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REVIEW

β-ARRESTINS AS KEY SWITCHES IN GPCR SIGNALING: FROM MOLECULAR STRUCTURE TO CLINICAL IMPLICATIONS — A NARRATIVE REVIEW

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Abstract: For many years, β-arrestins have been primarily recognized for their role in the desensitization and internalization of G protein-coupled receptors (GPCRs). More recently, however, they have emerged as versatile molecular switches that not only terminate G protein-dependent signaling but also initiate distinct intracellular pathways, shaping both the strength and duration of receptor responses. Advances in structural biology have revealed that β-arrestins adopt multiple conformations determined by receptor-specific phosphorylation "barcodes," enabling functional diversity across tissues and receptor subtypes. This review summarizes the current insights into β-arrestin structure, activation mechanisms, and signaling roles, with particular emphasis on their contribution to neuronal function, synaptic plasticity, and neurodegenerative processes. The emerging concept of functional selectivity (biased agonism), whereby ligands preferentially engage either β-arrestin- or G protein-mediated pathways, is also discussed. Clinically relevant examples—including carvedilol, oliceridine, tirzepatide, and biased dopamine or serotonin receptor ligands—illustrate how selective pathway targeting can improve therapeutic efficacy while minimizing side effects. Taken together, these advances redefine β-arrestins as dynamic regulators of GPCR signaling and highlight their potential as promising targets for next-generation therapeutics in neuropsychiatric and neurodegenerative disorders.

Keywords: β-arrestins; GPCR; signal transduction; receptor internalization; functional selectivity; biased agonism; central nervous system diseases.

G protein-coupled receptors (GPCRs) constitute the largest family of membrane receptors in the human body. The human genome encodes over 800 GPCR genes, and approximately one-third of all clinically approved drugs (over 500 compounds) exert their effects through this receptor family [1]. In recent years, however, attention has increasingly shifted beyond the receptors themselves to include the regulatory and signaling proteins that modulate their activity. Among these, β-arrestins have emerged as particularly important players [2, 3].

β-arrestins (β-arrestin-1 and β-arrestin-2) are 44–48 kDa proteins that act as key regulators of GPCR function. Their activity extends well beyond the classical "silencing" of receptor signaling. Although for many years they were regarded primarily as mediators of receptor desensitization, recent studies have revealed their broader signaling roles, including the initiation of alternative intracellular cascades independent of G proteins [2, 4–8].

As pharmacology and neurobiology continue to advance, elucidating the roles of β-arrestins has become essential for a comprehensive understanding of the complexity of GPCR signaling. Thus, the present review integrates structural, molecular, and pharmacological perspectives, emphasizing the therapeutic potential of β-arrestin-targeted drug design for enhanced efficacy and safety.

Structure and Activation Mechanisms of β-Arrestins

Crystallographic and cryo-EM studies have revealed that β-arrestin-1 and β-arrestin-2 share a conserved two-domain architecture composed of

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an N-terminal and C-terminal domain connected by a flexible hinge [9–11]. In the inactive state, these domains form a compact arrangement stabilized by two key intramolecular interactions: the polar core—a network of electrostatic contacts among Asp, Arg, and Lys residues—-and the three-element interaction, which tethers the C-terminal tail to the N-domain. This conformation maintains β-arrestins in an autoinhibited state, preventing spontaneous engagement with receptors or signaling partners [12].

Upon ligand binding and activation of a GPCR, G protein-coupled receptor kinases (GRKs) phosphorylate serine and threonine residues on the cytoplasmic domains of the receptor. These phosphorylation events generate high-affinity docking sites for β-arrestins, which translocate from the cytosol to the plasma membrane to engage the receptor. This process follows the phosphorylation barcode mechanism, in which distinct phosphorylation patterns on the receptor's C-terminal tail and/or intracellular loops encode specific β-arrestin conformations and activation states [5, 13–16].

Recognition of these phosphorylated motifs by positively charged residues within β-arrestin leads to disruption of the internal polar core, allowing interdomain rotation and release of the finger loop, a structural element capable of inserting into the transmembrane cavity of the receptor. Depending on the phosphorylation pattern and receptor context, β-arrestins can adopt at least two major modes of interaction [5, 13, 17].

In the core conformation, the released finger loop penetrates the transmembrane cavity of the receptor, occupying the site that normally binds the C-terminal α5 helix of the Gα subunit (Figure 1). This configuration sterically prevents further G protein coupling and fully desensitizes canonical G protein-dependent signaling while stabilizing β-arrestin in an active conformation that can scaffold downstream effectors, such as ERK1/2, Src, or JNK [5, 11, 18, 19].

In contrast, in the tail conformation, β-arrestin binds primarily to the phosphorylated receptor tail without finger loop insertion. In this partially engaged state, the receptor may remain coupled to its G protein, forming a megaplex that enables sustained or spatially restricted signaling from endosomes [20]. Within these endosomal megaplexes, the receptor remains in an active, G protein-coupled state despite β-arrestin association, allowing continued generation of second messenger,s such as cAM,P from internal compartments [21]. This spatially confined signaling prolongs and diversifies GPCR responses,

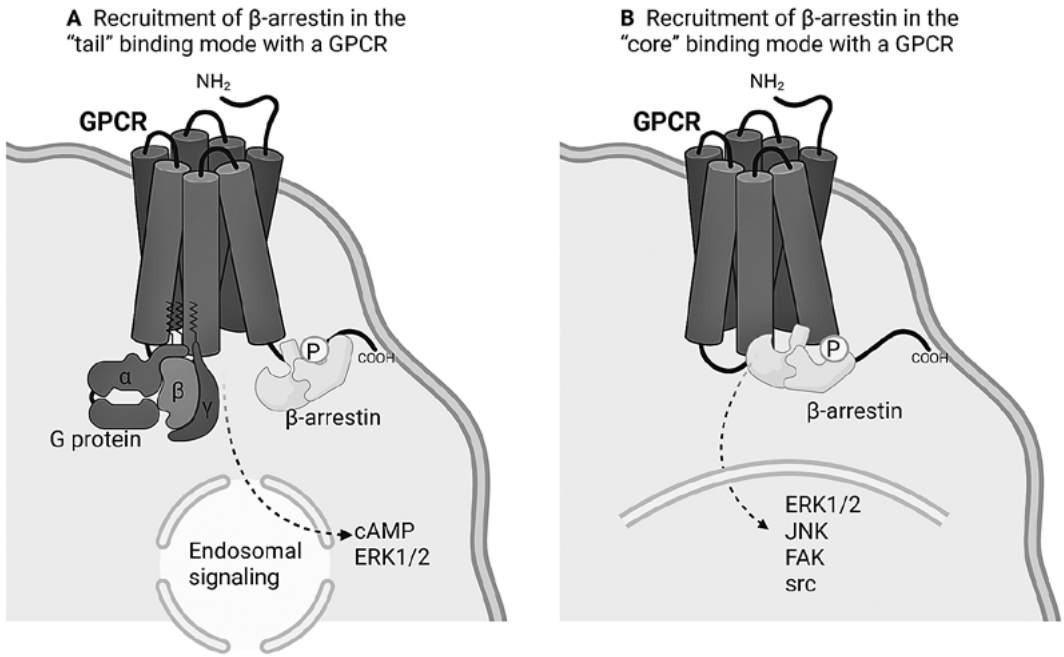

Figure 1. Two binding modes of β-arrestin to G protein–coupled receptors (GPCRs) A. Tail conformation - β-arrestin primarily interacts with the phosphorylated C-terminal tail of the receptor, with minimal insertion into its transmembrane core. This configuration permits simultaneous G-protein coupling, forming a receptor-G protein-β-arrestin "megaplex" that supports sustained endosomal signaling, including cAMP and ERK activation. B. Core conformation - β-arrestin inserts its "finger loop" between the transmembrane helices of the GPCR, occupying the position of the G protein and thereby inhibiting classical G protein-dependent signaling. This fully engaged state enables β-arrestin-dependent signaling through alternative pathways, including ERK1/2, JNK, FAK, and Src kinases. The figure was created with BioRender.com.

providing a mechanistic basis for ligand-specific kinetic bias and for the sustained physiological effects observed with certain class B receptors, including PTH_1R and V_2R [21–23].

These structural states illustrate how receptor-specific phosphorylation barcodes can dictate distinct β-arrestin conformations and, consequently, distinct signaling outcomes. Rather than acting as simple terminators of GPCR activity, β-arrestins serve as dynamic and selective modulators integrating receptor desensitization, internalization, and alternative signaling (Figure 2).

Functionally, β-arrestin activity can be conceptualized on three hierarchical levels [5, 8]:

(1) Desensitization, involving attenuation of cellular responsiveness through steric blockade of G protein coupling;

(2) Receptor internalization, mediated via β-arrestin-dependent recruitment of adaptor proteins such as AP-2 and clathrin, initiating clathrin-coated pit formation and receptor endocytosis; and

(3) β-arrestin-dependent signaling, which triggers alternative intracellular pathways independent of G proteins.

Through these mechanisms, β-arrestins not only terminate receptor activity at the plasma membrane but also define the spatial and temporal dimensions of cellular signaling—from the plasma

