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Review Article

Biased Agonism in Drug Discovery: Clinical Promise and Pitfalls

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ABSTRACT

The discovery of biased agonism as a pharmacological technique that enables specific receptor pathway activation through ligands transformed receptor pharmacology. The analysis evaluates the fundamental mechanisms and medical implications alongside the development hurdles for biased agonist drug discovery. The research analyzed PubMed alongside Scopus and Web of Science databases for articles between 2000 and 2024 under keywords that included "biased agonism" "GPCR signalling" and "functional selectivity." The review included articles about biased agonist mechanistic aspects together with clinical applications and regulatory frameworks. The study demonstrates how biased agonism enables therapeutic benefits through reduced unwanted effects specifically within opioid and adrenergic signalling pathways. Clinical studies of oliceridine and carvedilol demonstrate proof-of-concept yet their transition from laboratory research to clinical applications faces ongoing challenges. The context-dependent nature of receptor signalling together with methodological inconsistencies prevents accurate translation. Our analysis reveals the main challenges of assay inconsistency together with regulatory ambiguity and the reduction of complex signalling to simple dichotomies. New technologies which include cryo-EM organoids and AI-driven ligand screening systems provide predictive frameworks to scientific research. The practice of precision pharmacotherapy shows great potential through biased agonism. Biased agonism requires collaboration between different fields together with improved biomarkers and revised regulatory standards to achieve full therapeutic benefits.

Keywords: Biased Agonism, GPCR Signalling, Functional Selectivity, Therapeutic Window, Drug Discovery, Translational Pharmacology.

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INTRODUCTION

According to traditional receptor theory agonist binding produces equivalent activation of every linked signalling pathway. Biased agonists produce different receptor shapes that lead to the activation of particular intracellular signalling molecules (Kenakin, 2011). The first description of biased agonism occurred in G-Protein-Coupled Receptors (GPCRs) since they represent the largest drug-targeted receptor family in pharmacology.

The dual-pathway activation (e.g., G protein vs. β-arrestin) opens avenues to fine-tune therapeutic responses. Through biased activation of μ-opioid receptors oliceridine achieves analgesic effects through G protein pathways while reducing adverse effects related to β-arrestin activation (DeWire *et al.*, 2013). The method now applies to drug development beyond GPCRs through Receptor Tyrosine Kinases (RTKs) and nuclear receptors (Rittiner *et al.*, 2023). In this review aims to explain the mechanistic basis of biased agonism, evaluate current methodologies to quantify it, highlight clinically validated biased agonists, examine its therapeutic potential and pitfalls, and suggest future research directions.

METHODOLOGY

This is a narrative review. A literature search was conducted using PubMed, Scopus, and Web of Science (2000-2024) with keywords: biased agonism, GPCR signalling, functional selectivity, β-arrestin, drug discovery. This review included peer-reviewed English-language articles focusing on mechanistic and preclinical or clinical aspects of biased agonists. The research excluded studies written in non-English languages together with preprints and non-peer-reviewed literature. This review was not registered in PROSPERO because it fails to meet systematic review criteria.

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MECHANISTIC BASIS OF BIASED AGONISM

Biased agonism occurs through ligand-induced stabilization of receptor conformations that activate particular intracellular signalling pathways (Van der Westhuizen *et al.*, 2014). Research indicates that traditional views about receptors having a single "active" conformation do not apply because receptors instead exist in equilibrium between various active and inactive states. The chemical structure along with binding kinetics of ligands determines which receptor conformations become preferred to interact with specific effectors.

GPCRs function as the fundamental model of biased agonism because one receptor interacts with both G proteins and β-arrestins among its downstream effectors.

The rapid second-messenger signals cyclic AMP (cAMP), Inositol Trisphosphate (IP3) and calcium mobilization originate from G protein interactions.

The GPCR signalling process is desensitized through β-arrestin interaction which leads to receptor internalization alongside the activation of ERK1/2 p38 MAPK and JNK pathways without G protein involvement (Luttrell and Lefkowitz, 2002).

