Pharmacophore modelling of $GABA_B$ receptor PAMs – methodology and application for virtual screening

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γ-Aminobutyric acid B ($GABA_B$) receptors are postulated as potential therapeutic targets for the treatment of several brain disorders, including drug dependence. Apart from classical orthosteric ligands, the positive allosteric modulators (PAMs) have emerged as potential theraputic agents mimicking effects of agonists but having significantly reduced side-effects [1].

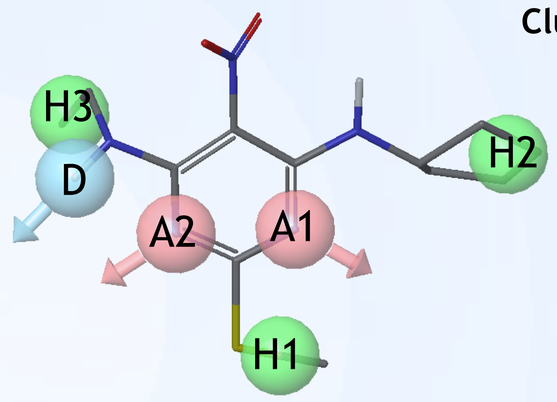
Due to the increasing numbers of published PAMs (74 structures in February 2014) some standard *in silico* approaches, such as pharmacophore modelling, may be utilized for the discovery of new active compounds. In this study, all known PAMs were hierarchicaly clustered using Canvas [2] with manual refinements to ensure proper chemotypes classification. Multiple hypotheses were developed for each cluster, employing the previously utilized approach [3]. After aplication of DUD-like [4] test set, one model per cluster was selected (according to Yourden's statistics value, Figure 1.) to form the linear combination of pharmacophore models, i.e. the first, general pharmacophore hypothesis of $GABA_B$ PAMs (Figure 2.).

$$Y = \frac{TP \cdot TN - FN \cdot FP}{(TP + FN) \cdot (TN + FN)}$$

Figure 1. Yourden's statistic formula. TP is the number of true positives (actives labeled as actives), TN the number of true negatives (inactives labeled as inactives), FP the number of false positives (inactives labeled as actives) and FN the number of false negatives (actives labeled as inactives).

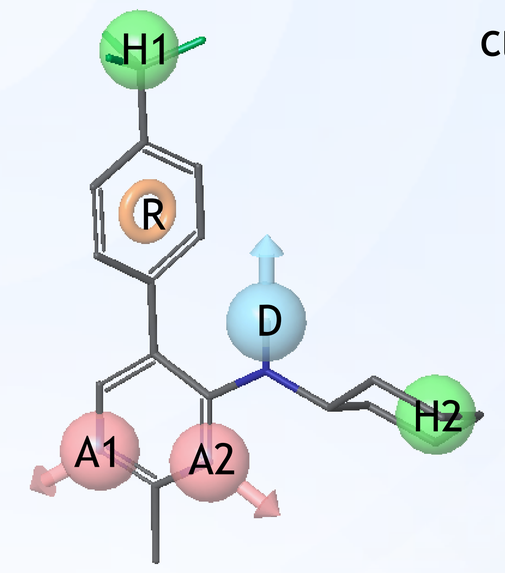
Developed combination of pharmacophore models was applied as one of the steps in the virtual screening protocol reducing space of 5.3M of compounds from seven commercial databases (Vitas M, Enamine, Chemdiv, Chembridge, UORSY, Specs and Maybridge) to ~8K structures for further investigation (Figure 3). In the next step these compounds are docked to homology models of $GABA_B$ receptors developed on diffrent templates from GCPR family, including recently solved structures of metabotropic glutamate receptors 1 and 5. The best performing compounds from docking studies will be purchased and evaluated in *in vitro* tests.

Figure 3. Virtual screening workflow.



