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Discovery of aryl-biphenyl-2-ylmethylpiperazines as novel scaffolds for 5-HT$_7$ ligands and role of the aromatic substituents in binding to the target receptor

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ABSTRACT

It has been reported that 5-HT$_7$ receptors are promising targets of depression and neuropathic pain. 5-HT$_7$ receptor antagonists have exhibited antidepressant-like profiles, while agonists have represented potential therapeutics for pain. In the course of our ongoing efforts to discover novel 5-HT$_7$ modulators, we designed an arylpiperazine scaffold with a substituted biphenyl-2-ylmethyl group. A series of biphenyl-2-yl-arylpiperazinylmethanes were then prepared, which showed a broad spectrum of binding affinities to the 5-HT$_7$ receptor depending upon the substituents attached to the biphenyl and aryl functionalities. Among those synthesized compounds, the compounds 1–24 and 1–26 showed the best binding affinities to the 5-HT$_7$ receptor with K_i values of 43.0 and 46.0 nM, respectively. Structure–activity relationship study in conjunction with molecular docking study proposed that the 5-HT$_7$ receptor might have two distinctive hydrophobic binding sites, one specific for aromatic 2-OCH$_3$ substituents within the arylpiperazine and the other for biphenyl methoxy group.

1. Introduction

As a neurotransmitter, serotonin (5-HT) interacts with various serotonin receptors to effect on the central and peripheral nervous system. The serotonin receptors are classified into seven families (5-HT$_1$–5-HT$_7$) according to sequence similarity and function. Most 5-HT receptors (except 5-HT$_3$ receptor) are G protein-coupled receptors (GPCRs),[1] and dysfunction of this system has been implicated in cardiovascular, digestive, and psychiatric disorders.[2,3] Among the seven 5-HT receptor subtypes, 5-HT$_7$ receptor has been most recently cloned,[4] and studies on the localization of the 5-HT$_7$ receptor gave important indications on its pathophysiological roles; the 5-HT$_7$ receptor mRNA is distributed in the central nervous system and particularly high levels have been detected in thalamus, hippocampus and hypothalamus (especially within the suprachiasmatic nucleus).[5,6] It has also been reported that the 5-HT$_7$ receptor may play a role in control of circadian rhythms, sleep, cognitive processes, pain and migraine, as well as in the pathophysiology of many psychiatric disorders including depression and anxiety.[4] Therefore, chemical entities which can modulate the 5-HT$_7$ receptor have been actively pursued,[7,8] but to date only a few selective 5-HT$_7$ receptor antagonists (SB-258719 and SB-269970)[9,10] and agonists (AS-19)[11] have been discovered (Fig. 1).

These 5-HT$_7$ receptor modulators showed interesting physiological effects in animal model studies. While the 5-HT$_7$ selective antagonist SB-269970 exhibited antidepressant-like activity,[12–14] systemic administration of the 5-HT$_7$ receptor agonist AS-19 sig-

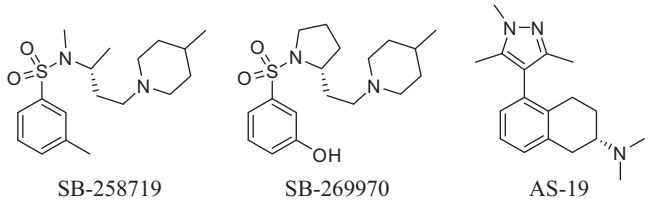

Figure 1. 5-HT$_7$ receptor antagonists and an agonist.

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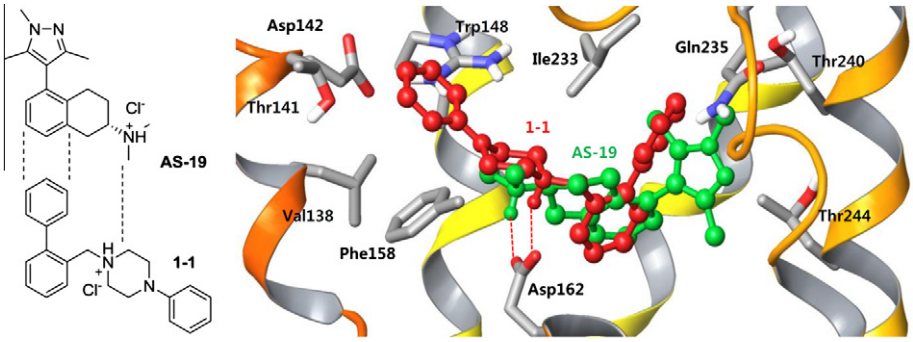


Figure 2. Docking mode of compound **1-1** (red stick) to the ligand binding site of the modeled 5-HT$_7$ receptor in comparison with that of AS-19 (green stick).

nificantly inhibited mechanical hypersensitivity and thermal hyperalgesia in the neuropathic pain animal model.[15] These results suggest that the 5-HT$_7$ receptor antagonists and agonists can be used for treatment of depression and neuropathic pain, respectively. In the course of our ongoing efforts to discover novel 5-HT$_7$ modulators, we designed an arylpiperazine scaffold with a substituted biphenyl-2-ylmethyl group. Herein we report design, synthesis and biological evaluation of the biphenyl-2-yl-arylpiperazinylmethane derivatives to the 5-HT$_7$ receptor.

2. Results and discussion

2.1. 5-HT$_7$ ligand design

For the purpose of designing novel ligands with potent binding affinity to 5-HT$_7$ receptor, various 5-HT$_7$ ligands previously reported in the literature were structurally investigated.[7,8] Based on this study, a combination of a biphenyl group and an arylpiperazine moiety, a structural mimic for the known 5-HT$_7$ ligand AS-19, biphenylpiperazines[8h] and phenylpyrroles,[8g] was proposed to serve as a novel scaffold for 5-HT$_7$ ligand. This hypothesis was then evaluated by computational docking study of a biphenyl-2-ylmethyl-phenylpiperazine (**1-1**, Fig. 2) to the modeled structure of the 5-HT$_7$ receptor in comparison with AS-19 (Fig. 2). The homology model structure of the 5-HT$_7$ receptor was constructed through the SwissModel server, and the geometry-optimized structures of the designed compound **1-1** and a 5-HT$_7$ agonist AS-19 were docked to the receptor by Glide 4.0 implemented in Maestro 7.5 (Schrödinger, Inc.) using the previously developed protocols.[16]

Overall, the biphenyl-2-ylmethylpiperazinyl moiety of the compound **1-1** showed similar docking mode as the phenylpyrazole group of AS-19. In particular, a characteristic salt bridge between the 5-HT$_7$ ligand and an aspartate residue of 5-HT$_7$ (Asp162) was commonly observed in the docking modes of the piperazine group and the dimethylamino group forming the cationic ammonium ion in compound **1-1** and AS-19, respectively. In addition, the biphenyl functionality of the compound **1-1** was found to serve as a mimic for the phenylpyrazole group of AS-19 with the terminal phenyl ring projecting toward a hydrophobic pocket formed by Ile233, Gln235, Thr240, and Thr244 (Fig. 2). In contrast, a marked difference in the binding modes of the two compounds was observed in the hydrophobic pocket located on the opposite side of the ligand binding site which was composed of Phe158, Trp148, Thr141, Asp142, Val138, and Arg367 (Fig. 2). While the phenylpiperazinyl group of the compound **1-1** was located in the middle of pocket, the relatively small dimethylamino group of AS-19 was not able to fill this hydrophobic space. Taken together, due to the structural similarity to the known 5-HT$_7$ ligand (AS-19) as well as possible additional hydrophobic interactions, biphenyl-2-yl-phenylpiperazinylmethane **1-1** was anticipated to serve as a novel scaffold to show potent binding affinity to the 5-HT$_7$ receptor. Moreover, introduction of various aromatic substituents on the biphenyl as well as the piperazinylphenyl functionalities would provide in depth information about the two hydrophobic pockets located in the ligand binding site of the 5-HT$_7$ receptor. Thus, as shown in Figure 3, a focused chemical library was designed through modifications on both of the aromatic groups of the compound **1-1**.

