

New Imide 5-HT_{1A} Receptor Ligands – Modification of Terminal Fragment Geometry

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Abstract: Two sets of new *o*-methoxyphenylpiperazine (MPP; series **a**) and 1,2,3,4-tetrahydroisoquinoline (THIQ; series **b**) derivatives, containing various imide moieties derived from NAN190, were synthesized and evaluated *in vitro* for their ability to bind to the serotonin 5-HT_{1A} and 5-HT_{2A} receptors. All new derivatives from series **a** demonstrated high 5-HT_{1A} affinities, whereas THIQ analogues were much less active. With respect to 5-HT_{2A} receptors, three MPP derivatives presented moderate activity but the rest of the investigated compounds were practically inactive. The influence of changes in terminus geometry on 5-HT_{1A} receptor affinity was analyzed in regard to model compounds NAN190 and MM199.

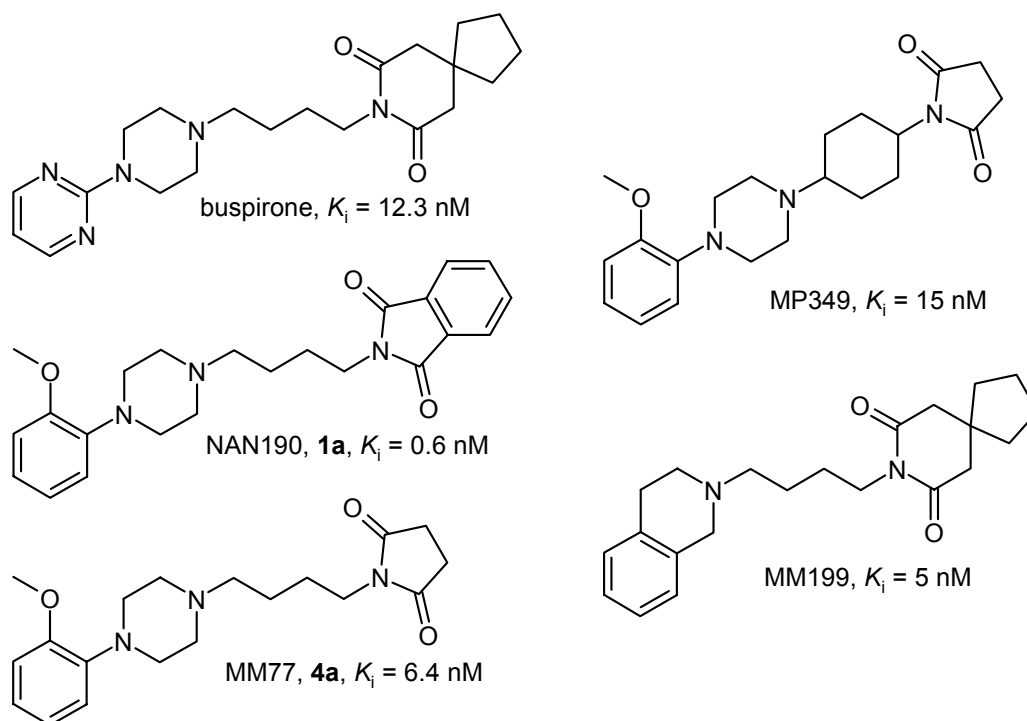
Keywords: 5-HT_{1A} ligands, arylpiperazine derivatives, 1,2,3,4-tetrahydroisoquinoline derivatives.

Introduction

During the last decade a large number of structurally different compounds have been proposed as 5-HT_{1A} receptor ligands. Among these, 4-substituted long chain 1-arylpiperazines (LCAPs) have been extensively studied. In particular, much effort has been devoted to the role of the terminal part in a ligand-receptor interaction, and in consequence, a great many different fragments were used [1]. The imide containing fragments constituted one of the most thoroughly investigated termini type and

among others, compounds like buspirone (anxiolytic drug; 5-HT_{1A} partial agonist [2]) or NAN190 (postsynaptic antagonist [3,4]) were found (Figure 1).

Figure 1. Structure and binding constants (K_i) of the selected 5-HT_{1A} receptor ligands.

