STRUCTURAL PARAMETERS OF ARYLPIPERAZINE TYPE OF LIGANDS DETERMINING THEIR 5-HT_{1A}/5-HT_{2A} SELECTIVITY

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Introduction

Serotonin (5-hydroxytryptamine, 5-HT) has been implicated in the etiology of many disease states, particularly may be important in mental illnesses, such as depression, anxiety, schizophrenia, and panic disorder. Indeed, many currently used treatments of these disorders are thought to act by modulating serotoninergic tone. A relatively new concept suggests that the promising psychotropic therapy can result from the application of drugs with a mixed 5-HT_{1A} and 5-HT_{2A} activity.

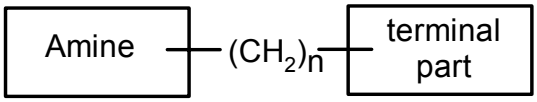
Two general strategies in design of new ligands acting at central serotonin (5-HT) receptors can be distinguished. The highly selective agents are desired pharmacological tools, whereas multireceptorial ligands are of interest from therapeutic point of view. In both cases, a knowledge of structural features controlling affinity/selectivity for different receptors is needed.

Since many years we were engaged in structure-activity relationship studies within 5-HT_{1A}/5-HT_{2A} receptor agents, especially of arylpiperazine type – one of the biggest and thoroughly investigated class of 5-HT receptor ligands. Having a large and relatively coherent database of compounds we decided to look at it from broader perspective and to check whether general structural parameters determining 5-HT_{1A}/5-HT_{2A} selectivity ($S_{1A/2A}$) can be found.

Results and discussion

Of all compounds in the local database only those with existing 5-HT_{1A} and 5-HT_{2A} receptors binding data (445) were selected (360 published and 85 yet unpublished). In the next step data set was narrowed down to arylpiperazine and 1,2,3,4-tetrahydroisoquinoline (THIQ) derivatives (389 compounds). And finally, only ligands with terminal group connected via methylene chain of different length (2–4 -CH_2- groups) to amine part were subjected to further analysis.

Table 1. Structures and quantity of the analyzed compounds



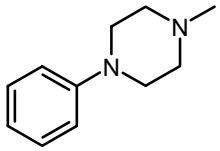
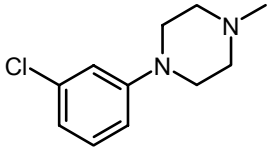
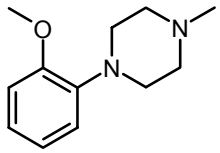
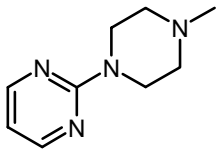
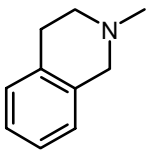
Amine	Abbr.	n = 2	n = 3	n = 4	∑
	PhP	0	38	4	42
	mCPP	4	62	8	104
	OMePhP	24	48	32	74
	PP	1	1	2	4
	THIQ	17	22	36	75
∑		46	171	82	**299**

Table 2. 5-HT_{1A} *vs* 5-HT_{2A} receptor binding constants (pK_i) for arylpiperazine and THIQ derivatives with different length of alkyl chain spacer