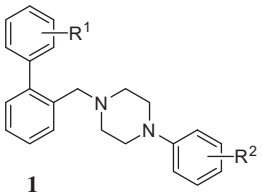
2.2. Chemistry

The title compounds, aryl-biphenyl-2-ylmethylpiperazines **1**, were synthesized in three steps from commercially available 2-bromobenzaldehyde **2** and arylboronic acid **3** (Scheme 1). Suzuki coupling of **2** with arylboronic acids **3** (R^1 = H, halogen, CH_3, or OCH_3) was performed in the presence of catalytic amount of $Pd(PPh_3)_4$ and Na_2CO_3 in refluxing DMF to afford biphenyl-2-carbaldehydes **4** in 60–70% yields.[17] Biphenyl-2-carbaldehydes **4** were reacted with various arylpiperazines **5** under reductive amination conditions to afford the title compounds **1**.[18] Total 26 aryl-biphenyl-2-ylmethylpiperazines **1** were synthesized.

2.3. Biological results

The synthesized aryl-biphenyl-2-ylmethylpiperazines **1** were biologically evaluated against the 5-HT$_7$ receptor by [^{3}H]LSD radioligand binding assays in transfected CHO-K1 cells and the results are summarized in Table 1.[19–21]

The binding affinity of the initially designed compound **1-1** with no aromatic substituent on either biphenyl or piperazinylphenyl moiety was first evaluated to show moderate K_i value of 537 nM (Table 1). Then, in order to understand the role of the piperazinylphenyl substituent R^2 in binding affinity of the corresponding aryl-biphenyl-2-ylmethylpiperazine derivatives, a series of analogues (**1-2** to **1-20**) with the unsubstituted biphenyl moiety (R^1 = H) and variously substituted piperazinylphenyl group ($R^2 \neq$ H) were



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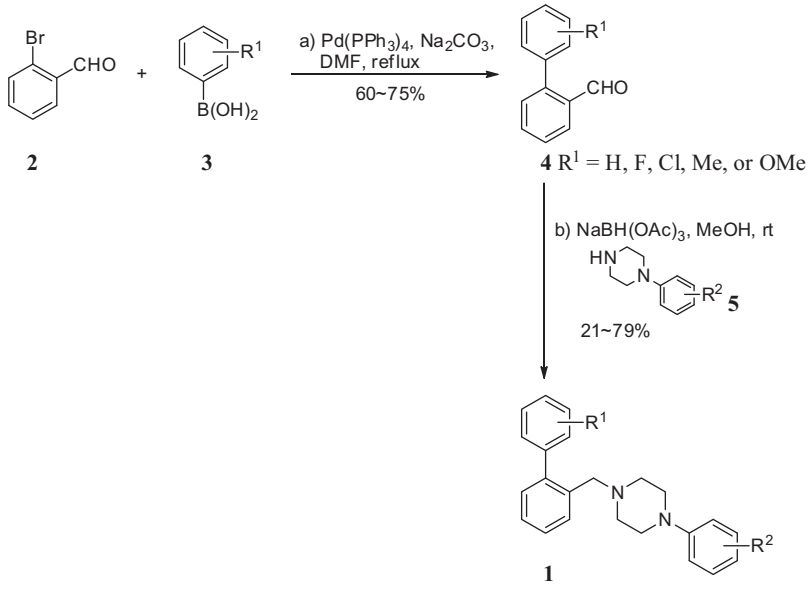
R^1 = H, F, Cl, Me, and OMe

R^2 = H, F, Cl, Me, diMe, OMe, and diOMe,

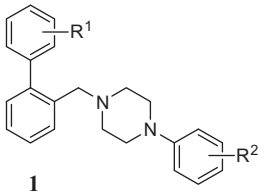
Figure 3. A designed focused chemical library.



Scheme 1. Synthesis of aryl-biphenyl-2-ylmethylpiperazines **1.**

tested for 5-HT_7 binding. First, a fluorine atom (R^2 = F) demolished the binding affinities of the resulting derivatives (**1-2** to **1-4**) to the target receptor (K_i >10,000 nM) regardless of its site of substitution on the aromatic ring. Considering the similar sizes of hydrogen and fluorine, this striking difference in binding affinities suggests hydrophobic nature of the aromatic-binding site of the 5-HT_7 receptor, to which a highly electronegative fluorine atom might not be suitable for binding. Electronegativity of chlorine, though chlorine is bigger than both hydrogen and fluorine, seems to be responsible for the lack of binding affinities of the chlorine-substituted derivatives (**1-5** and **1-6**; K_i >10,000 nM). Among the compounds **1-7** to **1-9** with methoxy substituents, the compound **1-7** with *ortho*-methoxy substituent only showed good binding affinity with a K_i value of 432 nM and the compound **1-10** with 3,4-dimethoxy substituent showed marginal binding affinity. The compounds **1-11** to **1-13** with methyl substituents showed only marginal binding affinities with K_i values of 1750, 1200, and 2760 nM for *ortho*-, *meta*-, and *para*-position, respectively. The compounds **1-14** to **1-17** with two methyl substituents showed no binding affinities against 5-HT_7 receptors. The compound **1-18** with *meta*-trifluoromethyl substituent showed only marginal binding affinity. Taken together, these data strongly suggest that the 5-HT_7 receptor has a specific aryl binding pocket with an open cavity at the site corresponding to the 2-position of the aryl ring, which is as large as a methoxy group. This hypothesis of a methoxy open cavity inside of the aryl binding pocket is supported by ~4 times lower binding affinity of 2-CH_3 substituted derivative **1-11** (R^2 = 2-CH_3; K_i = 1750 nM) compared with that of **1-7** (R^2 = 2-OCH_3; K_i = 432 nM). At this point, it is worth to note that the synthesized aryl-biphenyl-2-ylmethylpiperazines are much weaker binders to the 5-HT_7 receptor compared with the known 5-HT_7 ligand, AS-19 (K_i = 0.6 nM).[11] Considering the major structural difference of title compounds compared with AS-19 is located at the steric bulk around the aryl-substituted piperazinyl moiety, the aforementioned aryl binding pocket does not seem to be big enough to accommodate the aryl-substituted piperazinyl moiety. By the same token, 8-fold lower binding affinity of the phenylpyrrole with an arylpiperazinyl group (K_i = 4.7 nM)[8g] compared with AS-19 provides another evidence that the aryl-substituted piperazine moiety gives some negative effect on binding at the aryl binding pocket of 5-HT_7 receptor. This hypothesis can be further supported by the potent 5-HT_7-binding affinities of biphenylpiperazines of which piperazinyl moiety was left unsubstituted.[8h]

