Non-basic 5-HT$_6$ Receptor Ligands

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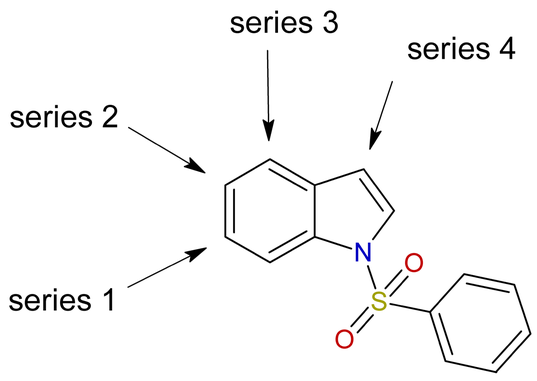
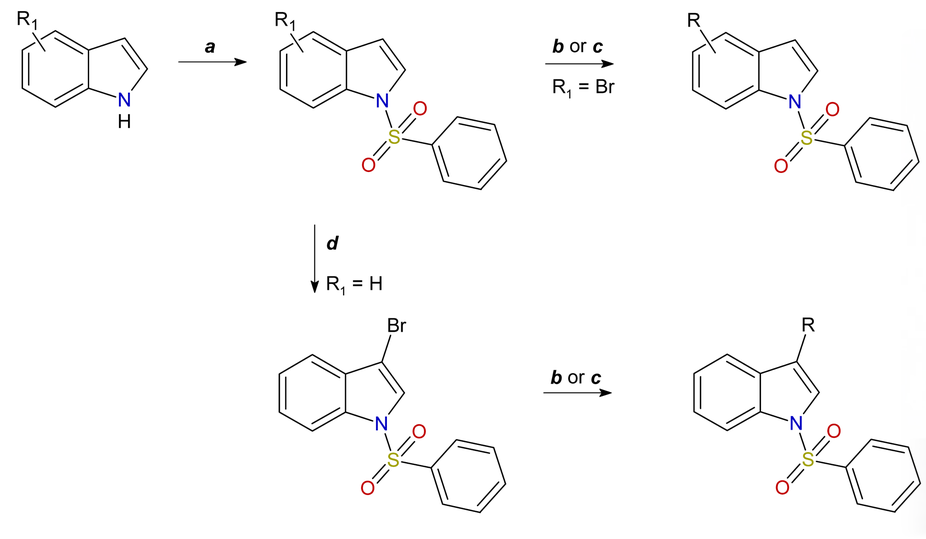
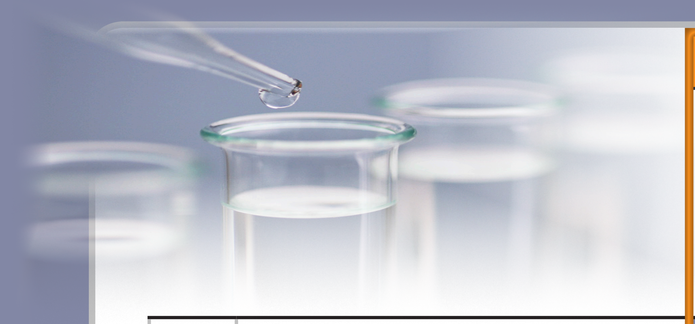
Recently, a progress has been made in finding new non-basic ligands of serotonin receptors – mainly 5-HT$_6$ subtype. Until recently it was believed that only compounds with a basic nitrogen atom can act as aminergic receptor ligands. The discovery of the non-basic ligands has changed the longstanding views in medicinal chemistry. This phenomenon has been recently studied and some hypotheses were formulated,[1,2] but the mechanism of non-basic ligands-receptor interaction is still unclear.

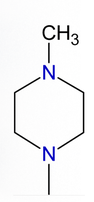
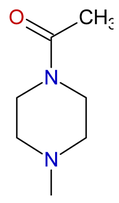
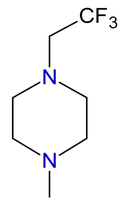
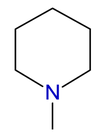
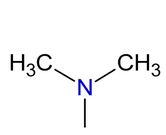
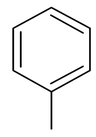
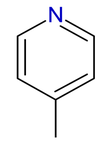
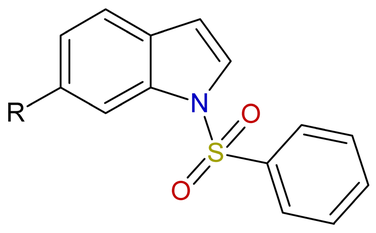
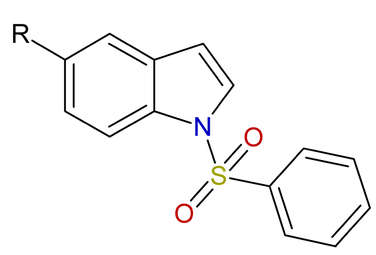
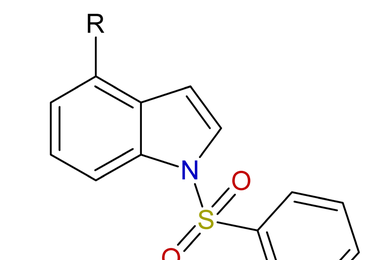
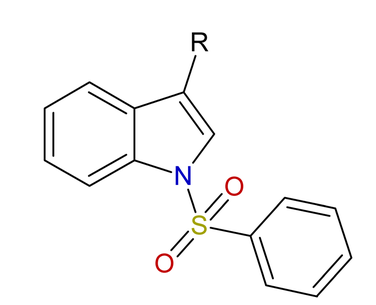


