SUPPORTING INFORMATION

The Physicochemical Challenges of Designing Multiple Ligands

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Tables of differences in the median property values and related p values for the target families.
Definition of Hydrogen Bond Donors and Acceptor and Rotatable bonds.

	GPCRs (all)	GPCRs (monoamine)	GPCRs (peptide)	GPCR / oxidases	GPCR / transporters	kinases	nuclear receptors	oxidases	proteases
GPCRs (peptide)		227 **0.0000**							
GPCR / oxidases	-51 0.2729	72 **0.0031**	-148.5 **0.0004**						
GPCR / transporters	-130.5 **0.0003**	14.5 0.5277	-213 **0.0000**	-58 **0.0016**					
kinases	-50.5 0.3089	106.5 **0.0005**	-124 **0.0002**	35 0.2582	91 **0.0003**				
nuclear receptors	-65 **0.0991**	61 **0.0131**	-157 **0.0001**	-13 0.7431	59 **0.0187**	-29.5 0.2477			
oxidases	-182.5 **0.0000**	-54 **0.0424**	-273 **0.0000**	-124 **0.0002**	-56 **0.0055**	-148 **0.0001**	-115 **0.0006**		
proteases	-74 **0.0134**	40 **0.0349**	-168 **0.0000**	-27 0.3171	39 **0.0564**	-46 0.1076	-18 0.5188	95 **0.0002**	
transporters	-208 **0.0000**	-87 **0.0027**	-312 **0.0000**	-163 **0.0010**	-99.5 **0.0014**	-198.5 **0.0002**	-153.5 **0.0005**	-35 0.1059	-129.5 **0.0002**

Table 8 Differences in the median MWs between the subsets and Mann-Whitney p values. Bold text indicates significance at the 90% level ($p < 0.1$)

	GPCRs (all)	GPCRs (monoamine)	GPCRs (peptide)	GPCR / oxidases	GPCR / transporters	kinases	nuclear receptors	oxidases	proteases
GPCRs (peptide)		2 **0.0009**							
GPCR / oxidases	0.2 0.6553	1.3 **0.0085**	-0.8 0.2569						
GPCR / transporters	-0.2 0.6393	0.85 **0.0086**	-1 **0.0106**	-0.4 0.4598					
kinases	-0.4 0.4270	0.9 0.1095	-1.1 **0.0320**	-0.3 0.4739	-0.1 0.7450				
nuclear receptors	2.1 **0.0001**	3.2 **0.0000**	1.2 **0.0302**	1.9 **0.0008**	2.3 **0.0000**	2.4 **0.0002**			
oxidases	-0.4 0.3689	0.8 **0.0941**	-1.3 **0.0177**	-0.5 0.1655	-0.2 0.5240	-0.2 0.5052	-2.5 **0.0000**		
proteases	-1.5 **0.0002**	-0.4 0.3888	-2.4 **0.0000**	-1.7 **0.0007**	-1.2 **0.0014**	-1.2 **0.0119**	-3.65 **0.0000**	-1.1 **0.0183**	
transporters	-0.65 0.3531	0.7 0.1608	-1.5 **0.0288**	-0.6 **0.0793**	-0.45 0.2863	-0.55 0.2027	-2.75 **0.0001**	-0.3 0.4188	0.9 0.1056

Table 9 Differences in the median cLogP values between the subsets and Mann-Whitney p values. Bold text indicates significance at the 90% level ($p < 0.1$)

	GPCRs (all)	GPCRs (monoamine)	GPCRs (peptide)	GPCR / oxidases	GPCR / transporters	kinases	nuclear receptors	oxidases	proteases
GPCRs (peptide)		36 **0.0001**							
GPCR / oxidases	11.5 0.1936	38 **0.0002**	-2 0.8136						
GPCR / transporters	-18 **0.0048**	5 0.2672	-31 **0.0000**	-31 **0.0000**					
kinases	12 0.1310	36 **0.0001**	1 0.9463	1 0.8951	32 **0.0000**				
nuclear receptors	-0.5 0.9903	26 **0.0008**	-14 **0.0833**	-12 **0.0435**	20 **0.0002**	-12 **0.0261**			
oxidases	-12 0.1094	9 **0.0753**	-26 **0.0021**	-25 **0.0022**	4 0.3573	-27 **0.0005**	-14.5 **0.0153**		
proteases	20 **0.0019**	43 **0.0000**	8 0.1823	11 0.2403	38 **0.0000**	6 0.1861	20 **0.0002**	33 **0.0000**	
transporters	-40 **0.0000**	-16 **0.0083**	-55 **0.0000**	-54 **0.0001**	-21 **0.0005**	-52 **0.0001**	-42 **0.0001**	-27 **0.0006**	-60 **0.0000**

Table 10 Differences in the median PSA values between the subsets and Mann-Whitney p values. Bold text indicates significance at the 90% level ($p < 0.1$)