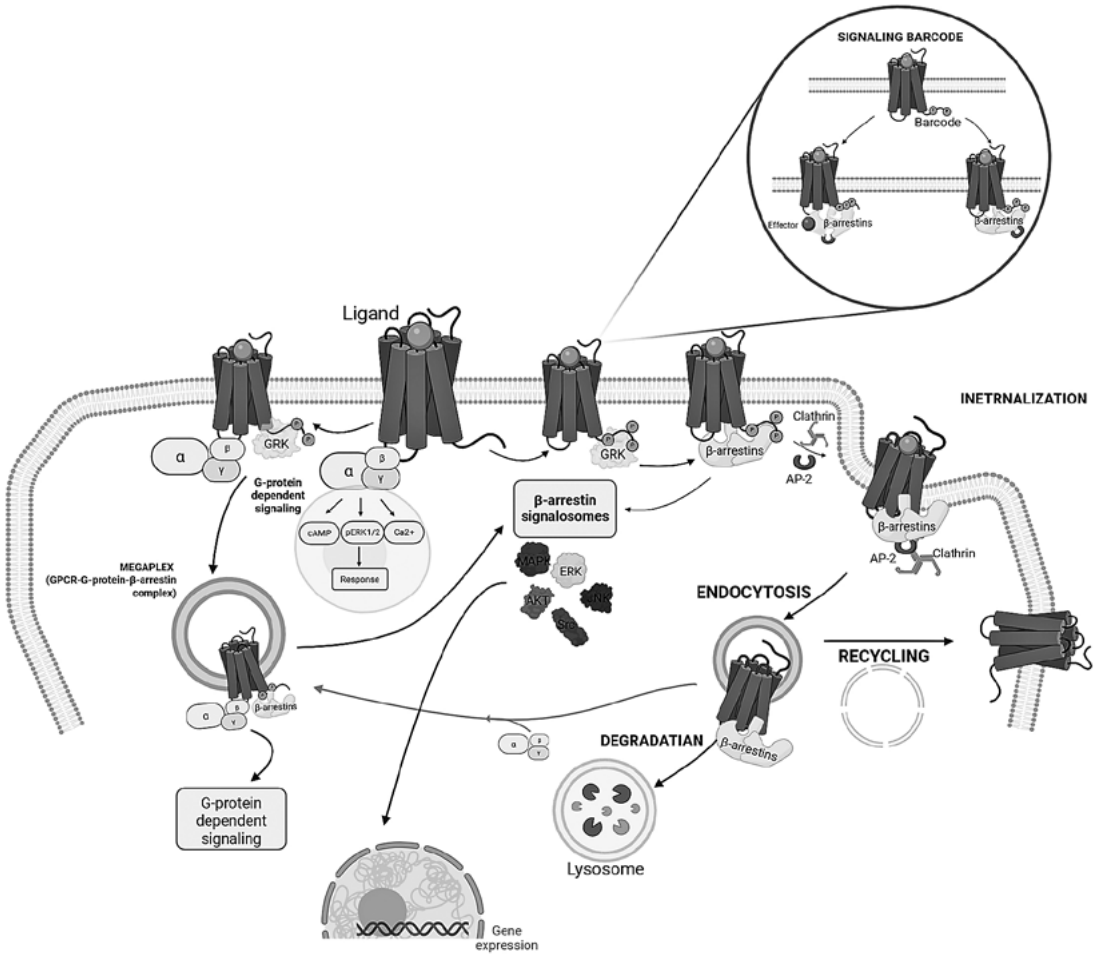

Figure 2. Schematic overview of β-arrestin recruitment and signaling following GPCR activation. Upon ligand binding, the G protein–coupled receptor (GPCR) undergoes a conformational change that enables coupling to the heterotrimeric Gαβγ complex and/or recruits β-arrestins. This activates classical G protein–dependent signaling pathways through membrane-associated effectors such as adenylyl cyclase or phospholipase C, leading to the generation of second messengers (cAMP, Ca^{2+}) and downstream activation of kinases including ERK1/2. Receptor phosphorylation by G protein-coupled receptor kinases (GRKs) creates a receptor-specific "phosphorylation barcode" on its cytoplasmic tail. This barcode determines the mode of β-arrestin engagement-either in the core or in the tail conformation, which allows a megaplex formation. β-arrestin engagement promotes receptor desensitization and internalization via AP-2 and clathrin, while also scaffolding downstream kinases such as ERK1/2, JNK, Src, and AKT. Within endosomes, β-arrestin-receptor complexes mediate G-protein–independent signaling, whereas megaplexes sustain prolonged G-protein–dependent signaling from internalized receptors. Internalized GPCRs are subsequently recycled or degraded, and β-arrestin-mediated kinase activation can modulate long-term nuclear responses. The figure was created with BioRender.com.

membrane to endosomes and even the nucleus. Their subcellular localization can thus be regarded as a pharmacodynamic biomarker reflecting the mode of receptor engagement and signaling bias. Distinct ligands can selectively stabilize one of these functional states, providing a structural basis for biased agonism and expanding the repertoire of GPCR-mediated cellular responses [19].

Activation of MAPK and JNK Pathways by β-Arrestins

β-Arrestin-1 and β-arrestin-2 play crucial roles in the regulation of mitogen-activated protein kinase (MAPK) signaling cascades. Upon GPCR activation and receptor phosphorylation by GRKs, β-arrestins act as scaffold proteins for the sequential assembly of Raf, MEK, and ERK kinases, thereby promoting spatially organized signal propagation independent of G protein activation [24, 25].

In canonical MAPK signaling, ERK activation is mediated through G protein-dependent mechanisms, leading to transient nuclear translocation of phosphorylated ERK (pERK) and subsequent transcriptional responses, such as cell proliferation or differentiation. In contrast, β-arrestin-dependent MAPK activation occurs primarily in the cytoplasm or within endosomal compartments. Here, β-arrestins anchor active ERK molecules in the cytosol, producing non-transcriptional outcomes such as cell migration and cytoskeletal remodeling [14, 26, 27].

Beyond scaffolding, β-arrestins can also promote allosteric activation of ERK [26]. Structural and biochemical data indicate that conformational rearrangements of β-arrestins can directly modulate ERK activity independently of classical upstream kinases. Such mechanisms have been described for β_2-adrenergic, angiotensin AT_1A, vasopressin V_2, and protease-activated receptor-2 (PAR_2) systems [5, 26]. These findings highlight the dual role of β-arrestins, as both scaffolds and allosteric activators, within MAPK signaling networks [25].

Activation of c-Jun N-terminal kinase (JNK) family members by β-arrestins shows distinct isoform selectivity compared to ERK signaling. Specifically, β-arrestin-2 can activate JNK3 by recruiting upstream kinases ASK1, MKK4, and MKK7, and this process can occur independently of receptor activation [17, 28]. β-Arrestin-2 can adopt an active conformation capable of binding and activating JNK3 directly, demonstrating its intrinsic signaling capacity. Two mechanistic modes of β-arrestin-dependent JNK3 activation have been proposed [28]:

(1) a receptor-dependent mode, in which GPCR activation stabilizes β-arrestin-2, promoting ASK1/MKK4/7/JNK3 assembly; and

(2) a receptor-independent mode, in which β-arrestin-2 conformation, ubiquitination state, and kinase-binding ability suffice to initiate signaling autonomously.

The subcellular localization of these β-arrestin-associated kinase complexes—at the plasma membrane, endosomes, cytoplasm, or nucleus—determines distinct biological outcomes (Table 1). Cytoplasmic pERK typically drives migratory and cytoskeletal responses, whereas nuclear pERK promotes transcriptional programs underlying differentiation and adaptation. Importantly, β-arrestins can also initiate intracellular signaling independent of active GPCRs. Conformational changes induced by interactions with other cytoplasmic proteins can recruit kinases and propagate signaling cascades in the absence of receptor engagement [29]. This challenges the traditional view of β-arrestins as passive downstream effectors and supports their role as autonomous signaling regulators within the cell.

Role of β-Arrestins in Central Nervous System

Studies in β-arrestin knockout mice have demonstrated that both β-arrestin-1 and β-arrestin-2 modulate diverse physiological processes, including cardiovascular regulation, metabolism, and central nervous system (CNS) function (Table 2) [37–40]. Decreased β-arrestin activity has been linked to the development of insulin resistance, diabetes, hypertension, neurodegenerative diseases, and cancer [7, 38, 41–45]. This wide functional range underscores their status as multifunctional signaling adaptors and potential therapeutic targets rather than simple regulators of GPCR desensitization [39, 46].

β-Arrestins and Antidepressant Mechanisms

Clinical and preclinical data highlight the critical role of β-arrestin-2 in the action of antidepressant drugs [47–49]. Distinct antidepressant classes modulate β-arrestin-2 expression and subcellular localization in neurons. High β-arrestin expression is observed in brain regions involved in emotional regulation, including the hypothalamus, amygdala, and hippocampus [50]. Altered β-arrestin-2 expression was reported in the hippocampus of rodent depression models, with normalization linked to antidepressant efficacy, while data from the prefrontal cortex and amygdala are supportive but less conclusive [51–55].

β-arrestin-2 knockout mice fail to respond behaviorally to fluoxetine, indicating that β-arrestin-2 is necessary for the therapeutic effects of selective serotonin reuptake inhibitors (SSRIs). Chronic fluoxetine treatment restores β-arrestin-1 and β-arrestin-2 levels in the hypothalamus, but not in the hippocampus or amygdala of corticosterone-exposed animals. Interestingly, antidepressants produce drug-specific effects on β-arrestin-2: fluvoxamine decreases β-arrestin-2 levels in the hippocampus, while imipramine and desipramine increase them [51, 56]. Increased cortical β-arrestin-2 levels after fluvoxamine suggest region-specific redistribution or receptor-specific modulation of β-arrestin signaling complexes. These findings support a tight relationship between β-arrestin-2, serotonergic receptor function, and mood regulation [57, 58].

β-Arrestin Signaling Pathways in Neurons

β-arrestins do not possess intrinsic enzymatic activity but serve as molecular adaptors connecting GPCR activation to downstream signaling cascades, including the MAPK/ERK, PI3K/Akt, and CREB/BDNF pathways [59, 60]. Overexpression or mutation of β-arrestins may activate stress-related kinases, such as JNK, potentially leading to maladaptive responses [61]. β-arrestin regulation of NF-κB signaling appears tissue- and receptor-dependent, with some evidence suggesting that β-arrestin-2 inhibits NF-κB activation and inflammation [62].

Increasing evidence indicates that ERK1/2 and related kinase cascades act as critical mediators of antidepressant responses, partly via the modulation of transcriptional regulators, such as CREB and BDNF [40, 63–66]. β-arrestins serve as scaffolding intermediates that can influence these pathways indirectly by organizing the ERK and Akt/mTOR signaling complexes. From a therapeutic perspective, modulation of β-arrestin-linked kinase networks, rather than direct alteration of β-arrestin expression, may offer a more refined means of

Table 1. Activation of kinases by β-arrestins – mechanisms, localization, and functional outcomes.

Kinase	Gene symbol	β-Arrestin isoform	Activation mechanism	Signal localization	Biological effect/functional outcome
ERK1/2	*MAPK 3 / MAPK1*	β-arrestin-1/β-arrestin-2	Scaffolding of Raf-MEK-ERK complex downstream of GPCR activation	Cytoplasm, endosomes	Cell migration, cytoskeletal remodeling [27, 30]
ERK1/2	*MAPK 3 / MAPK1*	β-arrestin-1/β-arrestin-2	Sustained, non-canonical ERK activation independent of G proteins	Cytoplasm	G protein-independent ERK activation; non-transcriptional signaling [5]
ERK1/2	*MAPK 3 / MAPK1*	β-arrestin-1	Nuclear translocation and interaction with transcriptional regulators (e.g., CREB, HDACs)	Nucleus	Regulation of gene expression, neuroplasticity [31]
JNK3	*MAPK 10*	β-arrestin-2 (specific)	Scaffolding of ASK1-MKK4/7-JNK3 complex	Endosomes, cytoplasm	Stress response, apoptosis, learning and memory modulation [32]
JNK3	*MAPK 10*	β-arrestin-2	Receptor-independent activation following β-arrestin ubiquitination	Cytoplasm	GPCR-independent stress signaling; potential role in neuroprotection [33]
p38 MAPK	*MAPK 14*	β-arrestin-1/β-arrestin-2	β-Arrestin-dependent recruitment of TAB1-TAK1 complex	Cytoplasm	Inflammatory regulation, cytokine production, neuroimmune modulation [34]
Akt/ PI3K	*AKT1/ AKT1/ PIK3CA*	β-arrestin-2	Recruitment of Src-PI3K complex and interaction with insulin receptor substrates	Cytoplasm, plasma membrane	Cell survival, metabolism, anti-apoptotic signaling [35]
NF-κB	*NFKB1 / NFKB2 / RELA*	β-arrestin-2	Modulation of IκB degradation and NF-κB nuclear translocation	Cytoplasm, nucleus	Inhibition of pro-inflammatory gene transcription (context-dependent) [36]

engaging neuroplastic and antidepressant mechanisms [67].

β-Arrestins and Neuronal Plasticity

β-Arrestin-2 is essential for neuronal plasticity and adult neurogenesis [51]. It is required for the SSRI-induced proliferation of neural progenitor cells in the dentate gyrus and hippocampus [68]. Acting as scaffold proteins, β-arrestins coordinate kinase complexes that regulate the phosphorylation of synaptic proteins and thereby modulate processes underlying long-term potentiation (LTP) and long-term depression (LTD) [7]. Moreover, β-arrestin-2-mediated signaling has been implicated in memory reconsolidation processes, with potential therapeutic implications for post-traumatic stress disorder (PTSD) and addiction [7, 60, 69]. Further research is needed to evaluate the possible risks associated with memory modulation through β-arrestin-dependent signaling.

