Hybridization of β-Adrenergic Agonists and Antagonists Confers G Protein Bias

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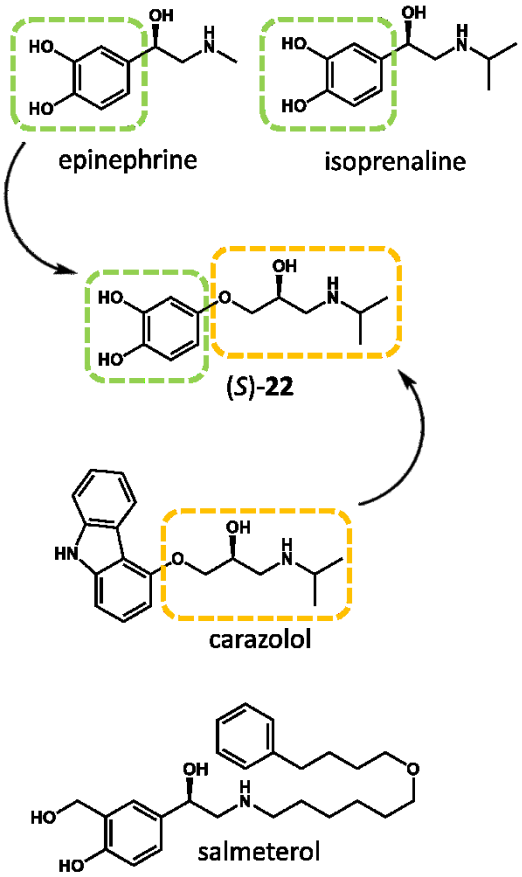
Starting from the β-adrenoceptor agonist isoprenaline and beta-blocker carvedilol, different chemotypes of agonist/antagonist hybrids were synthesized.

Investigations of ligand-mediated receptor activation revealed a predominant effect of the aromatic head group on the intrinsic activity of our ligands, whereas ligands with a carvedilol head group were devoid of agonistic activity.

Ligands composed of a catechol head group and an antagonist-like oxypropylene spacer possess significant intrinsic activity for the activation of $G\alpha_s$, while only showing weak or even no β-arrestin-2 recruitment at both β_1- and β_2-AR.

Unbiased MD simulations were performed to elucidate the binding mode of compound (*S*)-**22** in comparison to the full agonist epinephrine and the partial agonist salmeterol at the β_2-AR.

Thereby we gained insights into the origins of the functionally selective partial agonist activity for this type of catechol-beta blocker hybrid compounds.



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Hybridization of β-Adrenergic Agonists and Antagonists Confers G Protein Bias. *Journal of Medicinal Chemistry,* **2019**, 62, 5111-5131.
DOI: 10.1021/acs.jmedchem.9b00349