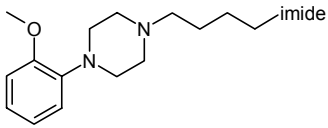
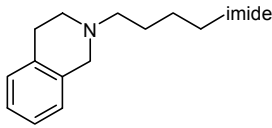
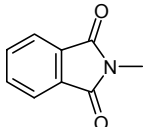
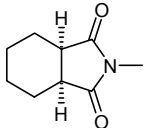
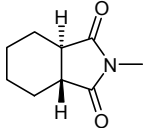
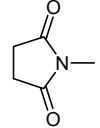
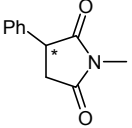
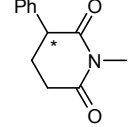
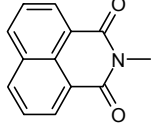


Our systematic SAR studies of the long chain 5-HT_{1A} ligands resulted in identification of several new imide derivatives with interesting biological activity. Two NAN190 analogues: MM77 (postsynaptic antagonist [5]) and its constrained form MP349 (full antagonist [6,7]) exhibited anxiolytic-like activity in some animal models [7,8]. Replacement of 1-pyrimidinylpiperazine fragment of buspirone with 1,2,3,4-tetrahydroisoquinoline (THIQ) led to the compound MM199 [9] (Figure 1), for which anxiolytic-like and antidepressant-like effects in rats were described [10]. Continuing exploration of this type of agents we synthesized two sets of new *o*-methoxyphenylpiperazine (MPP) and THIQ derivatives and evaluated their affinity for 5-HT_{1A} and 5-HT_{2A} receptors.

Results and Discussion

The structures of NAN190 and its simplified analog MM77 were chosen as lead molecules for modification of imide terminus. All the new compounds were examined *in vitro* for their ability to displace [³H]-OH-DPAT and [³H]-ketanserin binding to rat 5-HT_{1A} and 5-HT_{2A} receptors respectively, as described in the Experimental Section. The results are presented in Table 1, where additionally, the affinities of parent compounds and previously reported derivatives **1b**, **2a**, **2b** and **4b** are also included [9,11].

Table 1. Structure and 5-HT_{1A} and 5-HT_{2A} binding affinities of compounds 1–7.

No.	Imide moiety	a: 		b: 	
		K _i ± SEM (nM)		K _i ± SEM (nM)	
		5-HT _{1A}	5-HT _{2A}	5-HT _{1A}	5-HT _{2A}
1		0.55 ± 0.14 ^{a,b}	451 ± 65	355 ± 28 ^b	2770 ± 130
2		4.0 ± 0.2 ^b	109 ± 22	50 ± 11 ^b	880 ± 12
3		1.7 ± 0.5	185 ± 42	157 ± 17	1780 ± 25
4		6.4 ± 0.3 ^c	1510 ± 95	2920 ± 90 ^d	NT
5		6.8 ± 0.5	690 ± 40	453 ± 15	4000 ± 30
6		7.5 ± 0.7	835 ± 45	690 ± 20	4400 ± 40
7		46 ± 3	86 ± 2	620 ± 18	1230 ± 34

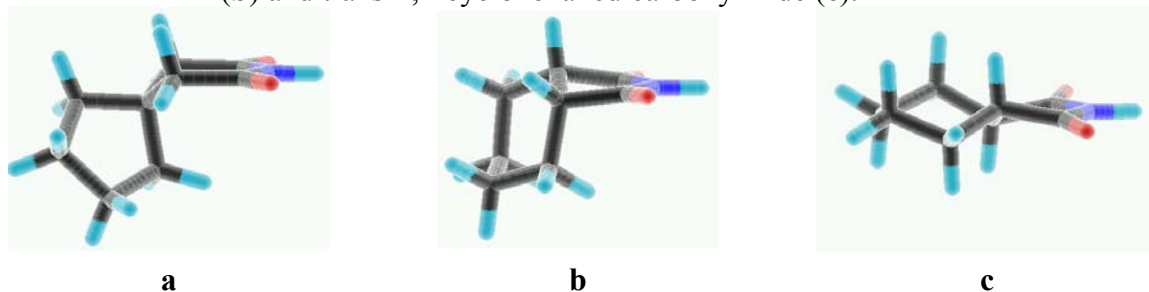
^a K_i value according to Glennon et al. was 0.58 nM [3]. ^b K_i value from ref 11. ^c ref 5. ^d ref 9.