The structural mechanisms behind biased agonism have become clearer through recent advances in cryo-Electron Microscopy (cryo-EM) combined with molecular dynamics simulations. The techniques reveal that different ligands produce distinct receptor shapes which lead to particular effector coupling patterns (Shukla *et al.*, 2011; Weis and Kobilka, 2018).

The binding kinetics between ligands and receptors can be monitored through NMR spectroscopy to show how they affect the degree and direction of signalling bias (Manglik *et al.*, 2015). Non-orthosteric receptor conformations become stabilized by allosteric modulators which can either enhance or inhibit bias (Christopoulos, 2014).

The cellular environment plays a vital role in the modulation process. Different factors including receptor density and G protein subtypes and scaffolding proteins and membrane lipid composition determine both the magnitude and type of biased signalling (Smith and Rajagopal, 2016; Thomsen *et al.*, 2016). Research shows that the duration a ligand stays on a receptor surface determines receptor conformational changes which lead to signalling results (Copeland, 2016).

Biased agonism arises from the dynamic interactions between receptors and ligands and effectors within cellular environments rather than being a ligand property. The drug development process needs to include this mechanistic complexity to achieve reproducible and clinically meaningful results (Eddy *et al.*, 2018).

QUANTIFICATION AND MEASUREMENT OF BIASED AGONISM

Biased agonism is quantified by comparing ligand-induced responses across different signalling pathways:

- Operational Model of Agonism (Black-Leff Model),
- Transduction Coefficient,
- Equiactive Comparison: comparing ligand responses at the same effect level (Michel *et al.*, 2020).

BRET, FRET and impedance-based label-free assays serve as tools for functional bias profiling. Standardized protocols remain essential because assay system variability such as receptor expression levels generates biased results (Dahan *et al.*, 2020). Machine learning tools predict bias from ligand-receptor interaction datasets (Rodríguez *et al.*, 2021).

CLINICALLY RELEVANT BIASED AGONISTS

Oliceridine

The FDA approved oliceridine (TRV130) as a μ-opioid Receptor (MOR) agonist to treat moderate-to-severe acute pain in adults when traditional pain treatments fail (U.S. FDA, 2020). Oliceridine differs from traditional opioids because it activates G protein-biased agonism at the μ-opioid receptor (Table 2). The μ-opioid receptor agonist oliceridine activates G protein pathways that produce analgesia without triggering β-arrestin-2 activation which leads to adverse effects such as respiratory depression and constipation and opioid tolerance (DeWire *et al.*, 2013). The drug's selective signalling properties are thought to provide enhanced safety benefits.

Preclinical experiments on animals revealed that oliceridine produced strong pain relief together with substantially decreased respiratory and gastrointestinal adverse effects when compared to morphine administration (DeWire *et al.*, 2013; Manglik *et al.*, 2016). The experimental findings created hope that biased agonism could lead to a breakthrough in opioid treatment methods. The pharmacokinetic profile of oliceridine shows rapid intravenous delivery which starts pain relief within 2-5 min while having a short elimination period between 1.3 to 3 hr. The drug undergoes primary metabolism through CYP3A4 and CYP2D6 enzymes while showing 77% plasma protein binding according to the U.S. FDA (2020). The compound leaves the body through liver processing along with urinary waste.

The positive results from preclinical studies failed to translate into substantial benefits during clinical trial phases. The Phase 3 clinical trials APOLLO-1 and APOLLO-2 showed that oliceridine delivered analgesia equivalent to morphine for postoperative pain management (Viscusi *et al.*, 2019; Singla *et al.*, 2019). The clinical trials showed a possible decrease in respiratory safety complications alongside reduced gastrointestinal side effects

although these results failed to reach statistical significance. Oliceridine preserves its potential for abuse despite being classified as a Schedule II controlled substance by the U.S. FDA (U.S. FDA, 2020). The adverse effects of oliceridine include nausea, vomiting, sedation and respiratory depression but their intensity may be lower in particular clinical contexts.

