NEW DERIVATIVES OF ARYLSULFONYLPIPERIDINES – THE INFLUENCE OF STRUCTURAL MODIFICATIONS ON 5-HT$_7$ AND 5-HT$_{1A}$ RECEPTOR AFFINITY

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Introduction

In recent years among 5-HT receptors much attention has been focused on the newest member of serotoninergic receptors family – 5-HT$_7$. The numerous papers that have been published successively provided evidences that 5-HT$_7$ receptor ligands can find potential applications in therapy of various mental disorders i.e. anxiety and depression.[1]

Inspired by appearing reports discovering new potent and selective 5-HT$_7$ receptor ligands[2] we designed and synthesized a new series of arylsulfonamide derivatives. The structural modifications included replacement of amine fragment, changes of aromatic substituent in arylsulfonylpiperidine moiety and length of alkyl chain.

Synthesis

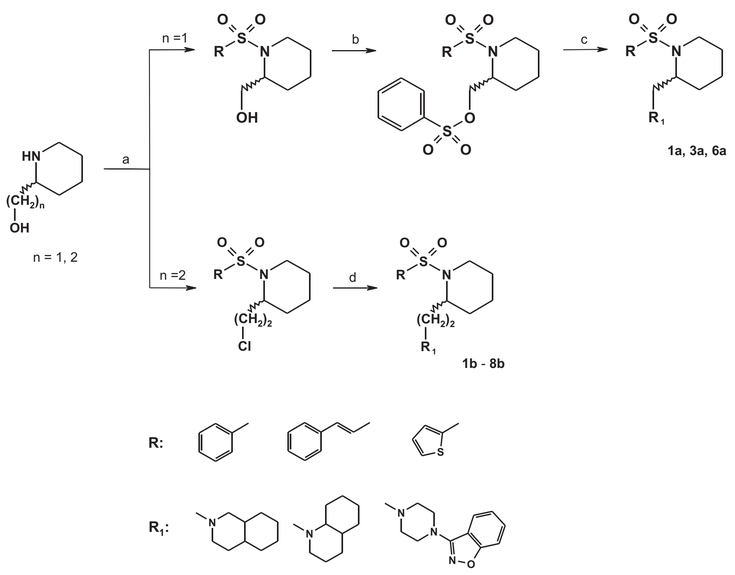
The synthesis of the target compounds **1** - **8** are illustrated in Scheme 1. Compounds **1a**, **3a** and **6a** were prepared in a three-step sequence. The synthesis started off by coupling piperidine-2-methanol with equimolar amount of appropriate derivative of sulfonyl chloride. Afterwards, without isolating of received alcohol, to the reaction mixture 1 equiv. of benzenesulfonyl chloride was added. The final compounds **1a**, **3a** and **6a** were obtained as racemates by reaction of received esters of benzenesulfonic acid with appropriate secondary amines in the presence of sodium iodide.

Synthesis of the derivatives **1b** - **8b** started with reaction of piperidine-2-ethanol with 2 equiv. of appropriate derivative of sulfonyl chloride to give derivatives of 2-(2-chloro-ethyl)piperidine.[3] Displacement of the chloride with appropriate secondary amines using sodium iodide to catalyze the reaction gave the racemic sulfonamides **1b** - **8b**.

Decahydroquinoline and decahydroisoquinoline are commercially available; 3-piperazin-1-yl-benzo[d]isoxazole was synthesized according to the published procedures.[4,5]

The structures of new derivatives **1** - **8** were confirmed by ^{1}H NMR spectra and for pharmacological experiments free bases were converted into hydrochloride or fumarate salts which molecular formulae and molecular weights were established based on elemental analysis.

Scheme 1. Methods of new compounds **1** - **8** synthesis.

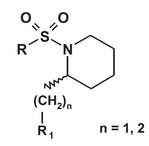


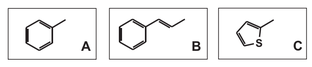
Reagents and conditions: (a) RSO_2Cl, diisopropylethylamine, $CHCl_3$, r.t.; (b) $PhSO_2Cl$, diisopropylethylamine, $CHCl_3$, reflux; (c) amine, NaI, K_2CO_3, DMF, reflux; (d) amine, NaI, K_2CO_3, CH_3CN, reflux.