Table 1
Binding affinities (K_is) to the 5-HT_7 receptor



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Entry	Compd	R^1	R^2	pK_i	K_i (nM)
1	**1-1**	H	H	6.27 ± 0.08	537
2	**1-2**	H	2-F	—[a]	>10000
3	**1-3**	H	3-F	—[a]	>10000
4	**1-4**	H	4-F	—[a]	>10000
5	**1-5**	H	2-Cl	—[a]	>10000
6	**1-6**	H	4-Cl	—[a]	>10000
7	**1-7**	H	2-OCH_3	6.36 ± 0.09	432
8	**1-8**	H	3-OCH_3	—[a]	>10000
9	**1-9**	H	4-OCH_3	—[a]	>10000
10	**1-10**	H	3,4-diOCH_3	5.73 ± 0.09	1850
11	**1-11**	H	2-CH_3	5.76 ± 0.09	1750
12	**1-12**	H	3-CH_3	5.9 ± 0.1	1200
13	**1-13**	H	4-CH_3	5.56 ± 0.08	2760
14	**1-14**	H	2,3-diCH_3	—[a]	>10000
15	**1-15**	H	2,4-diCH_3	—[a]	>10000
16	**1-16**	H	2,5-diCH_3	—[a]	>10000
17	**1-17**	H	3,5-diCH_3	—[a]	>10000
18	**1-18**	H	3-CF_3	5.78 ± 0.07	1660
19	**1-19**	2-F	2-OCH_3	6.18 ± 0.05	658
20	**1-20**	2-Cl	2-OCH_3	6.53 ± 0.08	297
21	**1-21**	3-Cl	2-OCH_3	6.66 ± 0.08	219
22	**1-22**	4-Cl	2-OCH_3	6.7 ± 0.1	220
23	**1-23**	2-CH_3	2-OCH_3	6.51 ± 0.08	311
24	**1-24**	2-OCH_3	2-OCH_3	7.37 ± 0.06	43.0
25	**1-25**	3-OCH_3	2-OCH_3	7.1 ± 0.1	77
26	**1-26**	4-OCH_3	2-OCH_3	7.34 ± 0.08	46.0
27	Chlorpromazine			7.97 ± 0.09	11.0

[a] Not available or determined.

Table 2
Docking results of the selected compounds to the model structure of 5-HT_7 receptor

Compd	R^1	R^2	K_i (nM)	G-Score[a]	HBnd[b]	$E_{elec+vdW}$[c]	E_{elec}[d]	E_{vdW}[e]
1-24	2-OCH_3	2-OCH_3	43	−7.64	1	−39.00	−2.90	−36.09
1-26	4-OCH_3	2-OCH_3	46	−7.56	1	−46.63	−3.88	−42.75
1-25	3-OCH_3	2-OCH_3	77	−7.60	1	−46.46	−3.67	−42.79
1-20	2-Cl	2-OCH_3	297	−6.87	1	−30.75	−2.55	−28.20
1-7	H	2-OCH_3	432	−6.52	1	−32.44	−1.99	−32.44
1-1	H	H	537	−6.21	1	−31.01	−2.83	−28.18
1-11	H	2-CH_3	1750	−6.27	0	−23.41	−3.16	−20.25
1-5	H	2-Cl	>10,000	−5.71	0	−20.57	+0.10	−20.67

[a] Glide Score.
[b] Number of hydrogen bonds between ligands and 5-HT_7 receptor.
[c] Total binding energy of the ligands to 5-HT_7 receptor.
[d] Electrostatic component of the total binding energy of the ligands to 5-HT_7 receptor.
[e] Hydrophobic component of the total binding energy of the ligands to 5-HT_7 receptor.

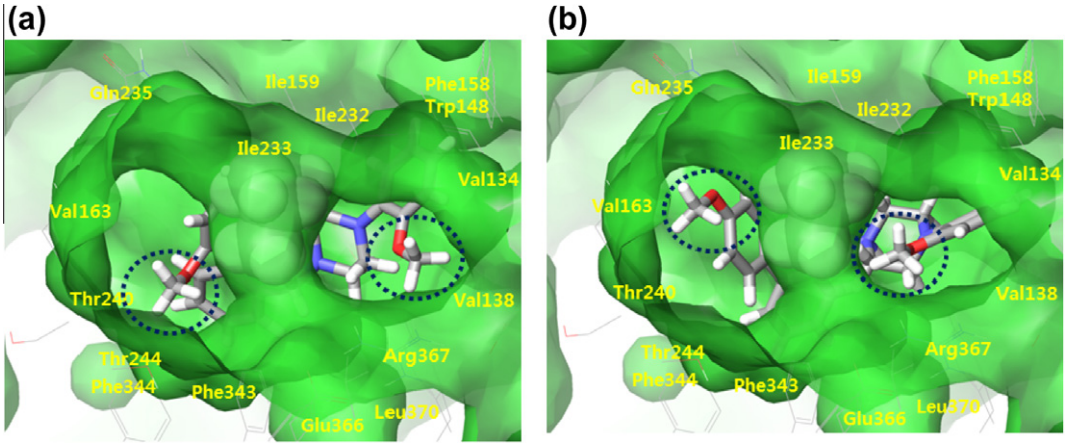

Figure 4. Docking modes of (a) **1-24** and (b) **1-26** to the model structure of 5-HT_7 receptor with the binding pockets for piperazinylphenyl 2-OCH_3 (right) and biphenyl methoxy (left) groups.

Among the series, 1-(2-biphenyl)piperazine showed the best binding affinity with a K_i value of 1.4 nM, which is comparable to that of AS-19.

Also noteworthy in those 1-biphenylpiperazines was that the substituents such as 2-OCH_3 and 4-OCH_3 attached to the biphenyl moiety endowed the corresponding derivatives with good binding affinities. Thus, we then attempted to optimize the binding affinity of the title compound through introduction of a substituent (R^1) at the biphenyl moiety (**1-19** to **1-26**). The compounds **1-19** to **1-23** with halogen and methyl susbstituents showed good binding affinities with K_i values between 219 and 658 nM. The activities are not much improved compared with that of the compound **1-7**. Surprisingly, the alkoxy group was also found to be a substituent of choice for the biphenyl group to significantly enhance the binding affinity of the resulting bis-methoxypiperazinyl derivatives (**1-24** to **1-26**; K_i = 43, 77, and 46 nM). However, unlike the phenyl group which showed exclusive selectivity for 2-alkoxy substituent, the binding affinities of the alkoxy-biphenylmethylpiperazines (**1-24** to **1-26**) were not sensitive to the position of the alkoxy group, which suggests that the biphenyl-binding pocket of the 5-HT_7 receptor might be larger than the aryl-binding pocket.

2.4. Molecular modeling

These biphenyl- and aryl-binding pocket hypotheses were then tackled by molecular docking study. The geometry-optimized structures of several ligands with a broad spectrum of binding affinities (**1-1**, **1-5**, **1-7**, **1-11**, **1-20**, **1-24**, **1-25**, and **1-26**) were docked to the previously constructed homology model structure of the 5-HT_7 receptor by Glide 4.0 implemented in Maestro 7.5 (Schrödinger, Inc.) using the previously developed protocols.[16] The docking results are summarized in Table 2, which shows a good correlation between the binding affinities (K_i) and docking scores (Glide scores) of the 5-HT_7 ligands. While ligands with moderate to potent binding affinities were docked to the target receptor with formation of a critical hydrogen bond to Asp162 (HBnd = 1, Table 2),[16] two weak binders (**1-11** and **1-5**) show abortive binding modes lacking the hydrogen bond (HBnd = 0). Also, analysis of the total binding energies ($E_{vdW+elec}$) reveals that hydrophobic interaction (E_{vdW}) determines the binding affinities of the 5-HT_7 ligands to the receptor. In particular, comparison of the hydrophobic energies of **1-7** with those of **1-1**, **1-11**, and **1-5** shows that the 2-OCH_3 group at the piperazinylphenyl moiety (R^2 = 2-OCH_3) is a stronger contributor to the hydrophobic interaction energy (E_{vdW}) than 2-CH_3 or 2-Cl substituent. Also noteworthy is that the total hydrophobic interaction energy between the ligands and the 5-HT_7 receptor can be significantly enhanced by combination with the second methoxy substituent at the biphenyl ring (R^1 = 2-OCH_3, 3-OCH_3, or 4-OCH_3).

