Revolutionizing Asthma Treatment: A Breakthrough in LABA Design Enhances Both Selectivity and Efficacy

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Purpose

To design the first selective and fully efficacious analog of long-acting β2-agonist (LABA)

- Propose and test a new method of drug design: creating analogs by combining structural groups of different LABAs
- Overcome the challenges posed by highly conserved ligand-binding sites of target receptor β2AR and off-target receptor β1AR
- Leverage known connections between LABAs' structural groups, receptor interactions, and physiological effects

Methods

1. Molecular Docking of Control Groups (Approved LABAs) to β2AR and β1AR for Five Trials Each in AutoDock Vina
2. 2D and 3D Designing of Analogs using ChemAxon and Avogadro
3. Testing of Analogs for Drug-likeness using SwissADME
4. Molecular Docking of Analogs to β2AR and β1AR for Five Trials Each in AutoDock Vina
5. Qualitative and Quantitative Analysis in UCSF Chimera, Excel, and Discovery Studio Visualizer to Find Insights for Designing Better Analogs
6. Steps 2-6 were repeated, totaling to 76 novel analogs.

Results

- **Full Efficacy**: Novel analog 20 had a ΔG of -9.9 kcal/mol when docked to β2AR, corresponding to a 1.5-fold increase in binding affinity for β2AR compared to the most efficacious LABA. When docked to β2AR, analog 20 formed all hydrogen bonds (Ser203, Ser207, Asn293, Asp113, Asn293, and Phe193) and π interactions necessary for full β2AR activation.
- **Selectivity**: Analog 20 had a ΔG of -8.3 kcal/mol when docked to β1AR, corresponding to a 4-fold decrease in binding affinity for β1AR compared to the most selective LABA.

Conclusion

- This study successfully designed novel analog 20, which is not only the first analog of LABA to be selective and fully efficacious but also the first to outperform current LABAs in both efficacy and selectivity *in silico*.
- Given that β2AR and β1AR are some of the most conserved pairs of receptors in humans this study's ability to overcome the challenges of designing a selective and efficacious drug would help many current and future works create drugs that target highly conserved receptors.