

Cite this as: Weiwei WANG, Jiangrong ZHANG, Jiahua ZHANG, Yixin YANG, Yan ZHANG. Structure-guided development of G protein-biased apelin receptor agonists for cardiovascular disease. *Journal of Zhejiang University-SCIENCE B*, 2026, 27(10):1059-1065. <https://doi.org/10.1631/jzus.B2600160>

Structure-guided development of G protein-biased apelin receptor agonists for cardiovascular disease

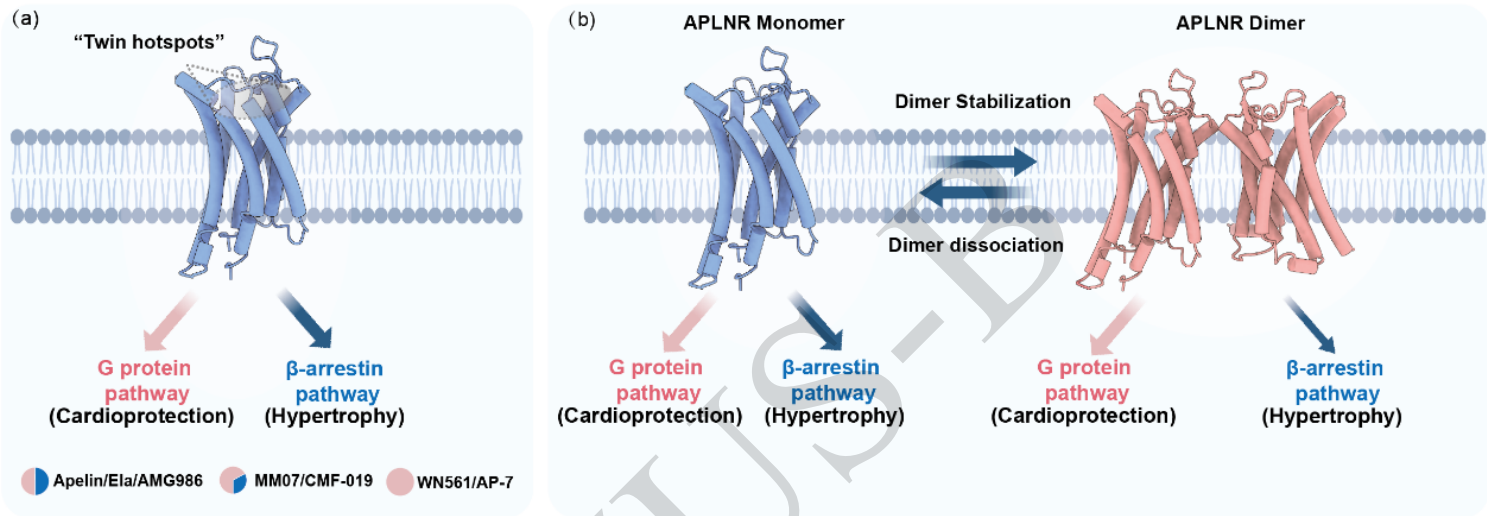
Key words: Apelin receptor (APLNR); G protein-coupled receptor; Biased signaling; Drug design

Research Summary

This review summarizes the physiological and cardiovascular roles of APLNR, elucidates the structural basis of receptor activation and biased signaling, and highlights the structure-guided development of G protein-biased agonists that preserve beneficial G_i signaling while minimizing β -arrestin-mediated adverse effects. Emerging strategies integrating artificial intelligence and oligomer-selective targeting are further discussed.

- Physiological roles and therapeutic potential of APLNR in the cardiovascular system**
- Structural mechanisms underlying APLNR activation and biased signaling**
- Structure-guided development and future design of G protein-biased APLNR agonists**

Innovation points



- Establishment of a structural framework linking ligand binding to APLNR activation and downstream signaling bias.
- Identification of complementary mechanisms governing biased signaling through ligand-dependent "twin hotspots" and receptor monomer–dimer transitions.
- Translation of structural insights into the rational development of exclusive G protein-biased agonists with precisely defined signaling profiles.

Future perspectives

Future directions for precision targeting of APLNR

- 1 | AI-guided design of peptide and small-molecule APLNR agonists based on expanding structural datasets and predefined signaling profiles.**
- 2 | State-selective ligand design targeting dynamic APLNR conformational ensembles rather than a single static receptor structure.**
- 3 | Oligomer-selective targeting as a potential strategy to favor Gi signaling by modulating the APLNR monomer–dimer equilibrium.**

Challenge for clinical application: APLNR-directed designs require experimental validation of ligand binding, receptor selectivity, Gi activation, β -arrestin recruitment, and oligomeric-state effects rather than relying on structural predictions alone.