ISSN Print: 2664-6781
ISSN Online: 2664-679X
IJACR 2022; 4(2): 401-403
www.chemistryjournals.net
Received: 07-09-2022
Accepted: 11-10-2022

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Advances in the design of allosteric modulators for GPCRs

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DOI: https://doi.org/10.33545/26646781.2022.v4.i2f.196

Abstract
G protein-coupled receptors (GPCRs) represent one of the largest and most diverse families of membrane proteins involved in signal transduction. They are crucial targets for a significant portion of therapeutic drugs. Allosteric modulators, which bind to sites distinct from the orthosteric ligand-binding site, offer several advantages, including improved selectivity and reduced side effects. This review provides a comprehensive overview of recent advances in the design of allosteric modulators for GPCRs, discussing key principles, methodologies, and therapeutic implications. The review also explores the structural basis of allosteric modulation, computational strategies for identifying allosteric sites, and the latest developments in the therapeutic targeting of GPCRs using allosteric modulators.

Keywords: GPCRs, allosteric modulators, drug design, signal transduction, therapeutic targeting, computational strategies

Introduction
G protein-coupled receptors (GPCRs) are integral membrane proteins that play a pivotal role in cellular signal transduction. They respond to a wide array of external stimuli, including hormones, neurotransmitters, and sensory signals, to mediate numerous physiological processes. Due to their central role in various biological pathways, GPCRs are prominent targets in drug discovery, with approximately one-third of all marketed drugs targeting these receptors. Traditional drug discovery has focused on orthosteric ligands, which compete with endogenous ligands for binding to the primary active site. However, the limitations of orthosteric ligands, such as poor selectivity and potential side effects, have driven interest in allosteric modulators, which bind to alternative sites on the receptor.
Allosteric modulators can fine-tune receptor activity by altering the conformation of the receptor and, consequently, its response to endogenous ligands. This review aims to provide a detailed discussion of recent advances in the design of allosteric modulators for GPCRs. We will explore the structural basis of allosteric modulation, key principles guiding the discovery and optimization of allosteric modulators, computational strategies employed in their identification, and the therapeutic potential of these novel compounds.

Structural basis of allosteric modulation
Allosteric modulation involves the binding of a modulator to a site on the receptor that is distinct from the orthosteric site. This binding induces conformational changes in the receptor, which can enhance or inhibit the receptor's response to its endogenous ligand. The structural elucidation of GPCRs through techniques such as X-ray crystallography and cryo-electron microscopy (cryo-EM) has provided significant insights into the locations and characteristics of allosteric sites.
Recent structural studies have identified several key features of allosteric sites on GPCRs. These sites are often located within the transmembrane domain, where they can influence the conformation of the receptor's intracellular and extracellular regions. For example, the binding of an allosteric modulator to the M2 muscarinic receptor has been shown to stabilize a specific receptor conformation that enhances the binding affinity of acetylcholine, the endogenous ligand [1]. Similarly, the structure of the glucagon-like peptide-1 receptor (GLP-1R) bound to an allosteric modulator has revealed how allosteric binding can modulate receptor activation and downstream signaling pathways [2].

Principles in the design of allosteric modulators

The design of allosteric modulators involves several key principles that distinguish them from orthosteric ligands. These principles include:

Allosteric modulators offer improved selectivity for their target receptors due to the unique and less conserved nature of allosteric sites compared to orthosteric sites. This selectivity reduces the likelihood of off-target effects. Additionally, allosteric modulators can exhibit positive or negative cooperativity with the orthosteric ligand, enhancing or inhibiting the receptor's response in a more nuanced manner than orthosteric ligands alone [3].

Unlike orthosteric ligands, the effects of allosteric modulators are saturable, meaning that once the allosteric site is fully occupied, further increases in modulator concentration do not increase the effect. This property can reduce the risk of overstimulation and associated side effects, providing a safety advantage in therapeutic applications [4].

Allosteric modulators can promote biased signalling by preferentially stabilizing specific receptor conformations that favor particular signalling pathways. This ability to selectively modulate downstream signalling responses opens new avenues for therapeutic intervention by targeting specific physiological processes while minimizing unwanted effects [5].

Computational strategies for identifying allosteric sites

Advances in computational chemistry have significantly contributed to the identification and characterization of allosteric sites on GPCRs. Computational strategies include:

Molecular docking and virtual screening are widely used to predict the binding of potential allosteric modulators to GPCRs. These techniques involve the use of computational algorithms to simulate the binding of small molecules to receptor structures, allowing researchers to identify and rank potential modulators based on their predicted binding affinities and interactions [6].

Molecular dynamics (MD) simulations provide dynamic insights into the conformational changes and interactions of GPCRs in the presence of allosteric modulators. MD simulations can reveal the stability of allosteric binding, the impact on receptor conformation, and the potential for cooperative interactions with orthosteric ligands. These simulations are particularly useful for understanding the mechanistic basis of allosteric modulation and guiding the design of more effective modulators [7].

Machine learning (ML) and artificial intelligence (AI) techniques are increasingly being applied to the discovery of allosteric modulators. ML algorithms can analyze large datasets of known modulators and receptor structures to identify patterns and predict novel allosteric sites and modulators. AI-driven approaches can accelerate the drug discovery process by automating the identification and optimization of potential modulators [8].

