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Novel aminoethylbiphenyls as 5-HT$_7$ receptor ligands

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Abstract—The synthesis of a series of aminoethylbiphenyls as novel 5-HT$_7$ receptor ligands is described. The novel derivatives exhibit high affinity for the 5-HT$_7$ receptor with selectivity toward 5-HT$_{1A}$ receptor.

The 5-HT$_7$ receptor (5-HT$_7$R) is the most recent subtype identified of the serotonin (5-HT) receptor family.[1] Application of molecular cloning has led to the identification and the characterization of the 5-HT$_7$ receptor subtype from rat,[2–5] mouse,[6] human,[7] guinea-pig[8], and pig.[9] The 5-HT$_7$ receptors have been located in the central nervous system (thalamus, hypothalamus, hippocampus, cortex) and in peripheral tissues (pancreas, spleen, coronary artery, ileum).[3,5,7] Although biological functions of these receptors are poorly understood, recent reports suggest that 5-HT$_7$ receptors are involved in the pathophysiology of several disorders such as anxiety,[10] depression,[10,11] schizophrenia,[12] control of circadian rhythm,[13] migraine,[14] nociception,[15] epilepsy,[16] and relaxation of blood vessels.[17] The 5-HT$_7$ receptors are also involved in different endocrine functions.[18,19]

Several 5-HT$_7$R ligands have been reported,[20] including aporphine analogues **1**[20e] and aminotetralins **2a**–**b**[20g] (Fig. 1).

We also recently described a novel series of phenylpyrroles as 5-HT$_7$R ligands (Fig. 2).[21] However, these compounds were also potent ligands of the 5-HT$_{1A}$ receptor.

We postulated that the 5-HT$_{1A}$R affinity was due to the presence of the 2-methoxyphenylpiperazine moiety, which is a key fragment in many 5-HT$_{1A}$ receptor ligands.[22–25]

We now wish to report our efforts in identifying a new series of 5-HT$_7$R ligands with good selectivity toward the 5-HT$_{1A}$ receptor.

We analyzed the structural homology of the phenylpyrroles **6** with the fused polycyclic analogues **5** (left) and aminotetralin (right) (Fig. 3).[26,27] This led to a hypothesis that simple phenylpyrroles **6** would be interesting structures to investigate.

From these observations, we decided to synthesize a series of phenylpyrroles bearing an ethylamine chain in position 3 of the pyrrole (Scheme 1, compounds **9a**–**c** and **10a**–**b**).

These compounds were prepared from **7a**–**c**[21] as outlined in Scheme 1. Nitrovinyl compounds **8a**–**c** were obtained by the reaction of nitromethane with aldehydes **7a**–**c**, in the presence of ammonium acetate. Primary amines **9a**–**c** were prepared by reduction of nitrovinyl **8a**–**c** with $LiAlH_4$.[28] Compounds **9a**–**b** were then subjected to Eschweiler–Clarke conditions, with formaldehyde and sodium cyanoborohydride in acetic acid, to give the *N*,*N*-dimethyl derivatives **10a**–**b**.[29–31]

The results of binding assays on 5-HT$_7$[4,5] and 5-HT$_{1A}$ [32] receptors are given in Table 1. Contrary to our

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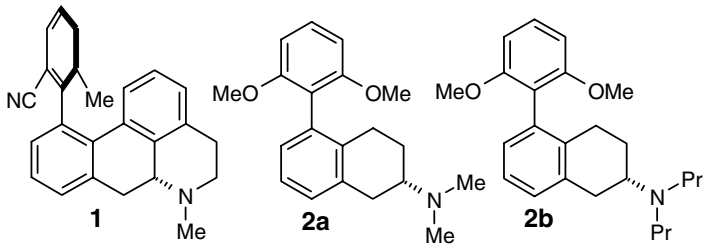
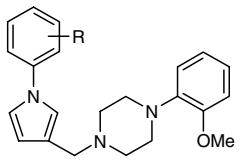


Figure 1. 5-HT_7 antagonist **1**, **2a** and agonist **2b** of the aporphine and 2-aminotetralin series.



