Lessons learned from analysis of bioisosteric substitution in ligands of a serotonin receptor family

Dawid Warszycki, Jakub Staroń, Rafał Kafel, Andrzej J. Bojarski

Institute of Pharmacology, Polish Academy of Sciences, 12 Smetna Street, 31-343 Kraków, Poland

e-mail:warszyc@if-pan.krakow.pl

A bioisosteric replacement transforms an active compound by exchanging a group of atoms with broadly similar groups (in terms of physicochemical properties). Implementations of this technique are aimed to achieve an increase the affinity, improvement of the pharmacokinetic properties or exploration of new, unknown scaffolds. One of the most spectacular examples of bioisosteric replacement application is the discovery of pindolol (a non-selective beta blocker), by replacing naphthalene system of propranolol, with indole moiety.
For compounds with determined affinity for any serotonin receptor stored in the ChEMBL database[1] (version 16 May 2013) all possible bioisosteres were generated in Pipeline Pilot[2]. Analysis of this collection, consisting of more than 1 million structures, showed that in average 31% of known ligands of a particular target are mutual bioisosteres. Here we present further data exploration revealing e.g. the most frequent and the most efficient replacements in modulating ligands activity for different subtypes of serotonin receptors with special emphasis on 5-HT_6 receptor ligands.

The analysis of the chemical space of ligands of the serotonin receptors showed, that there are many cases, where the given ligand was identified as bioisostere of compound active towards different member of 5-HTR family (Table 1). The number of such cases allows making the assumption, that the bioisosteric replacement may be a viable method of discovery of novel, promising ligands for serotonin receptors. This statement is also supported by a large number (averagely 30% of the population) of "self-bioisosteres" — compounds being bioisosteres active towards the same receptor. Such large set of self-bioisosteres is caused by extensive Structure-Activity Relationship (SAR) studies, exploring significant space of substitutions, however, the trend to replace terminal and rather simple groups makes the full potential of the bioisosteric substitution yet to be revealed.

For the self-bioisosteres the most frequent substitution types is halogen replacing, ring modification and substitution (Table 1.).

As regards analysis of bioisostere database for 5-HT_6R ligands (Figure 1.) activity is improved when 2-pyrimidine rings are substituted by other aromatic systems, especially phenyl (Table 2.). Another undesired molecular fragment is nitrile group, which can be substituted by any halogen with high possibility of higher affinity. In addition, after the introduction of sulfonamide instead amide usually caused an increase in affinity (Table 3.).

Modification of 5-HT_6R ligands structure may lead to novel compounds acting on a different member of serotonin receptor family. Statistical analysis of bioisosteres between developed for different receptor types proved that substitution of fluorine by chlorine can increase activity for 5-HT_{1A}R, 5-HT_{1B}R and 5-HT_{1D}R. On the other hand, ring modifications as it linearization or its expanding decrease K_i for 5-HT_{1A}R, 5-HT_{1B}R, 5-HT_{1D}R, 5-HT_{1F}R, 5-HT_{2A}R, 5-HT_{2C}R and 5-HT_{5A}R as well as 5-HT_{2B}R and 5-HT_{2C}R, respectively.

Table 1. Abundance of bioisosteric replacements types for each class of self-bioisosteres.

Receptor	Ligands	Bioisteres	Fraction of self-bioisosteres	Replacement class						Total
				Ring biois	Amide	Carbonyl	Halogen	Hydroxyl	Ring mod	
5-HT_{1A}	6709	293477	0.306	362	142	108	692	14	735	2053
5-HT_{1B}	1145	50084	0.276	66	44	48	82	2	74	316
5-HT_{1D}	1319	59318	0.287	68	64	46	90	2	108	378
5-HT_{1E}	132	5905	0.197	-	-	-	16	-	10	26
5-HT_{1F}	125	5868	0.488	20	14	-	6	2	19	61
5-HT_{2A}	3864	167910	0.338	114	18	16	804	2	352	1306
5-HT_{2B}	1017	44248	0.335	34	8	10	214	2	73	341
5-HT_{2C}	3019	126863	0.305	56	30	26	596	2	211	921
5-HT_4	532	36453	0.244	8	24	2	58	-	38	130
5-HT_{5A}	271	8453	0.144	2	2	2	26	-	7	39
5-HT_6	4806	165675	0.454	278	26	142	1054	2	678	2180
5-HT_7	3019	64212	0.242	52	12	24	154	4	101	347

Table 2. Affinity of compounds acting on 5-HT_6R depending on the presence 2-pyridine or phenyl