Role of β-Arrestins in Neurodegenerative Diseases and CNS Disorders

An expanding body of evidence links β-arrestins to the pathophysiology of several CNS disorders, including Alzheimer's disease (AD), frontotemporal dementia (FTD) with tau pathology, and Parkinson's disease (PD) [60, 88–90]. Recent studies indicate that β-arrestins serve as key molecular intermediates connecting GPCR signaling with cellular processes that regulate proteostasis, autophagy, and neuronal survival [7, 91].

β-Arrestin-2 in Alzheimer's Disease and Tauopathies

In Alzheimer's disease, β-arrestin-2 has been shown to interact with the α1a subunit of the γ-secretase complex, promoting its translocation into cholesterol-rich lipid raft domains of the plasma membrane. This redistribution enhances

Table 2. Functional roles of β-arrestins in the central nervous system (CNS).

Function	Description	Representative Literature
Receptor regulation (desensitization, internalization)	β-arrestins bind phosphorylated GPCRs, switch signaling from G-protein-dependent to β-arrestin-mediated, recruit AP-2 and clathrin, and direct receptors to endocytosis.	[70–72]
Modulation of neurotransmission (D_2R)	β-arrestin-2 forms the Akt-PP2A complex, inhibiting Akt and disinhibiting GSK3, thereby affecting dopaminergic behaviors.	[73]
ERK pathway activation	β-arrestins scaffold Raf/MEK/ERK components, enhancing ERK activation and retaining pERK in the cytoplasm/endosomes, distinct from G-protein signaling dynamics.	[74,75]
Endosomal signaling	Certain GPCRs form stable receptor-G protein-β-arrestin complexes that sustain long-term signaling from endosomes.	[20,76]
JNK3 activation (β- arrestin-2 specific)	β-arrestin-2 scaffolds the ASK1-MKK4/7-JNK3 axis; activation may occur in receptor-dependent or receptor-independent modes	[17]
cAMP regulation in microdomains (PDE4)	β-arrestins recruit PDE4 to β_2-AR, locally reducing cAMP and PKA activity.	[77]
Wnt/Frizzled signaling (non-classical GPCR)	β-arrestin-2 bridges Dvl and Axin, mediating FZD4 endocytosis and β-catenin modulation.	[78]
Nuclear functions (transcriptional regulation)	β-arrestin-1 translocates to the nucleus and interacts with p300/E2F1, modulating gene expression.	[79]
Opioid tolerance	$Arrb2^{-/-}$ mice display enhanced morphine analgesia and reduced tolerance; β-arrestin-2 is critical for opioid tolerance.	[80, 81]
Role in SSRI action	β-arrestin-2 contributes to fluoxetine's antidepressant effects (neurogenesis, chronic mild stress models).	[51, 82]
5-HT_2A: psychedelic-like behaviors	5-HT_2AR-dependent behaviors are partly β-arrestin-2-dependent and ligand-specific.	[83, 84]
5-HT_1A: pERK/ERK	Moderate β-arrestin recruitment accompanying a high ERK phosphorylation observed of compounds with strong antidepressant activity in rat.	[85, 86]
Allosteric modulation of ERK	β-arrestins can allosterically activate ERK2 independently of upstream kinases.	[26]
Phosphoinositide signaling and endocytosis	β-arrestins enhance local $PI(4,5)P_2$ synthesis via PIP5K recruitment, strengthening GPCR endocytosis.	[87]

amyloid-β (Aβ) peptide generation and accelerates amyloidogenesis. Moreover, the G protein-coupled receptor GPR3 modulates Aβ production through β-arrestin-2 recruitment, further supporting the pathogenic role of this signaling pathway in AD-related mechanisms [91].

In frontotemporal dementia with tau pathology, oligomeric forms of β-arrestin-2 have been implicated in disease progression. Unlike the monomeric form, which appears to be non-pathogenic, oligomerized β-arrestin-2 impairs p62/SQSTM1-dependent autophagy, reducing the clearance of aggregated tau protein and promoting the accumulation of neurotoxic tau species [92]. This impairment of autophagic flux contributes to neurodegenerative progression and highlights the importance of β-arrestin structural state in maintaining neuronal proteostasis.

β-Arrestin Signaling in Parkinson's Disease

In the striatum of patients with Parkinson's disease, increased expression of β-arrestins and GRKs, particularly β-arrestin-2, has been reported [90]. One mechanistic link involves the β_2-adrenergic receptor (β_2AR), which regulates the transcription of the *SNCA* gene encoding α-synuclein. Activation of β_2AR by agonists such as clenbuterol reduces α-synuclein expression and exerts neuroprotective effects, most likely through G protein-mediated signaling [93]. Conversely, β-arrestin-2-dependent signaling has been associated with increased α-synuclein levels, potentially via epigenetic modulation of the *SNCA* promoter. These opposing mechanisms may explain how β-arrestin-2 contributes to disease progression and the emergence of drug-induced dyskinesias during dopaminergic therapy.

β-Arrestin Signaling and its Role in Schizophrenia

The therapeutic efficacy of most antipsychotic agents is generally attributed to their ability to antagonize dopamine D_2-class receptors, supporting the view that hyperactive dopaminergic transmission within the mesolimbic pathway represents a key mechanism underlying the pathophysiology of schizophrenia [40, 94]. Beyond canonical G protein signaling, the activation of D_2 receptors recruits β-arrestin-2, leading to the formation of a signaling complex composed of Akt and protein phosphatase 2A (PP2A) [95]. This β-arrestin-2-dependent complex mediates dopamine-induced dephosphorylation and functional inactivation of Akt, resulting in the disinhibition of glycogen synthase kinase-3 (GSK3) signaling in the striatum [96]. Dysregulation of this pathway contributes to abnormal dopaminergic behaviors that serve as preclinical correlates of psychotic symptoms [97]. Conversely, antipsychotic drugs can normalize Akt/GSK3 activity, and several atypical agents—including aripiprazole and brexpiprazole—have been shown to modulate β-arrestin-2-dependent signaling at D_2 receptors, suggesting that the arrestin pathway itself may contribute to their therapeutic efficacy [98].

β-Arrestin-2 in Addiction and Reward Circuitry

Beyond neurodegeneration, β-arrestin-2 plays a critical role in addiction-related processes, including tolerance, reward, and withdrawal. Studies on opioid receptor signaling have shown that β-arrestin-2 knockout mice exhibit stronger and longer-lasting analgesic effects following morphine administration and develop tolerance more slowly [80]. These findings led to the concept of biased agonism, in which ligands preferentially activate G protein pathways while minimizing β-arrestin recruitment, thereby retaining therapeutic efficacy with fewer adverse effects such as respiratory depression or constipation [99]. Similar mechanisms have been described for psychostimulants such as cocaine and amphetamine, as well as for ethanol [99, 100]. In vivo studies using β-arrestin-2 knockout mice demonstrated its involvement in the consolidation of reward-related contextual memory. Within the nucleus accumbens, β-arrestin-2 modulates dopamine D_3 receptor (D_3R) signaling, influencing drug-seeking behavior and motivational drive [95, 101, 102]. Growing evidence suggests that selective targeting of β-arrestin-mediated signaling may allow the separation of therapeutic and adverse effects by modulating specific signaling nodes within the reward circuitry.

Collectively, data from neurodegenerative and psychiatric disease models indicate that β-arrestins not only intersect multiple signaling pathways but also participate directly in cellular repair and adaptive mechanisms, or conversely, in maladaptive, disease-promoting responses. The rapid effects of neurotransmitters or psychotropic drugs typically rely on G protein signaling, whereas β-arrestin-mediated processes govern long-term adaptations, including tolerance, synaptic remodeling, and endosome-dependent signaling [11].

This duality positions β-arrestin-2 as a crucial regulator of signal homeostasis in the brain [70]. Its oligomerization state, subcellular localization, and interactions with autophagic and transcriptional

machinery critically influence disease progression. Understanding these mechanisms opens new avenues for the development of therapeutic strategies aimed at limiting neurodegeneration and maladaptive plasticity while minimizing side effects through selective modulation of β-arrestin-dependent pathways [40, 88, 92].

Functional Selectivity ("Biased Agonism") in GPCR-Targeted Therapies: From Bench to Bedside

The concept of biased agonism, or functional selectivity**,** refers to the ability of certain ligands to preferentially activate one intracellular signaling branch—most often G protein or β-arrestin—while sparing others [103]. Such pathway bias may enhance therapeutic efficacy and limit adverse effects. Nonetheless, translation into clinical benefit remains challenging, as biased signaling depends on receptor expression, cellular context, ligand efficacy, and kinetic parameters [104, 105].

This chapter reviews selected examples of clinically approved and investigational biased ligands, covering both classical systems (β-adrenergic, opioid, angiotensin, and incretin) and more recent areas, such as psychedelics and serotonin 5-HT_1A bias.

Clinically Approved Drugs Exhibiting Functional Selectivity

Carvedilol

The non-selective β-adrenergic blocker carvedilol, which is used to treat heart failure and hypertension, is a prototypical β-arrestin-biased ligand at β_2-adrenergic receptors. It promotes β-arrestin-mediated ERK activation and EGFR transactivation while antagonizing Gs-coupled cAMP signaling [106,107]. This bias has been proposed to contribute tothe cardioprotective properties of carvedilol.

Alprenolol

Alprenolol, a non-selective β-adrenergic antagonist, similarly induces β-arrestin-dependent ERK activation of β_1-adrenergic receptor despite inhibiting Gs-signaling, highlighting that even classical "blockers" can exhibit pathway bias [108].

Oliceridine (Olinvyk)

Oliceridine, approved by the FDA in 2020, is a G protein-biased agonist at the μ-opioid receptor (MOR) designed to retain analgesic efficacy while reducing β-arrestin-2 recruitment [109]. Although preclinical data supported this rationale, later studies indicated that its improved safety profile may arise from low intrinsic efficacy rather than pure bias [110, 111].

Nalfurafine

Nalfurafine, a κ-opioid receptor (KOR) agonist approved in Japan for the treatment of uremic pruritus, shows a G protein-biased signaling pattern, producing antipruritic effects with minimal dysphoria [112–114].

Tirzepatide

The dual GIP/GLP-1 receptor agonist tirzepatide (approved 2022) shows G protein-biased agonism at GLP-1R, characterized by stronger cAMP generation over β-arrestin recruitment. Weaker recruitment of β-arrestin results in reduced internalization of GLP-1R, thereby enabling a more complete manifestation of the beneficial effects associated with receptor activation. This mechanism may underlie its high clinical efficacy [115,116].

Aripiprazole, Cariprazine

Third-generation antipsychotics act as partial agonists at dopamine D_{2L} receptors and display complex, system-dependent bias-often favoring Gi/o signaling with limited β-arrestin-2 recruitment [97, 117]. The relative sparing of β-arrestin pathways may prevent excessive receptor desensitization and internalization, maintaining dopaminergic tone within a physiological range. In neuronal systems, this translates to a "dopamine stabilizing" effect-attenuating excessive D_2 activation in hyperdopaminergic states while preserving signaling where dopamine tone is low. Clinically, such bias is thought to contribute to a reduced incidence of extrapyramidal symptoms and improved efficacy against negative and cognitive symptoms compared to conventional D_2 antagonists. It should also be considered that the partial agonism of cariprazine at D_3 receptors may be involved in the reduction of negative symptoms [98, 118, 119].