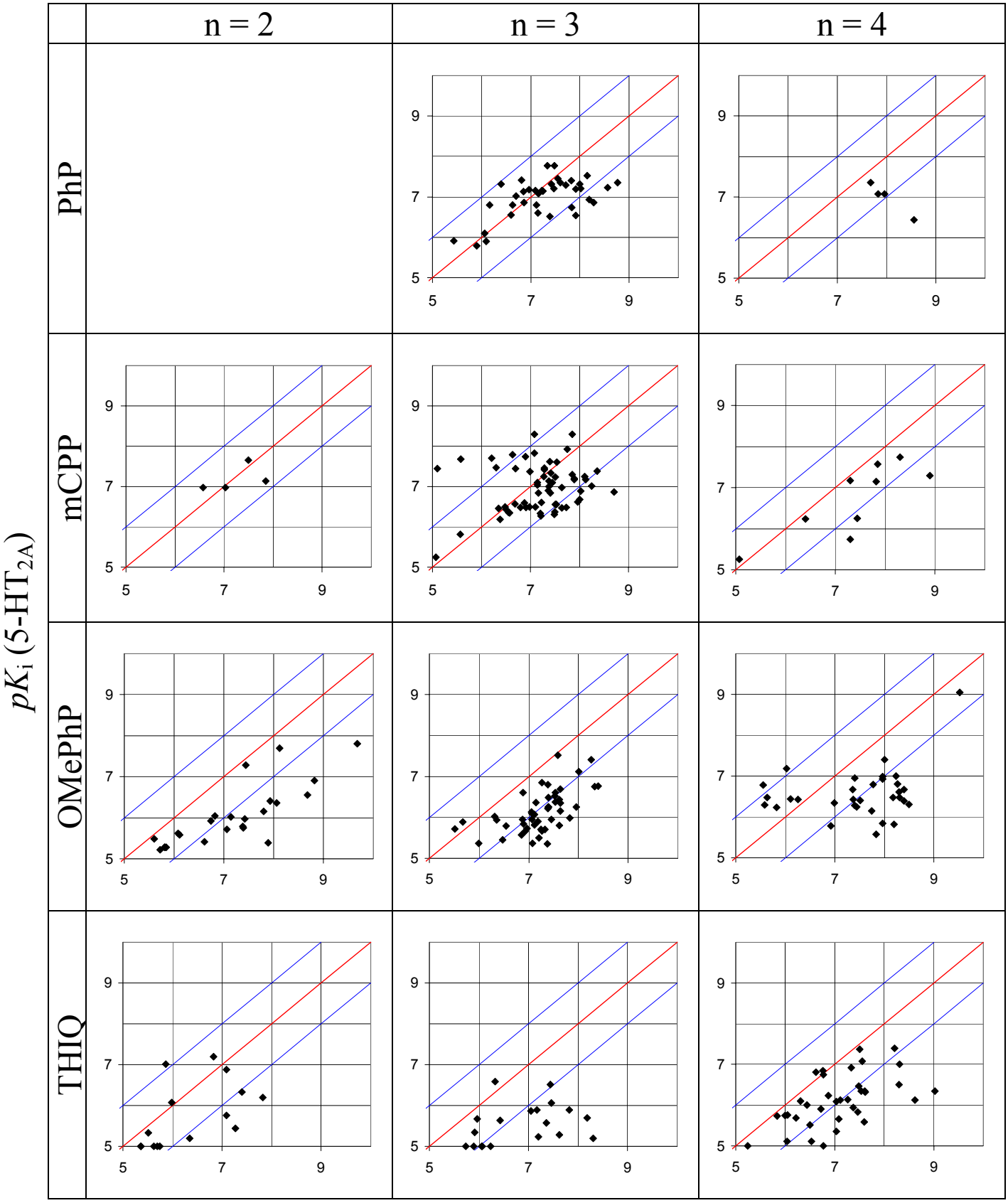
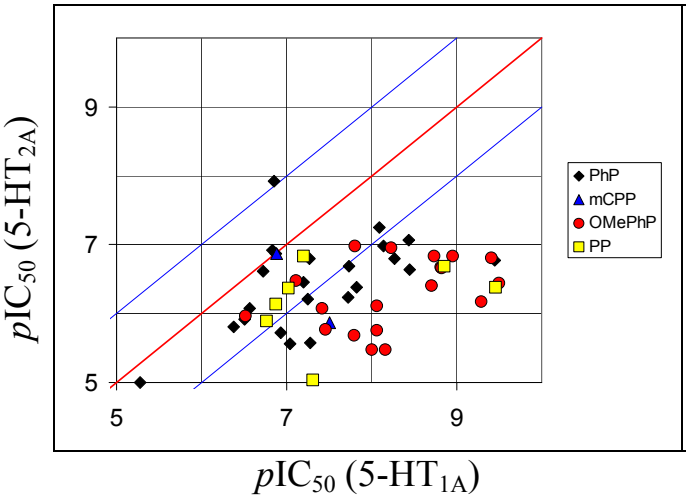
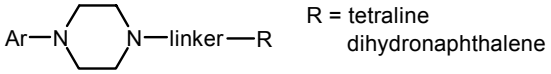