The clinical advantages of oliceridine as a G protein-biased opioid approved by the FDA are restricted because it does not offer substantial benefits over conventional opioids. Oliceridine serves only as a short-term treatment under hospital supervision due to its fast-acting IV formulation. The drug functions primarily to validate biased agonism concepts rather than provide a revolutionary pain management solution. Research into new biased ligands continues because they show promise to improve both efficacy and safety while maintaining high selectivity (Manglik *et al.*, 2016; Kliewer *et al.*, 2020).

Carvedilol

Carvedilol functions as a non-selective β-adrenergic receptor blocker which provides additional α_1-adrenergic blocking properties and serves as a common medication for heart failure and hypertension treatment. Research has elevated carvedilol's status to a β-arrestin-biased ligand at the β_1-Adrenergic Receptor (β_1-AR) in addition to its established function as a G Protein-Coupled Receptor (GPCR) antagonist (Table 1). Carvedilol functions differently from standard β-blockers since it blocks G protein pathways while stimulating β-arrestin-dependent pathways particularly EGFR transactivation which results in its beneficial cardioprotective effects (Wisler *et al.*, 2007).

Carvedilol blocks the Gs protein-coupled signalling cascade that produces cyclic AMP thus decreasing heart rate and contractility which helps patients with reduced ejection fraction heart failure. Unlike other β-blockers carvedilol both blocks the β_1-AR from G protein signalling and recruits β-arrestin to activate downstream pathways that do not need G proteins. The activation of ERK1/2 pathways through EGFR transactivation occurs as part of β-arrestin signalling which leads to cardiomyocyte survival and prevents cell death (Kim *et al.*, 2008). The drug functions beyond antagonist properties to exhibit functional selectivity which positions it as an early clinical application of biased ligands.

Research demonstrates carvedilol triggers β-arrestin-mediated signalling to enhance cardiac remodeling processes and reduce oxidative stress while protecting myocytes from death particularly during β-adrenergic receptor overactivation found in heart failure patients (Noma *et al.*, 2007). These therapeutic advantages operate independently from blood pressure reduction and do not apply to all β-blockers. Research comparing carvedilol to metoprolol in animal experiments confirmed that carvedilol specifically triggered β-arrestin-dependent ERK signalling because of its unique signalling bias (Wisler *et al.*, 2007; Kim *et al.*, 2008).

Carvedilol comes in oral form and its bioavailability reaches 25-35% before undergoing extensive first-pass metabolism through CYP2D6 and CYP2C9 enzymes. The half-life of carvedilol ranges between 7 to 10 hr and it binds heavily to proteins while primarily eliminating through bile and feces. The drug presents as a racemic mixture where the S-enantiomer performs β-blockade functions and the R-enantiomer provides more α_1-blocking activity (Rehsia and Dhalla, 2010). Its dual pharmacological properties create an effective treatment solution for lowering blood pressure and managing afterload while reducing sympathetic nervous system activity.

The medical literature shows carvedilol lowers death rates together with hospital readmissions among patients who have chronic heart failure based on results from both COPERNICUS and COMET trials. The biased signalling properties of carvedilol have gained recognition as vital contributors to its protective effects on the heart although its clinical benefits are traditionally linked to its dual β- and α-blocking activities (Lymperopoulos *et al.*, 2013). Research continues to develop β-arrestin-biased ligands beyond carvedilol to optimize heart protection while minimizing standard β-blocker adverse effects.

The therapeutic application of carvedilol demonstrates how biased agonism functions through blocking dangerous G protein-mediated β_1-AR signalling while simultaneously activating protective β-arrestin pathways. The drug's distinct pharmacological characteristics introduce a new concept of adrenergic drug action which will guide development of future cardio-selective agents that use signalling bias advantages.

TRV027

A β-arrestin-biased AT1R ligand explored for acute heart failure. The BLAST-AHF trial demonstrated unsuccessful clinical outcomes although the drug exhibited promising mechanisms (Felker *et al.*, 2017).

