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Human Rhinovirus Inhibition through Capsid "Canyon" Perturbation: Structural Insights into the Role of a Novel Benzothiophene Derivative

The challenge in targeting human rhinoviruses (HRV) over the years has been attributed to the wide variety in HRV serotypes. Nonetheless, the search for therapeutic agents against HRV continues unabated. These efforts have been augmented by the recent discovery of the novel benzothiophene derivative shown to inhibit HRV viral replication. Bound to subtype HRV-B14, the compound showed similar inhibitory activity as Pleconaril, a known capsid inhibitor. However, the molecular and structural basis of this inhibition remains unclear. In this in silico report, residue interaction network analysis revealed that the binding of the benzothiophene derivative into the "canyon" region of the active site of HRV-B14 distorts its initially extensively networked and compact residue profile. This was characterized by fewer inter-residue hydrogen bonds, reduced van der Waal interactions, and increased residue flexibility. Interestingly, however, the binding of this benzothiophene derivative decreased the flexibility of the north-south wall around the canyon region possibly impeding the "breathing motion" of HRV-B14, hence its inhibition. Atomistic insights also revealed the cruciality of Tyr152 towards inhibitor binding at HRV-B14. This was justified by the amino acid's high intermolecular interaction with both inhibitors. Findings provide important structural insights in the inhibitory activity the novel benzothiophene derivative, and reaffirm its promising potential as an alternative capsid inhibitor towards common cold therapy upon further experimental validation.

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