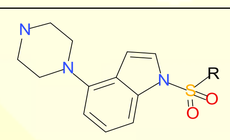
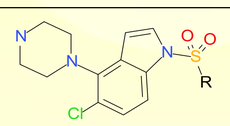
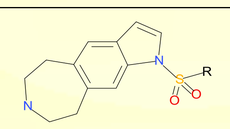
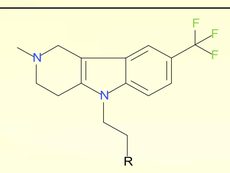
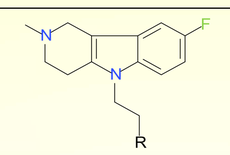
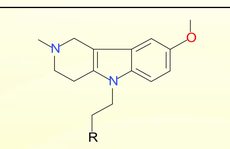
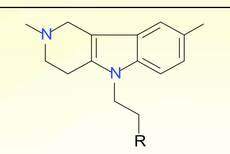
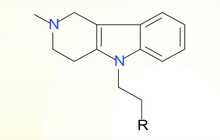
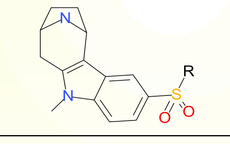
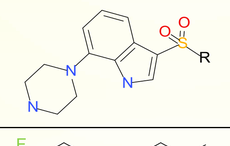
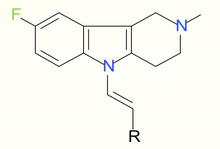
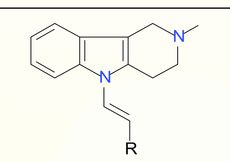
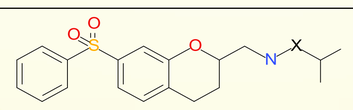
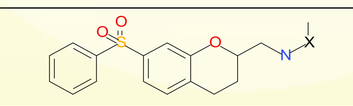
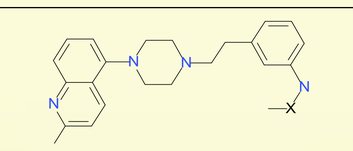
Compound	Affinity	
	R=2-pyridine	R= Ph
	Log K_i=9.00	K_i=1nM
	Log K_i=9.30	Log K_i=9.00
	K_i=100nM	K_i=1.58nM
	IC_{50}=1590nM	IC_{50}=974nM
	IC_{50}=2980nM	IC_{50}=692nM
	IC_{50}=8360nM	IC_{50}=1057nM
	IC_{50}=860nM	K_i=2nM
	IC_{50}=15750nM	K_i=100nM
	K_i=10nM	K_i=9.6nM
	K_i=1054nM	K_i=0.5nM
	IC_{50}=25300nM	IC_{50}=4940nM
	IC_{50}=45900nM	IC_{50}=3790nM

Table 3. Affininty of compounds acting on 5-HT_6R depending on the presensce of amide or sulfonamide.

Compound	Affinity	
	X=CO	X=SO_2
	K_i=3981nM	K_i=2512nM
	K_i=4.4nM	K_i=0.4nM
	K_i=3.0nM	K_i=0.3nM

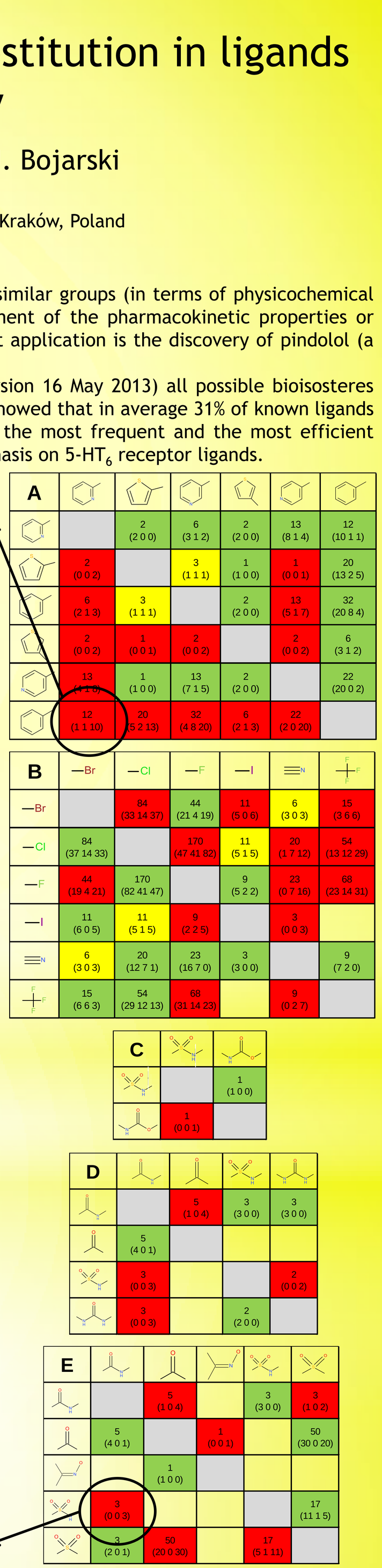


Figure 1. All bioisosteric replacements for 5-HT_6R ligands belonging to: phenyl (panel A), amide (B), hydroxyl (C), halogen (D) and carbonyl (E) modifications. Total number of such replacements are given in the intersection field, along with the number of replacements which increase (X _ _), do not change (_ X _) and decrease (_ _ X). Desirable substitutions are backgrounded in green, ones decreasing the activity in red and not statistically influencing the activity in yellow.

References

[1] ChEMBL: a large-scale bioactivity database for drug discovery, *Nucleic Acids Research*. Volume 40. Issue D1. Pages D1100-D1107. **2011**.
[2] Pipeline Pilot 8.5, San Diego: Accelrys Software Inc., **2011**.

Acknowledgements

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