Table 1: Comparison of G Protein vs β-Arrestin Signalling.

Feature	G Protein Pathway	β-Arrestin Pathway
Activation	cAMP, Ca^{2+}	ERK, JNK, receptor internalization
Signal Duration	Transient	Sustained.
Therapeutic Role	Primary response	Modulatory/ counter-regulatory
Associated with	Analgesia, cardiac effects	Desensitization, side effects
Tools for detection	cAMP assay, calcium flux	BRET/FRET, phosphorylation assays

ERK-Extracellular Signal-Regulated Kinase, JNK-c-Jun N-terminal Kinase, BRET-Bioluminescence Resonance Energy Transfer, FRET-Fluorescence Resonance Energy Transfer.

Table 2: Key Examples of Clinically Relevant Biased Agonists.

Drug	Target Receptor	Bias Direction	Clinical Indication	Status
Oliceridine	μ-Opioid receptor	G protein-biased	Acute pain	Approved
Carvedilol	β1-Adrenergic receptor	β-arrestin-biased	Heart failure	Approved
TRV027	AT1R (angiotensin)	β-arrestin-biased	Acute HF	Failed Phase II
Biased 5-HT2A ligands	Serotonin receptor	G protein-biased	Mood disorders	Preclinical
Biased D2 agonists	Dopamine receptor	G protein-biased	Schizophrenia	Early Clinical

AT1R- Angiotensin II Type 1 Receptor, HF- Heart Failure, 5-HT2A- 5-Hydroxytryptamine 2A Receptor, TRV027 = Compound number 027 developed by Trevena Inc

Other Examples

Schizophrenia research explores biased ligands for D2 dopamine receptors as do studies on mood disorders that use 5-HT2A serotonin receptor targets (Schmid *et al.*, 2017).

Biased agonism offers several benefits during drug discovery processes

- Enhanced Therapeutic Selectivity: Tailored pathway activation reduces side effects
- Reduced Tolerance: The absence of β-arrestin-mediated desensitization leads to sustained efficacy.
- Drug Repurposing: Biased signalling can rescue previously abandoned ligands.
- Precision Medicine: Biased ligands allow context-specific receptor targeting.
- Intellectual Property Advantages: Novel scaffolds enable extended patent lifespans (Christopoulos, 2002).

Pitfalls and Limitations

- *In vitro* vs. *In vivo* Disconnect: Ligand bias often fails to predict clinical efficacy,
- Context Dependence: Cell type, receptor reserve and assay systems influence the results of bias experiments (Onaran and Costa, 2012),
- Over-Simplification: Pathway categorization into beneficial or harmful types can lead to errors since β-arrestins exhibit detrimental effects in particular situations,
- Regulatory Barriers: The drug approval systems do not have established criteria for pathway-selectivity (Iijima *et al.*, 2020),
- Interpretation Risks: Small differences in bias may be over-interpreted.

Emerging Trends and Future Directions

- AI/ML Tools: Predicting ligand bias using structural fingerprints and deep learning,
- Allosteric Modulators: Targeting non-orthosteric sites to promote functional selectivity,
- Beyond GPCRs: Biased signalling now observed in RTKs, cytokine receptors, and nuclear receptors,
- Organoids and Organ-on-Chip: Enhancing physiological relevance of functional assays. (Low *et al.*, 2021),
- Regulatory Innovations: Emphasis on novel biomarkers, patient stratification, and adaptive trials for biased ligands.

CONCLUSION

The drug discovery approach of biased agonism transforms drug development by providing improved selectivity and efficacy. Its clinical application remains limited due to methodological inconsistencies and regulatory gaps as well as the complex nature of receptor signalling. Future success will depend on Standardized functional assays, Robust translational models, Clear regulatory guidelines, Interdisciplinary collaboration, Biased agonism will serve as a fundamental element in the development of upcoming precision pharmacotherapy treatments.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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