Table 3. 5-HT_{1A} *vs* 5-HT_{2A} receptor binding constants (pIC_{50}) for arylpiperazine derivatives of R. Perrone, G. Caliendo and M.H. Norman groups

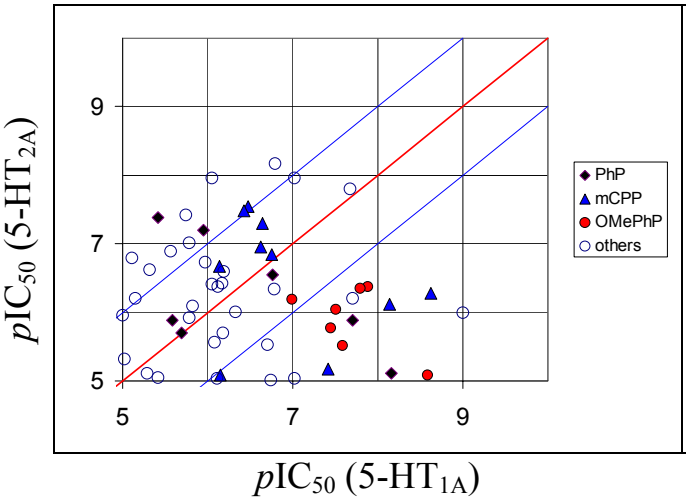
a



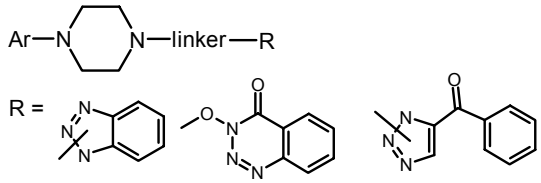
Data from publications of R. Perrone et al. (*J. Med. Chem.* **1994**, *37*, 99-104; *J. Med. Chem.* **1995**, *38*, 942-949; *J. Med. Chem.* **1996**, *39*, 3195-3202; *J. Med. Chem.* **1996**, *39*, 4928-4934) – PhP–23, mCPP–2, OMePhP–19, PP–7 derivatives.



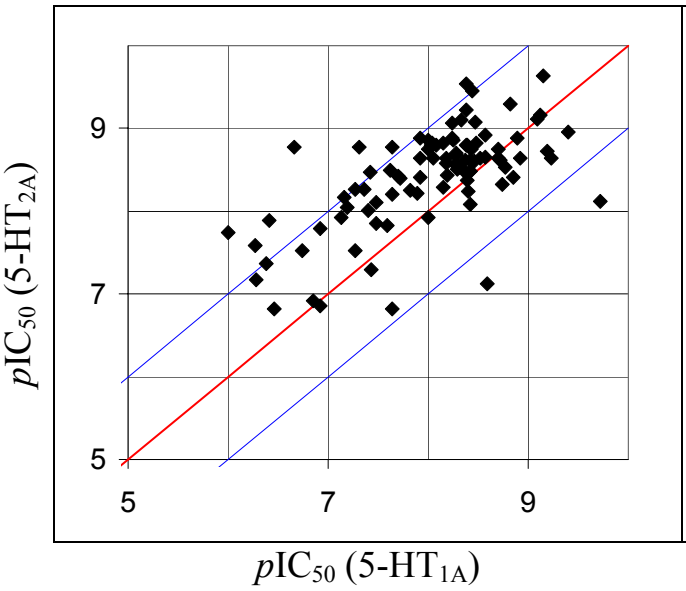
b



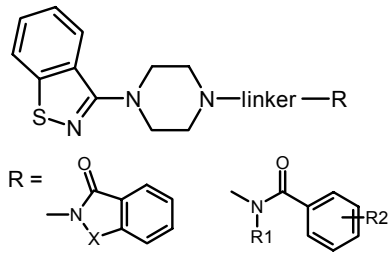
Data from pulications of G. Caliendo et al. (*Bioorg. Med. Chem.* **2000**, *8*, 533-538; *Eur. J Med. Chem.* **1996**, *31*, 207-213; *Eur. J. Med. Chem.* **1999**, *34*, 719-727) – PhP–10, mCPP–11, OMePhP–9, others–37 derivatives.



c



Data from publications of M.H. Norman et al. (*J. Med. Chem.* **1994**, *37*, 2552-2563; *J. Med. Chem.* **1996**, *39*, 149-157; *J. Med. Chem.* **1996**, *39*, 1172-1188; *J. Med. Chem.* **1996**, *39*, 4692-4703) – 94 compounds.



