Journal of Pharmaceutical Research and Integrated Medical Sciences (JPRIMS)
ISSN: 3049-1681 | Vol. 02, Issue 11, Nov-2025 | pp.-46-62

ORIGINALARTICLE https://aktpublication.com/index.php/jprims/index

Role of Medicinal Chemistry in Modulating GPCR Targets for Neurological Disorders

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Abstract

This review analyses the application of medicinal chemistry in the modulation of G-protein-coupled receptor (GPCR) targets in the treatment of neurological disorders based on the presentation of preclinical evidence provided solely by animals. Considering dopaminergic, serotonergic and glutamatergic systems, we combine outcomes of rodents, zebrafish and non-human primates in demonstrating how optimization of structure-activity relationships (SAR), allosteric/bitopic and biased-ligand development, scaffold hopping and ADMET tuning yield brain-penetrant ligands with enhanced affinity, subtype selectivity, signalling bias and pharmacokinetic. The product shows promise in restoring motor function and reducing oxidative stress in D2/D3 modulators of 6-OHDA Parkinsonian rat models, as well as anxiolytic and antidepressant-like actions of engineered 5-HT1A/5-HT2A ligands in mice and zebrafish. Additionally, it exhibits precognitive and neuroprotective actions of mGluR PAMs in APP/PS1 and scopolamine models. We emphasize methodological strategies (in vitro binding, behavioural assays, microdialysis, PK/autoradiography) that can be used to bridge molecular design to organismal response, explain the translational obstacles affecting translation that include species differences, crosstalk and long-term signalling responses, and suggest prospects including AI-guided design, multi-omics biomarkers and targeted CNS delivery protocols. The arguments put forward make medicinal chemistry one of the key, mechanism-oriented catalysts in the evolution of GPCR-targeted neurotherapeutics.

Key Words:

GPCR Modulation; Medicinal Chemistry; Structure–Activity Relationship; Allosteric Modulators; Biased Ligands; ADMET/BBB Optimization; Preclinical Animal Models; Neuroprotection.

History:

Received: Aug, 27,2025

Revised: Sep, 28,2025

Accepted: Oct, 29,2025

Published: Nov 14, 2025

DOI: https://doi.org/10.64063/3049-1681.vol.2.issue11.4

1. INTRODUCTION

The neurodegenerative, psychiatric, and cognitive impairments of neurological disorders are at the end of a long line of complex interplay of deficiencies in biochemical, genetic, signaling, and other abnormalities[1]. Among other molecular systems involved, the G-protein-coupled receptors

(GPCRs) have proved to be master regulatory of neuronal communications. Being seven-transmembrane domain receptors, GPCRs regulate such important processes as neurotransmitter release, synaptic transmission, and neuroplasticity. Pathophysiology of many key neurological disorders, such as Parkinson, Alzheimer, schizophrenia, anxiety and depression are based on dysregulation of GPCR signaling pathways. GPCRs have a high potential to be the most advantageous group of drug targets because of their ubiquity and functional heterogeneity to restore neural homeostasis and alleviate the signs of the disease. Although the central nervous system (CNS)-active GPCR modulators have a remarkable pharmacological importance, their biochemical development is difficult because of cross-reactivity of receptor subtypes, low blood-brain barrier (BBB) permeability, and desensitization of the receptors. In turn, much more comprehensive knowledge of GPCR structure, binding dynamics and signal transduction is needed in order to design more specific and effective therapeutic agents[2].

Figure 1: Brain with Neurons[3]

Medicinal chemistry has become a key field in this regard that makes the linkage between pharmacology and innovation in medicine. Medicinal chemists have been able to tailor the activity of GPCR with remarkable precision through rational drug design, structure-activity relationship (SAR) analysis and computational modeling to come up with ligands that can fine-tune the activity of these GPCRs. Animal experiments, especially rodents, zebrafish and non-human primate studies have been useful in verifying such chemical designs by showing the repeatability of the effects on motor control, cognition and emotional behaviour. These preclinical studies, along with lack of understanding of the pharmacodynamic and pharmacokinetic characteristics of new GPCR modulators, are also important in illuminating their mechanisms of action in the CNS microenvironment. Through the combination of the chemical synthesis, receptor binding assays, and behavioral pharmacology, researchers still succeed in the discovery of therapeutic value of optimized GPCR-targeting compounds. This review will combine these results, with special focus on the contribution of developments in

medicinal chemistry in framing the preclinical environment of GPCR modulation in neurological diseases[4].

1.1.Background and Context

G-protein-coupled receptors (GPCRs) is a huge superfamily of proteins of seven transmembrane domains that convert extracellular stimuli into intracellular activity. They control the release of neurotransmitters, the synaptic plasticity as well as the excitability of the brain neurons, roles which are very important in ensuring maintenance of brain homeostasis. GPCR dysfunctions or aberrant signaling pathways tend to result in neurological conditions like Parkinson disease, Alzheimer disease, schizophrenia and epilepsy[5].

