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CHEMMEDCHEM Concepts

Bioisosteric Matrices for Ligands of Serotonin Receptors

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The concept of bioisosteric replacement matrices is applied to explore the chemical space of serotonin receptor ligands, aiming to determine the most efficient ways of manipulating the affinity for all 5-HT receptor subtypes. Analysis of a collection of over 1 million bioisosteres of compounds with measured activity towards serotonin receptors revealed that an average of 31% of the ligands for each target are mutual bioisosteres. In addition, the collected dataset allowed the development of bioisosteric matrices—qualitative and quantitative descriptions of the biological effects of each predefined type of bioisosteric substitution, providing favored paths of modifying the compounds. The concept exemplified here for serotonin receptor ligands can likely be more broadly applied to other target classes, thus representing a useful guide for medicinal chemists designing novel ligands.

Bioisosteric replacement is a technique of transforming a compound by exchanging a group of atoms for a different group that is similar in terms of its physicochemical properties. The underlying purpose of this modification is the enhancement of a certain biological or chemical property, such as affinity towards a given target, pharmacodynamics, pharmacokinetics, or the exploration of new, unknown scaffolds. Although fundamentally simple, the method has been successfully applied in numerous drug design projects and has led to some spectacular results, such as the discovery of prontosil (its active metabolite, sulfanilamide, is a bioisostere of *para*-aminobenzoic acid)[1] and pindolol (a nonselective beta blocker, developed from propranolol by replacing the naphthalene moiety with indole). Given its capabilities, the full potential of bioisosterism has not yet been utilized, especially in the field of serotonin receptor ligands; to the best of our knowledge, only four reports in the literature explicitly applying the strategy of bioisosteric replacement.[2–5]

In May 2013, approximately 22000 unique ligands with known activity against any serotonin receptor were annotated in the ChEMBL database.[6] Despite this quantity and the relatively high diversity within this set, the vast majority of compounds contain two typical pharmacophore features characteristic of serotonergic ligands: an aromatic system and a polarizable nitrogen atom. Following the classification of 5-HT receptor ligands described in the literature, ten key structural classes of ligands can be highlighted: tryptamines, phenylalkylamines, aminotetralines, aporphines, ergolines, arylpiperazines, piperidines, tricycles, indole and sulfonamide derivatives;[7–16] these classes were used in this research.

To apply the concept of bioisosterism to serotonin receptors, we conducted a detailed exploration of the bioisosteric data available. The methodology of using substitution matrices, as demonstrated here for 5-HT_6R, allows the identification of the most frequent and most efficient replacements in terms of biological activity and provides valuable suggestions for modifications to existing ligands for the rational design of new, potent and selective ligands for serotonin receptors.

The source of the compounds was the ChEMBL database version 16 (May 2013). To preserve the coherence of the data, only compounds with defined K_i values or equivalent (IC_{50}, assumed to be $2\times K_i$; pK_i and pIC_{50} values were converted to K_i), as assayed on human cloned, rat cloned or native receptors, were considered. In the case of multiple data for a single ligand, the K_i value and data against human receptors were preferred; a median value was used in the case of multiple biological results. Among the 14 members of the 5-HTR family, two were rejected: 5-HT_3R because it is an ion channel and 5-HT_{5B}R due to an insufficient number of ligands to perform a comprehensive analysis. The set of 5-HT_6R ligands fetched from the ChEMBL database (2277 compounds) was enriched by data extracted from approximately 40 patents (2529 compounds). For each compound acting on the remaining 5-HTR subtypes (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_4, 5-HT_{5A}, 5-HT_6, 5-HT_7), all classic bioisosteric replacements implemented in Pipeline Pilot[17] (divided into six classes: ring, amide, carbonyl, halogen and hydroxyl substitutions and ring modifications) were applied. The input structures and duplicates were removed from the original collections, leading to 12 sets of unique bioisosteres. Each compound was then queried against all other sets (regardless of target). Finding the same structure in the ligand and bioisostere set indicated that bioisostere replacement between those repositories exists. This procedure was repeated for all bioisostere collections and led to the identification of all bioisosteres between all targets as well as within the chemical space of single receptor (self-bioisosteres) (Table 1). The collections of

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Table 1. The number of bioisosteres found for different serotonin receptor subtypes.

