Application of computational methods in rational design of multi-target ligands as potential antipsychotics and antidepressants

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Nowadays, polypharmacological strategy represents an increasingly important approach in the treatment of neuropsychiatric diseases with complex pathophysiological mechanisms. For that reason, drugs that selectively act on a single target have been successfully replaced with multi-target compounds, which modulate the activity of different biological targets involved in pathogenesis of complex brain disorders. Atypical antipsychotics (AAPs), such as clozapine, ziprasidone and risperidone, simultaneously act on a wide range of aminergic G protein-coupled receptors (GPCRs). In particular, their well-established therapeutic efficacy against the positive and negative symptoms of psychosis is based on the antagonism of 5-HT_{2A} and D_2 receptors. AAPs may also influence neurotransmission of glutamate, interacting with N-methyl-D-aspartate (NMDA) receptors or by potentiating the release of glutamate in corticolimbic regions. However, their off-target activity on H_1 receptor (H_1-R) has been related to metabolic side effects, especially weight gain, as well as drowsiness and sedation. Moreover, AAPs are frequently used in anxiety, bipolar disorder, and agitation associated with neurodegenerative disorders. Lumateperone was recently approved for the treatment of schizophrenia and bipolar disorder. Besides blocking 5-HT_{2A} and D_2 receptors, it also acts as a modulator of glutamate and inhibitor of serotonin reuptake providing the basis for treatment of unipolar major depression. In this regard, searching for novel multi-target compounds with an optimal polypharmacological profile and fewer side effects could provide a new perspective in the treatment of complex brain disorders. Application of computational methods has an important role in the early stages of drug discovery process, enabling analysis of large compound libraries, the optimization of lead compounds as well as the design of novel promising candidates for biological evaluation. Rational drug design of multi-target ligands with optimal antagonistic activity on 5-HT_{2A}/D_2 receptors, as well as lower affinity for H_1-R presents a promising strategy for treatment of multifactorial brain disorders. Polypharmacological profiling of compounds requires integration of different computational methods, which are classified into structure-based drug design (SBDD) and ligand-based drug design (LBDD). Molecular dynamics (MD) simulations combined with molecular docking methods were used to evaluate dynamic behavior of studied receptors in complex with clozapine, ziprasidone and lumateperone as lead molecules, as well as to obtain their bioactive conformations. Relying on available structural data, these SBDD approaches revealed how structurally different antagonists bind and modulate activity of 5-HT_{2A}, D_2, and H_1 receptors, providing a basis for further LBDD study. With the aim to precisely define the pharmacophore of multi-target compounds with dual antagonistic activity on 5-HT_{2A}/D_2 receptors (5-HT_{2A}/D_2-R) and better selectivity against off-target H_1-R, 3D-Quantitative Structure

Activity Relationship (3D-QSAR) modeling was employed. Previously selected conformers from SBDD study were used to develop linear regression models between GRID-independent molecular descriptors and studied biological activities. Validated 3D-QSAR models could be used for further optimization of lead molecules as well as for accurate activity prediction of new designed analogues. Considering the structural features required for the optimal polypharmacological profile of studied compounds, a fragment-based drug design approach was used in rational drug design of new dual antagonists. Commercially available libraries were screened to identify the best aligned fragments for the design of potent 5-HT_{2A}-R/D_2-R antagonists, with a lower activity on H_1-R. Early stage *in silico* prediction of ADMET properties plays an important role in optimization of new designed compounds. Besides, the *in vitro* parallel artificial membrane permeability assay (PAMPA) followed with the quantitative structure permeability relationship (QSPR) analysis represent a promising tool in successful drug discovery process. These methods were combined with the aim to create predictable QSPR models for *in silico* assessment of blood-brain barrier (BBB) permeability of CNS related compounds. Overall, obtained results provided new methodologies that could be used as guidelines for rational drug design of new multi-target compounds for neuropsychiatric diseases.