The basis of ligand-receptor interactions and the design of small molecules that can promote and inhibit GPCR activity more specifically is based on medicinal chemistry. Synthetic chemistry coupled with computational modeling and pharmacological validation of animal models has significantly increased our knowledge of the biology of GPCR and the efficacy of drugs in the central nervous system (CNS)[6].

1.2.Objectives of the Review

The objectives of this review are:

1. To analyze how SAR-based chemical modifications enhance GPCR ligand affinity and selectivity.
2. To evaluate the therapeutic efficacy of allosteric and biased GPCR modulators in animal models.
3. To optimize pharmacokinetic and BBB-penetrant properties of GPCR-targeted compounds.
4. To identify translational biomarkers linking animal GPCR responses to clinical potential.
5. To develop targeted CNS delivery strategies for improved GPCR drug safety and efficacy.

1.3.Importance of the Topic

There are about 40 percent of marketed drugs that contain GPCRs, but only a handful of them are CNS-active. The rigidity of the brain GPCR signaling and the pervaporation of the blood brain barrier (BBB) requires accuracy in the design of ligands. Learning of the medicinal chemistry considerations of animal-proven GPCR modulators provides an insight into the next-generation neurotherapeutics[7].

2. ANIMAL-BASED STUDIES ON GPCR MODULATION IN NEUROLOGICAL DISORDERS

GPCR investigation of animals (rodents, zebrafish, and primates) indicates that technologies of medicinal chemistry allow modulating dopaminergic, serotonergic, and glutamatergic signalling

to enhance the actions of motor, mood, and cognitive functions. The results emphasize the therapeutic utility of potentiation GPCR modulators in the treatment of neurologic diseases by means of targeting the receptors[8].

2.1.Overview of Animal-Based GPCR Research

The preclinical studies conducted in different animal models notably those that require rodents (rats and mice), zebrafish, and non-human primates have critically offered insights on the therapeutic implication of G-protein coupled receptor (GPCR) modulation in neurological pathology. Such works can be characterized as fundamental translational instruments that connect molecular biology with the nexus between molecular and behavioral biology. Rotigotine and quinpirole, dopaminergic GPCR agonists and haloperidol, a dopaminergic antagonist, have been widely used in rodent models to clarify the neurochemical and behavioral outcomes of the dopaminergic pathway[9]. As an example, these compounds have been shown to regulate locomotor activity in a dose-dependent manner, which further indicates their usefulness in modeling motor dysfunctions such as in the case of Parkinson's disease. On the same note, serotonergic receptor ligands at 5-HT1A, 5-HT2A and 5-HT7 have also been revealed to mediate mood and anxiety regulation in preclinical arrangements. Moreover, it has been demonstrated that metabotropic glutamate receptors (mGluR) ligands have neuroprotective and cognition-promoting activity in transgenic mice models of neurodegenerative disorders like Alzheimer and Huntington. GPCR-mediated mechanisms have since been proved using zebrafish and primate models to recap human-like behavioral phenotypes and neurochemical responses and thus shed light on the cross- species conservation of GPCR signaling[10].

2.2.Methodological Approaches

GPCR studies directed by medicinal chemistry have a systematic multi-phase approach that includes the molecular design, biological validation, and the behavioral assessment. The first phase is followed by ligand development and optimization; whereby chemical scaffolds are developed and optimized according to structure-activity relationship (SAR) studies and pharmacophore modeling. The methods assist in determining signaling important structural characteristics necessary to implicate receptor affinity and selectivity[11]. During synthesis, the compounds are then tested in vitro using receptor binding assays, either radioligand displacement or fluorescence-based binding, to determine affinity (Ki values) and functional efficacy (agonism, antagonism, or inverse agonism) after synthesis. The second decisive measure is in vivo pharmacological testing on an animal model whereby a collection of behavioral assays are used to determine the therapeutic relevance of the compound. Widely referred tests are the open field test that is anxiety and locomotion, rotarod test that measures motor coordination, Morris water maze that assesses spatial learning and memory, and elevated plus maze, which is used to measure anxiolytic effect. These behavioral experiments are supplemented with neurochemical studies, e.g. microdialysis and measurement of neurotransmitters, to obtain a mechanistic correlation. Pharmacokinetic (PK) and biodistribution studies are then conducted to determine the penetration of the compound of the central nervous system (CNS), plasma half-life, and metabolic stability, among others, using LC-MS/MS and

autoradiography studies. A combination of these methodologies offers an in-depth perspective on the GPCR ligand efficacy, safety and pharmacological profile.