A majority of our compounds contained as a terminal part an amide, cyclic amide or imide moieties, benzotriazole fragments or its analogues.

Analysis of data presented in Table 2 shows that PhP and mCPP derivatives are generally nonselective 5-HT_{1A}/5-HT_{2A} ligands of different potency. In contrast, OMePhP analogues clearly prefer 5-HT_{1A} receptors. Moreover, in a series of compounds which structure differs only by an amine moiety, OMePhP derivatives are characterized by higher 5-HT_{1A} and lower 5-HT_{2A} receptor affinity than the respective PhP and mCPP analogues.

THIQ ligands also favor 5-HT_{1A} receptor binding site over 5-HT_{2A} one, however they are less potent than the corresponding OMePhP derivatives. Additionally, an introduction of substitutuents in the aromatic part of the THIQ moiety reduces 5-HT_{1A} and simultaneously slightly increases 5-HT_{2A} receptor affinity, what leads to a decrease of 5-HT_{1A}/5-HT_{2A} selectivity in comparison to unsubstituted analogues.

Further analysis of charts presented in Table 1 reveals that the length of an alkyl chain spacer has some influence on $S_{1A/2A}$ parameter. Compounds with even number of methylene groups (n = 2 and 4) are more frequent 5-HT_{1A} ligands, whereas 3-membered chain derivatives exhibit similar activity for both receptor subtypes.

The role of terminal fragment in the stabilization of ligand-receptor complex is still far from explanation. As already has been suggested,

Table 4. Phthalimide and isoindolinone derivatives with conforma-

tionally constrained linker – binding data and 5-HT_{1A}/5-HT_{2A} selectivity (M.H. Norman et al. *J. Med. Chem.* **1996**, *39*, 149-157)

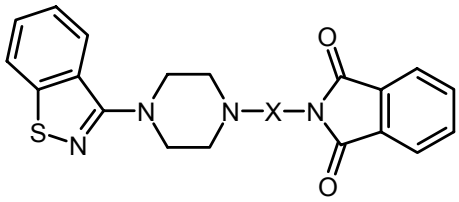
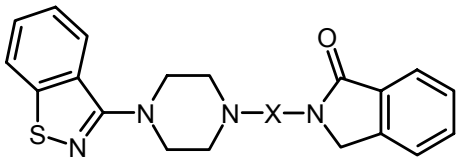
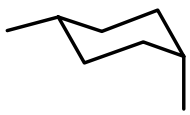
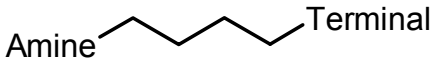
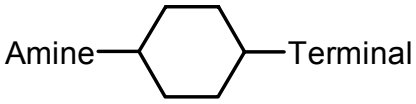
No.	X						
		IC_{50} (nM)		$S_{1A/2A}$	IC_{50} (nM)		$S_{1A/2A}$
		5-HT_{1A}	5-HT_{2A}		5-HT_{1A}	5-HT_{2A}	
		a			**b**		
1		0.19	7.6	0.03	7.0	5.1	1.37
2		420	43	9.77	1000	18	55.56
3		4.7	0.78	6.03	23	1.7	13.53
4		24	3.2	7.50	44	5.5	8.00
5		19	4.0	4.75			
6					140	120	1.17