All four newly synthesized MPP derivatives (**3a** and **5a–7a**) showed a high affinity for 5-HT_{1A} receptors ($K_i = 1.7\text{--}46$ nM), however, lower than that of NAN190. This is thus another confirmation that the flat phthalimide terminus optimally binds to the respective receptor region. All modifications of this fragment, namely saturation (**2a** and **3a**), removal of the aromatic ring (**4a**), changes in its position (**5a** and **6a**) or enlargement (**7a**) decreased the observed 5-HT_{1A} receptor affinity. Compound **7a**, the least active at the 5-HT_{1A} sites, was found to be the most potent 5-HT_{2A} ligand. All the other MPP derivatives displayed a moderate to low affinity for 5-HT_{2A} receptors ($K_i = 109\text{--}1510$ nM), and

except for **2a**, were at the same time at least 100-fold selective 5-HT_{1A} agents. This is not unexpected, since it is known that the MPP system prefers 5-HT_{1A} binding sites.

The THIQ moiety has often been used as a replacement for the arylpiperazine fragment in our studies on the role of individual pharmacophoric groups of LCAPs. Although THIQ itself does not show any affinity for the 5-HT_{1A} receptors ($K_i > 50\,000$ nM) [12] its substitution with butyl-azaspiro[4.5]decane-7,9-dione (MM199, Figure 1) increased the affinity to nanomolar level [9]. The same was observed in the case of the 1-adamantoyloaminobutyl THIQ derivative, for which $K_i = 0.95$ nM was determined [13]. It was then concluded that bulky alicyclic termini should be especially well accommodated by the 5-HT_{1A} binding site. This finding is additionally confirmed by the results obtained for the second group of imide derivatives **b**. Indeed, the highest 5-HT_{1A} receptor affinity was observed for the alicyclic systems (**2b** and **3b**), whereas aromatic groups were less favorable, although they were better than the small succinimide alone (**4b**, $K_i = 2920$ nM). Thus, the replacement of MPP by a THIQ fragment caused a decrease of 5-HT_{1A} affinity and we did not obtain any more active compounds than the previously examined **2b** [11]. A more detailed comparison of terminal fragments of MM199, **2b** and **3b** reveals that their geometry may play a role, and that a bent configuration of the cycloalkyl part (Figure 2) is preferred. With regard to 5-HT_{2A} receptors, we did not detect a significant activity in the investigated THIQ derivatives.

Figure 2. The geometry of terminal fragments: azaspiro[4.5]decane-7,9-dione (**a**), cis- (**b**) and trans-1,2-cyclohexanedicarboxyimide (**c**).



As a result of present investigation three new highly active 5-HT_{1A} ligands were found (**3a**, **5a** and **6a**), which displayed a 100-fold selectivity over 5-HT_{2A} receptors. During the preparation of this manuscript, Hackling and coworkers published a paper in which compound **7a** was investigated as a dopamine D₂ and D₃ receptor ligand [14]. In our hands this derivative was a dual 5-HT_{1A}/5-HT_{2A} ligand and based on the data obtained by Hackling, it is also a potent but unselective D₂/D₃ agent ($K_i = 40$ and 29 nM, respectively). Pharmacological work is currently in progress to evaluate the 5-HT_{1A} functional profile of these four compounds.

Experimental

General

Melting points were determined on a Boetius apparatus and are uncorrected. ^1H -NMR spectra were obtained on a Varian EM-360L (60 MHz) in the CDCl_3 solution with Me_4Si as an internal reference. Elemental analyses were performed in the Institute of Organic Chemistry PAS (Warsaw, Poland), and were within 0.5% of the theoretical values. The syntheses of 2-(4-aminobutyl)-1,2,3,4-tetrahydroisoquinoline [9] and 4-(4-aminobutyl)-1-(2-methoxyphenyl)piperazine [15] have been previously reported.