Losartan and Other ARBs

Angiotensin II type 1 receptor (AT_1R) antagonists can elicit β-arrestin-mediated responses even while blocking Gq-coupled effects, although the clinical relevance of such bias remains uncertain [120, 121]. However, subsequent studies have revealed that some Angiotensin Receptor Blockers (ARBs) can stabilize receptor conformations capable of recruiting β-arrestins, thereby initiating G protein-independent signaling pathways [120]. These

β-arrestin-mediated responses include ERK1/2 activation, EGFR transactivation, and modulation of cardiomyocyte survival and contractility, suggesting that AT_1R ligands may exert tissue-specific or context-dependent signaling bias [122].

Buprenorphine

Buprenorphine, a partial agonist at the μ-opioid receptor (MOR), has often been described as a G protein-leaning ligand. Experimental assays show that it exhibits only minimal recruitment of β-arrestin-2 relative to full MOR agonists and maintains activity in G protein signaling pathways despite low intrinsic efficacy [111, 123]. The clinical benefits of buprenorphine—including a ceiling effect on respiratory depression, reduced risk of dependence, and better safety profile—are thought to stem in part from this signaling profile; by engaging G protein pathways with limited β-arrestin engagement, receptor desensitization and internalization are attenuated, thereby prolonging therapeutic signaling while limiting many side-effects [124]. It is worth noting, however, that the improved therapeutic window associated with buprenorphine may derive as much from its low efficacy as from true signaling bias, and therefore, interpretation of its G protein bias remains subject to ongoing debate [125].

Setmelanotide

Setmelanotide, a selective MC4R agonist approved for the treatment for monogenic obesity, preferentially activates Gαq-PLC signaling with limited β-arrestin recruitment [126–128]. Functional studies indicate that the bias profile of setmelanotide may contribute to its favorable metabolic efficacy and reduced cardiovascular side effects, providing a molecular explanation for its clinical benefits in patients with POMC (proopiomelanocortin), PCSK1 (proprotein convertase subtilisin/kexin type 1), or LEPR (leptin receptor) deficiency-associated obesity [129].

Experimental and Preclinical Biased Ligands

TRV027

TRV027 (TRV120027) is a peptide, β-arrestin-biased AT_1R ligand, designed to block deleterious Gq-mediated vasoconstrictive signaling while preserving or enhancing β-arrestin-dependent cardioprotective pathways. Preclinical studies demonstrated that TRV027 improved cardiac contractility, reduced afterload, and limited adverse remodeling in heart failure models. However, despite these promising mechanistic and animal data, Phase II clinical trials (NCT01966601) in patients with acute heart failure failed to show significant clinical benefits [130].

TRV-023

TRV-023 (TRV120023), another peptide AT_1R ligand, selectively recruits β-arrestin while minimizing Gq-mediated signaling, thereby promoting cardioprotective responses such as ERK1/2 activation, anti-apoptotic signaling, and improved cardiac function following ischemic injury [131, 132]. It was under development for acute heart failure but never entered clinical trials in humans. Instead, it was primarily used as a research tool to elucidate the mechanism of action of TRV027, and likely served as a backup molecule within the same drug development program [133].

Neladenoson Bialanate

Neladenoson bialanate (BAY-1067197) is a small molecule, orally available partial A_1-adenosine receptor (A_1R) agonist that preferentially engages β-arrestin-dependent signaling while minimizing G protein-mediated effects, such as bradycardia and atrioventricular block. This biased pharmacology was expected to confer cardioprotective benefits without the adverse hemodynamic effects associated with full A_1R agonists. Although preclinical data suggested improved mitochondrial function and cardiac remodeling, Phase II clinical trials (NCT03098979) in chronic heart failure failed to demonstrate meaningful efficacy [134, 135].

UNC9994 and UNC9975

UNC9994 and its analogue UNC9975 are β-arrestin-biased D_2R agonists. In preclinical studies, both compounds demonstrated antipsychotic-like efficacy in rodent behavioral models, including the reversal of amphetamine-induced hyperlocomotion and improvement of prepulse inhibition deficits [136]. These effects were absent in β-arrestin-2 knockout mice, confirming that their activity depends on β-arrestin-mediated signaling. The development of these compounds provided the first in vivo evidence that selective engagement of D_2R-β-arrestin-2 signaling may represent a novel mechanism for antipsychotic drug action with potentially reduced extrapyramidal side effects [98].

SBI-553 and SBI-810

SBI-553 and SBI-810 are β-arrestin-biased PAMs of neurotensin receptor 1 (NTSR1) that exhibit potent analgesic and anti-addictive properties

without inducing sedation or hypothermia in rodent models [137, 138]. The compounds stabilize a β-arrestin-preferring NTSR1 conformation, promoting ERK and Akt pathway activation that mediates neuroprotective and antinociceptive responses [138]. Both SBI-553 and SBI-810 are currently in the preclinical stage of development.

Among the experimental opioid ligands, several compounds have been developed to preferentially engage G protein signaling while minimizing β-arrestin recruitment, aiming to preserve analgesia with reduced adverse effects.

PZM21, SR-17018, RB-64 and 6′-GNTI

PZM21 and SR-17018 exemplify such μ-opioid receptor (MOR) selective G protein-biased agonists. Both compounds promote robust G_i/o-mediated inhibition of cAMP accumulation while eliciting minimal β-arrestin-2 recruitment [99, 139]. In preclinical studies, they produced potent analgesia with reduced respiratory depression and tolerance, although subsequent work has shown that the extent of their bias may be system-dependent [140].

In contrast, RB-64 (also known as 19-epi-salvinorin A) and 6′-GNTI are κ-opioid receptor (KOR) agonists that likewise display a marked preference for G protein signaling over β-arrestin pathways [141, 142]. Such KOR-biased ligands have been proposed to dissociate the desirable antinociceptive and antipruritic effects of KOR activation from the dysphoria and sedation typically associated with β-arrestin recruitment.

Exendin-P5

Exendin-P5 is a GLP-1R agonist with a G protein bias, characterized by the strong activation of Gs-mediated cAMP production [143]. This signaling preference enhances insulinotropic and anorectic effects while reducing tachyphylaxis and gastrointestinal side effects associated with prolonged β-arrestin engagement. In preclinical models, Exendin-P5 demonstrated improved glucose tolerance, enhanced insulin secretion, and reduced body weight, highlighting its potential as a next-generation incretin-based therapeutic with sustained efficacy and improved tolerability [144].

Psychedelics and Hallucinogens: 5-HT$_2$A Receptor Bias

Hallucinogens such as LSD and psilocybin—acting primarily through the 5-HT$_2$A receptor—have long been proposed to signal via β-arrestin-dependent mechanisms. Early structural and functional studies suggested that LSD stabilizes a receptor conformation favoring prolonged β-arrestin engagement [145, 146], and β-arrestin-2 knockout mice showed attenuated head-twitch responses, supporting the potential role of arrestin pathways in psychedelic behaviors [146–148]. However, more recent pharmacological and genetic data challenge this view, indicating that activation of the Gq/11–phospholipase C pathway—leading to intracellular Ca^{2+} mobilization and cortical excitation—is both necessary and sufficient for the hallucinogenic-like response [149]. These findings suggest that β-arrestin signaling may modulate receptor trafficking or temporal dynamics, but that the core psychedelic effect arises primarily from G protein-mediated activation. Consistent with this, Wallach et al. (2023) showed that disrupting Gq-PLC signaling markedly attenuates the head-twitch response and that a threshold level of Gq activation is required to elicit hallucinogenic effects, explaining why certain partial agonists such as lisuride, despite activating G protein signaling, remain non-psychedelic. Current models thus emphasize that the magnitude and kinetics of Gq-mediated activation, rather than β-arrestin recruitment, determine whether 5-HT$_2$A receptor engagement produces hallucinogenic or purely therapeutic outcomes [148, 149].

5-HT$_1$A Receptor Biased Agonists: NLX-101 (F15599) and NLX-204

Highly selective 5-HT$_1$A receptor biased agonists such as NLX-101 (F15599) and NLX-204 exemplify how functional selectivity can yield rapid-acting antidepressant profiles. These ligands preferentially engage postsynaptic cortical 5-HT$_1$A receptors, promoting ERK/CREB/BDNF-linked neuroplasticity while avoiding autoreceptor desensitization [3,6,150–153].

NLX-101 displays nanomolar affinity and a strong bias toward ERK phosphorylation over Gi-mediated responses, producing sustained antidepressant-like and pro-cognitive effects in rodents [151,153,154]. Importantly, NLX-101 has also been studied for potential use in the treatment of Fragile X syndrome, reflecting its promising procognitive and neuroplastic effects demonstrated in preclinical models [155]. Medicinal-chemistry optimization led to NLX-204 and related aryloxyethyl derivatives maintaining ERK-preferring profiles and exhibiting ketamine-like rapid-acting antidepressant efficacy in a chronic mild stress model [150,156,157]. Mechanistically, their bias promotes cortical pyramidal disinhibition and neurotrophic activation, offering a non-hallucinogenic route for rapid-acting antidepressant therapy [152, 158].

Functional selectivity is now recognized across diverse GPCR families. Clinically approved agents such as carvedilol, oliceridine, and setmelanotide demonstrate that bias can be therapeutically relevant, while compounds such as TRV027, neladenoson, or certain psychedelics reveal their limitations. Structural biology continues to elucidate the conformational bases of bias [159]. In psychiatry, biased 5-HT_2A and 5-HT_1A agonists suggest a path toward rapid-acting yet non-hallucinogenic therapies.

In conclusion, biased agonism is a powerful but nuanced principle: it can separate desired from adverse effects, yet requires rigorous mechanistic validation and thoughtful translational design.

DISCUSSION

Over the past two decades, the view of β-arrestins has shifted from that of simple terminators of GPCR signaling to multifunctional scaffolding and signaling proteins that diversify receptor output. The accumulated structural, biochemical, and functional data demonstrate that β-arrestins operate as dynamic modulators capable of integrating spatial and temporal signaling information. The concept of phosphorylation barcodes provides a unifying framework explaining how receptors encode distinct β-arrestin conformations and signaling profiles [5, 13]. This mechanistic plasticity translates directly into cellular and physiological diversity, positioning β-arrestins at the crossroads of receptor desensitization, trafficking, and signal propagation.

In the central nervous system, β-arrestins have emerged as critical regulators of synaptic plasticity, mood regulation, and neurodegeneration [7]. Their dual role in both adaptive and maladaptive processes exemplifies the "signaling homeostasis" model, wherein G protein-mediated signaling provides rapid responses, whereas β-arrestin-dependent pathways shape long-term adaptations [11]. Dysregulation of these pathways, whether through altered β-arrestin expression, post-translational modification, or oligomerization, may contribute to the pathophysiology of depression, addiction, and neurodegenerative disorders such as Alzheimer's and Parkinson's disease [88,89]. Importantly, these effects are not merely secondary to receptor desensitization but also reflect the intrinsic signaling properties of β-arrestins themselves.

