Molecular Dynamic Simulations to Probe Stereoselectivity of Tiagabine Binding with Human GAT1

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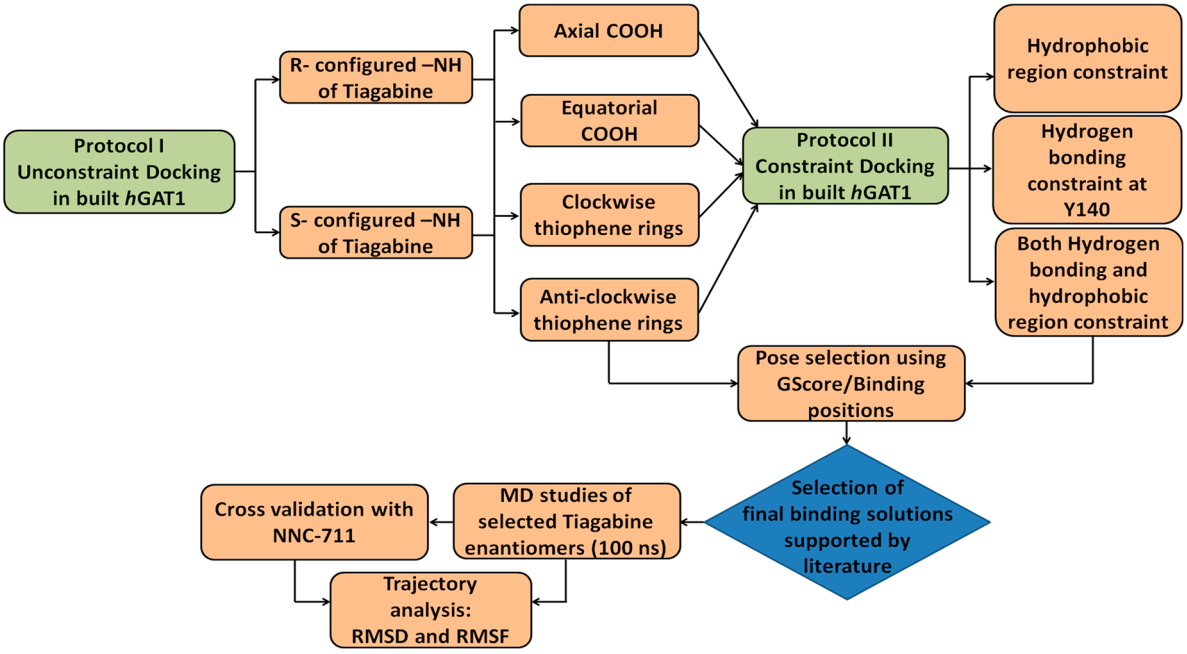

Figure 1. Workflow of selection of stable docking pose of hGAT1—Tiagabine complex followed by MD studies.