Receptor	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{1E}$	5-HT$_{1F}$	5-HT$_{2A}$	5-HT$_{2B}$	5-HT$_{2C}$	5-HT$_{4}$	5-HT$_{5A}$	5-HT$_{6}$	5-HT$_{7}$
5-HT$_{1A}$	2053	204	248	27	48	384	60	156	30	34	113	165
5-HT$_{1B}$	204	316	297	29	51	60	40	64	23	22	75	59
5-HT$_{1D}$	248	297	378	32	52	72	47	75	31	25	89	66
5-HT$_{1E}$	27	29	32	26	13	27	18	27	22	19	35	28
5-HT$_{1F}$	48	51	52	13	61	13	13	13	9	3	27	15
5-HT$_{2A}$	384	60	72	27	13	1306	288	818	25	61	129	103
5-HT$_{2B}$	60	40	47	18	13	288	341	282	19	13	59	42
5-HT$_{2C}$	156	64	75	27	13	818	282	921	25	30	140	105
5-HT$_{4}$	30	23	31	22	9	25	19	25	130	15	28	19
5-HT$_{5A}$	34	22	25	19	3	31	13	30	15	39	31	23
5-HT$_{6}$	113	75	89	35	27	129	59	140	28	31	2180	131
5-HT$_{7}$	165	59	66	28	15	103	42	105	19	23	131	347

bioisosteres belonging to the same class of ligands were gathered into matrices, revealing the amount of positive, neutral and negative substitutions in terms of affinity towards a given target.

Self-bioisosteres represent the largest portion of the analyzed population of ligands (with the exception of 5-HT$_{1E}$R). Unsurprisingly, the number of self-bioisosteres is proportional to the quantity of ligands (Table 2). The highest rate of self-bioisosteres was observed for the 5-HT$_{1F}$R and 5-HT$_{6}$R, due to enrichment of the original sets retrieved from ChEMBL with patent data (5-HT$_{6}$R) and to exploration of structure—activity relationship studies in a limited number of published papers (5-HT$_{1F}$R). A relatively high number of bioisosteres is also observed for closely related targets (e.g., 5-HT$_{2}$Rs).

The most frequent replacements for self-bioisosteres are the following: halogen replacements (nearly 50% of all substitutions), ring modifications, and substitutions. Apparently, the hydroxyl class of substitutions was the least frequently explored within the investigated dataset. The analysis of bioisosteric substitutions for 5-HT$_{6}$R ligands showed two types of substitutions that enhanced activity: 2-substituted pyridine ring substituted by other aromatic systems, especially phenyl (Table 3), and nitrile group, which are interchangeable with any halogen (Figure 1). Moreover, the introduction of sulfonamide (Table 4) and urea increases affinity towards 5-HT$_{6}$R in all cases.

Analogous analysis for 5-HT$_{1A}$R ligands proves that the introduction of 2-pyridine or replacement of the trifluoromethyl group usually leads to increased affinity (see Supporting Information). For 5-HT$_{2A}$R ligands, 2-pyridine, 2-thiophene, nitrile and trifluoromethyl are undesirable, and the removal of a bromo substituent negatively affects the activity. On the contrary, substitutions introducing a bromo group are the most desirable for the modulation of activity towards 5-HT$_{2C}$R. 2-Pyridine, nitrile and iodo should be replaced similarly to other targets. An amide moiety is preferred over a nitrile in potent 5-HT$_{4}$R ligands. For 5-HT$_{7}$R ligands, substitution of phenyl or 2-thiophene increases activity, as does replacement of the amide linker, especially with sulfonamide.[18]