Docking modes of the two most potent 5-HT_7 ligands, **1-24** and **1-26**, show that the 2-OCH_3 group on the piperazinylphenyl ring and the biphenyl methoxy group bind to the corresponding binding pockets separated by Ile233 (Fig. 4). Due to the difference in size, the smaller piperazinylphenyl binding pocket seems to be specific for 2-OCH_3 while the biphenyl binding pocket can accommodate both 2-OCH_3 (Fig. 4a) and 4-OCH_3 (Fig. 4b).

3. Conclusion

A series of aryl-biphenyl-2-ylmethylpiperazines **1** were designed, synthesized, and biologically evaluated against the 5-HT_7 receptor. Total 31 compounds were prepared and those compounds showed a broad spectrum of binding affinities to the 5-HT_7 receptor depending upon the substituents attached to the biphenyl and aryl functionalities. Among those, the compounds **1-24** and **1-26** showed the best binding affinities to the 5-HT_7 receptor with K_i values of 43.0 and 46.0 nM, respectively. Structure-activity relationship study in conjunction with molecular docking study proposed that the 5-HT_7 receptor might have two distinctive hydrophobic binding sites, one specific for aromatic 2-OCH_3 within the arylpiperazine and the other for biphenyl methoxy group. With the most potent compounds **1-24** and **1-26**, further evaluations such as functionality, selectivity over other serotonin receptor subtypes, and pharmacokinetics are in progress.

4. Experimental section

4.1. 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 using a rotary evaporator. Analytical thin layer chromatography (TLC) was performed using glass plates precoated with silica gel (0.25 mm). TLC plates were visualized 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 using silica gel 60 (230–400 mesh, Merck) with the indicated solvents. ^1H and ^{13}C spectra were recorded on Bruker 300, Bruker 400 or Varian 300 NMR spectrometers. ^1H 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, br s = broad singlet, br t = broad triplet), integration, and coupling constant (J) in Hertz (Hz). ^1H NMR chemical shifts are reported relative to $CDCl_3$ (7.26 ppm). ^{13}C NMR was recorded relative to the central line of $CDCl_3$ (77.0 ppm). LC/MS analyses were performed on either Micromass QUATTRO micro™ or Agilent 6410 Triple Quad system.

4.2. Synthesis of biphenyl-2-carbaldehydes (4) derivatives

4.2.1. Representative procedure for synthesis of [1,1′-biphenyl]-2-carbaldehyde (4a)

To a solution of 2-bromobenzaldehyde (315 μl, 2.70 mmol) in DMF (20 ml) was added phenyl boronic acid (395 mg, 3.24 mmol), tetrakis-(triphenylphosphine)-palladium (31 mg, 0.027 mmol) and Na_2CO_3 (430 mg, 4.05 mmol). The result solution was stirred and refluxed for 6 h. After the reaction completed, the solution was cooled to room temperature, then partitioned between satd $NaHCO_3$ and EtOAc, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/diethyl ether = 8:1) to afford the product (369 mg, 2.03 mmol, 75% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 10.00(s, 1H), 8.05 (dd, J = 6.6, 1.2 Hz, 1H), 7.65 (dd, J = 6.1, 1.4 Hz, 1H), 7.51–7.46 (m, 5H), 7.40 (dd, J = 5.9, 2.0 Hz, 2H).

4.2.2. 2′-Fluoro-[1,1′-biphenyl]-2-carbaldehyde (4b)

Following the same procedure used for the synthesis of **4a**, the reaction of 2-bromobenzaldehyde (315 μl, 2.70 mmol), 2-fluorophenylboronic acid (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** (536 mg, 2.68 mmol, 99% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.05 (dd, J = 7.7, 1.5 Hz, 1H), 7.68 (td, J = 7.5, 1.5 Hz, 1H), 7.55 (m, 1H), 7.49–7.40 (m, 2H), 7.35 (td, J = 7.5, 1.9 Hz, 1H), 7.27 (td, J = 7.2, 1.1 Hz, 1H), 7.19 (td, J = 8.2, 1.1 Hz, 1H).

4.2.3. 2′-Chloro-[1,1′-biphenyl]-2-carbaldehyde (4c)

Following the same procedure used for the synthesis of **4a**, the reaction of 2-bromobenzaldehyde (277 μl, 2.37 mmol), 2-chlorophenylboronic acid (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). ^1H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.06 (dd, J = 7.6, 1.3 Hz, 1H), 7.68 (td, J = 7.6, 1.5 Hz, 1H), 7.58–7.50 (m, 2H), 7.43–7.33 (m, 4H).

4.2.4. 3′-Chloro-[1,1′-biphenyl]-2-carbaldehyde (4d)

Following the same procedure used for the synthesis of **4a**, the reaction of 2-bromobenzaldehyde (277 μl, 2.37 mmol), 3-chlorophenylboronic acid (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 **4d** (345 mg, 1.59 mmol, 67% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.04 (dd, J = 8.3, 1.5 Hz, 1H), 7.66 (td, J = 7.5, 1.5 Hz, 1H), 7.54 (t, J = 7.9 Hz, 1H), 7.47–7.39 (m, 4H), 7.28–7.24 (m, 1H).

4.2.5. 4′-Chloro-[1,1′-biphenyl]-2-carbaldehyde (4e)

Following the same procedure used for the synthesis of **4a**, the reaction of 2-bromobenzaldehyde (277 μl, 2.37 mmol), 4-chlorophenylboronic acid (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 **4e** (281 mg, 1.30 mmol, 55% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.04 (dd, J = 7.9, 1.5 Hz, 1H), 7.66 (td, J = 7.5, 1.5 Hz, 1H), 7.56–7.41 (m, 4H), 7.35–7.31 (m, 2H).

4.2.6. 2′-Methyl-[1,1′-biphenyl]-2-carbaldehyde (4f)

Following the same procedure used for the synthesis of **4a**, the reaction of 2-bromobenzaldehyde (315 μl, 2.70 mmol), 2-methylphenylboronic acid (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 **4f** (432 mg, 2.20 mmol, 82% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.03 (dd, J = 7.8, 1.2 Hz, 1H), 7.64 (td, J = 7.5, 1.5 Hz, 1H), 7.53–7.47 (m, 1H), 7.34–7.24 (m, 4H), 7.21–7.18 (m, 1H), 2.10 (s, 3H).

4.2.7. 2′-Methoxy-[1,1′-biphenyl]-2-carbaldehyde (4g)

Following the same procedure used for the synthesis of **4a**, the reaction of 2-bromobenzaldehyde (315 μl, 2.70 mmol), 2-methoxyphenylboronic acid (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 **4g** (350 mg, 1.65 mmol, 61% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.00 (dd, J = 7.8, 1.3 Hz, 1H), 7.65 (td, J = 7.5, 1.5 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.42 (td, J = 8.3, 1.8 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 7.29(dd, J = 7.5, 1.7 Hz, 1H), 7.09 (td, J = 7.5, 1.0 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 3.74 (s, 3H).