3a R = 2-Me; 5-HT_7 Ki = 4.7 nM; 5-HT_{1A} Ki = 9.9 nM
3b R = 2-CN; 5-HT_7 Ki = 5.4 nM; 5-HT_{1A} Ki = 33.7 nM
3c R = 2-Me, 6-CO_2Me; 5-HT_7 Ki = 18nM; 5-HT_{1A} Ki = 18.5 nM

Figure 2. Phenylpyrroles **3a**–**c** as novel 5-HT_7 receptor ligands.

hypothesis, the 5-HT_7R affinity was not improved by shifting the ethylamine chain from position 2 to position 3 of the pyrrole and alkylation of the amino group did not result in an increase in affinity (compounds **10a**–**b**). However, these compounds showed no affinity for the 5-HT_{1A} receptor. These results support the hypothesis that the 2-methoxyphenylpiperazine moiety could be responsible for the lack of selectivity.

In order to better align with both phenylaporphine and aminotetraline compounds, we chose to replace the pyrrole by a second phenyl group.

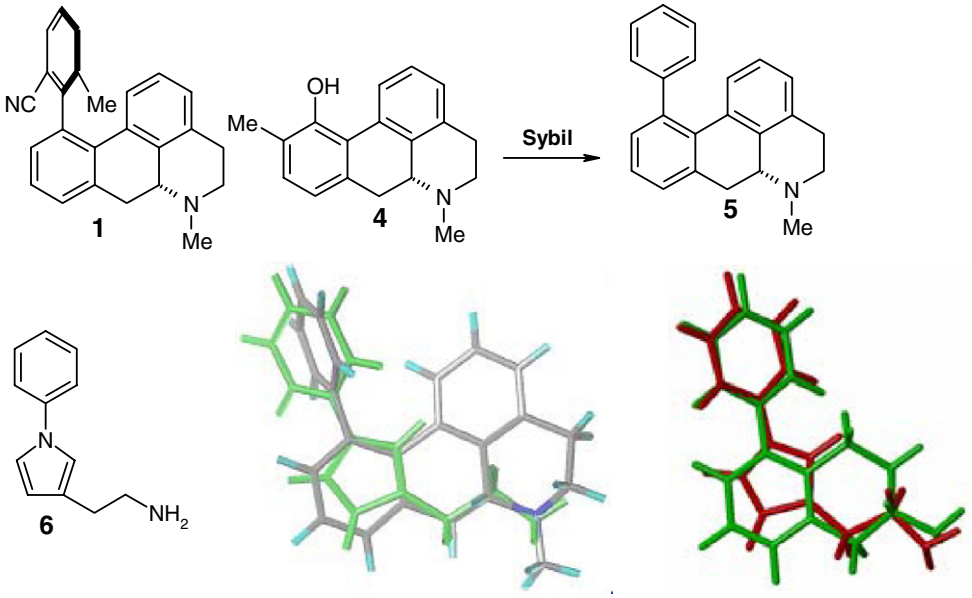
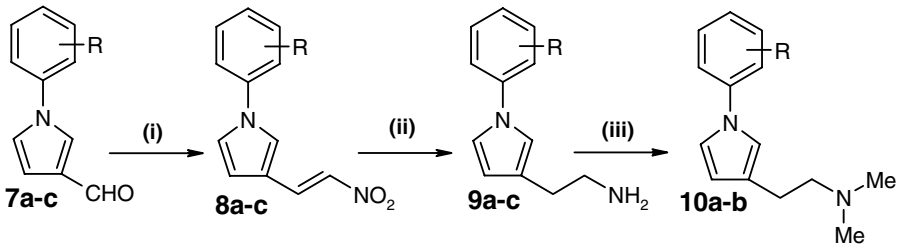


Figure 3. Alignment between phenylpyrrole **6** and phenylaporphine **5** (left) or aminotetralin (right).



Scheme 1. Reagents and conditions: (i) 2.5 equiv ammonium acetate, CH_3NO_2, reflux, 5 h, 80–99%; (ii) 4 equiv $LiAlH_4$, THF, reflux, 4 h, 81–94%; (iii) 2.7 equiv $NaBH_3CN$, 4 equiv HCHO, AcOH, MeOH, rt, 8 h, 42%.