The concept of biased agonism has provided a powerful pharmacological framework for exploiting β-arrestin-mediated signaling. Ligands such as oliceridine [109], nalfurafine [113, 114], or carvedilol [106] illustrate how selective pathway engagement can dissociate therapeutic effects from adverse events. However, translating receptor bias into clinical success remains challenging. Quantifying bias in vivo requires context-dependent assessment of receptor expression, signal amplification, and effector coupling [104]. Moreover, the same ligand may display opposite biases across tissues or species, complicating the prediction of clinical outcomes [8].

Recent developments in structural pharmacology and cryo-EM have begun to reveal the conformational basis of functional selectivity [5]. In psychiatry, this opens the possibility of designing ligands that mimic the rapid antidepressant effects of psychedelics without hallucinogenic liability, an idea supported by recent data on ERK/BDNF-biased 5-HT_1A agonists [156, 157].

Nevertheless, major questions remain. The physiological relevance of β-arrestin bias across receptor families is still not completely understood, and distinguishing true bias from differences in efficacy or kinetics remains experimentally demanding. Additionally, the long-term consequences of selectively activating β-arrestin pathways, particularly in the CNS, require careful evaluation given their involvement in processes such as memory reconsolidation, autophagy, and protein aggregation. Future research should combine high-resolution structural approaches with cellular and behavioral models to define the therapeutic "sweet spot" of β-arrestin signaling.

CONCLUSIONS

β-Arrestins represent a paradigm shift in our understanding of GPCR biology—from passive desensitizers to active, versatile signaling regulators. Their ability to integrate receptor phosphorylation patterns, spatial localization, and protein–protein interactions enables diverse cellular outcomes with profound physiological relevance. In the nervous system, β-arrestins bridge receptor activation with neuroplasticity, mood regulation, and proteostatic balance, suggesting that modulation of β-arrestin-dependent signaling could support the development of innovative therapies for neuropsychiatric and neurodegenerative disorders.

The concept of biased agonism offers a rational framework for drug discovery within this landscape. By selectively modulating G protein versus β-arrestin signaling, it becomes possible to dissociate efficacy from side effects—a principle already

validated by clinically approved biased ligands. Experimental compounds such as NLX-101 and NLX-204 further illustrate how this approach can translate into next-generation drug candidates with rapid and sustained efficacy.

Ultimately, the therapeutic exploitation of β-arrestin biology will depend on bridging molecular mechanisms with system-level physiology. Integrating structural pharmacology, computational modeling, and translational neuroscience promises to unlock the full clinical potential of β-arrestin-biased signaling, ushering in a new era of precision GPCR pharmacology.

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Conflict of Interest

The authors declare no conflicts of interest.

Author's Contribution

Research concept: M.G-L., J.Ś., M.K;
Writing the article: M.G-L., J.Ś;
Critical revision of the article: M.G-L., J.Ś., M.K;
Final approval of the article: M.K.

REFERENCES

1. Chilmonczyk Z, Bojarski AJ, Pilc A, Sylte I. Functional selectivity and antidepressant activity of serotonin 1A receptor ligands. *Int J Mol Sci*. 2015; 16: 18474–18506. doi:10.3390/ijms160818474.
2. Gurevich VV, Gurevich EV. GPCR signaling regulation: the role of GRKs and arrestins. *Front Pharmacol*. 2019; 10: 125. doi: 10.3389/fphar.2019.00125.
3. Głuch-Lutwin M, Sałaciak K, Gawalska A, et al. The selective 5-HT1A receptor biased agonists, F15599 and F13714, show antidepressant-like properties after a single administration in the mouse model of unpredictable chronic mild stress. *Psychopharmacology (Berl)* 2021; 238(8): 2249–2260 doi:10.1007/s00213-021-05849-0.
4. Seyedabadi M, Gharghabi M, Gurevich EV, Gurevich VV. Receptor-arrestin interactions: the GPCR perspective. *Biomolecules* 2021; 11(2): 218. doi: 10.3390/biom11020218.
5. Cahill TJ, Thomsen ARB, Tarrasch JT, et al. Distinct conformations of GPCR-β-arrestin complexes mediate desensitization, signaling, and endocytosis. *Proc Natl Acad Sci U S A* 2017; 114: 2562–2567. doi: 10.1073/pnas.1701529114.
6. Sniecikowska J, Newman-Tancredi A, Kolaczkowski M. From receptor selectivity to functional selectivity: the rise of biased agonism in 5-HT1A receptor drug discovery. *Curr Top Med Chem*. 2019; 19: 2393–420. doi: 10.2174/1568026619666190911122040.
7. Kee TR, Khan SA, Neidhart MB, et al. The multifaceted functions of β-arrestins and their therapeutic potential in neurodegenerative diseases. *Exp Mol Med*. 2024; 56: 129–141. doi:10.1038/s12276-023-01144-4.
8. Reiter E, Ahn S, Shukla AK, Lefkowitz RJ. Molecular mechanism of β-arrestin-biased agonism at seven-transmembrane receptors. *Annu Rev Pharmacol Toxicol*. 2012; 52: 179–197. doi: 10.1146/annurev.pharmtox.010909.105800.
9. Kang Y, Zhou XE, Gao X, et al. Crystal structure of rhodopsin bound to arrestin by femtosecond X-ray laser. *Nature* 2015; 523: 561–567. doi: 10.1038/nature14656.
10. Shukla AK, Manglik A, Kruse AC, et al. Structure of active β-arrestin-1 bound to a G-protein-coupled receptor phosphopeptide. *Nature* 2013; 497: 137–141. doi: 10.1038/nature12120.
11. Xie W, Lai J, Cai H, et al. Structural features of arrestin-mediated GPCR signaling. *Med Drug Discov*. 2024; 24: 100201. doi: 10.1016/j.medidd.2024.100201.
12. Gurevich VV, Gurevich EV. Structural determinants of arrestin functions. *Prog Mol Biol Transl Sci*. 2013; 118: 57–92. doi: 10.1016/B978-0-12-394440-5.00003-6.
13. Nobles KN, Xiao K, Ahn S, et al. distinct phosphorylation sites on the β2-adrenergic receptor establish a barcode that encodes differential functions of β-arrestin. *Sci Signal*. 2011; 4: ra51–ra51. doi: 10.1126/scisignal.2001707.
14. Smith JS, Rajagopal S. The β-arrestins: multifunctional regulators of G protein-coupled receptors. J *Biol Chem*. 2016; 291: 8969–8977. doi: 10.1074/jbc.R115.713313.
15. Liggett SB. Phosphorylation barcoding as a mechanism of directing GPCR signaling. *Sci Signal*. 2011; 4: pe36. doi: 10.1126/scisignal.2002331.
16. Latorraca NR, Masureel M, Hollingsworth SA, et al. How GPCR phosphorylation patterns orchestrate arrestin-mediated signaling. *Cell* 2020; 183(7): 1813–1825. e18. doi:10.1016/j.cell.2020.11.014.
17. Chen Q, Perry NA, Vishnivetskiy SA, et al. Structural basis of arrestin-3 activation and signaling. *Nat Commun*. 2017; 8: 1427. doi: 10.1038/s41467-017-01218-8.
18. Vishnivetskiy SA, Huh EK, Gurevich EV, Gurevich VV. The finger loop as an activation sensor in arrestin. *J Neurochem*. 2021; 157: 1138–1152. doi: 10.1111/jnc.15232.
19. Luttrell LM, Lefkowitz RJ. The role of beta-arrestins in the termination and transduction of G-protein-coupled

receptor signals. *J Cell Sci.* 2002; 115: 455–465. doi: 10.1242/jcs.115.3.455.

20. Nguyen AH, Thomsen ARB, Cahill TJ, et al. Structure of an endosomal signaling GPCR-G protein-β-arrestin megacomplex. *Nat Struct Mol Biol.* 2019; 26: 1123–1131. doi: 10.1038/s41594-019-0330-y.
21. Peña KA. Endosomal parathyroid hormone receptor signaling. *Am J Physiol - Cell Physiol*. 2022; 323: C783–90. doi: 10.1152/ajpcell.00452.2021.
22. Aydin Y, Böttke T, Lam JH, et al. Structural details of a Class B GPCR-arrestin complex revealed by genetically encoded crosslinkers in living cells. *Nat Commun*. 2023; 14: 1151. doi: 10.1038/s41467-023-36797-2.
23. Gesty-Palmer D, Flannery P, Yuan L, et al. A beta-arrestin-biased agonist of the parathyroid hormone receptor (PTH1R) promotes bone formation independent of G protein activation. *Sci Transl Med.* 2009; 1(1): 1ra1. doi: 10.1126/scitranslmed.3000071.
24. Luttrell LM, Roudabush FL, Choy EW, et al. Activation and targeting of extracellular signal-regulated kinases by beta-arrestin scaffolds. *Proc Natl Acad Sci U S A* 2001; 98: 2449–2454. doi: 10.1073/pnas.041604898.
25. Haider RS, Reichel M, Matthees ESF, Hoffmann C. Conformational flexibility of β-arrestins – How these scaffolding proteins guide and transform the functionality of GPCRs. *BioEssays* 2023; 45: 2300053. doi: 10.1002/bies.202300053.
26. Kahsai AW, Shah KS, Shim PJ, et al. Signal transduction at GPCRs: Allosteric activation of the ERK MAPK by β-arrestin. *Proc Natl Acad Sci U S A* 2023; 120: e2303794120. doi: 10.1073/pnas.2303794120.
27. Tohgo A, Pierce KL, Choy EW, et al. beta-Arrestin scaffolding of the ERK cascade enhances cytosolic ERK activity but inhibits ERK-mediated transcription following angiotensin AT1a receptor stimulation. *J Biol Chem*. 2002; 277: 9429–9436. doi: 10.1074/jbc.M106457200.
28. McDonald PH, Chow C-W, Miller WE, et al. β-Arrestin 2: a receptor-regulated MAPK scaffold for the activation of JNK3. *Science* 2000; 290: 1574–1577. doi: 10.1126/science.290.5496.1574.
29. Song X, Raman D, Gurevich EV, et al. Visual and both non-visual arrestins in their "Inactive" conformation bind JNK3 and Mdm2 and relocalize them from the nucleus to the cytoplasm. *J Biol Chem*. 2006; 281: 21491–21499. doi: 10.1074/jbc.M603659200.
30. Eishingdrelo H, Sun W, Li H, et al. ERK and β-arrestin interaction: a converging-point of signaling pathways for multiple types of cell-surface receptors. *J Biomol Screen*. 2015; 20: 341–349. doi: 10.1177/1087057114557233.
31. Kang J, Shi Y, Xiang B, et al. A nuclear function of beta-arrestin1 in GPCR signaling: regulation of histone acetylation and gene transcription. *Cell* 2005; 123: 833–847. doi:10.1016/j.cell.2005.09.011.
32. Guo C, Whitmarsh AJ. The β-arrestin-2 scaffold protein promotes c-Jun N-terminal Kinase-3 activation by binding to its nonconserved N terminus. *J Biol Chem*. 2008; 283: 15903–15911. doi: 10.1074/jbc.M710006200.
33. Gurevich VV, Gurevich EV. GPCR-dependent and -independent arrestin signaling. *Trends Pharmacol Sci*. 2024; 45: 639–650. doi: 10.1016/j.tips.2024.05.007.
34. Oh DY, Talukdar S, Bae EJ, et al. GPR120 is an Omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin sensitizing effects. *Cell* 2010; 142: 687–698. doi: 10.1016/j.cell.2010.07.041.
35. Goel R, Phillips-Mason PJ, Raben DM, Baldassare JJ. alpha-Thrombin induces rapid and sustained Akt phosphorylation by beta-arrestin1-dependent and -independent mechanisms, and only the sustained Akt phosphorylation is essential for G1 phase progression. *J Biol Chem*. 2002; 277: 18640–18648. doi: 10.1074/jbc.M108995200.
36. Witherow DS, Garrison TR, Miller WE, Lefkowitz RJ. β-Arrestin inhibits NF-κB activity by means of its interaction with the NF-κB inhibitor IκBα. *Proc Natl Acad Sci U S A* 2004; 101: 8603–8607. doi: 10.1073/pnas.0402851101.
37. Patel PA, Tilley DG, Rockman HA. Beta-arrestin-mediated signaling in the heart. *Circ J Off J Jpn Circ Soc*. 2008; 72: 1725–1729. doi: 10.1253/circj.cj-08-0734.
38. Pydi SP, Cui Z, He Z, et al. Beneficial metabolic role of β-arrestin-1 expressed by AgRP neurons. *Sci Adv.* 2020; 6: eaaz1341. doi: 10.1126/sciadv.aaz1341.
39. Zhai R, Snyder J, Montgomery S, Sato PY. Double life: How GRK2 and β-arrestin signaling participate in diseases. *Cell Signal*. 2022; 94: 110333. doi: 10.1016/j.cellsig.2022.110333.
40. Beaulieu J-M, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacol Rev*. 2011; 63: 182–217. doi: 10.1124/pr.110.002642.
41. Mathieu NM, Nakagawa P, Grobe CC, et al. ARRB2 (β-Arrestin-2) deficiency alters fluid homeostasis and blood pressure regulation. *Hypertension* 2022; 79: 2480–2492. doi: 10.1161/HYPERTENSIONAHA.122.19863.
42. Song Q, Ji Q, Li Q. The role and mechanism of β-arrestins in cancer invasion and metastasis (Review). *Int J Mol Med*. 2018; 41: 631–639. doi: 10.3892/ijmm.2017.3288.
43. Barella LF, Rossi M, Pydi SP, et al. β-Arrestin-1 is required for adaptive β-cell mass expansion during obesity. *Nat Commun*. 2021; 12: 3385. doi: 10.1038/s41467-021-23656-1.
44. Zhu L, Almaça J, Dadi PK, et al. β-arrestin-2 is an essential regulator of pancreatic β-cell function under