General method for the preparation of compounds **3a**, **3b**, **5a**, **5b**, **6a**, **6b**, **7a** and **7b**.

Equimolar amounts (1 mmol) of the respective, commercially available acid anhydride and 4-(4-aminobutyl)-1-(2-methoxyphenyl)piperazine or 2-(4-aminobutyl)-1,2,3,4-tetrahydroisoquinoline were refluxed in xylene (20 mL) for 3 h. After the mixture was allowed to cool to room temperature, the xylene was evaporated under reduced pressure and the products were isolated on a silica gel column. Free bases were converted into the hydrochloride salts in CHCl_3 or acetone solution by treatment with excess of Et_2O saturated with gaseous HCl .

4-{4-[2-(*trans*-1,2-Cyclohexanedicarboxyimido)]butyl}-1-(2-methoxyphenyl)piperazine (**3a**).

Oil, yield (base) 90%; M.p. (salt) 192–194°C (acetone); $R_f = 0.45$ ($\text{CHCl}_3/\text{MeOH}$ 19:1); ^1H -NMR (base): δ (ppm) = 7.1–6.7 (m, 4H, arom), 3.9 (s, 3H, OCH_3), 3.7–3.3 (m, 2H), 3.3–2.9 (m, 4H), 2.9–2.1 (m, 8H), 2.1–1.2 (m, 12H); $\text{C}_{23}\text{H}_{33}\text{N}_3\text{O}_3 \cdot 2\text{HCl}$ (472.03), Calcd. C 58.52, H 7.90, N 8.90; Found C 58.37, H 7.52, N 8.90.

1-(2-Methoxyphenyl)-4-[4-(3-phenylsuccinimido)butyl]piperazine (**5a**).

Oil, yield (base) 76%; M.p. (salt) 205–207°C (acetone); $R_f = 0.46$ ($\text{CHCl}_3/\text{MeOH}$ 19:1); ^1H -NMR (base): δ (ppm) = 7.5–7.1 (m, 5H, arom), 7.1–6.7 (m, 4H, arom), 4.2–3.8 (m, 1H), 3.8 (s, 3H, OCH_3), 3.8–3.3 (m, 2H), 3.3–2.2 (m, 12H), 2.9–1.3 (m, 4H); $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_3 \cdot 2\text{HCl}$ (494.464), Calcd. C 60.72, H 6.72, N 8.49; Found C 60.24, H 6.90, N 8.43.

1-(2-Methoxyphenyl)-4-[4-(3-phenylmaleicimido)butyl]piperazine (**6a**).

Oil, yield (base) 56%; M.p. (salt) 209–210°C (acetone); $R_f = 0.53$ ($\text{CHCl}_3/\text{MeOH}$ 19:1); ^1H -NMR (base): δ (ppm) = 7.5–7.0 (m, 5H, arom), 7.0–6.8 (m, 4H, arom), 4.1–3.6 (m, 3H), 3.8 (s, 3H, OCH_3),

3,3-2.9 (m, 4H), 2.9-2.1 (m, 10H), 1.9-1.3 (m, 4H); $C_{26}H_{33}N_3O_3 \cdot 2HCl$ (508.49), Calcd. C 61.41, H 6.93, N 8.26; Found C 61.00, H 6.99, N 8.08.

1-(2-Methoxyphenyl)-4-[4-(1,8-naphthalimido)butyl]piperazine (7a).

Oil, yield (base) 84%; M.p. (salt) 280-281°C (acetone); $R_f = 0.52$ ($CHCl_3/MeOH$ 19:1); 1H -NMR (base): δ (ppm) = 8.6(d, $J=8Hz$, 2H, arom), 8.2 (d, $J=8Hz$, 2H, arom), 7.7 (t, $J=8Hz$, arom), 7.1-6.7 (m, 4H, arom.), 4.5-4.0 (m, 2H), 3.9 (s, 3H, OCH_3), 3,3-2.9 (m, 4H), 2.9-2.3 (m, 6H), 2.1-1.5 (m, 4H); $C_{27}H_{32}N_3O_3 \cdot 2HCl$ (552.926), Calcd. C 58.65, H 5.83, N 7.60; Found C 58.83, H 6.36, N 7.63.