4.2.8. 3′-Methoxy-[1,1′-biphenyl]-2-carbaldehyde (4h)

Following the same procedure used for the synthesis of **4a**, the reaction of 2-bromobenzaldehyde (145 μl, 1.24 mmol), 3-methoxyphenylboronic acid (227 mg, 1.49 mmol), tetrakis-(triphenylphosphine)-palladium (14 mg, 0.012 mmol), and Na_2CO_3 (197 mg, 1.86 mmol) in DMF (10 ml) gave the title compound **4h** (200 mg, 0.94 mmol, 76% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H),

8.02 (dd, J = 7.6, 1.2 Hz, 1H), 7.64 (td, J = 7.5, 1.5 Hz, 1H), 7.53–7.44 (m, 2H), 7.38 (t, J = 7.8 Hz, 1H), 7.00–6.94 (m, 3H), 3.85 (s, 3H).

4.2.9. 4′-Methoxy-[1,1′-biphenyl]-2-carbaldehyde (4i)

Following the same procedure used for the synthesis of **4a**, the reaction of 2-bromobenzaldehyde (315 μl, 2.70 mmol), 4-methoxyphenylboronic acid (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 **4i** (535 mg, 2.52 mmol, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.00 (s, 1H), 8.01 (dd, J = 7.9, 1.2 Hz, 1H), 7.62 (td, J = 7.5, 1.2 Hz, 1H), 7.49–7.43 (m, 2H), 7.34–7.28 (m, 2H), 7.03–6.98 (m, 2H), 3.88 (s, 3H)

4.3. Synthesis of aryl-biphenyl-2-ylmethylpiperazines (1)

4.3.1. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-phenylpiperazine (1-1)

To a solution of 1-phenylpiperazine (266 mg, 1.64 mmol) in methanol (10 ml) was added [1,1′-biphenyl]-2-carbaldehyde (150 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 2 h, and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) was added. The resulting mixture was stirred for 8 h. After termination of the reaction, the solution was partitioned between sat. $NaHCO_3$ and CH_2Cl_2, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/diethyl ether = 8:1) to afford the product (50 mg, 0.15 mmol, 18% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 6.9 Hz, 1H), 7.64–7.44 (m, 8H), 7.21–7.01 (m, 4H), 3.65 (s, 2H), 3.20 (br s, 4H), 2.71 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.49, 142.88, 141.53, 135.61, 130.21, 130.12, 130.07, 129.60, 129.19, 129.11, 127.19, 126.94, 119.57, 116.03, 59.9, 52.84, 49.28; LC/MS (ESI$^+$): m/z: calcd for $C_{23}H_{24}N_2$: 328.46, $[M+H]^+$; found: 329.30.

4.3.2. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(2-fluorophenyl)piperazine (1-2)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2-fluorophenyl)piperazine (296 mg, 1.64 mmol), [1,1′-biphenyl]-2-carbaldehyde (150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in methanol (10 ml) gave the title compound **5–2** (20 mg, 0.06 mmol, 7% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 6.9 Hz, 1H), 7.64–7.44 (m, 8H), 7.21–7.01 (m, 4H), 3.65 (s, 2H), 3.20 (br s, 4H), 2.71 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.89 (d, J = 244.5 Hz), 143.01, 141.65, 140.48 (d, J = 8.25 Hz), 135.77, 130.33, 130.26, 129.74, 128.60, 128.04, 127.30, 124.58 (d, J = 3.75 Hz), 122.39 (d, J = 7.5 Hz), 119.09, 119.05, 116.22 (d, J = 21 Hz), 60.03, 53.01, 50.85, 50.81; LC/MS (ESI$^+$): m/z: calcd $C_{23}H_{23}FN_2$: 346.45, $[M+H]^+$; found:.347.30

4.3.3. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(3-fluorophenyl)piperazine (1-3)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(3-fluorophenyl)piperazine (296 mg, 1.64 mmol), [1,1′-biphenyl]-2-carbaldehyde (150 mg, 0.82 mmol), and $NaBH(OAc)_3$ 529 mg, 2.46 mmol) in methanol (10 ml) gave the title compound **1-3** (80 mg, 0.23 mmol, 28% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.57 (m, 1H), 7.50–7.30 (m, 8H), 7.24–7.16 (m, 1H), 6.69–6.51 (m, 3H), 3.50 (s, 2H), 3.17 (br t, J = 4.8 Hz, 4H), 2.53 (br t, J = 5.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.94 (d, J = 240.75 Hz), 153.12 (d, J = 6.75 Hz), 153.06, 142.88, 141.51, 135.51, 130.25, 130.17, 130.04, 129.59, 127.94, 127.23, 126.00 (d, J = 3.75 Hz), 111.09, 111.06, 105.64 (d, J = 21.75 Hz), 102.57 (d, J = 25.5 Hz), 60.45, 52.62, 48.75; LC/MS (ESI$^+$): m/z: calcd for $C_{23}H_{23}FN_2$: 346.45, $[M+H]^+$; found: 347.20.

4.3.4. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(4-fluorophenyl)piperazine (1-4)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(4-fluorophenyl)piperazine (296 mg, 1.64 mmol), [1,1′-biphenyl]-2-carbaldehyde (150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in methanol (10 ml) gave the title compound **1-4** (96 mg, 0.28 mmol, 34% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.33 (m, 9H), 7.05–6.89 (m, 4H), 3.65 (s, 2H), 3.13 (br t, J = 4.8 Hz, 4H), 2.68 (br t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.12 (d, J = 230 Hz), 148.18, 142.88, 141.52, 135.59, 130.16 (d, J = 16.6 Hz), 129.62, 128.91, 127.94, 127.21, 126.99, 117.78, 117.71, 115.51(d, J = 4 Hz), 59.88, 52.83, 50.30; LC/MS (ESI$^+$): m/z: calcd for $C_{23}H_{23}FN_2$: 346.45, $[M+H]^+$; found: 347.30.

4.3.5. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(2-chlorophenyl)piperazine (1-5)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2-chlorophenyl)piperazine (382 mg, 1.64 mmol), [1,1′-biphenyl]-2-carbaldehyde (150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in methanol (10 ml) gave the title compound **1-5** (60 mg, 0.17 mmol, 21% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 6.6 Hz, 1H), 7.52–7.31 (m, 9H), 7.27–7.21 (m, 1H), 7.06 (dd, J = 8.1 Hz, 1.5 Hz, 1H), 6.98 (td, J = 7.5 Hz, J = 1.5 Hz, 1H), 3.53 (s, 2H), 3.05 (br s, 4H), 2.59 (br s, 4H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.49, 142.84, 141.51, 135.74, 130.65, 130.17, 130.07, 129.62, 128.79, 127.90, 127.56, 127.15, 126.61, 126.87, 123.54, 120.39, 59.87, 53.00, 51.40, 29.76; LC/MS (ESI$^+$): m/z: calcd for $C_{23}H_{23}ClN_2$: 362.90, $[M+H]^+$; found: 363.20.

4.3.6. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(4-chlorophenyl)piperazine (1-6)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(4-chlorophenyl)piperazine (382 mg, 1.64 mmol), [1,1′-biphenyl]-2-carbaldehyde (150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in methanol (10 ml) gave the title compound **1-6** (20 mg, 0.06 mmol, 7% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63–7.23 (m, 11H), 6.89–6.85 (m, 2H), 3.54 (s, 2H), 3.16 (br t, J = 5.1 Hz, 4H), 2.57 (br t, J = 5.1 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.09, 142.87, 141.50, 135.51, 130.22, 129.57, 127.91, 127.19, 126.98, 126.94, 124.32, 117.15, 59.85, 52.66, 49.27; LC/MS (ESI$^+$): m/z: calcd for $C_{23}H_{23}ClN_2$: 362.90, $[M+H]^+$; found: 363.20.

