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PHARMACOPHORE MODELING OF $GABA_B$ RECEPTOR LIGANDS – 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) to form the linear combination of pharmacophore models, i.e. the first, general pharmacophore hypothesis of $GABA_B$ PAMs.

This combination was applied as one of the steps in the virtual screening protocol reducing space of 5.3M of compounds from seven commericial databases to ~8K structures for further investigation.

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References:

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