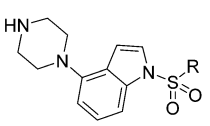
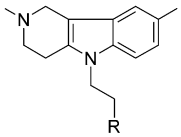
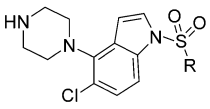
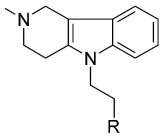
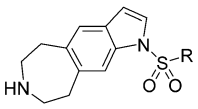
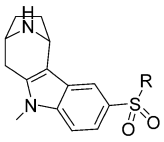
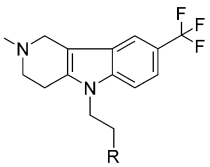
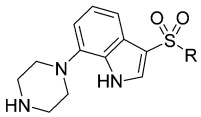
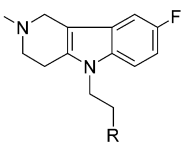
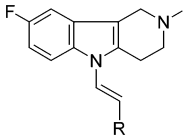
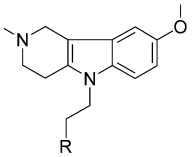
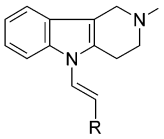
Here, some restrictions were applied to investigate the replacement of groups, with the knowledge that different targets might have different activity thresholds. For each receptor–receptor pair, only substitutions appearing at least five times in the global analysis and with at least twofold more examples of increasing affinity than decreasing (or vice versa) were considered. In general, ring modifications (linearization or expansion) decreased activity towards all targets. Substitution of an amide with a carbonyl moiety in 5-HT$_{1A}$R ligands enhances affinity towards 5-HT$_{1B}$R and 5-HT$_{1D}$R but decreases affinity toward 5-HT$_{7}$R. Transition from amide to sulfonamide or urea shifts activity towards 5-HT$_{1B}$R and 5-HT$_{1D}$R, respectively, in the

Table 2. Abundance of types of bioisosteric replacements by class.

Receptor	Ligands	Bioisosteres	Self-bioisosteres[a]	Replacement class						Total
				Ring bios[b]	Amide	Carbonyl	Halogen	Hydroxyl	Ring mod.[c]	
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	0	0	0	16	0	10	26
5-HT$_{1F}$	125	5868	0.488	20	14	0	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	0	38	130
5-HT$_{5A}$	271	8453	0.144	2	2	2	26	0	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

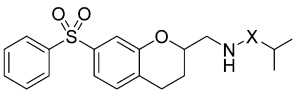
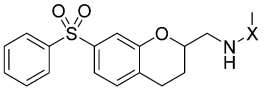
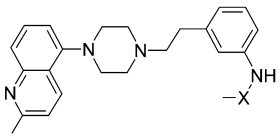
[a] Fraction of self-bioisosteres; [b] Substitution of the entire ring systems; [c] Ring modifications only (e.g., opening, contraction, etc.).

Table 3. Affinity of compounds for the 5-HT_6R, depending on the presence of a 2-pyridine or a phenyl group.

Compd	R = 2-pyridine		R = Ph		Compd	R = 2-pyridine		R = Ph	
	K_i [nM]	IC_{50} [nM]	K_i [nM]	IC_{50} [nM]		K_i [nM]	IC_{50} [nM]	K_i [nM]	IC_{50} [nM]
	1[19]	–	1[20]	–		–	860[22]	2[23]	–
	0.5[19]	–	1[19]	–		–	15750[22]	100[23]	–
	100[21]	–	1.58[21]	–		10[24]	–	9.6[24]	–
	–	1590[22]	–	974[23]		1054[25]	–	0.5[26]	–
	–	2980[22]	–	692[23]		–	25300[27]	–	4940[27]
	–	8360[22]	–	1057[23]		–	45900[27]	–	3790[27]

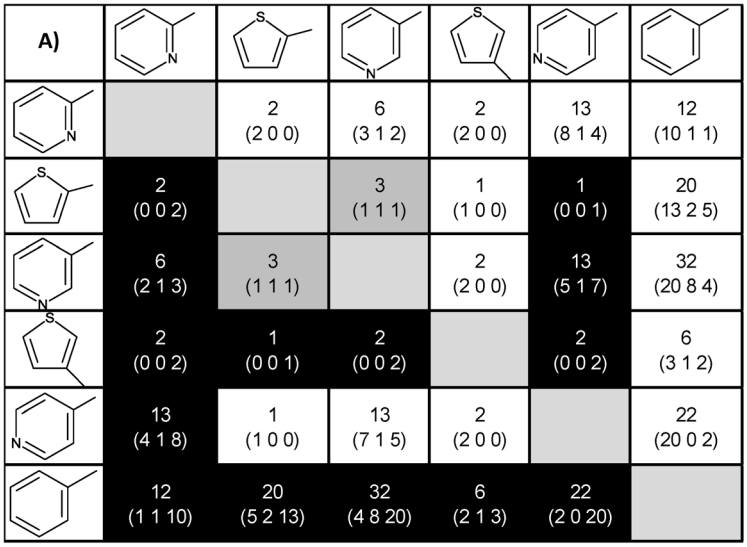
majority of cases. Conversely, reverse substitution (sulfonamide to amide) in 5-HT_{1A}R ligands enhances the activity of compounds against subtypes 1D and 2A. Exchanging a fluoro with a chloro group in 5-HT_6R ligands increases the activity for receptors 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D}, whereas a chloro group in 5-HT_{1A}R ligands replaced with other halogens leads to decreased affinity towards 1B, 1D and 2C subtypes. All ring modifications of 5-HT_{1A}R ligands decrease the affinity for 5-HT_{1B}R, 5-HT_{1D}R and 5-HT_{1F}R and 5-HT_2R.