	GPCRs (all)	GPCRs (monoamine)	GPCRs (peptide)	GPCR / oxidases	GPCR / transporters	kinases	nuclear receptors	oxidases	proteases
GPCRs (peptide)		3 **0.0000**							
GPCR / oxidases	0 0.5949	2 **0.0003**	-1 0.2569						
GPCR / transporters	-2 **0.0015**	0 0.3656	-3 **0.0000**	-2 **0.0001**					
kinases	0 0.4081	2.5 **0.0003**	0 0.5150	0 0.4975	2 **0.0002**				
nuclear receptors	0 0.4271	2 **0.0002**	0 0.4679	0 0.7043	2 **0.0001**	0 0.8630			
oxidases	-2 **0.0017**	0 0.8342	-3 **0.0000**	-2 **0.0013**	0 0.5520	-2 **0.0007**	-2 **0.0006**		
proteases	0 0.7613	2 **0.0003**	-1 **0.0185**	0 0.3343	1 **0.0003**	-1 0.1392	-1 0.1654	2 **0.0010**	
transporters	-3 **0.0001**	-1 **0.0178**	-4 **0.0000**	-3 **0.0001**	-1 **0.0017**	-3.5 **0.0001**	-3 **0.0001**	-1 **0.0165**	-3 **0.0000**

Table 11 Differences in the median HBA values between the subsets and Mann-Whitney p values. Bold text indicates significance at the 90% level ($p < 0.1$)

	GPCRs (all)	GPCRs (monoamine)	GPCRs (peptide)	GPCR / oxidases	GPCR / transporters	kinases	nuclear receptors	oxidases	proteases
GPCRs (peptide)		0 0.2418							
GPCR / oxidases	0 0.1432	1 **0.0564**	0 0.2476						
GPCR / transporters	0 0.5250	1 0.2065	0 0.7113	0 0.6898					
kinases	1 **0.0293**	1 **0.0141**	1 **0.0578**	0 0.3558	0 0.2198				
nuclear receptors	0 0.3284	0 0.8886	0 0.1524	-1 **0.0044**	-1 **0.0772**	-1 **0.0005**			
oxidases	0 0.1924	1 **0.0719**	0 0.3162	0 0.9569	0 0.6102	0 0.4387	1 **0.0139**		
proteases	2 **0.0000**	2 **0.0000**	2 **0.0000**	1 **0.0001**	2 **0.0000**	1 **0.0025**	2 **0.0000**	1 **0.0002**	
transporters	0 0.3725	0 1.0000	0 0.2184	-1 **0.0219**	-1 0.1449	-1 **0.0051**	0 0.8571	-1 **0.0433**	-2 **0.0000**

Table 12 Differences in the median HBD values between the subsets and Mann-Whitney p values. Bold text indicates significance at the 90% level ($p < 0.1$)

	GPCRs (all)	GPCRs (monoamine)	GPCRs (peptide)	GPCR / oxidases	GPCR / transporters	kinases	nuclear receptors	oxidases	proteases
GPCRs (peptide)		4 **0.0014**							
GPCR / oxidases	1 0.2616	4 **0.0018**	0 0.9106						
GPCR / transporters	-3 **0.0003**	0 0.5166	-4 **0.0000**	-4 **0.0000**					
kinases	-1 0.3247	1 0.2035	-2 **0.0482**	-3 **0.0418**	1 **0.0444**				
nuclear receptors	1 0.2408	4 **0.0008**	0 1.0000	0 0.9862	4 **0.0000**	3 **0.0353**			
oxidases	-5 **0.0000**	-2 **0.0061**	-6 **0.0000**	-6 **0.0000**	-2 **0.0053**	-3 **0.0003**	-6 **0.0000**		
proteases	-1 0.4915	2 **0.0332**	-2 **0.0340**	-2 **0.0392**	2 **0.0004**	1 0.4492	-2 **0.0239**	4 **0.0000**	
transporters	-4 **0.0060**	-1 0.3165	-5 **0.0004**	-5 **0.0007**	0 0.5716	-2 **0.0508**	-5 **0.0002**	1 0.1383	-3 **0.0059**

Table 13 Differences in the median RB values between the subsets and Mann-Whitney p values. Bold text indicates significance at the 90% level ($p < 0.1$)

Definition of Hydrogen Bond Donors and Acceptor

The perception of hydrogen bond donors and acceptors is performed in two steps:

1. A simple default rule is applied to determine the donors and acceptors.
2. Then, a list of exceptions to the default rules is applied.

Default Rule

- Any nitrogen or oxygen atom with at least one pair of free electrons is considered as an acceptor.
- Any hydrogen atom that is bonded to a nitrogen or oxygen atom is considered as a donor.

Exceptions

- The nitrogen atoms of amides, sulfonamides, and equivalent structures are not considered as acceptors.
- Only one nitrogen atom of guanidines, amidines, and equivalent groups is considered as an acceptor.
- The nitrogen atoms of aromatic amines are not considered as acceptors.
- The nitrogen atoms of five-membered aromatic rings like pyrrole are not considered as acceptors.
- The sulfur atoms of thiocarbonyl compounds are considered as acceptors.

Definition of Rotatable Bonds

A bond is considered as being rotatable, if:

- it is not in a ring, or if it is in a ring larger than 8;
- it is a single or a triple bond;
- none of the two atoms is terminal;
- it is not adjacent to a triple bond;
- it is not an amide, amidine, guanidine bond.