physiological and pathophysiological conditions. *Nat Commun*. 2017; 8: 14295. doi: 10.1038/ncomms14295.

45. Luan B, Zhao J, Wu H, et al. Deficiency of a beta-arrestin-2 signal complex contributes to insulin resistance. *Nature 2009*; 457: 1146–1149. doi: 10.1038/nature07617.
46. Wess J, Oteng A-B, Rivera-Gonzalez O, et al. β-arrestins: structure, function, physiology, and pharmacological perspectives. *Pharmacol Rev.* 2023; 75: 854–884. doi: 10.1124/pharmrev.121.000302.
47. Beaulieu J-M, Marion S, Rodriguiz RM, et al. A beta-arrestin 2 signaling complex mediates lithium action on behavior. *Cell* 2008; 132: 125–136. doi: 10.1016/j.cell.2007.11.041.
48. Mendez-David I, Boursier C, Domergue V, et al. Differential peripheral proteomic biosignature of fluoxetine response in a mouse model of anxiety/depression. *Front Cell Neurosci*. 2017; 11. doi: 10.3389/fncel.2017.00237.
49. Petit A-C, El Asmar K, David DJ, et al. The association of β-arrestin2 polymorphisms with response to antidepressant treatment in depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; 81: 74–79. doi. 10.1016/j.pnpbp.2017.10.006.
50. Gurevich EV, Benovic JL, Gurevich VV. Arrestin2 and arrestin3 are differentially expressed in the rat brain during postnatal development. *Neuroscience* 2002; 109: 421–436. doi: 10.1016/s0306-4522(01)00511-5.
51. Li C, Zheng Y, Zhu H, et al. β-arrestin 2 is essential for fluoxetine-mediated promotion of hippocampal neurogenesis in a mouse model of depression. *Acta Pharmacol Sin* 2021; 42: 679–690. doi:10.1038/s41401-020-00576-2.
52. Liu Y, Song N, Yao H, et al. β-arrestin2-biased Drd2 agonist UNC9995 alleviates astrocyte inflammatory injury via interaction between β-arrestin2 and STAT3 in mouse model of depression. *J Neuroinflammation*. 2022; 19: 240. doi: 10.1186/s12974-022-02597-6.
53. Mahmoodkhani M, Amini M, Derafshpour L, et al. Negative relationship between brain α1A-AR neurotransmission and βArr2 levels in anxious adolescent rats subjected to early life stress. *Exp Brain Res*. 2020; 238: 2833–2844. doi: 10.1007/s00221-020-05937-1.
54. Li Y, Li H, Liu X, et al. Regulation of amygdalar PKA by β-arrestin-2/phosphodiesterase-4 complex is critical for fear conditioning. *Proc Natl Acad Sci*. 2009; 106: 21918–2123. doi: 10.1073/pnas.0906941106.
55. Ko MJ, Chiang T, Mukadam AA, et al. β-arrestin–dependent ERK signaling reduces anxiety-like and conditioned fear–related behaviors in mice. *Sci Signal*. 2021; 14: eaba0245. doi: 10.1126/scisignal.aba0245.
56. David DJ, Samuels BA, Rainer Q, et al. Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression. *Neuron* 2009; 62: 479–493. doi: 10.1016/j.neuron.2009.04.017.
57. Avissar S, Matuzany-Ruban A, Tzukert K, Schreiber G. β-arrestin-1 levels: reduced in leukocytes of patients with depression and elevated by antidepressants in rat brain. *Am J Psychiatry* 2004; 161: 2066–2072. doi: 10.1176/appi.ajp.161.11.2066.
58. Tejeda-Martínez AR, Ramos-Molina AR, Brand-Rubalcava PA, Flores-Soto ME. Involvement of serotonergic receptors in depressive processes and their modulation by β-arrestins: A review. *Medicine (Baltimore)* 2024; 103: e38943. doi: 10.1097/MD.0000000000038943.
59. Bagnato A, Rosanò L. New routes in GPCR/β-arrestin-driven signaling in cancer progression and metastasis. *Front Pharmacol*. 2019; 10: 114. doi: 10.3389/fphar.2019.00114.
60. Liu X, Ma L, Li HH, et al. β-arrestin–biased signaling mediates memory reconsolidation. P*roc Natl Acad Sci U S A* 2015; 112: 4483–4488. doi: 10.1073/pnas.1421758112.
61. Kook S, Zhan X, Kaoud TS, et al. Arrestin-3 binds c-Jun N-terminal kinase 1 (JNK1) and JNK2 and facilitates the activation of these ubiquitous JNK isoforms in cells via scaffolding. *J Biol Chem*. 2013; 288: 37332–37342. doi: 10.1074/jbc.M113.510412.
62. Wang W, Chen J, Li XG, Xu J. Anti-inflammatory activities of fenoterol through β-arrestin-2 and inhibition of AMPK and NF-κB activation in AICAR-induced THP-1 cells. *Biomed Pharmacother.* 2016; 84: 185–190. doi: 10.1016/j.biopha.2016.09.044.
63. Wang JQ, Mao L. The ERK pathway: molecular mechanisms and treatment of depression. *Mol Neurobiol*. 2019; 56: 6197–6205. doi: 10.1007/s12035-019-1524-3.
64. Dwivedi Y, Rizavi HS, Roberts RC, et al. Reduced activation and expression of ERK1/2 MAP kinase in the post-mortem brain of depressed suicide subjects. *J Neurochem*. 2001; 77: 916–928.
65. Dwivedi Y, Zhang H. Altered ERK1/2 signaling in the brain of learned helpless rats: relevance in vulnerability to developing stress-induced depression. *Neural Plast*. 2016: 7383724. doi:10.1155/2016/7383724.
66. Fernandes A, Li Y-W. Focused microwave irradiation-assisted immunohistochemistry to study effects of ketamine on phospho-ERK expression in the mouse brain. *Brain Res.* 2017; 1670: 86–95. doi: 10.1016/j.brainres.2017.05.008.
67. Schreiber G, Golan M, Avissar S. Beta-arrestin signaling complex as a target for antidepressants and as a depression marker. *Drug News Perspect.* 2009; 22: 467–480.
68. Tao Y, Ma L, Liao Z, et al. Astroglial β-arrestin1-mediated nuclear signaling regulates the expansion of neural precursor cells in adult hippocampus. *Sci Rep.* 2015; 5: 15506. doi: 10.1038/srep15506.