4.3.7. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(2-methoxyphenyl)piperazine (1-7)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2-methoxyphenyl)piperazine (211 mg, 1.10 mmol), [1,1′-biphenyl]-2-carbaldehyde (100 mg, 0.55 mmol), and $NaBH(OAc)_3$ (355 mg, 1.65 mmol) in methanol (10 ml) gave the title compound **1-7** (74 mg, 0.21 mmol, 38% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 6.8 Hz, 1H), 7.48–7.29 (m, 8H), 7.04–6.86 (m, 4H), 3.86 (s, 3H), 3.51 (s, 2H), 3.06 (br s, 4H), 2.60 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.32, 142.87, 141.53, 135.77, 130.17, 130.13, 129.64, 127.84, 127.10, 126.84, 122.76, 120.96, 118.20, 111.22, 59.87, 55.35, 53.04, 50.83; LC/MS (ESI$^+$): m/z: calcd for $C_{24}H_{26}N_2O$: 358.48, $[M+H]^+$; found: 359.30.

4.3.8. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(3-methoxyphenyl)piperazine (1-8)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(3-methoxyphenyl)piperazine (315 mg, 1.64 mmol), [1,1′-biphenyl]-2-carbaldehyde (150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in methanol (10 ml) gave the title compound **1-8** (124 mg, 0.35 mmol, 43% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.51 (m, 1H), 7.40–7.26 (m, 8H), 7.12 (t,

J = 8.0 Hz, 1H), 6.49–6.35 (m, 3H), 3.72 (s, 3H), 3.44 (s, 2H), 3.10 (br t, J = 5.1 Hz, 4H), 2.47 (br t, J = 5.0 Hz, 4H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.67, 152.93, 142.91, 141.57, 135.66, 130.27, 130.12, 129.83, 129.65, 127.98, 127.25, 127.01, 108.89, 104.35, 102.48, 59.96, 55.22, 52.84, 49.23; LC/MS (ESI^+): m/z: calcd for $C_{24}H_{26}N_2O$: 358.48, $[M+H]^+$; found: 359.30.

4.3.9. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(4-methoxyphenyl)piperazine (1-9)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(4-methoxyphenyl)piperazine (212 mg, 1.10 mmol), [1,1′-biphenyl]-2-carbaldehyde (100 mg, 0.55 mmol), and $NaBH(OAc)_3$ (355 mg, 1.65 mmol) in methanol (5 ml) gave the title compound **1-9** (128.8 mg, 0.36 mmol, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.57 (m, 1H), 7.45–7.26 (m, 9H), 6.93–6.84 (m, 3H), 3.80 (s, 3H), 3.50 (s, 2H), 3.07 (br t, J = 4.2 Hz, 4H), 2.56 (br t, J = 4.5 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.78, 145.99, 142.93, 141.60, 135.73, 130.31, 130.20, 129.72, 128.02, 127.28, 127.04, 118.20, 114.51, 59.99, 55.63, 53.03, 50.83; LC/MS (ESI^+): m/z: calcd for $C_{24}H_{26}N_2O$: 358.48, $[M+H]^+$; found: 359.30.

4.3.10. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(3,4-dimethoxyphenyl)piperazine (1-10)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(3,4-dimethoxyphenyl)piperazine (245 mg, 1.10 mmol), [1,1′-biphenyl]-2-carbaldehyde (100 mg, 0.55 mmol), and $NaBH(OAc)_3$ (355 mg, 1.65 mmol) in methanol (5 ml) gave the title compound **1-10** (167.9 mg, 0.43 mmol, 79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 6.3 Hz, 1H), 7.45–7.30 (m, 8H), 6.82 (d, J = 8.7 Hz, 1H), 6.59 (d, J = 2.4 Hz, 1H), 6.47 (dd, J = 8.7 Hz, J = 2.7 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.54 (s, 2H), 3.09 (br t, J = 4.5 Hz, 4H), 2.57 (br t, J = 4.5 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.51, 146.50, 143.47, 142.89, 141.52, 135.50, 130.26, 130.18, 129.66, 127.98, 127.24, 127.04, 126.99, 112.07, 107.95, 102.89, 59.84, 56.33, 55.86, 52.92, 50.84; LC/MS (ESI^+): m/z: calcd for $C_{25}H_{28}N_2O_2$: 388.51, $[M+H]^+$; found: 389.30.

4.3.11. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(2-methylphenyl)piperazine (1-11)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2-methylphenyl)piperazine (194 mg, 1.10 mmol), [1,1′-biphenyl]-2-carbaldehyde (100 mg, 0.55 mmol), and $NaBH(OAc)_3$ (355 mg, 1.65 mmol) in methanol (5 ml) gave the title compound **1-11** (140.7 mg, 0.41 mmol, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76–7.70 (m, 1H), 7.61–7.41 (m, 8H), 7.32–7.28 (m, 2H), 7.18–7.09 (m, 2H), 3.64 (s, 2H), 3.03 (br t, J = 4.5 Hz, 4H), 2.68 (br s, 4H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.81, 142.89, 141.66, 135.95, 132.68, 131.18, 130.30, 130.17, 129.76, 128.03, 127.28, 127.03, 126.97, 126.69, 123.12, 119.08, 60.12, 53.51, 52.02, 18.10; LC/MS (ESI^+): m/z: calcd for $C_{24}H_{26}N_2$: 342.49, $[M+H]^+$; found: 343.30.

4.3.12. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(3-methylphenyl)piperazine (1-12)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(3-methylphenyl)piperazine (289 mg, 1.64 mmol), [1,1′-biphenyl]-2-carbaldehyde (150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in methanol (10 ml) gave the title compound **1-12** (154 mg, 0.45 mmol, 55% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–7.79 (m, 1H), 7.67–7.51 (m, 8H), 7.36 (t, J = 7.5 Hz, 1H), 6.95–6.88 (m, 3H), 3.70 (s, 2H), 3.34 (br t, J = 5.1 Hz, 4H), 2.73 (br t, J = 4.8 Hz, 4H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.86, 143.15, 141.84, 135.85, 135.94, 130.52, 130.39, 129.90, 129.26, 128.21, 127.48, 127.27, 127.24, 120.76, 117.14, 113.51, 60.26, 53.17, 49.60, 22..20; LC/MS (ESI^+): m/z: calcd for $C_{24}H_{26}N_2$: 342.49, $[M+H]^+$; found: 343.30.

4.3.13. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(4-methylphenyl)piperazine (1-13)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(4-methylphenyl)piperazine (155 mg, 0.88 mmol), [1,1′-biphenyl]-2-carbaldehyde (80 mg, 0.44 mmol), and $NaBH(OAc)_3$ (284 mg, 1.32 mmol) in methanol (5 ml) gave the title compound **1-13** (70 mg, 0.21 mmol, 48% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.70 (m, 1H), 7.61–7.41 (m, 8H), 7.32–7.28 (m, 2H), 7.18–7.09 (m, 2H), 3.64 (s, 2H), 3.03 (br t, J = 4.5 Hz, 4H), 2.68 (br s, 4H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.49, 142.92, 141.59, 135.72, 130.29, 129.72, 129.69, 129.09, 127.99, 127.26, 127.01, 116.46, 59.98, 52.95, 49.92, 20.59; LC/MS (ESI^+): m/z: calcd for $C_{24}H_{26}N_2$: 342.49, $[M+H]^+$; found: 343.30.