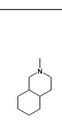
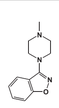
Pharmacology

The new compounds **1** - **8** were tested in competition binding experiments for serotonin 5-HT$_{1A}$ and 5-HT$_7$ receptors. The affinity data are collected in Table 1.

Table 1. Structure and affinity data on serotonin (5-HT$_{1A}$ and 5-HT$_7$) receptors of investigated compounds **1** - **8**. Selectivity has been defined by equation: $S_{1A/7}$ = 5-HT$_{1A}$/5-HT$_7$.



R:  A B C

No	R	R^1	n	K_i (nM) 5-HT$_7$	K_i (nM) 5-HT$_{1A}$	$S_{1A/7}$
1a	A		1	1225	NT	–
1b			2	44	2966	67
2b	B		2	126	NT	–
3a	C		1	10000	NT	–
3b			2	95	NT	–
4b	A		2	407	10000	25
5b	B		2	868	NT	–
6a	A		1	143	NT	–
6b			2	11	105	9.5
7b	B		2	4.5	43	9.5
8b	C		2	4.8	66	14

NT – not tested

New compounds vs. 5-HT$_7$ pharmacophore models

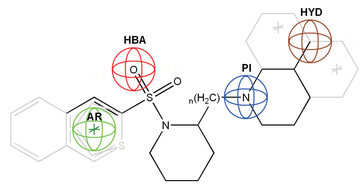
Recently, in our department two receptor-based pharmacophore models describing features necessary for the affinity and selectivity of 5-HT$_7$ receptor antagonists were generated.[6] On the basis of these models, comparison between 5-HT$_7$ pharmacophore and the global energy minimum conformations (antiperiplanar geometry of ethylene linker) of new compounds **1** - **8** was performed.

For compounds **1** - **5**, distances between four specific interaction points (AR, PI, HBA and HYD), and in the case of **6** - **8** between five specific features (AR1, AR2, PI, HBA1 and HBA2) were compared with optimal distances in the "selectivity" and "affinity" hypothesis,[6] respectively (Table 2 and 3).

Figures 1 and 2 illustrate ranges of optimal distances in both models (blue area) and individual measurement of distances for the analyzed compounds.

For each measurement that was out of range of the "blue area", a coefficient of variation (*CV*) was calculated (Table 2 and 3). Moreover, to describe the relationship between affinity for 5-HT$_7$ receptors and divergence towards pharmacophoric model, a plot of pK_i and total sum of *CV* was prepared (Figure 3).

Table 2. Distances between pharmacophoric features in the "selectivity" hypothesis.[6]



Optimal distances between pharmacophores x_A - x_B	Distances d [Å] in compounds **1** - **5** and their divergence (*CV*)* towards pharmacophoric model						
	1a	**1b**	**2b**	**3a**	**3b**	**4b**	**5b**
AR1–PI	6.3	7.1	7.7	6.4	7.4	7.7	8.8
6.9 - 7.7	(*0.08*)			(*0.07*)			(*0.15*)
HYD–PI	4.4	4.1	4.4	4.4	4.4	3.4	3.4
4.3 - 7.0		(*0.03*)				(*0.16*)	(*0.16*)
HBA1–PI	3.0	3.9	3.8	3.4	3.7	4.0	5.1
3.7 - 5.1	(*0.16*)			(*0.07*)			
AR1–HYD	9.1	11.1	10.8	10.0	10.8	10.9	12.1
11.1 - 13.2	(*0.08*)		(*0.02*)	(*0.09*)	(*0.02*)	(*0.02*)	
AR1–HBA1	3.8	3.8	3.7	3.7	3.7	3.8	3.8
3.7 - 3.8							
HBA1–HYD	6.2	9.4	8.0	6.9	8.2	7.7	8.7
8.3 - 10.1	(*0.23*)		(*0.03*)	(*0.15*)	(*0.01*)	(*0.06*)	
	Total *CV***						
	(*0.55*)	(*0.03*)	(*0.05*)	(*0.38*)	(*0.03*)	(*0.24*)	(*0.31*)

Abbreviations: (HBA) H-Bond accepting feature, (HYD) hydrophobic domain, (PI) positively ionizable feature.
* Coefficient of variation *CV* = 0 when distance is in range <x_A, x_B>. In the other case error were calculated according to equations: *CV* =2(x_A–d)/(x_A+x_B) for d (0, x_A) and *CV* = 2(d–x_A)/(x_A+x_B) for d (x_B, +). ** Calculated as sum of individual *CV*.