Table 1. Human 5-HT_7 receptor and rat 5-HT_{1A} affinities of compounds **9a–c** and **10a–b**[a]

Compound	R	5-HT_7 % Inhib.		5-HT_{1A} % Inhib.	
		10^{-6} M	10^{-8} M	10^{-6} M	10^{-8} M
9a	2-CH_3	62	5	16	0
9b	2,4,6-CH_3	0	0	0	0
9c	2,3-CH_3	48	25	17	0
10a	2-CH_3	87	16	41	14
10b	2,4,6-CH_3	56	3	20	0

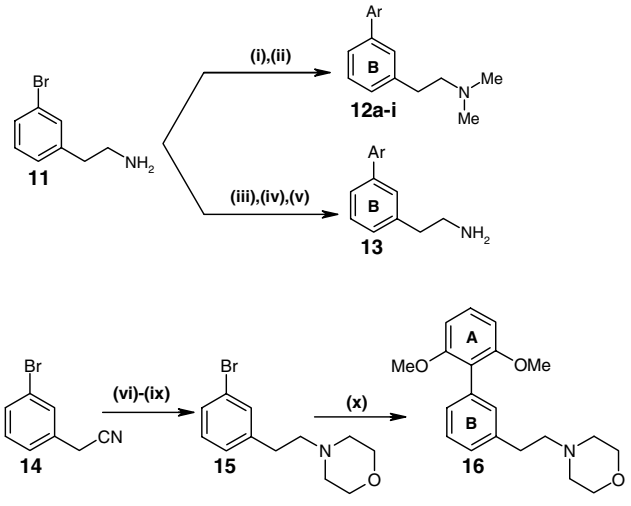
[a] 5-HT_7 receptors and radioligand used in binding assays: human cloned receptors in sf9 cells, [3H]LSD, according to Refs. 4 and 5. Binding experiments on 5-HT_{1A} receptors were realized according to Hall et al.'s procedure.[32]

The series of aminoethylbiphenyls were synthesized from the commercially available 3-bromophenethylamine **11**. *N*,*N*-dimethylation of the primary amine **11**, followed by Suzuki cross-coupling reactions, afforded the target compounds **12a–i** (Scheme 2). Boc-protection of **11**, followed by Suzuki cross-coupling reactions and acidic hydrolysis, led to compound **13**.

Compound **15** was obtained from the commercially available 3-bromophenylacetonitrile **14** after hydrolysis,[33] reduction[34], and amination by morpholine via the mesylate.[35] The Suzuki cross-coupling reaction between 2,6-dimethoxyphenylboronic acid and **15** led to **16** (Scheme 2).

These novel biaryls were evaluated for their affinity for the 5-HT_7 and 5-HT_{1A} receptors, according to methods previously described[4,5,32] and the results are summarized in Table 2.

In this series, the 5-HT_7 affinity and selectivity depend on the substitution of the phenyl ring **A**. Introduction of *ortho* substituents (Me or OMe) into the phenyl ring **A** increased the 5-HT_7R affinity (**12b** and **12c**) as described for other 5-HT_7 ligands.[20e,g,h] Moreover, these *ortho* substituted compounds showed a good selectivity toward 5-HT_{1A} receptor. The presence of a substituent in *ortho* position was essential for the 5-HT_7R affinity. We can hypothesize that the aryl groups **A** and **B** should not be placed in the same plane. The distributions of the dihedral angle between the two phenyl rings, not substituted and *ortho* substituted, were analyzed from CSD data.[36] The results showed clearly a different distribution between the two fragments (values of 0° highly probable without substitution and around 45° for *ortho* substituted). So, these results (compounds **12e–i**) support this hypothesis.



