BIOISOSTERISM, THE USE IN DESIGNING 5-HT$_6$ RECEPTOR LIGANDS

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1. Introduction:

Among the serotonin receptor family, the 5-HT$_6$ subtype was discovered as one of the latest. It's abundant number in limbic areas [1] and the fact that many antipsychotic drugs acts as antagonists, makes it a promising target for future psychotropic drugs. Up to date several thousands of ligands have been synthesized and their high structural diversity makes the binding mode difficult to define. By performing bioisostere analysis we might be able to get better insight into the structure of ligand-receptor complexes.

2. Bioisosterism:

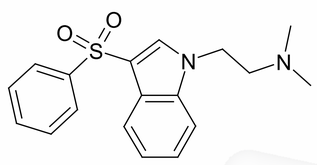
Bioisosterism is one of the main strategy in Medicinal Chemistry for designing new biologically active compounds. It is based on pursuing structural modification on the lead compound, which should maintain it's electrotopologic and/or stereospecific properties. These modifications may increase pharmacological activity, improve selectivity, reduce side effects or optimize pharmacokinetic properties [3,4].

3. *In silico* studies:

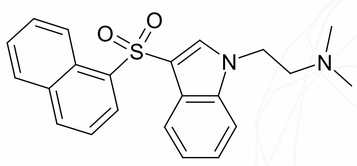
From several thousands of selective 5HT$_6$ ligands a group of 10 compounds was selected for initial study. Using specialized software (PipelinePilot - Accelrys, vBrood - OpenEye) thousands of molecular modifications were generated. Output compounds were selected based on virtual screening cascade protocol which screens output compounds by 2D and 3D-pharmacophores, physicochemical properties, ADME/Tox properties and docking to receptor model [5]. Final selection of compounds was based on visual inspection taking into account synthetic accessibility (verified with *Beilstein-Reaxys* database) and 3D Pharmacophore mapping performed in *Discovery Studio* (*Accelrys*) using *Ligand Pharmacophore Mapping* protocol. This protocol mapped conformations of selected compounds which were restricted within a 20 kcal/mol energy threshold to the lowest energy conformation, to a previously reported five-point pharmocophore [6]. FitValue of chosen compounds is presented in tab. 1.

Table. 1 FitValue of designed molecules to 5-HT$_6$ pharmacophore model compared with FitValue of parent compounds.

Structure ID	5-HT$_6$ Pharmacophore model FitValue
Compound 1 [7]	0.795
Compound 2 [7]	0.949
PKS-21	0.983
PKS-25	0.988
PKS-37	0.961
PKS-38	0.903
PKS-44	0.965
PKS-45	0.973
PKS-46	0.906
PKS-98	0.900



Compound 1



Compound 2

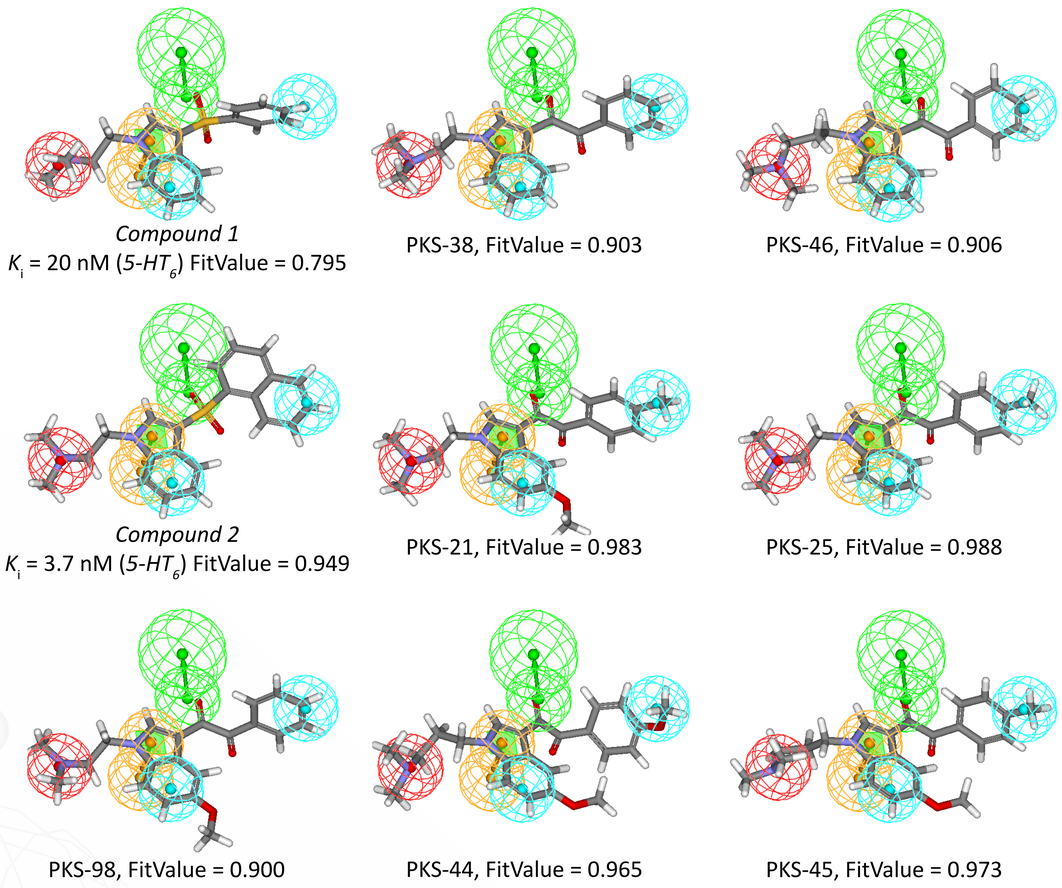


Fig. 1. Comparison of active compounds with those designed in bioisostere software mapped to pharmacophore model.