Figure 1. Individual measurement of distances for compounds **1** - **5** and ranges of optimal distances in "selectivity" pharmacophoric model (blue area).

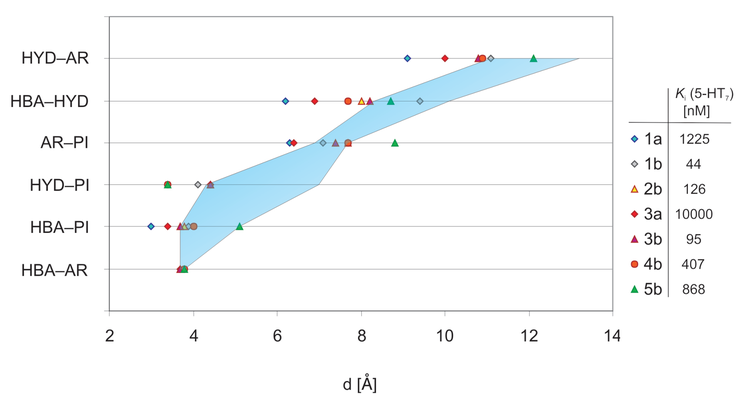
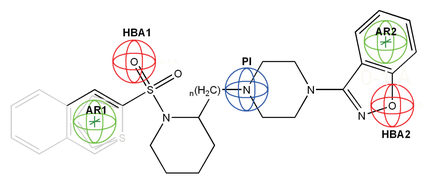


Table 3. Distances between pharmacophoric features in the "affinity" hypothesis.[6]



Optimal distances between pharmacophores x_A - x_B	Distances d [Å] in compounds **6** - **8** and their divergence (*CV*)* towards pharmacophoric model			
	6a	**6b**	**7b**	**8b**
AR1–PI	7.6	8.2	7.4	7.2
6.9 - 9.4				
AR2–PI	6.5	6.6	6.7	6.5
4.3 - 7.8				
HBA1–PI	4.3	4.7	4.5	4.5
3.7 - 5.1				
HBA2–PI	6.5	6.2	6.2	6.2
5.1 - 6.9				
AR2–AR1	14.1	12.2	12.5	12.2
11.1 - 14.4				
HBA1 - AR1	3.8	3.7	3.8	3.7
3.7-3.8				
HBA2–AR1	13.3	13.3	13.1	12.9
14.2	(*0.06*)	(*0.06*)	(*0.08*)	(*0.09*)
HBA1-AR2	10.5	9.4	9.0	8.9
8.3 - 10.1	(0.04)			
HBA2–AR2	2.7	2.7	2.7	2.7
2.8 - 3.7	(*0.03*)	(*0.03*)	(*0.03*)	(*0.03*)
	Total *CV***			
	(*0.13*)	(*0.09*)	(*0.11*)	(*0.12*)

Abbreviations: (HBA) H-Bond accepting feature, (HYD) hydrophobic domain, (PI) positively ionizable feature.
* Coefficient of variation *CV* = 0 when distance is in range <x_A, x_B>. In the other case error were calculated according to equations: *CV* =2(x_A–d)/(x_A+x_B) for x_i (0, x_A) and *CV* = 2(d–x_A)/(x_A+x_B) for x_i (x_B, +). ** Calculated as sum of individual *CV*.

Figure 2. Individual measurement of distances for compounds **6** - **8** and ranges of optimal distances in "affinity" pharmacophoric model (blue area).