Scheme 2. Reagents and conditions: (i) 2.7 equiv $NaBH_3CN$, 4 equiv HCHO, AcOH, MeOH, rt, 8 h, 77%; (ii) 1.8 equiv $ArB(OH)_2$, 5% $(PPh_3)_4Pd$, Tol/EtOH 9:1, 2.5 equiv Na_2CO_3, reflux, 24 h, 49–89%; (iii) 1.1 equiv $(Boc)_2O$, 2.5 equiv TEA, THF, N_2, rt, 12 h, 77%; (iv) 1.8 equiv $ArB(OH)_2$, 5% $(PPh_3)_4Pd$, Tol/EtOH 9:1, 2.5 equiv Na_2CO_3, reflux, 24 h, 84%; (v) HCl, Et_2O, rt, 12 h, 61%; (vi) 3 equiv LiOH, $MeOH/H_2O$ 3:1, 50°C, 72 h, 78%; (vii) 2 equiv BH_3.THF 1M, THF, 0°C, 4 h, 93%; (viii) 1.2 equiv CH_3SO_2Cl, Pyridine, rt, 12 h, 65%; (ix) 4 equiv morpholine, DMF, reflux, 24 h, 72%; (x) 2 equiv $ArB(OH)_2$, 5% $(PPh_3)_4Pd$, Tol/EtOH 9:1, 4.5 equiv Na_2CO_3, reflux, 24 h, 36%.

Introduction of a second substituent in *ortho* position does not modify the 5-HT_7R affinity (**12a**, **12d**) but improves the selectivity toward the 5-HT_{1A} receptor. Indeed, the 5-HT_{1A}/5-HT_7 affinity ratio is around 60 for compounds **12b** and **12c**, and increased respectively to 400 and 600 when we introduced a second substituent in *ortho* position of the phenyl group (**12a** and **12d**).

In addition, we observed that an increase of the steric hindrance on the basic nitrogen atom led to inactive compound (compare **16** and **12a**), whereas the free amino group was tolerated (compare **13** and **12b**). Other compounds will be synthesized to confirm this observation.

Compounds **12a** and **12b** were then evaluated for their pharmacological profile by using a specific test of aldosterone secretion from perifused rat adrenal cortex stimulated by serotonin through 5-HT_7R.[37,38] Compound **12b** behaved as 5-HT_7 antagonist with calculated pK_b value of 7.03. In contrast, compound **12a** was found to be a partial agonist with no antagonistic profile.

From our initial series of phenylpyrroles, with a moderate 5-HT_7 affinity, we obtained a new series of compounds with high 5-HT_7 affinity by replacement of the pyrrole cycle by a second phenyl cycle. Furthermore, a good selectivity toward 5-HT_{1A} receptor was observed for most of these compounds, in particular for the *diortho* substituted compounds.

These results show that aminoethylbiphenyles could be considered as interesting simplified structures of the phenylaporphine **5**, with an easier synthetic access.

Table 2. Binding affinities of compounds **12a–i**, **13**, and **16** to human 5-HT_7 and rat 5-HT_{1A} receptors[a]

Compound	Ar (**A**)	5-HT_7 % Inhib. 10^{-6} M/10^{-8} M	K_i (nM)[c]	5-HT_{1A} % Inhib. 10^{-6} M/10^{-8} M	K_i (nM)[c]
12a	2,6-DiMeOPh	100/50	8.6	18/3	4826
12b	2-MePh	81/72	7.6	85/1	443
12c	2-MeOPh	69/23	8.4	48/12	531
12d	2,6-DiMePh	93/73	6.2	33/6	2250
12e	Ph	70/18	ND[b]	18/2	ND
12f	4-MeOPh	52/9	ND	37/0	ND
12g	3,4-DiMeOPh	38/0	ND	52/12	ND
12h	2-Thienyl	75/12	ND	63/6	ND
12i	3-Thienyl	87/12	ND	64/20	ND
13	2-MePh	92/71	7.5	37/0	1470
16	2,6-DiMeOPh	9/0	ND	14/7	ND

[a] 5-HT_7 receptors and radioligand used in binding assays: human cloned receptors in *sf*9 cells, [^{3}H]LSD, according to Refs. 4 and 5. Binding experiments on 5-HT_{1A} receptors were realized according to Hall et al.'s procedure.[32]

[b] Not determined.

[c] The K_i-values are means of three experiments.

In conclusion, we have identified new leads in the search of 5-HT_7R ligands with antagonist or partial agonist profile. The best compounds **12a** and **12b** will be submitted to further pharmacological studies.

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