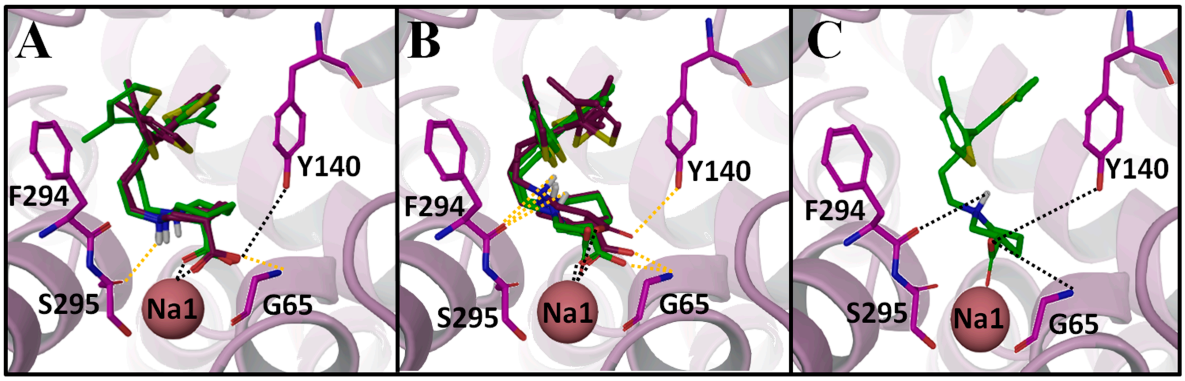

Figure 2. Unconstraint docking of *R*- and *S*-enantiomers of tiagabine in hGAT1. Ligand protein interactions of tiagabine enantiomers of (**A**) cluster $A_{unconstraint}$ and (**B**) cluster $B_{unconstraint}$ in hGAT1. (**C**) The more pronounce deviation of equatorial –COOH from Y140 (5.7Å) was observed in the *S*-configured S-S clockwise equatorial unconstraint enantiomer of tiagabine (Table 1, entry 10).

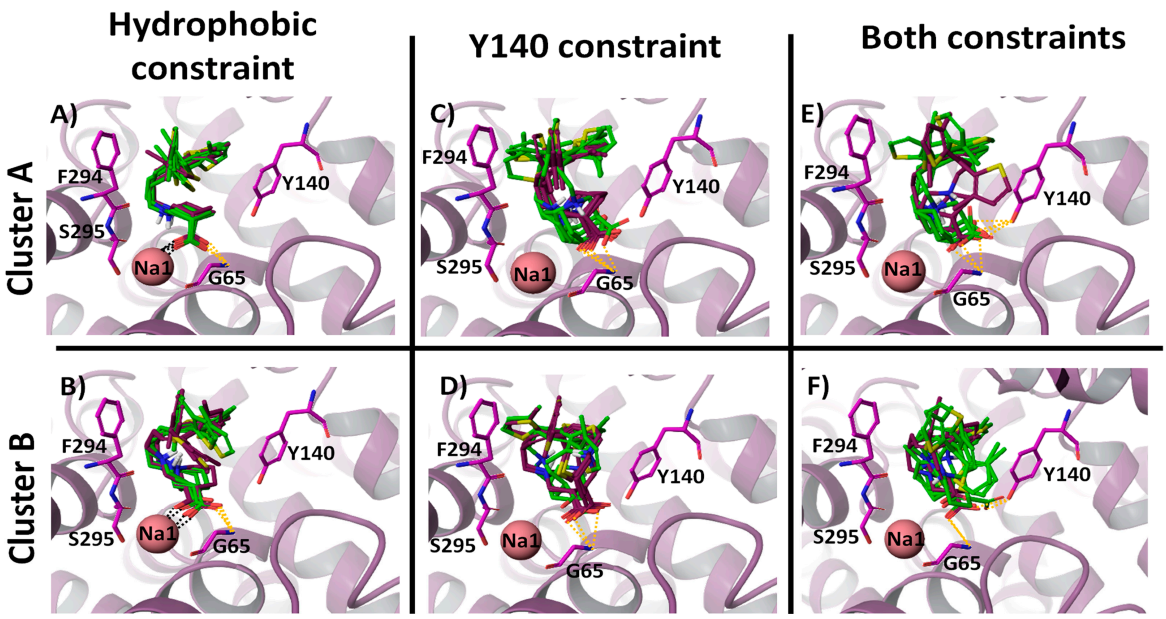

Figure 3. Application of hydrophobic constraint, Y140 constraint and both hydrophobic and hydrogen bond with Y140 constraint in docking of tiagabine enantiomers within hGAT1 binding pocket. (**A**) Distances of protonated –NH group and axial –COOH from S295 (3.21–3.50Å) and –OH of Y140 (4.43Å), respectively in enantiomers of cluster $A_{\text{hydrophobic constraint}}$, (**B**) Distances of protonated –NH group and equatorial –COOH of tiagabine enantiomers from F294 (3.84–3.99Å) and –OH of Y140 (2.46–3.09Å), respectively in cluster $B_{\text{hydrophobic constraint}}$. (**C,D**) Hydrogen bonding between OH of Y140 and few of the –NHs of G65 with –COOH groups of tiagabine enantiomers in both clusters (1 and 2 of Y140 constraint) was observed. (**E,F**) Lack of coordination between Na1 and –COOH groups in clusters $A_{\text{both constraints}}$ and $B_{\text{both constraints}}$ was observed due to increased distance (3.22–4.8Å). Interaction between F294 and protonated –NH group was also disrupted.