4.3.14. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(2,3-dimethylphenyl)piperazine (1-14)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2,3-dimethylphenyl)piperazine (312 mg, 1.64 mmol), [1,1′-biphenyl]-2-carbaldehyde (150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in methanol (10 ml) gave the title compound **1-14** (53 mg, 0.15 mmol, 18% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 6.9 Hz, 1H), 7.44–7.03 (m, 7H), 7.05 (t, J = 7.5 Hz, 2H), 6.88 (t, J = 7.2 Hz, 2H), 3.47 (s, 2H), 2.84 (br t, J = 4.5 Hz, 4H), 2.52 (br s, 4H), 2.24 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.80, 142.81, 141.59, 137.95, 135.89, 131.30, 130.19, 130.08, 129.67, 127.92, 127.17, 126.92, 126.85, 125.85, 124.87, 116.67, 60.04, 53.46, 52.36, 20.70, 14.04; LC/MS (ESI^+): m/z: calcd for $C_{24}H_{26}N_2$: 356.51, $[M+H]^+$; found: 357.30.

4.3.15. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(2,4-dimethylphenyl)piperazine (1-15)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2,4-dimethylphenyl)piperazine (312 mg, 1.64 mmol), [1,1′-biphenyl]-2-carbaldehyde (150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in methanol (10 ml) gave the title compound **1-15** (202 mg, 0.57 mmol, 69% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.75 (m, 1H), 7.62–7.42 (m, 8H), 7.14–7.06 (m, 3H), 3.67 (s, 2H), 3.01 (br t, J = 3.9 Hz, 4H), 2.69 (br s, 4H), 2.42 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.37, 142.94, 141.68, 135.74, 132.56, 132.43, 131.92, 130.29, 130.27, 129.75, 128.05, 127.30, 127.18, 127.04, 119.06, 60.01, 53.50, 52.15, 20.88, 17.89; LC/MS (ESI^+): m/z: calcd for $C_{24}H_{26}N_2$: 356.51, $[M+H]^+$; found: 357.30.

4.3.16. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(2,5-dimethylphenyl)piperazine (1-16)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2,5-dimethylphenyl)piperazine (312 mg, 1.64 mmol), [1,1′-biphenyl]-2-carbaldehyde (150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in methanol (10 ml) gave the title compound **1-16** (36 mg, 0.10 mmol, 12% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.26 (m, 7H), 7.05 (d, J = 7.5 Hz, 1H), 6.82–6.76 (m, 2H), 3.47 (s, 2H), 2.84 (br t, J = 4.5 Hz, 4H), 2.52 (br s, 4H), 2.24 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.54, 142.79, 141.55, 136.06, 135.84, 130.87, 130.17, 130.06, 129.65, 129.30, 127.90, 127.14, 126.90, 126.83, 126.62, 119.76, 59.99, 53.42, 51.90, 21.26, 17.52; LC/MS (ESI^+): m/z: calcd for $C_{24}H_{26}N_2$: 356.51, $[M+H]^+$; found: 357.30.

4.3.17. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(3,5-dimethylphenyl)piperazine (1-17)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(3,5-dimethylphenyl)piperazine (312 mg, 1.64 mmol), [1,1′-biphenyl]-2-carbaldehyde (150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in methanol (10 ml) gave

the title compound **1-17** (58 mg, 0.16 mmol, 20% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.54 (m, 1H), 7.47–7.20 (m, 8H), 6.53–6.50 (m, 3H), 3.45 (s, 2H), 3.10 (br t, J = 4.8 Hz, 4H), 2.49 (br t, J = 4.8 Hz, 4H), 2.26 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.66, 142.87, 141.55, 138.60, 135.68, 130.22, 130.07, 129.62, 127.92, 127.19, 126.93, 121.58, 114.09, 59.94, 52.93, 49.48, 21.74; LC/MS (ESI^+): m/z: calcd for $C_{24}H_{26}N_2$: 356.51, $[M+H]^+$; found: 357.30.

4.3.18. 1-([1,1′-Biphenyl]-2-ylmethyl)-4-(3-(trifluoromethyl)phenyl)piperazine (1-18)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(3-trifluoromethylphenyl)piperazine (437 mg, 1.64 mmol), [1,1′-biphenyl]-2-carbaldehyde (150 mg, 0.82 mmol), and $NaBH(OAc)_3$ (529 mg, 2.46 mmol) in methanol (10 ml) gave the title compound **1-18** (19 mg, 0.05 mmol, 6% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.54 (m, 1H), 7.41–7.25 (m, 9H), 7.07–7.00 (m, 3H), 3.47 (s, 2H), 3.17 (br t, J = 5.1 Hz, 4H), 2.51 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.52, 142.85, 141.46, 135.43, 130.21, 129.97, 129.53, 129.49, 127.90, 127.19, 126.99, 126.93, 118.64, 115.60, 112.02, 59.82, 52.57, 48.77; LC/MS (ESI^+): m/z: calcd for $C_{24}H_{23}F_3N_2$: 396.46, $[M+H]^+$; found: 397.30.

4.3.19. 1-((2′-Fluoro-[1,1′-biphenyl]-2-yl)methyl)-4-(2-methoxyphenyl)piperazine (1-19)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2-methoxyphenyl)piperazine (1.2 g, 6.20 mmol), 2′-fluorobiphenyl-2-carbaldehyde (620 mg, 3.10 mmol), and $NaBH(OAc)_3$ (2.0 g, 9.30 mmol) in methanol (50 ml) gave the title compound **1-19** (379 mg, 1.01 mmol, 33% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (dd, J = 6.8 Hz, 1.5 Hz, 1H), 7.44–7.11 (m, 7H), 7.03–6.92 (m, 3H), 6.86 (d, J = 7.9 Hz, 1H), 3.85 (s, 3H), 3.48 (s, 2H), 3.00 (br s, 4H), 2.52 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.69 (d, J = 246 Hz), 152.31, 141.59, 137.10, 136.16, 131.69 (d, J = 3.5 Hz), 130.32, 129.63, 129.05, 128.91 (d, J = 5.6 Hz), 127.91, 126.71, 123.69 (d, J = 3.5 Hz), 122.72, 120.95, 118.18, 115.28 (d, J = 22.4 Hz), 111.21, 59.99, 55.33, 53.08, 50.74; LC/MS (ESI^+): m/z: calcd for $C_{24}H_{25}FN_2O$: 376.47, $[M+H]^+$; found: 377.30.

4.3.20. 1-((2′-Chloro-[1,1′-biphenyl]-2-yl)methyl)-4-(2-methoxyphenyl)piperazine (1-20)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2-methoxyphenyl)piperazine (311 mg, 1.62 mmol), 2′-chlorobiphenyl-2-carbaldehyde (175 mg, 0.81 mmol), and $NaBH(OAc)_3$ (523 mg, 2.43 mmol) in methanol (15 ml) gave the title compound **1-20** (69 mg, 0.18 mmol, 22% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 7.46–7.24 (m, 6H), 7.17 (d, J = 7.6 Hz, 1H), 6.99–6.88 (m, 3H), 6.82 (d, J = 7.8 Hz, 1H), 3.81 (s, 3H), 3.44 (d, J = 13.5 Hz, 1H), 3.28 (d, J = 13.5 Hz, 1H), 2.96 (br s, 4H), 2.47 (br s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.29, 141.55, 140.14, 139.78, 136.72, 133.53, 131.38, 129.81, 129.45, 129.20, 128.53, 127.87, 126.64, 126.26, 122.76, 120.94, 118.19, 111.14, 59.89, 55.34, 53.17, 50.71; LC/MS (ESI^+): m/z: calcd for $C_{24}H_{25}ClN_2O$: 392.93, $[M+H]^+$; found: 393.30.