4. Chemistry:

A series of eight compounds was designed as a preliminary study. Bioisosteric replacement assumed substitution of sulfonyl with dicarbonyl group. Synthesis was planned with the use of *Beilstien-Reaxys* database and included three steps. (Fig. 2):

1) reaction of indole with oxalyl chloride
2) Friedl-Crafts arylation of acid chloride
3) substitution of indole nitrogen with appropriate alkil chloride

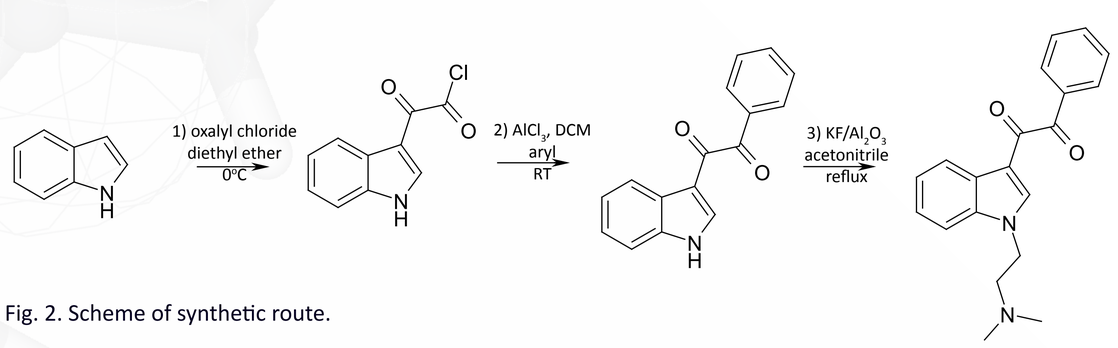


Fig. 2. Scheme of synthetic route.

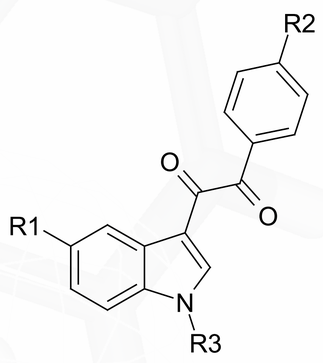
5. Biological activity:

Affinity towards 5-HT$_6$ receptor was evaluated using *in vitro* competition experiment with the use of [^{3}H]-LSD and HEK239 cell line with a stable expressiion of 5-HT$_6$.
K_i values are presented in tab. 2.

Table 2. Structures of compounds from designed series with their K_i values.

Structure ID	R1	R2	R3	*5-HT$_6$* K_i [nM]	*5-HT$_7$* K_i [nM]
PKS-21	OMe	Me	$CH_2CH_2N(CH_3)_2$	431	19480
PKS-25	H	Me	$CH_2CH_2N(CH_3)_2$	1170	ND
PKS-37	OMe	OMe	$CH_2CH_2N(CH_3)_2$	2583	26820
PKS-38	H	H	$CH_2CH_2N(CH_3)_2$	656	20170
PKS-44	OMe	OMe	$CH_2CH_2CH_2N(CH_3)_2$	4274	20470
PKS-45	OMe	Me	$CH_2CH_2CH_2N(CH_3)_2$	2331	30670
PKS-46	H	H	$CH_2CH_2CH_2N(CH_3)_2$	7361	12920
PKS-98	OMe	H	$CH_2CH_2N(CH_3)_2$	608	4259

ND - not determined



6. Conclusions:

A series of eight compounds was designed and synthesized. They showed high FitValue to pharmacophore model which suggested a potential high affinity towards 5-HT$_6$ receptor. Surprisingly their affinity was from 4 - 100 fold lower than their parent molecules. Changing tetrahedral sulfonyl group to planar dicarbonyl group seems to be not accepted by the receptor. This might imply that binding to 5-HT$_6$ receptor requires a tetrahedral (more flexible) linker between molecule core and aromatic ring. Despite having low affinity for 5-HT$_6$ receptor, synthesized compounds showed high selectivity between 5-HT$_6$ and 5-HT$_7$ receptors.

7. References:

[1] Sleight, A. J.; Boess, F. G.; Bos, M.; Bourson, A. Annals of the New York Academy of Sciences 1998, 861, 91-96.
[2] Hamon, M.; Doucet, E.; Lefèvre, K.; Miquel, M.-C.; Lanfumey, L.; Insausti, R.; Frechilla, D.; Del Rio, J.; Vergé, D. Neuropsychopharmacology 1999, 21, S68-S76.
[3] Lima, L. M.; Barreiro, E. J. Current medicinal chemistry 2005, 12, 23-49.
[4] Kier, L. B.; Hall, L. H. Chemistry & biodiversity 2004, 1, 138-51.
[5] Kurczab, R.; Nowak, M.; Chilmonczyk, Z.; Sylte, I.; Bojarski, A . J. Bioorganic & medicinal chemistry letters 2010, 20, 2465-8.
[6] Kim, H.-J.; Doddareddy, M. R.; Choo, H.; Cho, Y. S.; No, K. T.; Park, W.-K.; Pae, A. N. Journal of chemical information and modeling 2008, 48, 197-206.
[7] Bernotas, R.; Lenicek, S.; Antane, S.; Zhang, G. M.; Smith, D.; Coupet, J.; Harrison, B.; Schechter, L. E. Bioorganic & medicinal chemistry letters 2004, 14, 5499-502.

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