of cells expressing recombinant target were dispensed into each well. The reaction mixtures (250 μL in total) were incubated at room temperature and shielded from light for 1.5 h, then harvested by rapid filtration onto Whatman GF/B glass fiber filters presoaked with 0.3% polyethyleneimine, by using a 96-well Brandel harvester. Four rapid washes (500 μL) were performed with chilled standard binding buffer to decrease nonspecific binding. Filters were placed in 6 mL scintillation tubes and allowed to dry overnight. The next day, EcoScint scintillation cocktail (4 mL; National Diagnostics) was added to each tube. The tubes were capped, labeled, and counted by liquid scintillation counting. The filter mats were dried, then the scintillant was melted onto the filters, and the radioactivity retained on the filters was counted in a Microbeta scintillation counter. The IC_{50} values were obtained by using the Prism 4.0 program (GraphPad Software) and converted into K_i values.

cAMP accumulation assay: All of the synthesized compounds were evaluated for adenylate cyclase activity by using HEK293 cells transiently transfected with the human 5-HT_7R. To analyze cAMP levels, cAMP dynamic 2HTRF kits (Cisbio, USA), which provide homogeneous high throughput, were used. Transfected HEK293 cells were suspended in phosphate-buffered saline (PBS) containing 2 mM 3-isobutyl-1-methylxanthine (IBMX), which blocks the phosphodiesterase enzyme degradation of cAMP. Cells were stimulated by 5-HT for 30 min, with or without pretreatment with the compounds for 10 min. After 30 min, cAMP labeled with the dye d2 and anti-cAMP antibodies labeled with cryptate were added into the cell plates. The plates were incubated at room temperature for 1 h. The fluorescence intensity of the accumulated cAMP level was measured by using a Flexstation3 microplate reader (Molecular Devices, Downingtown, PA).

Molecular docking

The previously constructed model structure of the human 5-HT_7 serotonin receptor[10b] was used. Three dimensional structures of aryl biphenyl-3-ylmethylpiperazines were sketched by the "Build" module of the Maestro 7.5 software (Schrödinger Inc.). Energy minimization was performed by using a conjugate gradient minimization (0.05 convergence criteria), the OPLS-AA force field, and the GB/SA continuum water model. A torsional scan along every rotatable bond was then performed for the minimized structures. The "Conformational search" module implemented in the Maestro 7.5 software was used with the automatic setup. With the modeled structure, docking of the aryl biphenyl-3-ylmethylpiperazines was carried out. The protein preparation utilities in Maestro 7.5 were used to assign the charge state of ionizable residues, add hydrogen atoms, and carry out energy minimization. The ligands were then docked into the comparative model structure of the 5-HT_7R by using the GLIDE 4.0 program (http://www.schrodinger.com), with H-bond constraint between Asp162 and the protonated nitrogen atoms of the ligands. The default setting of the extreme precision mode of the GLIDE program was employed for the docking, and up to ten poses were saved for analysis.