2-{4-[2-(trans-1,2-Cyclohexanedicarboxyimido)]butyl}-1,2,3,4-tetrahydroisoquinoline (3b).

Oil, yield (base) 79%; M.p. (salt) 168-170°C (acetone); $R_f = 0.49$ ($CHCl_3/MeOH$ 19:1); 1H -NMR (base): δ (ppm) = 7.3-6.9 (m, 4H, arom), 3.7-3.3 (m, 4H) 3.1-2.0 (m, 8H), 2.0-1.2 (m, 12H); $C_{21}H_{28}N_2O_2 \cdot HCl \cdot 0.5H_2O$ (385.919), Calcd. C 65.35, H 7.83, N 7.26; Found C 64.99, H 7.89, N 7.08.

2-[4-(3-Phenylsuccinimido)butyl]-1,2,3,4-tetrahydroisoquinoline (5b).

Oil, yield (base) 81%; M.p. (salt) 127-129°C (acetone); $R_f = 0.39$ ($CHCl_3/MeOH$ 19:1); 1H -NMR (base): δ (ppm) = 7.6-7.2 (m, 5H, arom), 7.2-7.0 (m, 4H, arom), 4.1-3.3 (m, 5H), 3.3-2.3 (m, 8H), 2.1-1.3 (m, 4H); $C_{23}H_{26}N_2O_2 \cdot HCl \cdot 0.25H_2O$ (403.439), Calcd. C 68.47, H 6.87, N 6.94; Found C 68.47, H 6.89, N 6.85.

2-[4-(3-phenylmaleicimido)butyl]-1,2,3,4-tetrahydroisoquinoline (6b).

Oil, yield (base) 47%; M.p. (salt) 121-123°C (acetone); $R_f = 0.43$ ($CHCl_3/MeOH$ 19:1); 1H -NMR (base): δ (ppm) = 7.6-7.2 (m, 5H, arom), 7.2-6.9 (m, 4H, arom), 4.2-3.5 (m, 5H), 3.3-2.0 (m, 10H), 1.9-1.4 (m, 4H); $C_{24}H_{28}N_2O_2 \cdot HCl \cdot 1.25H_2O$ (435.482), Calcd. C 66.19, H 7.29, N 6.43; Found C 66.43, H 7.26, N 6.16.

2-[4-(1,8-naphthalimido)butyl]-1,2,3,4-tetrahydroisoquinoline (7b).

Oil, yield (base) 40%; M.p. (salt) 265-267°C (acetone); $R_f = 0.43$ ($CHCl_3/MeOH$ 19:1); 1H -NMR (base): δ (ppm) = 8.6 (d, $J=8Hz$, 2H, arom), 8.2 (d, $J=8Hz$, 2H, arom), 7.7 (t, $J=8Hz$, 2H arom), 7.3-6.9 (m, 4H, arom), 4.5-4.0 (m, 2H, CH_2), 3.8-3.5 (m, 2H), 3,1-2.4 (m, 6H), 2.1-1.5 (m, 4H); $C_{25}H_{24}N_2O_2 \cdot HCl \cdot 0.5H_2O$ (429.942), Calcd. C 69.84, H 6.09, N 6.51; Found C 70.17, H 5.63, N 6.17.

Radioligand binding studies

The *in vitro* affinity of the investigated compounds for 5-HT_{1A} and 5-HT_{2A} receptors was assessed on the basis of their ability to displace [³H]-8-OH-DPAT (222 Ci/mmol, Amersham, England) and [³H]-ketanserin (66.4 Ci/mmol, NEN Chemicals, USA), respectively. Radioligand binding experiments were carried out on rat brain using tissues from the hippocampus for 5-HT_{1A} receptors, and from the cortex for 5-HT_{2A} receptors, according to the previously published procedures [16].

K_i values were determined from at least three competitive binding experiments in which 10–14 sample concentrations, run in triplicate, were used. The Cheng and Prusoff [17] equation was used for *K_i* calculations.

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Sample Availability: Available from the authors.