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# Probing Binding Landscapes and Molecular Recognition Mechanisms of Atypical Antipsychotic Drugs towards the Selective Targeting of D2 Dopamine Receptor

Dopamine receptors constitute a unique class of G-protein coupled receptors that mediate the activities of dopamine, a neurotransmitter implicated in diverse neurological diseases when dysregulated. Over the years, antipsychotic drugs have been primarily directed towards D2 dopamine receptor (DRD2) while associable adverse effects have been centred on non-selective targeting. The recent crystal structure of DRD2 in complex with atypical antipsychotic could further aid the structure-based design of highly DRD2-selective antipsychotics. Therefore, in this study, we comprehensively investigate the molecular recognition and differential binding landscapes of class-I and II DRD2 atypical antipsychotics, using membrane-bilayer molecular dynamics simulation and binding free energy techniques. Findings revealed that selected class-I antipsychotics exhibited binding dynamics and poses dissimilar to the class-II types with different interactive mechanisms at the binding cavity of DRD2. More interestingly, the class-II drugs established a highly coordinated binding at the DRD2 active site with a pertinent and recurrent involvement of Asp114 via strong hydrogen interactions. Furthermore, while these compounds exert distinct effects on DRD2 structure, findings revealed that the class-II types favourably engaged the deep hydrophobic pocket of DRD2 compared to the class-I drugs. We speculate that these findings will be fundamental to the discovery of highly selective DRD2 antipsychotics.

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