Table 4. Affinity of compounds for the 5-HT_6R, depending on the presence of an amide or a sulfonamide functionality.

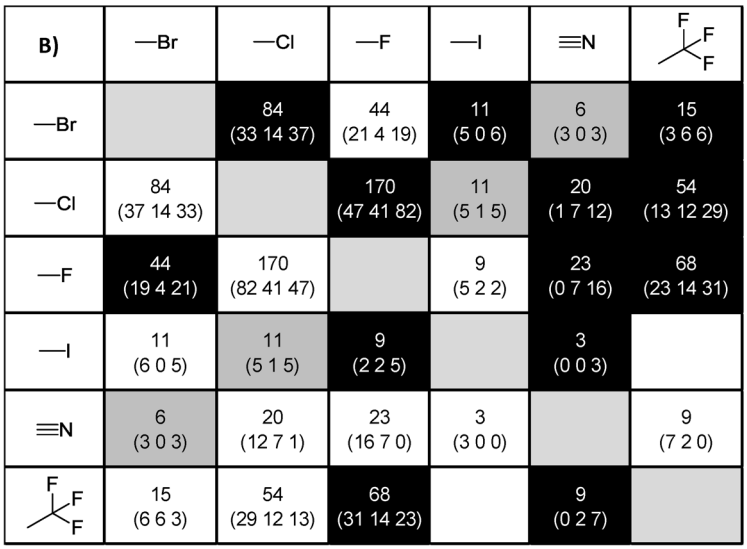
Compd	K_i [nM]	
	X = CO	X = SO_2
	3981[28]	2512[28]
	4.4[29]	0.4[29]
	3.0[29]	0.3[29]

We observed that the modification of 5-HT_{1B}R ligands results in highly potent 5-HT_{1D}R compounds, as shown with 16 different substitutions. Moreover, ring modifications in these ligands increase activity towards 5-HT_{1F}R, 5-HT_2Rs and 5-HT_7R subtypes. Ring contraction of 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F} receptors ligands leads to more active 5-HT_7R ligands as well; however, ring expansion in 5-HT_{1D}R ligands decreases activity towards 5-HT_2Rs. A bromo group in place of other halogens in 5-HT_{2A}R ligands enhances the affinity towards 5-HT_{2B}R. An identical effect is achieved if a fluoro group is substituted with another halogen; this replacement generates compounds that are active toward 5-HT_{2C}R and 5-HT_7R.

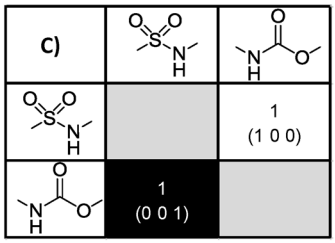
In summary, the concept of bioisosteric matrices has been applied to analyze the chemical space of ligands of the serotonin receptors. The results revealed that in many cases, the



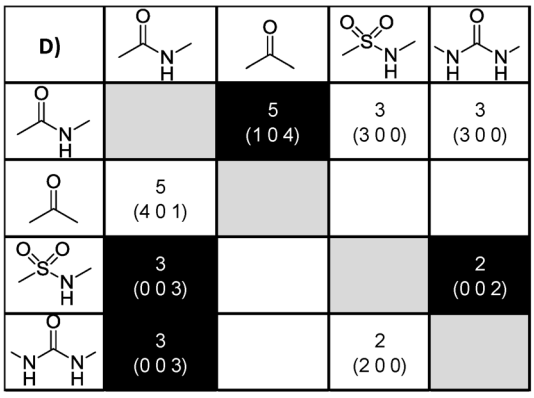
A)						
		2 (2 0 0)	6 (3 1 2)	2 (2 0 0)	13 (8 1 4)	12 (10 1 1)
	2 (0 0 2)		3 (1 1 1)	1 (1 0 0)	1 (0 0 1)	20 (13 2 5)
	6 (2 1 3)	3 (1 1 1)		2 (2 0 0)	13 (5 1 7)	32 (20 8 4)
	2 (0 0 2)	1 (0 0 1)	2 (0 0 2)		2 (0 0 2)	6 (3 1 2)
	13 (4 1 8)	1 (1 0 0)	13 (7 1 5)	2 (2 0 0)		22 (20 0 2)
	12 (1 1 10)	20 (5 2 13)	32 (4 8 20)	6 (2 1 3)	22 (2 0 20)	