69. Otis JM, Werner CT, Mueller D. Noradrenergic regulation of fear and drug-associated memory reconsolidation. *Neuropsychopharmacology* 2015; 40: 793–803. doi: 10.1038/npp.2014.243.
70. Shenoy SK, Lefkowitz RJ. β-arrestin-mediated receptor trafficking and signal transduction. *Trends Pharmacol Sci.* 2011; 32: 521–533. doi: 10.1016/j.tips.2011.05.002.
71. Laporte SA, Oakley RH, Zhang J, et al. The beta2-adrenergic receptor/betaarrestin complex recruits the clathrin adaptor AP-2 during endocytosis. *Proc Natl Acad Sci U S A* 1999; 96: 3712–3717. doi: 10.1073/pnas.96.7.3712.
72. Laporte SA, Oakley RH, Holt JA, et al. The interaction of beta-arrestin with the AP-2 adaptor is required for the clustering of beta 2-adrenergic receptor into clathrin-coated pits. *J Biol Chem*. 2000; 275: 23120–23126. doi: 10.1074/jbc.M002581200.
73. Beaulieu J-M, Sotnikova TD, Marion S, et al. An Akt/beta-arrestin 2/PP2A signaling complex mediates dopaminergic neurotransmission and behavior. *Cell* 2005; 122: 261–273. doi: 10.1016/j.cell.2005.05.012.
74. Luttrell LM, Roudabush FL, Choy EW, et al. Activation and targeting of extracellular signal-regulated kinases by beta-arrestin scaffolds. *Proc Natl Acad Sci U S A* 2001; 98: 2449–2454. doi: 10.1073/pnas.041604898.
75. Ahn S, Shenoy SK, Wei H, Lefkowitz RJ. Differential kinetic and spatial patterns of beta-arrestin and G protein-mediated ERK activation by the angiotensin II receptor. *J Biol Chem*. 2004; 279: 35518–35525. doi: 10.1074/jbc.M405878200.
76. Daly C, Guseinov AA, Hahn H, et al. β-arrestin-dependent and -independent endosomal G protein activation by the vasopressin type 2 receptor. eLife 2023; 12: RP87754. doi: 10.7554/eLife.87754.
77. Retraction for Baillie et al., β-Arrestin-mediated PDE4 cAMP phosphodiesterase recruitment regulates β-adrenoceptor switching from Gs to Gi. *Proc Natl Acad Sci*. 2022; 119: e2205198119. doi: 10.1073/pnas.2205198119.
78. Chen W, ten Berge D, Brown J, et al. Dishevelled 2 recruits ß-arrestin 2 to mediate Wnt5A-stimulated endocytosis of frizzled 4. *Science* 2003; 301: 1391–1394. doi: 10.1126/science.1082808.
79. Kang J, Shi Y, Xiang B, et al. A nuclear function of beta-arrestin1 in GPCR signaling: regulation of histone acetylation and gene transcription. *Cell* 2005; 123: 833–847. doi: 10.1016/j.cell.2005.09.011.
80. Bohn LM, Lefkowitz RJ, Gainetdinov RR, et al. Enhanced morphine analgesia in mice lacking β-arrestin 2. *Science* 1999; 286: 2495–2498. doi: 10.1126/science.286.5449.2495.
81. Bohn LM, Gainetdinov RR, Lin FT, et al. Mu-opioid receptor desensitization by beta-arrestin-2 determines morphine tolerance but not dependence. *Nature* 2000; 408: 720–723. doi: 10.1038/35047086.
82. Fang Y, Ding X, Zhang Y, et al. Fluoxetine inhibited the activation of A1 reactive astrocyte in a mouse model of major depressive disorder through astrocytic 5-HT2BR/β-arrestin2 pathway. *J Neuroinflammation*. 2022; 19: 23. doi: 10.1186/s12974-022-02389-y.
83. Schmid CL, Raehal KM, Bohn LM. Agonist-directed signaling of the serotonin 2A receptor depends on beta-arrestin-2 interactions *in vivo*. *Proc Natl Acad Sci U S A* 2008; 105: 1079–1084. doi: 10.1073/pnas.0708862105.
84. Rodriguiz RM, Nadkarni V, Means CR, et al. LSD-stimulated behaviors in mice require β-arrestin 2 but not β-arrestin 1. *Sci Rep.* 2021; 11: 17690. doi: 10.1038/s41598-021-96736-3.
85. Sniecikowska J, Gluch-Lutwin M, Bucki A, et al. Discovery of novel pERK1/2- or β-arrestin-preferring 5-HT1A receptor-biased agonists: diversified therapeutic-like versus side effect profile. *J Med Chem*. 2020; 63: 10946–10971. doi: 10.1021/acs.jmedchem.0c00814.
86. Sniecikowska J, Gluch-Lutwin M, Bucki A, et al. Discovery of NLX-266, an orally available and metabolically stable ERK1/2-Biased 5-HT1AR agonist with superior antidepressant and antiparkinsonian activity. *J Med Chem*. 2025; 68: 9706–9722. doi: 10.1021/acs.jmedchem.5c00484.
87. Jung S-R, Jiang Y, Seo JB, et al. β-arrestin-dependent PI(4,5)P2 synthesis boosts GPCR endocytosis. *Proc Natl Acad Sci U S A* 2021; 118: e2011023118. doi: 10.1073/pnas.2011023118.
88. Thathiah A, Horré K, Snellinx A, et al. β-arrestin 2 regulates Aβ generation and γ-secretase activity in Alzheimer's disease. *Nat Med.* 2013; 19: 43–49. doi: 10.1038/nm.3023.
89. Urs NM, Bido S, Peterson SM, et al. Targeting β-arrestin2 in the treatment of L-DOPA-induced dyskinesia in Parkinson's disease. *Proc Natl Acad Sci U S A* 2015; 112: E2517–E2526. doi: 10.1073/pnas.1502740112.
90. Bychkov ER, Gurevich VV, Joyce JN, et al. Arrestins and two receptor kinases are upregulated in Parkinson's disease with dementia. *Neurobiol Aging* 2008; 29: 379–396. doi: 10.1016/j.neurobiolaging.2006.10.012.
91. Nelson CD, Sheng M. Gpr3 stimulates Aβ production via interactions with APP and β-arrestin2. *PloS One* 2013; 8: e74680. doi: 10.1371/journal.pone.0074680.
92. Woo J-AA, Liu T, Fang CC, et al. β-arrestin2 oligomers impair the clearance of pathological tau and increase tau aggregates. *Proc Natl Acad Sci U S A* 2020; 117: 5006–5015. doi: 10.1073/pnas.1917194117.
93. Mittal S, Bjørnevik K, Im DS, et al. β2-Adrenoreceptor is a regulator of the α-synuclein gene driving risk of Parkinson's disease. *Science* 2017; 357: 891–898. doi: 10.1126/science.aaf3934.
94. Howes OD, Kapur S. The dopamine hypothesis of Schizophrenia: version III—the final common pathway.

Schizophr Bull. 2009; 35: 549–562. doi: 10.1093/schbul/sbp006.

95. Beaulieu J-M, Sotnikova TD, Marion S, et al. An Akt/beta-arrestin 2/PP2A signaling complex mediates dopaminergic neurotransmission and behavior. *Cell* 2005; 122: 261–273. doi: 10.1016/j.cell.2005.05.012.
96. Beaulieu J-M, Gainetdinov RR, Caron MG. The Akt-GSK-3 signaling cascade in the actions of dopamine. *Trends Pharmacol Sci*. 2007; 28: 166–172. doi: 10.1016/j.tips.2007.02.006.
97. Masri B, Salahpour A, Didriksen M, et al. Antagonism of dopamine D2 receptor/beta-arrestin 2 interaction is a common property of clinically effective antipsychotics. *Proc Natl Acad Sci U S A* 2008; 105: 13656–13661. doi: 10.1073/pnas.0803522105.
98. Allen JA, Yost JM, Setola V, et al. Discovery of β-arrestin-biased dopamine D2 ligands for probing signal transduction pathways essential for antipsychotic efficacy. *Proc Natl Acad Sci U S A* 2011; 108: 18488–18493. doi: 10.1073/pnas.1104807108.
99. Schmid CL, Kennedy NM, Ross NC, et al. Bias factor and therapeutic window correlate to predict safer opioid analgesics. *Cell* 2017; 171: 1165-1175.e13. doi: 10.1016/j.cell.2017.10.035.
100. Meinhardt MW, Giannone F, Hirth N, et al. Disrupted circadian expression of β-arrestin 2 affects reward-related μ-opioid receptor function in alcohol dependence. *J Neurochem*. 2022; 160: 454–468. doi: 10.1111/jnc.15559.
101. Xi Z-X, Li X, Li J, et al. Blockade of dopamine D3 receptors in the nucleus accumbens and central amygdala inhibits incubation of cocaine craving in rats. *Addict Biol*. 2013; 18: 665–677. doi: 10.1111/j.1369-1600.2012.00486.x.
102. Beaulieu J-M, Tirotta E, Sotnikova TD, et al. Regulation of akt signaling by D2 and D3 dopamine receptors *in vivo*. J Neurosci. 2007; 27: 881–885. doi: 10.1523/JNEUROSCI.5074-06.2007.
103. Kenakin T, Christopoulos A. Signalling bias in new drug discovery: detection, quantification and therapeutic impact. *Nat Rev Drug Discov*. 2013; 12: 205–216. doi: 10.1038/nrd3954.
104. Kenakin T. Biased receptor signaling in drug discovery. *Pharmacol Rev*. 2019; 71: 267–315. doi: 10.1124/pr.118.016790.
105. Eiger DS, Pham U, Gardner J, et al. GPCR systems pharmacology: a different perspective on the development of biased therapeutics. *Am J Physiol Cell Physiol*. 2022; 322: C887–95. doi:10.1152/ajpcell.00449.2021.
106. Wisler JW, DeWire SM, Whalen EJ, et al. A unique mechanism of β-blocker action: Carvedilol stimulates β-arrestin signaling. *Proc Natl Acad Sci*. 2007; 104: 16657–16662. doi: 10.1073/pnas.0707936104.
107. Wisler JW, Rockman HA, Lefkowitz RJ. Biased G protein–coupled receptor signaling. *Circulation* 2018; 137: 2315–2317. doi: 10.1161/CIRCULATIONAHA.117.028194.
108. Kim I-M, Tilley DG, Chen J, et al. β-Blockers alprenolol and carvedilol stimulate β-arrestin-mediated EGFR transactivation. *Proc Natl Acad Sci U S A* 2008; 105: 14555–14560. doi: 10.1073/pnas.0804745105.
109. Soergel DG, Subach RA, Burnham N, et al. Biased agonism of the μ-opioid receptor by TRV130 increases analgesia and reduces on-target adverse effects versus morphine: A randomized, double-blind, placebo-controlled, crossover study in healthy volunteers. *Pain* 2014; 155: 1829–1835. doi: 10.1016/j.pain.2014.06.011.
110. Urits I, Viswanath O, Orhurhu V, et al. The utilization of mu-opioid receptor biased agonists: oliceridine, an opioid analgesic with reduced adverse effects. *Curr Pain Headache Rep*. 2019; 23: 31. doi: 10.1007/s11916-019-0773-1.
111. De Neve J, Barlow TMA, Tourwé D, et al. Comprehensive overview of biased pharmacology at the opioid receptors: biased ligands and bias factors. *RSC Med Chem*. 2021;12: 828–870. doi: 10.1039/d1md00041a.
112. Schattauer SS, Kuhar JR, Song A, Chavkin C. Nalfurafine is a G-protein biased agonist having significantly greater bias at the human than rodent form of the kappa opioid receptor. *Cell Signal*. 2017; 32: 59–65. doi: 10.1016/j.cellsig.2017.01.016.
113. Mearimanan JK, Sutphen JC, Gao J, Kapusta DR. Nalfurafine, a G-protein-biased KOR (Kappa Opioid Receptor) Agonist, enhances the diuretic response and limits electrolyte losses to standard-of-care diuretics. *Hypertens Dallas Tex*. 1979 2022; 79: 379–390. doi: 10.1161/HYPERTENSIONAHA.121.18503.
114. Kaski SW, White AN, Gross JD, et al. Preclinical testing of nalfurafine as an opioid-sparing adjuvant that potentiates analgesia by the mu opioid receptor-targeting agonist morphine. *J Pharmacol Exp Ther*. 2019; 371: 487–499. doi: 10.1124/jpet.118.255661.
115. Willard F, Douros J, Gabe M, et al. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. *JCI Insight*. 2020; 5. doi: 10.1172/jci.insight.140532.
116. Hinds CE, Peace E, Chen S, et al. Abolishing β-arrestin recruitment is necessary for the full metabolic benefits of G protein-biased glucagon-like peptide-1 receptor agonists. *Diabetes Obes Metab*. 2024; 26: 65–77. doi: 10.1111/dom.15288.
117. Gao Y, Peterson S, Masri B, Hougland MT, et al. Cariprazine exerts antimanic properties and interferes with dopamine D2 receptor β-arrestin interactions. *Pharmacol Res Perspect*. 2015; 3: e00073. doi: 10.1002/prp2.73.