4.3.21. 1-((3′-Chloro-[1,1′-biphenyl]-2-yl)methyl)-4-(2-methoxyphenyl)piperazine (1-21)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2-methoxyphenyl)piperazine (603 mg, 3.14 mmol), 3′-chlorobiphenyl-2-carbaldehyde (340 mg, 1.57 mmol), and $NaBH(OAc)_3$ (1.0 g, 4.71 mmol) in methanol (25 ml) gave the title compound **1-21** (250 mg, 0.64 mmol, 41% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (br s, 1H), 7.56–7.52 (m, 1H), 7.43–7.30 (m, 6H), 7.06–6.92 (m, 3H), 6.90 (d, J = 7.5 Hz, 1H), 3.89 (s, 3H), 3.47 (s, 2H), 3.10 (br s, 4H), 2.65 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.36, 143.34, 141.63, 141.59, 135.75, 133.70, 130.73, 130.06, 129.07, 127.79, 127.46, 127.17, 126.97, 122.80, 121.03, 118.25, 111.31, 60.21, 55.38, 52.94, 50.84; LC/MS (ESI^+): m/z: calcd for $C_{24}H_{25}ClN_2O$: 392.93, $[M+H]^+$; found: 393.20.

4.3.22. 1-((4′-Chloro-[1,1′-biphenyl]-2-yl)methyl)-4-(2-methoxyphenyl)piperazine (1-22)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2-methoxyphenyl)piperazine (497 mg, 2.58 mmol), 4′-chlorobiphenyl-2-carbaldehyde (280 mg, 1.29 mmol), and $NaBH(OAc)_3$ (832 mg, 3.87 mmol) in methanol (20 ml) gave the title compound **1-22** (215 mg, 0.55 mmol, 42% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, J = 6.4 Hz, 2.3 Hz, 1H), 7.51–7.31 (m, 7H), 7.09–6.98 (m, 3H), 6.92 (d, J = 7.2 Hz, 1H), 3.91 (s, 3H), 3.52 (s, 2H), 3.12 (br s, 4H), 2.66 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.41, 141.76, 141.61, 140305, 135.78, 133.04, 121.10, 130.63, 130.15, 128.06, 127.43, 127.14, 122.87, 121.10 ,118.28, 111.43, 60.17, 55.44, 53.08, 50.89; LC/MS (ESI^+): m/z: calcd for $C_{24}H_{25}ClN_2O$: 392.93, $[M+H]^+$; found: 393.20.

4.3.23. 1-(2-Methoxyphenyl)-4-((2′-methyl-[1,1′-biphenyl]-2-yl)methyl)piperazine (1-23)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2-methoxyphenyl)piperazine (196 mg, 1.02 mmol), 2′-methyl-[1,1′-biphenyl]-2-carbaldehyde (100 mg, 0.51 mmol), and $NaBH(OAc)_3$ (329 mg, 1.53 mmol) in methanol (50 ml) gave the title compound **1-23** (186 mg, 0.50 mmol, 98% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, J = 7.5 Hz, 1.2 Hz, 1H), 7.35–7.10 (m, 7H), 6.96–6.86 (m, 3H), 6.79 (d, J = 7.5 Hz, 1H), 3.78 (s, 3H), 3.34 (d, J = 13.5 Hz, 1H), 3.22 (d, J = 13.5 Hz, 1H), 2.98 (br s, 4H), 2.47 (br s, 4H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.40, 142.13, 141.67, 141.05, 136.46, 136.06, 129.76, 129.68, 129.42, 127.29, 127.21, 126.68, 125.34, 122.84, 121.08, 118.29, 111.34, 59.84, 55.43, 53.48, 53.32, 50.86; LC/MS (ESI^+): m/z: calcd for $C_{25}H_{28}N_2O$: 372.51, $[M+H]^+$; found: 373.30.

4.3.24. 1-((2′-Methoxy-[1,1′-biphenyl]-2-yl)methyl)-4-(2-methoxyphenyl)piperazine (1-24)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2-methoxyphenyl)piperazine (634 mg, 3.30 mmol), 2′-methoxybiphenyl-2-carbaldehyde (350 mg, 1.65 mmol), and $NaBH(OAc)_3$ (1.1 g, 4.95 mmol) in methanol (25 ml) gave the title compound **1-24** (382 mg, 0.98 mmol, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 7.6 Hz, 1.0 Hz, 1H), 7.36–7.25 (m, 3H), 7.19–7.15 (m, 2H), 7.00–6.89 (m, 5H), 6.80 (d, J = 7.6 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.46 (d, J = 13.4 Hz, 1H), 3.33 (d, J = 13.4 Hz, 1H), 2.98 (br s, 4H), 2.48 (br s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.60, 152.34, 141.65, 138.95, 137.21, 131.30, 130.44, 130.28, 129.03, 128.38, 127.37, 126.53, 122.79, 121.03, 120.41, 118.25, 111.20, 110.51, 59.83, 55.40, 53.53, 53.25, 50.88; LC/MS (ESI^+): m/z: calcd for $C_{25}H_{28}N_2O_2$: 388.51, $[M+H]^+$; found: 389.30.

4.3.25. 1-((3′-Methoxy-[1,1′-biphenyl]-2-yl)methyl)-4-(2-methoxyphenyl)piperazine (1-25)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2-methoxyphenyl)piperazine (181 mg, 0.94 mmol), 3′-methoxybiphenyl-2-carbaldehyde (100 mg, 0.47 mmol), and $NaBH(OAc)_3$ (303 mg, 1.41 mmol) in methanol (10 ml) gave the title compound **1-25** (176 mg, 0.45 mmol, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.53 (m, 1H), 7.34–7.26 (m, 4H), 7.03–6.80 (m, 7H), 3.80 (s, 6H), 3.48 (s, 2H), 3.02 (br s, 4H), 2.58 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.26, 152.38, 142.98, 142.80, 141.61, 135.70, 130.39, 130.10, 128.93, 127.24, 126.93, 122.87, 122.23, 121.07, 118.26, 115.42, 112.60, 111.29, 60.03, 55.42, 55.37, 53.18, 50.91; LC/MS (ESI^+): m/z: calcd for $C_{25}H_{28}N_2O_2$: 388.51, $[M+H]^+$; found: 389.30.

4.3.26. 1-((4′-Methoxy-[1,1′-biphenyl]-2-yl)methyl)-4-(2-methoxyphenyl)piperazine (1-26)

Following the same procedure used for the synthesis of **1-1**, the reaction of 1-(2-methoxyphenyl)piperazine (181 mg, 0.94 mmol), 4′-methoxybiphenyl-2-carbaldehyde (100 mg, 0.47 mmol), and $NaBH(OAc)_3$ (303 mg, 1.41 mmol) in methanol (10 ml) gave the title compound **1-26** (149 mg, 0.38 mmol, 82% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.51 (m, 1H), 7.38–7.24 (m, 5H), 6.95–6.87 (m, 5H), 6.80 (d, J = 7.2 Hz, 1H) 3.80 (s, 3H), 3.79 (s, 3H), 3.46 (s, 2H), 3.02 (br s, 4H), 2.57 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.76, 152.41, 142.66, 141.66, 135.91, 134.00, 130.89, 130.42, 130.39, 126.98, 126.91, 122.88, 121.10, 118.31, 113.39, 111.33, 60.12, 55.44, 55.35, 53.16, 50.95; LC/MS (ESI^+): m/z: calcd for $C_{25}H_{28}N_2O_2$: 388.51, $[M+H]^+$; found: 389.30.

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21. For the more detailed explanation of radioligand binding affinity assay, see the website of NIMH Psychoactive Drug Screening Program: http://pdsp.med.unc.edu/.