As a part of our study on 5-HT$_6$R the consistent four series of indole derivatives has been designed in an attempt to describe the interactions of non-basic ligands in the binding pocket. Following the examples of literature ligands with 3, 4, 5 or 6-substituted 1-(phenylsulfonyl)-1H-indole with N-methylpiperazine fragment (first column in below table), their counterparts with reduced and/or removed basicity were synthesized.



a: $PhSO_2Cl$, NaH; ***b***: amine, Cs_2CO_3, XPhOS, $Pd(OAc)_2$; ***c***: $ArB(OH)_2$, K_2CO_3, $Pd[(C_6H_5)_3P]_4$; ***d***: Br_2



		Reference basic compounds	R							
										
		7.4	**0.6**	**3.6**	**4.5**	**4.2**	**-7.5**	**5.0**	**pK$_a$**	
series 1		247	>10 000	> 10 000	> 10 000	> 10 000	> 10 000	> 10 000		5-HT$_{1A}$
		2809	>10 000	> 10 000	> 10 000	> 10 000	1039	1050		5-HT$_{2A}$
		9	**97**	**1201**	**403**	**211**	**178**	**38**	K_i [nM]	**5-HT$_6$**
		1818	ND	> 10 000	> 10 000	> 10 000	> 10 000	> 10 000		5-HT$_7$
		241	6993	> 10 000	> 10 000	> 10 000	9587	> 10 000		D$_2$
		7.3	**0.8**	**3.9**	**5.4**	**5.0**	**-6.8**	**4.9**	**pK$_a$**	
series 2		> 10 000	> 10 000	> 10 000	> 10 000	> 10 000	> 10 000	> 10 000		5-HT$_{1A}$
		4197	> 10 000	> 10 000	> 10 000	> 10 000	> 10 000	>10000		5-HT$_{2A}$
		27	**4853**	**5252**	**360**	**82**	**558**	**409**	K_i [nM]	**5-HT$_6$**
		> 10 000	> 10 000	> 10 000	> 10 000	> 10 000	> 10 000	> 10 000		5-HT$_7$
		802	> 10 000	> 10 000	7767	> 10 000	> 10 000	> 10 000		D$_2$
		7.4	**0.9**	**3.4**	**1.9**	**3.3**	**-7.6**	**4.5**	**pK$_a$**	
series 3		164	>10 000	> 10 000	> 10 000	> 10 000	> 10 000	> 10 000		5-HT$_{1A}$
		41	>10 000	> 10 000	> 10 000	> 10 000	> 10 000	> 10 000		5-HT$_{2A}$
		1	**714**	**1743**	**128**	**65**	**162**	**1508**	K_i [nM]	**5-HT$_6$**
		5462	ND	8920	7153	> 10 000	> 10 000	> 10 000		5-HT$_7$
		353	>10 000	> 10 000	8472	> 10 000	5611	> 10 000		D$_2$
		8.2	**-0.4**	**3.6**	**-0.4**	**-0.3**	**-7.3**	**4.9**	**pK$_a$**	
series 4		1404	ND	>10 000	ND	ND	>10 000	>10 000		5-HT$_{1A}$
		657	ND	>10 000	ND	ND	>10 000	7676		5-HT$_{2A}$
		4	**ND**	**2029**	**ND**	**ND**	**146**	**124**	K_i [nM]	**5-HT$_6$**
		> 10 000	ND	ND	ND	ND	ND	ND		5-HT$_7$
		532	ND	>10 000	ND	ND	5650	8491		D$_2$

ND – Not Determined

The aqueuos pKa were calculated using the Jaguar program of the Schrödinger suite.

Membrane preparation and general assay procedures for 5-HT$_{1A}$ [3], 5-HT$_{2A}$ [3], 5-HT$_7$ [4,5], 5-HT$_6$ [6], and D$_2$ [7] receptors were performed exactly as previously described.

For binding experiments 7–9 sample concentrations were used to determine inhibition constant (K_i) on the base of Cheng-Prusoff equation: $K_i = IC_{50} / (1 + L/K_D)$. Values are means of three experiments run in triplicate, SEM ≤ 16%.

[1] Ivachtchenko A. V. et al. *J. Med. Chem.* **2011**, *54*, 8161–8173.
[2] Van Loevezijn A. at al. *J. Med. Chem.* **2011**, *54*, 7030–7054.
[3] Bojarski A. J. et al. *Pharmazie*. **1993**, *48*(4), 289–94.
[4] Bojarski A. J. et al. *Bioorg. Med. Chem. Lett.* **2004**, *14*(23), 5863–6.
[5] Paluchowska M. H. et al. *Bioorg. Med. Chem.* **2007**, *15*(22), 7116–25.
[6] Duszyńska B. et al. poster, 25–29.05.2008 Krasiczyn, *Book of Abstract*, 23–24.
[7] Bojarski A. J. et al. *Bioorg. Med. Chem.* **2005**, *13*(6), 2293–303.

All the reference structures with a basic nitrogen atom as well as their synthesized non-basic counterparts will be docked to the 5-HT$_6$R homology models in order to determine binding modes for both classes of ligands. Data obtained in docking experiment will be used to describe the interactions of non-basic ligands in the binding pocket and to develop a pharmacophore model.

ACKNOWLEDGMENTS

NATIONAL SCIENCE CENTRE POLAND

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