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[1] a) P. B. Hedlund, J. G. Sutcliffe, *Trends Pharmacol. Sci.* **2004**, *25*, 481; b) D. Hoyer, J. P. Hannon, G. R. Martin, *Pharmacol. Biochem. Behav.* **2002**, *71*, 533.
[2] M. Ruat, E. Traiffort, R. Leurs, J. Tardivel-Lacombe, J. Diaz, J.-M. Arrang, J.-C. Schwartz, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 8547.
[3] T. W. Lovenberg, B. M. Baron, L. Delecea, J. D. Miller, R. A. Prosser, M. A. Rea, P. E. Foye, M. Racke, A. L. Slone, B. W. Siegel, P. E. Danielson, J. G. Sutcliffe, M. G. Erlander, *Neuron* **1993**, *11*, 449.
[4] J. A. Bard, J. Zgombick, N. Adham, P. Vaysse, T. A. Branchek, R. L. Weinshank, *J. Biol. Chem.* **1993**, *268*, 23422.
[5] P. Vanhoenacker, G. Haegeman, J. E. Leysen, *Trends Pharmacol. Sci.* **2000**, *21*, 70.
[6] a) M. Guscott, L. J. Bristow, K. Hadingham, T. W. Rosahl, M. S. Beer, J. A. Stanton, F. Bromidge, A. P. Owens, I. Huscroft, J. Myers, N. M. Rupniak, S. Patel, P. J. Whiting, P. H. Hutson, K. C. Fone, S. M. Biello, J. J. Kulagowski, G. McAllister, *Neuropharmacology* **2005**, *48*, 492; b) P. B. Hedlund, S. Huitron-Resendis, S. J. Henriksen, J. G. Sutcliffe, *Biol. Psychiatry* **2005**, *58*, 831.
[7] J. P. P. Foong, J. C. Bornstein, *Neuroreport* **2009**, *20*, 325.
[8] a) G. Sarkisyan, A. J. Roberts, P. B. Hedlund, *Behav. Brain Res.* **2010**, *209*, 99; b) O. Mnie-Filali, C. Faure, L. Lambas-Senas, M. El Mansari, H. Belblidia, E. Gondard, A. Etievant, H. Scarna, A. Didier, A. Verod, P. Blier, N. Haddjeri, *Neuropsychopharmacology* **2011**, *36*, 1275.
[9] a) A. Meneses, G. Perez-Garcia, G. Liy-Salmeron, D. Flores-Galvez, C. Castillo, E. Castillo, *Behav. Brain Res.* **2008**, *195*, 112; b) A. Brenchat, L. Romero, M. Garcia, M. Pujol, J. Burgueno, A. Torrens, M. Hamon, J. M. Baeyens, H. Buschmann, D. Zamaillo, J. M. Vela, *Pain* **2009**, *141*, 239; c) A. Brenchat, X. Nadal, L. Romero, S. Ovalle, A. Muro, R. Sanchez-Arroyos, E. Portillo-Salido, M. Pujol, A. Montero, X. Codony, J. Burgueno, D. Zamanillo, M. Hamon, R. Maldonado, J. M. Vela, *Pain* **2010**, *149*, 483; d) M. I. Díaz-Reval, R. Ventura-Martinez, M. Déciga-Campos, J. A. Terrón, F. Cabre, F. J. López-Muños, *Eur. J. Pharmacol.* **2004**, *483*, 241; e) A. Dogrul, M. H. Ossipov, F. Porreca, *Brain Res.* **2009**, *1280*, 52; f) A. Dogrul, M. Seyrek, *Br. J. Pharmacol.* **2006**, *149*, 498; g) S. E. Harte, R. G. Kender, G. S. Borszcz, *Pain* **2005**, *113*, 405; h) T. Meuser, C. Pietruck, A. Gabriel, G. X. Xie, K. J. Lim, P. P. Palmer, *Life Sci.* **2002**, *71*, 2279; i) H. I. Rocha-González, A. Meneses, S. M. Carlton, V. Granados-Soto, *Pain* **2005**, *117*, 182.
[10] a) M. Paillet-Loilier, F. Fabis, A. Lepailleur, R. Bureau, S. Butt-Gueulle, F. Dauphin, C. Delarue, H. Vaudry, S. Rault, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3753; b) M. Paillet-Loilier, F. Fabis, A. Lepailleur, R. Bureau, S. Butt-Gueulle, F. Dauphin, A. Lesnard, C. Delarue, H. Vaudry, S. Rault, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3018; c) E. Lacivita, D. Patarnello, N. Stroth, A. Caroli, M. Niso, M. Contino, P. De Giorgio, P. Di Pilato, N. A. Colabufo, F. Berardi, R. Perrone, P. Svenningsson, P. B. Hedlund, M. Leopoldo, *J. Med. Chem.* **2012**, *55*, 6375; d) Y. H. Na, S. H. Hong, J. H. Lee, W.-K. Park, D.-J. Baek, H. Y. Koh, Y. S. Cho, H. Choo, A. N. Pae, *Bioorg. Med. Chem.* **2008**,

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16, 2570; e) M. K. Kim, H. S. Lee, S. Kim, S. Y. Cho, B. L. Roth, Y. Chong, H. Choo, *Bioorg. Med. Chem.* **2012**, *20*, 1139; f) Y. Kim, J. Kim, J. Tae, B. L. Roth, H. Rhim, G. Keum, G. Nam, H. Choo, *Bioorg. Med. Chem.* **2013**, *21*, 2568.

[11] T. Ogawa, N. Kurose, S. Tanaka, K. Nishi, (Shionogi & Co. Ltd.), Eur. Pat. No. EP1894919A1, **2008**.