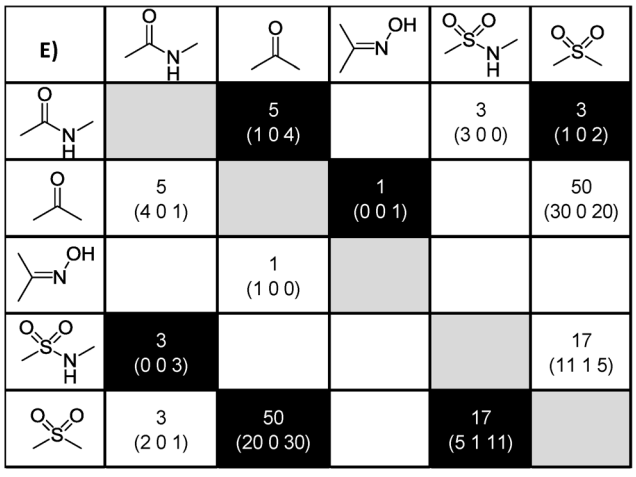
B)	—Br	—Cl	—F	—I	≡N	F F F
—Br		84 (33 14 37)	44 (21 4 19)	11 (5 0 6)	6 (3 0 3)	15 (3 6 6)
—Cl	84 (37 14 33)		170 (47 41 82)	11 (5 1 5)	20 (1 7 12)	54 (13 12 29)
—F	44 (19 4 21)	170 (82 41 47)		9 (5 2 2)	23 (0 7 16)	68 (23 14 31)
—I	11 (6 0 5)	11 (5 1 5)	9 (2 2 5)		3 (0 0 3)	
≡N	6 (3 0 3)	20 (12 7 1)	23 (16 7 0)	3 (3 0 0)		9 (7 2 0)
F F F	15 (6 6 3)	54 (29 12 13)	68 (31 14 23)		9 (0 2 7)	



C)		
		1 (1 0 0)
	1 (0 0 1)	



D)				
		5 (1 0 4)	3 (3 0 0)	3 (3 0 0)
	5 (4 0 1)			
	3 (0 0 3)			2 (0 0 2)
	3 (0 0 3)		2 (2 0 0)	



E)					
		5 (1 0 4)		3 (3 0 0)	3 (1 0 2)
	5 (4 0 1)		1 (0 0 1)		50 (30 0 20)
		1 (1 0 0)			
	3 (0 0 3)				17 (11 1 5)
	3 (2 0 1)	50 (20 0 30)		17 (5 1 11)	

Figure 1. All bioisosteric replacements for 5-HT_6R ligands belonging to A) halogen, B) phenyl, C) hydroxyl, D) amide, and E) carbonyl modifications. The total number of a given replacement is given in the intersection field. The three numbers in parentheses represent the number of replacements that increase (X__), do not change (_X_) and decrease (__X) the affinity. Color code: desirable substitutions (□); substitutions that decrease activity (■); substitutions that do not influence activity (■).

given ligand is a bioisostere of a compound active towards a different member of the 5-HTR family. The number of such cases allows the assumption that bioisosteric replacement could be a viable method for discovering novel, promising ligands for serotonin receptors. This statement is also supported by a large number (30% of the population on average) of self-bioisosteres. The size of this set results from extensive structure–activity relationship studies, exploring a significant number of substitutions. However, the trend to replace terminal and relatively simple groups indicates that the full potential of the bioisosteric substitution has yet to be revealed. All bioisosteres analyzed in this study are available from the authors upon request.

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Keywords: bioisosterism · bioisosteric matrices · bioisosteric substitutions · chemical space · serotonin receptors

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