118. Urs NM, Peterson SM, Caron MG. New concepts in dopamine D2 receptor biased signaling and implications for schizophrenia therapy. *Biol Psychiatry*. 2017; 81: 78–85. doi: 10.1016/j.biopsych.2016.10.011.
119. Laszlovszky I, Barabássy Á, Németh G. Cariprazine, A Broad-spectrum antipsychotic for the treatment of schizophrenia: pharmacology, efficacy, and safety. *Adv Ther*. 2021; 38: 3652–3673. doi: 10.1007/s12325-021-01797-5.
120. Violin JD, Crombie AL, Soergel DG, Lark MW. Biased ligands at G-protein-coupled receptors: promise and progress. *Trends Pharmacol Sci*. 2014; 35: 308–316. doi: 10.1016/j.tips.2014.04.007.
121. Ikeda Y, Kumagai H, Motozawa Y, et al. Biased Agonism of the angiotensin II type I receptor. *Int Heart J*. 2015; 56: 485–488. doi: 10.1536/ihj.15-256.
122. Gekle M, Dubourg V, Schwerdt G, et al. The role of EGFR in vascular AT1R signaling: From cellular mechanisms to systemic relevance. *Biochem Pharmacol*. 2023; 217: 115837. doi: 10.1016/j.bcp.2023.115837.
123. Virk MS, Arttamangkul S, Birdsong WT, Williams JT. Buprenorphine is a weak partial agonist that inhibits opioid receptor desensitization. *J Neurosci Off J Soc Neurosci*. 2009; 29: 7341–7348. doi: 10.1523/JNEUROSCI.3723-08.2009.
124. Davis M. Buprenorphine pharmacodynamics: a bridge to understanding buprenorphine clinical benefits. *Drugs* 2025; 85: 215–230. doi: 10.1007/s40265-024-02128-y.
125. Infantino R, Mattia C, Locarini P, et al. Buprenorphine: far beyond the "Ceiling." *Biomolecules* 2021; 11: 816. doi: 10.3390/biom11060816.
126. Clément K, van den Akker E, Argente J, et al. Efficacy and safety of setmelanotide, an MC4R agonist, in individuals with severe obesity due to LEPR or POMC deficiency: single-arm, open-label, multicentre, phase 3 trials. *Lancet Diabetes Endocrinol*. 2020; 8: 960–970. doi: 10.1016/S2213-8587(20)30364-8.
127. Heyder NA, Kleinau G, Speck D, et al. Structures of active melanocortin-4 receptor–Gs-protein complexes with NDP-α-MSH and setmelanotide. *Cell Res*. 2021; 31: 1176–1189. doi: 10.1038/s41422-021-00569-8.
128. Israeli H, Degtjarik O, Fierro F, et al. Structure reveals the activation mechanism of the MC4 receptor to initiate satiation signaling. *Science* 2021; 372: 808–814. doi: 10.1126/science.abf7958.
129. Liu Z, Hruby VJ. MC4R biased signalling and the conformational basis of biological function selections. *J Cell Mol Med*. 2022; 26: 4125–4136. doi: 10.1111/jcmm.17441.
130. Pang PS, Butler J, Collins SP, et al. Biased ligand of the angiotensin II type 1 receptor in patients with acute heart failure: a randomized, double-blind, placebo-controlled, phase IIB, dose ranging trial (BLAST-AHF). *Eur Heart J*. 2017; 38: 2364–2373. doi: 10.1093/eurheartj/ehx196.
131. Singh KD, Karnik SS. Implications of β-arrestin biased signaling by angiotensin II type 1 receptor for cardiovascular drug discovery and therapeutics. *Cell Signal*. 2024; 124: 111410. doi: 10.1016/j.cellsig.2024.111410.
132. Monasky MM, Taglieri DM, Henze M, et al. The β-arrestin-biased ligand TRV120023 inhibits angiotensin II-induced cardiac hypertrophy while preserving enhanced myofilament response to calcium. *Am J Physiol - Heart Circ Physiol*. 2013; 305: H856–H866. doi: 10.1152/ajpheart.00327.2013.
133. Violin JD, DeWire SM, Yamashita D, et al. Selectively engaging β-arrestins at the angiotensin II type 1 receptor reduces blood pressure and increases cardiac performance. *J Pharmacol Exp Ther*. 2010; 335: 572–579. doi: 10.1124/jpet.110.173005.
134. Voors AA, Düngen H-D, Senni M, et al. Safety and Tolerability of neladenoson bialanate, a novel oral partial adenosine A1 receptor agonist, in patients with chronic heart failure. *J Clin Pharmacol*. 2017; 57: 440–451. doi: 10.1002/jcph.828.
135. Voors AA, Shah SJ, Bax JJ, et al. Rationale and design of the phase 2b clinical trials to study the effects of the partial adenosine A1-receptor agonist neladenoson bialanate in patients with chronic heart failure with reduced (PANTHEON) and preserved (PANACHE) ejection fraction. *Eur J Heart Fail*. 2018; 20: 1601–1610. doi: 10.1002/ejhf.1295.
136. Park SM, Chen M, Schmerberg CM, et al. Effects of β-arrestin-biased dopamine d2 receptor ligands on schizophrenia-like behavior in hypoglutamatergic mice. *Neuropsychopharmacology* 2016; 41: 704–715. doi: 10.1038/npp.2015.196.
137. Guo R, Chen O, Zhou Y, et al. Arrestin-biased allosteric modulator of neurotensin receptor 1 alleviates acute and chronic pain. *Cel*l 2025; 188: 4332-4349.e21. doi: 10.1016/j.cell.2025.04.038.
138. Slosky LM, Bai Y, Toth K, et al. β-arrestin biased allosteric modulator of NTSR1 selectively attenuates addictive behaviors. *Cell* 2020; 181: 1364-1379.e14. doi: 10.1016/j.cell.2020.04.053.
139. Manglik A, Lin H, Aryal DK, et al. Structure-based discovery of opioid analgesics with reduced side effects. *Nature* 2016; 537: 185–190. doi: 10.1038/nature19112.
140. Kliewer A, Gillis A, Hill R, et al. Morphine-induced respiratory depression is independent of β-arrestin2 signalling. *Br J Pharmacol*. 2020; 177: 2923–2931. doi: 10.1111/bph.15004.
141. White KL, Robinson JE, Zhu H, et al. The G protein–biased κ-opioid receptor agonist RB-64 Is analgesic with a unique spectrum of activities *in vivo*. *J Pharmacol Exp Ther*. 2015; 352: 98–109. doi: 10.1124/jpet.114.216820.

142. Rives M-L, Rossillo M, Liu-Chen L-Y, Javitch JA. 6'-Guanidinonaltrindole (6'-GNTI) is a G protein-biased κ-opioid receptor agonist that inhibits arrestin recruitment. *J Biol Chem*. 2012; 287: 27050–27054. doi: 10.1074/jbc.C112.387332.
143. Li B, Maruszko K, Kim S-K, et al. Structure and molecular mechanism of signaling for the glucagon-like peptide-1 receptor bound to Gs protein and exendin-P5 biased agonist. *J Am Chem Soc*. 2023; 145: 20422–20431. doi: 10.1021/jacs.3c05996.
144. El Eid L, Reynolds CA, Tomas A, Ben Jones. Biased agonism and polymorphic variation at the GLP-1 receptor: Implications for the development of personalised therapeutics. *Pharmacol Res*. 2022; 184: 106411. doi: 10.1016/j.phrs.2022.106411.
145. Wacker D, Wang S, McCorvy JD, et al. Crystal structure of an LSD-bound human serotonin receptor. *Cell* 2017; 168: 377-389.e12. doi: 10.1016/j.cell.2016.12.033.
146. Kim K, Che T, Panova O, et al. Structure of a hallucinogen-activated Gq-Coupled 5-HT2A serotonin receptor. *Cell* 2020; 182: 1574-1588.e19. doi: 10.1016/j.cell.2020.08.024.
147. Rodriguiz RM, Nadkarni V, Means CR, et al. LSD-stimulated behaviors in mice require β-arrestin 2 but not β-arrestin 1. *Sci Rep*. 2021; 11: 17690. doi: 10.1038/s41598-021-96736-3.
148. Pogorelov VM, Rodriguiz RM, Roth BL, Wetsel WC. The G protein biased serotonin 5-HT2A receptor agonist lisuride exerts anti-depressant drug-like activities in mice. *Front Mol Biosci*. 2023; 10: 1233743. doi: 10.3389/fmolb.2023.1233743.
149. Wallach J, Cao AB, Calkins MM, et al. Identification of 5-HT2A receptor signaling pathways associated with psychedelic potential. *Nat Commun*. 2023; 14: 8221. doi: 10.1038/s41467-023-44016-1.
150. Sniecikowska J, Gluch-Lutwin M, Bucki A, et al. Novel aryloxyethyl derivatives of 1-(1-benzoylpiperidin-4-yl) methanamine as the extracellular regulated kinases 1/2 (ERK1/2) phosphorylation-preferring serotonin 5-HT1A receptor-biased agonists with robust antidepressant-like activity. *J Med Chem*. 2019; 62: 2750–2771. doi: 10.1021/acs.jmedchem.9b00062.
151. Cabanu S, Pilar-Cuéllar F, Zubakina P,, et al. Molecular signaling mechanisms for the antidepressant effects of NLX-101, a selective cortical 5-HT1A receptor biased agonist. *Pharm Basel Switz*. 2022; 15: 337. doi: 10.3390/ph15030337.
152. Newman-Tancredi A, Depoortere RY, et al. Translating biased agonists from molecules to medications : Serotonin 5-HT 1A receptor functional selectivity for CNS disorders. *Pharmacol Ther*. 2022; 229. doi: 10.1016/j.pharmthera.2021.107937.
153. Depoortère R, Auclair AL, Newman-Tancredi A. NLX-101, a highly selective 5-HT1A receptor biased agonist, mediates antidepressant-like activity in rats via prefrontal cortex 5-HT1A receptors. *Behav Brain Res*. 2021; 401: 113082. doi: 10.1016/j.bbr.2020.113082.
154. Jastrzębska-Więsek M, Partyka A, Rychtyk J, et al. Activity of serotonin 5-HT1A Receptor Biased Agonists in Rat: Anxiolytic and Antidepressant-like properties. ACS *Chem Neurosci*. 2018; 9: 1040–1050. doi: 10.1021/acschemneuro.7b00443.
155. Tao X, Croom K, Newman-Tancredi A, et al. Acute administration of NLX-101, a serotonin 1A receptor agonist, improves auditory temporal processing during development in a mouse model of Fragile X Syndrome. *J Neurodev Disord*. 2025; 17: 1. doi: 10.1186/s11689-024-09587-0.
156. Papp M, Gruca P, Lason M, et al. The 5-HT1A receptor biased agonists, NLX-204 and NLX-101, display ketamine-like RAAD and anti-TRD activities in rat CMS models. *Psychopharmacology (Berl)* 2023; 240: 2419–2433. doi: 10.1007/s00213-023-06389-5.
157. Papp M, Gruca P, Litwa E, et al. The 5-HT1A receptor biased agonists, NLX-204 and NLX-101, like ketamine, elicit rapid-acting antidepressant activity in the rat chronic mild stress model via cortical mechanisms. *J Psychopharmacol Oxf Engl*. 2024; 38: 661–671. doi: 10.1177/02698811241254832.
158. Newman-Tancredi A. Biased agonism at serotonin 5HT1A receptors: preferential postsynaptic activity for improved therapy of CNS disorders. *Neuropsychiatry* 2011; 1(2): 149–164.
159. Zhang M, Chen T, Lu X, et al. G protein-coupled receptors (GPCRs): advances in structures, mechanisms and drug discovery. *Signal Transduct Target Ther*. 2024; 9(1): 88. doi: 10.1038/s41392-024-01803-6.