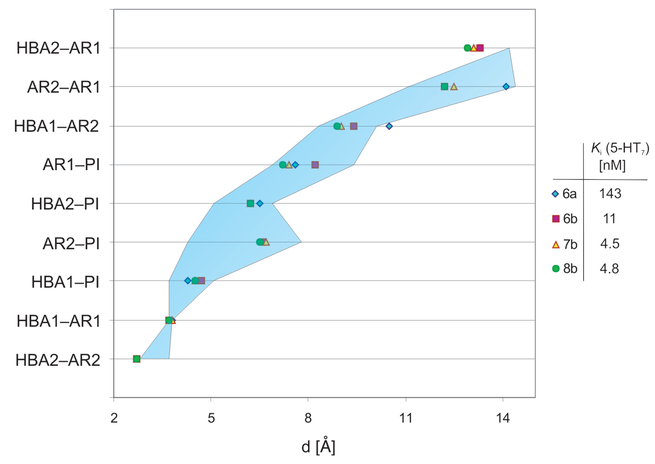
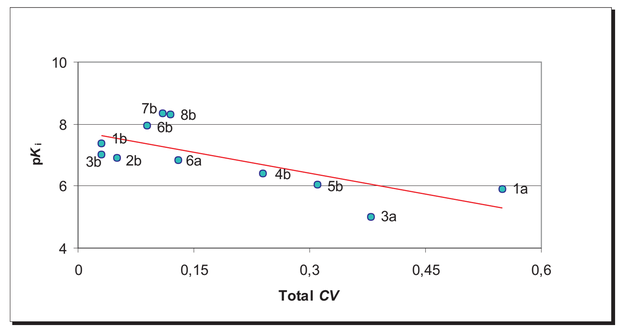


Figure 3. Relationship between affinity for 5-HT$_7$ receptors (pK_i) and divergence towards pharmacophoric model (Total *CV*).



Results and Discussion

➪ Ligand **1b** with decahydroisoquinoyl substituent showed the highest selectivity ($S_{1A/7}$ = 67) and about 10-fold higher affinity for 5-HT$_7$ receptors than its decahydroquinoline analogue **4b**.

➪ Interestingly, the examination of the binding data of 5-HT$_7$ receptors revealed that the decahydroisoquinoyl substituent (compounds **1b** and **2b**) was more preferable than decahydroquinoyl (compounds **4b** and **5b**). It suggests that the binding pocket of this receptor is very sensitive on the geometry of hydrophobic fragment at the N-terminal part of the molecule.

➪ Introduction of 3-piperazin-1-ylbenzo[d]isoxazole moiety instead of decahydroisoquinoline increased affinity for the both examined receptors but diminished $S_{1A/7}$ selectivity.

➪ In contrast to derivatives with completely hydrogenated quinoline moieties (**1b** - **5b**), for the series of compounds **6b** - **8b** the variation in the aryl part at the sulfonyl group seldom influenced the 5-HT$_7$ receptor affinity (K_i = 4.5 - 11 nM).

➪ Compounds with one methylene group spacer **1a** and **3a** were generally less active at 5-HT$_7$ receptor than their longer counterparts **1b** and **3b**, what emphasize the role of distance between pharmacophoric groups. Only compounds with 3-piperazin-1-ylbenzo[d]isoxazole moiety **6a** showed moderate affinity for this receptor binding sites.

➪ A linear correlation between total sum of *CV* and pK_i (Figure 3) was found. The results obtained for this plot suggest that the Total *CV* of approximately 0.15 can be regarded as a limit for a good affinity (<150 nM) to 5-HT$_7$ receptor.

Conclusion

Summing up, the new derivatives of arylsulfonylpiperidines were synthesized, next, their 5-HT$_7$ receptor affinity was measured, and the obtained coherent results were analyzed on the basis of the recently published receptor based pharmacophore models.

At first, we have succeeded in getting very active ligands either selective and nonselective to 5-HT$_7$ receptor subtype. Structures of these compounds deliver a lot of useful information in recognizing receptor binding sites geometry. Next, we showed that the affinity of the investigated compounds depends on the length of the methylene spacer, the kind of amine substituent and the type of aromatic system connected by a sulfonamide bond with the piperidine moiety.

The comparison of mutual spatial arrangement of particular structural fragments of compounds **1** - **8** with pharmacophoric hypothesis confirms the usability of these models in preliminary testing of newly designed compounds prior to their synthesis.

The present study provided initial data for further investigations concerning 5-HT$_7$ receptor agents. In order to study structure-intrinsic activity relationships, in the next step, functional profile of the analyzed compounds will be established.

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References

[1] Wesołowska A. et al..; *Neuropharmacology* **2006**, *51*, 578–86. [2] Raubo P. et al.; *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1255–1258. [3] Lovell, P. J. et al.; *J. Med. Chem.* **2000**, *43*, 342–345. [4] Friary, R. et al.; *J. Heterocyclic Chem.* **1979**, *16*, 1277–1278. [5] Yevich, J. P. et al.; *J. Med. Chem.* **1986**, *29*, 359–369. [6] Kołaczkowski M. et al.; *J. Med. Chem.* **2006**, *49*, 6732–6741.