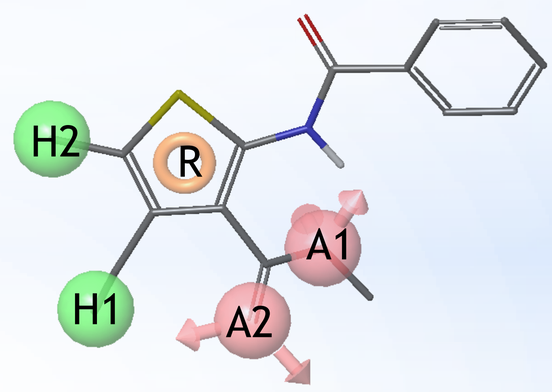
Cluster 1 (12 cmpds) - AADHHH

	A2	D	H1	H2	H3
A1	2.38	4.58	2.62	4.55	5.19
A2		2.38	3.30	6.86	3.48
D			5.60	8.77	2.37
H1				6.07	6.41
H2					8.79



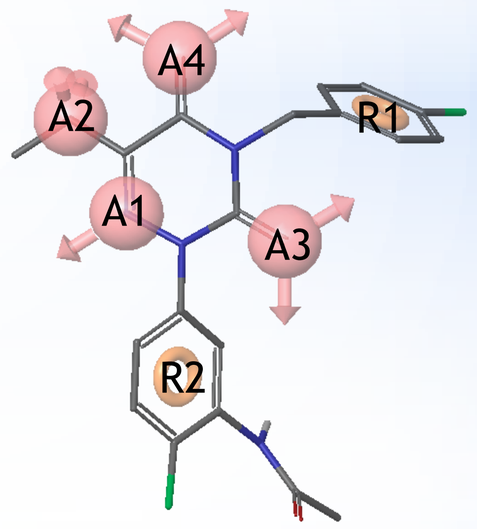
Cluster 2 (10 cmpds) - AADHHR

	A2	D	H1	H2	R
A1	2.38	4.74	8.35	7.02	5.12
A2		3.27	8.42	4.73	5.17
D			5.94	3.83	3.26
H1				9.31	3.29
H2					7.00



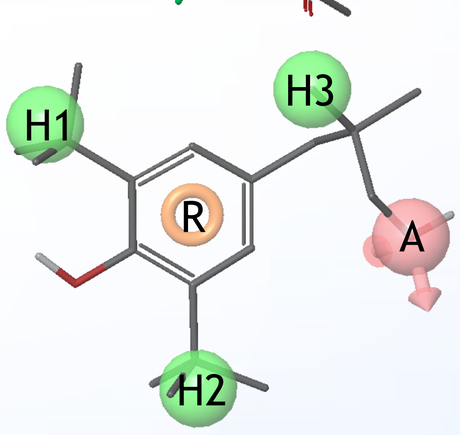
Cluster 3 (13 cmpds) - AAHHR

	A2	H1	H2	R
A1	2.26	5.08	6.09	3.49
A2		3.30	5.57	3.54
H1			3.66	3.56
H2				2.77



Cluster 4 (32 cmpds) - AAAARR

	A2	A3	A4	R1	R2
A1	2.36	3.55	3.51	6.02	3.67
A2		5.40	2.71	6.72	5.98
A3			4.58	4.17	3.75
A4				4.73	6.81
R1					7.32



Cluster 5 (7 cmpds) - AHHHR

	H1	H2	H3	R
A	7.80	5.47	3.78	4.58
H1		6.28	5.68	3.56
H2			6.95	3.56
H3				4.10

Figure 2. The additive model of pharmacophore models of $GABA_B$ ligands. For each hypothesis the best fitting compound is presented, along with a matrix of distances (in angstroms) between features. The feature abbreviations used are: hydrogen bond acceptor – A, hydrogen bond donor – D, hydrophobic group – H, aromatic ring – R.

References

[1] Filip, M. et al Neuropharmacology, 2014, xxx, 1-12.
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Acknowledgements

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