[12] A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849.

[13] a) D. A. Shapiro, S. Renock, E. Arrington, L. A. Chiodo, L. X. Liu, D. R. Sibley, B. L. Roth, R. Mailman, *Neuropsychopharmacology* **2003**, *28*, 1400; b) B. L. Roth, K. Baner, R. Westkaemper, D. Siebert, K. C. Rice, S. Steinberg, P. Ernsberger, R. B. Rothman, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 11934; c) For a more detailed explanation of the radioligand binding affinity assay, see the NIMH Psychoactive Drug Screening Program website: http://pdsp.med.unc.edu/.

[14] a) E. Chojnacka-Wójcik, E. Tatarczyńska, K. Golembiowska, E. Przegaliński, *Neuropharmacology* **1991**, *30*, 711; b) M. W. Hamblin, M. A. Metcalf, R. W. McGuffin, S. Karpells, *Biochem. Biophys. Res. Commun.* **1992**, *184*, 752.

[15] a) G. Quesseveur, H. T. Nguyen, A. M. Gardier, B. P. Guiard, *Expert Opin. Invest. Drugs* **2012**, *21*, 1701; b) A. Kovács, I. Gacsályi, J. Wellmann, É. Schmidt, Z. Szücs, V. Dubreuil, J. P. Nicolas, J. Boutin, D. Bózsing, A. Egyed, K. Tihanyi, M. Spedding, G. Szénási, *Cardiovasc. Drugs Ther.* **2003**, *17*, 427.

[16] J. D. Hutcheson, V. Setola, B. L. Roth, W. D. Merryman, *Pharmacol. Ther.* **2011**, *132*, 146.

[17] Y. Chong, H. Choo, *Expert Opin. Invest. Drugs* **2010**, *19*, 1309.

[18] G. Rossé, H. Schaffhauser, *Curr. Top. Med. Chem.* **2010**, *10*, 207.

[19] A. Lepailleur, R. Bureau, M. Paillet-Loilier, F. Fabis, N. Saettel, S. Lemaître, F. Dauphin, A. Lesnard, J. C. Lancelot, S. Rault, *J. Chem. Inf. Model.* **2005**, *45*, 1075.

[20] R. A. Medina, J. Sallander, B. Benhamú, E. Porras, M. Campillo, L. Pardo, M. L. López-Rodríguez, *J. Med. Chem.* **2009**, *52*, 2384.

[21] P. Kowalski, J. Jaśkowska, A. J. Bojarski, B. Duszyńska, A. Bucki, M. Kołaczkowski, *J. Heterocycl. Chem.* **2011**, *48*, 192.

[22] Z. Y. Yang, W. Lv, R. Tian, H. W. Jin, H. H. Zeng, *J. Chin. Pharm. Sci.* **2009**, *18*, 151.

[23] T. Varin, H. Gutiérrez-de-Terán, M. Castro, J. Brea, F. Fabis, F. Dauphin, J. Åqvist, A. Lepaileur, P. Perez, J. Burgueño, J. M. Vela, M. I. Loza, J. Rodrigo, *Br. J. Pharmacol.* **2010**, *159*, 1069.

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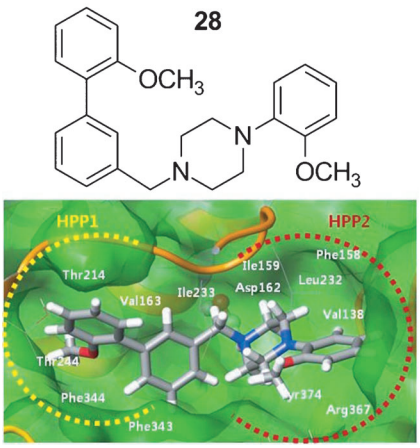
Vacancies filled: 2′-Methoxybiphenyl-3-ylmethyl(2-methoxyphenyl)piperazine (**28**) is shown to serve as a selective 5-HT_7 receptor antagonist. From a comparison with the docking modes of other known 5-HT_7 receptor agonists and antagonists, it is suggested that occupancy of both hydrophobic ligand binding sites of the 5-HT_7 receptor by the ligand is crucial for its antagonistic property.



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Aryl Biphenyl-3-ylmethylpiperazines as 5-HT_7 Receptor Antagonists

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