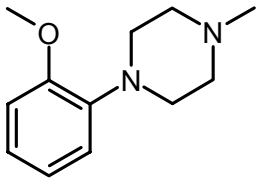
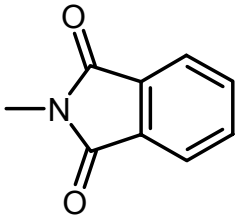
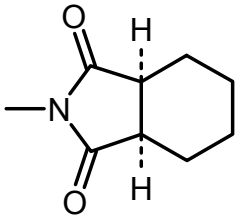
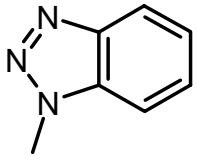
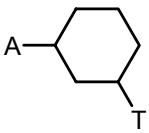
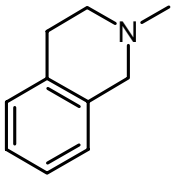
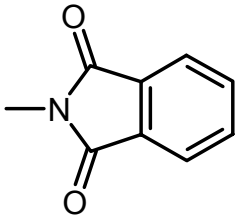
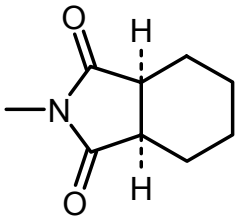
Table 5. Flexible/constrained pairs of compounds: structure, 5-HT_{1A} and 5-HT_{2A} receptor binding data and selectivity

a:



b:



No.	Amine	Linker	Terminal part	K_i (nM)		$S_{1A/2A}$
				5-HT_{1A}[a]	5-HT_{2A}	
7		**a**		0.55[b]	451	0.001
		b		8	2602	0.003
8		**a**		4	109	0.037
		b		72	1932	0.037
9a				15	1040	0.014
9b				47	300	0.157
10		**a**		355	2774	0.128
		b		34	210	0.162
11		**a**		50	886	0.056
		b		1600	40000	0.040

[a] K_i data for 5-HT_{1A} receptors from Paluchowska et al. *J. Med. Chem.* **1999**, *42*, 4952–4960

[b] K_i value according to Glennon et al. (*Eur. J. Pharmacol.* **1988**, *154*, 339–341) was 0.58 nM

it is caused by highly flexible structure of arylpiperazine type of ligands. Thus, position of this terminal part within receptor pocket is equivocal and can differ depending on its nature as well as the length of an alkyl spacer. These conclusions also resulted from CoMFA analysis conducted for the interactions of arylpiperazines with 5-HT_{1A} receptors (P. Gaillard et al. *J. Med. Chem.* **1996**, *39*, 126-134).

Comparison with an external datasets

During a survey of the literature only three large sets of arylpiperazines with 5-HT_{1A} and 5-HT_{2A} receptor binding data were found (Table 3). The similar conclusions can be drawn regarding an influence of the core amine structure on 5-HT_{1A}/5-HT_{2A} selectivity within the compounds of Perrone and Caliendo (Tab. 3 **a** and **b**). A majority of highly active and selective 5-HT_{1A} ligands belongs to OMePhP derivatives. Almost all of the compounds presented by Norman et al. (Tab. 3 **c**) are very potent but in general nonselective 5-HT_{1A}/5-HT_{2A} receptor ligands.

Constrained arylpiperazines

Due to highly flexible character of arylpiperazine structure and probable different requirements of both receptor binding sites rigid analogues are desired for more precise description of ligand receptor interactions. In Table 4 constrained phthalimide (**2a**–**5a**) and

isoindolinone (**2b**–**4b** and **6b**) derivatives extracted from the Norman's set are presented. Partially limited conformational freedom causes a decrease of affinity for 5-HT_{1A} receptor and clear preference for 5-HT_{2A} one can be observed. In the case of cyclohexyl derivative **6b**, affinities for both receptors are significantly lower than the flexible analogue **1b** but a selectivity ratio remains unchanged. Similar conclusions can be drawn from the comparison of the respective pairs (**a**, **b**) of our compounds presented in Table 5. A replacement of *n*-butyl spacer by the 1e,4e-cyclohexyl ring reduces both receptor affinities in a similar manner, thus does not influences the selectivity ratio. In the case of 1e,3e-cyclohexyl derivative (**3b**), an applied modification forces bend the conformation, and interestingly the affinity for 5-HT_{2A} receptor increases by three times in comparison to the flexible *n*-propyl chain analogue **3a**.

These results may suggest different conformational preferences of both receptors during interactions with the arylpiperazine type of ligands.