The therapeutic potential of allosteric modulators for GPCRs is vast, with applications across numerous disease areas. Allosteric modulators offer several advantages over traditional orthosteric drugs, including improved selectivity, reduced side effects, and the ability to modulate receptor activity in a more nuanced manner.

GPCRs play a critical role in the central nervous system, and allosteric modulators have shown promise in treating various neurological disorders. For example, positive allosteric modulators (PAMs) of the metabotropic glutamate receptor 5 (mGluR5) have demonstrated potential in treating schizophrenia and other cognitive disorders by enhancing glutamatergic signalling without the side effects associated with direct agonists [9].

Allosteric modulators targeting GPCRs involved in metabolic regulation offer new therapeutic options for conditions such as diabetes and obesity. The GLP-1R, a key receptor in glucose homeostasis, has been targeted by allosteric modulators to enhance insulin secretion and improve glycemic control in patients with type 2 diabetes [10]. GPCRs are also implicated in cardiovascular function, and allosteric modulators have been explored for the treatment of hypertension and heart failure. Allosteric modulators of the beta-adrenergic receptors, for example, have the potential to provide more targeted modulation of cardiac function compared to traditional beta-blockers [11].

The role of GPCRs in cancer progression and metastasis has led to the exploration of allosteric modulators as anticancer agents. Modulators of the chemokine receptors CXCR4 and CCR5 have shown promise in inhibiting tumor growth and metastasis by disrupting chemokine signalling pathways [12].

Recent advances in the field of allosteric modulation for GPCRs include the development of more sophisticated computational models, the discovery of novel allosteric sites, and the design of modulators with improved pharmacokinetic properties. Structural biology techniques, such as cryo-EM, continue to provide high-resolution insights into GPCR-allosteric modulator complexes, guiding the rational design of new modulators.

Future directions in the field include the integration of multi-scale modelling approaches that combine atomic-level simulations with systems biology to understand the broader physiological impact of allosteric modulation. Advances in AI and ML will likely further enhance the identification and optimization of allosteric modulators, accelerating the drug discovery process. Additionally, the exploration of combination therapies that leverage both orthosteric and allosteric modulators offers a promising avenue for achieving more precise and effective therapeutic outcomes.

Conclusion

The design of allosteric modulators for GPCRs represents a significant advancement in drug discovery, offering improved selectivity, reduced side effects, and the potential for biased signalling. Advances in structural biology, computational chemistry, and AI have significantly contributed to the identification and optimization of allosteric modulators. The therapeutic potential of these modulators spans various disease areas, including neurological disorders, metabolic diseases, cardiovascular conditions, and cancer. As research in this field continues to evolve, allosteric modulators are poised to play an increasingly important role in the development of novel therapeutics.

References

1. Kruse AC, Ring AM, Manglik A, *et al*. Activation and allosteric modulation of a muscarinic acetylcholine receptor. Nature. 2013;504(7478):101-106.
2. Wootten D, Reynolds CA, Koole C, *et al*. A hydrogen-bond network between transmembrane helices drives the activation of the glucagon-like peptide-1 receptor. Nature Communications. 2016;7:12484.

3. May LT, Leach K, Sexton PM, Christopoulos A. Allosteric modulation of G protein-coupled receptors. Annual Review of Pharmacology and Toxicology. 2007;47:1-51.
4. Conn PJ, Christopoulos A, Lindsley CW. Allosteric modulators of GPCRs: A novel approach for the treatment of CNS disorders. Nature Reviews Drug Discovery. 2009;8(1):41-54.
5. Kenakin T. Functional selectivity through protean and biased agonism: Who steers the ship? Molecular Pharmacology. 2007;72(6):1393-1401.
6. Morris GM, Huey R, Olson AJ. Using AutoDock for ligand-receptor docking. Current Protocols in Bioinformatics. 2008;24:8-14.
7. Dror RO, Dirks RM, Grossman JP, Xu H, Shaw DE. Biomolecular simulation: A computational microscope for molecular biology. Annual Review of Biophysics. 2012;41:429-452.
8. Vamathevan J, Clark D, Czodrowski P, *et al*. Applications of machine learning in drug discovery and development. Nature Reviews Drug Discovery. 2019;18(6):463-477.
9. Nicoletti F, Bruno V, Catania MV, *et al*. Group I metabotropic glutamate receptors: Hypothesis and mechanisms of action in neurodegenerative diseases. Neuropharmacology. 1996;35(7):1009-1021.
10. Knudsen LB, Lau J. The discovery and development of liraglutide and semaglutide. Frontiers in Endocrinology. 2019;10:155.
11. Woo AY, Xiao RP. β-Adrenergic receptor subtype signaling in heart: from bench to bedside. Acta Pharmacologica Sinica. 2012;33(3):335-341.
12. Duda DG, Kozin SV, Kirkpatrick ND, *et al*. CXCL12 (SDF1α)-CXCR4/CXCR7 pathway inhibition: An emerging sensitizer for anticancer therapies? Clinical Cancer Research. 2011;17(8):2074-2080.