Biased Unmatched Bivalent Ligands Targeting Asymmetrically Signaling GPCR Homodimers

Technology #20170276

Targets Asymmetrically Signaling Homodimers

A new technology targets asymmetrically signaling homodimers using biased unmatched bivalent ligands (BUmBLs). Four new compounds have a functional effect on melanocortin 4 receptor (MC4R) signaling and are the first-ever melanocortin biased ligands that favor cAMP signaling pathways over \(\beta\)-arrestin recruitment pathways when targeting the MC4R. This strategy is the first to pharmacologically target allosteric signaling between G protein-coupled receptors (GPCR) homodimers and can be applied easily both in vitro and in vivo to various GPCR systems. In addition, the technology can create other bivalent ligands for different GPCRs because the pharmacophores on either end are easily swapped out to target different receptors, making it a mix-and-match pharmacophore system that should be able to use any known pharmacophore. These valuable chemical probes can be used to study melanocortin signaling in disease states and disorders in which melanocortin receptors are implicated (e.g., cancer, skin pigmentation disorders, social disorders, sexual function disorders, Alzheimer’s disease, cachexia and obesity).

Bivalent Ligand with Two Different Pharmacophores

While G protein-coupled receptors (GPCRs) are typically targeted as monomers, they also form dimers and oligomers that have recently become new therapeutic targets. GPCRs that form homodimers that can asymmetrically signal are usually targeted by using two monovalent ligands and a complicated, time consuming dosing strategy that is difficult to apply in vivo. Currently, no therapeutics exist that can target asymmetric signaling of GPCR homodimers. This new technology allows for targeting this asymmetric signaling since each end of the bivalent ligand can contain a different pharmacophore. The two identical receptors that form the homodimers are targeted by these new bivalent ligands that have a C-terminal scaffold and N-terminal scaffold linked by a PEG or Pro-Gly linker. Differential functional effects are possible, depending on the pharmacophore used. Linking two pharmacophores to create a bivalent ligand solves the
difficult dosing problem with monovalent compounds, making these molecules more effective in vivo than current therapeutics. These novel pharmacological probes may be useful in studying biased ligand signaling and may offer novel drug targeting strategies.

**BENEFITS AND FEATURES:**

- Biased unmatched bivalent ligands (BUmBLs) target asymmetrically signaling homodimers
- Functional effect on melanocortin 4 receptor (MC4R) signaling
- First-ever melanocortin biased ligands to favor cAMP signaling pathways over β-arrestin recruitment pathways when targeting MC4R
- Easily applied both in vitro and in vivo to various GPCR systems
- Mix-and-match pharmacophore system uses known pharmacophores to create bivalent ligands with a biased pharmacology for different GPCRs

**APPLICATIONS:**

- Probe compounds
- Potential use as a therapeutic
- Studying various GPCR systems or melanocortin signaling in disease states and disorders in which melanocortin receptors are implicated (e.g., cancer, skin pigmentation disorders, social disorders, sexual function disorders, Alzheimer’s disease, cachexia and obesity)
- Studying biased ligand signaling
- Developing more bivalent ligands that target dimers (both homo- and hetero-) of GPCRs

**Phase of Development** - In vitro assessment: synthesis of all compounds, in vitro cellular assays

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