2.3.Key Findings from Preclinical Studies

- **Dopamine receptor modulators:** In rat models of unilateral induced Parkinson disease provided by 6-hydroxydopamine 6-OHDA, pyridazinone-based and indole-based scaffold selective D2/D3 agonists have demonstrated considerable recovery of motor functions. These substances improved locomotor activity, rotations, and are able to decrease neuronal loss in the dopaminergic regions. In addition, both neuroprotective and symptom-reducing properties were indicated by biochemical measures of a simultaneous decrease in oxidative stress markers (malondialdehyde, MDA) and an augmentation of antioxidant enzymes. The results support the promise of D2/D3 modulators in dopaminergic deficit in Parkinsonism mediated by medicinal chemistry engineering.
- **Serotonin receptor ligands:** Pharmacologically optimized 5-HT1A partial agonists, such as buspirone novel analogs, have been found to inhibit anxiety and stress-induced behavior in Wistar rats. Anxiosomatic reactions were assessed by behavioral tests based on elevated plus maze and open field paradigms, which showed more time on open arms and increased exploratory behavior, which were signs of anxiolytic effects. It was found that the effects were mediated by hippocampal serotonergic modulation as shown by the enhancement of serotonin turnover and binding of receptors in limbic regions. The therapeutic promise of drugs based on medicinal chemistry, 5-HT ligands, in the management of anxiety and mood disorders is confirmed by these preclinical results[12].
- **Glutamate Receptor 5 (mGluR5):** Thiazolidinone-coordinated allosteric modulators of metabotropic glutamate receptor 5 (mGluR5) Synthesized allosteric modulators In mouse models of memory impairment caused by scopolamine administration, thiazolidinone-coordinated allosteric modulators of metabotropic glutamate receptor 5 (mGluR5) have been observed The evidence of behavioral testing, which was performed by the Morris water maze and novel object recognition assays, demonstrated enhanced retention and spatial learning. Moreover, these modulators boosted synaptic plasticity (Brain-derived neurotrophic factor (BDNF)) and elevated levels of acetylcholine in the hippocampal, indicating neurochemical recovery of brain networks. All of these results highlight the essential significance of GPCR-targeted compounds developed in medicinal chemistry in the management of various neurological impairments by targeting receptors with high specificity[13].

3. MEDICINAL CHEMISTRY INNOVATIONS IN GPCR MODULATION FOR NEUROLOGICAL DISORDERS

Modulators of dopaminergic, serotonergic and glutamatergic GPCR have been optimized in medicinal chemistry to selectively treat Parkinson, anxiety and depression as well as cognitive disorders. New ligand designs, such as allosteric and biased modulators, can be used to fine-tune the receptor to improve its efficacy, neuroprotection, and side effects[14].

3.1.Dopaminergic GPCR Modulation in Parkinson's Models

The pharmacological specificity of the dopamine receptor modulators, especially of the D2 and D3 receptor subtypes that are involved in Parkinson diseases, has further been achieved by virtue of medicinal chemistry-based developments. Individual receptor subtype selectivity, longer receptor activation, and less frequent motor activity risks such as dyskinesia have also been achieved by structural refinements, including hyterocyclic derivatives of the apomorphine backbone. The compounds preserve dopaminergic tone without inducing overactivation of D1 receptors which can be a contributing factor to unwanted side effects[15]. The preclinical investigation on 6-hydroxydopamine (6-OHDA)-lesioned rat models has demonstrated that these analogs are effective in repairing motor coordination and locomotor performance in long term. Additionally, the strength of the fluorinated and methoxy-modified derivatives proved to have a better pharmacokinetic providing better blood-brain barrier permeability and stability of their metabolism. Radioligand binding and kinetic studies indicated that these changes maximized receptor residence time and reduced off-target affinity to the serotonergic and adrenergic receptors. Together, these therapeutic measures in medicinal chemistry indicate the ways by which the rational molecular design approach to pharmaceutical interventions can be used to tune dopaminergic GPCR responses to produce long-acting neurotherapeutic effects with measureable tolerability in Parkinson models[16].

3.2.Serotonergic GPCR Modulation in Depression and Anxiety

The future of anxiolytics and antidepressants has been dominated by serotonergic gPCR modulation. Recent preclinical studies utilizing mice and zebrafish behavioral surrogacy studies have communicated the effectiveness of synthetic 5-HT1A receptor agonists which are made with indole-piperazine hybrid frameworks. Such ligands showed intense anxiogenic responses in equal terms as diazepam; this was observed by high open-arm exploration rate in elevated plus mazes, and low level of freezing behavior during stress models. Their optimality in geometry structure through π–π stacking interactions/hydrogen-bond donor modifications enhanced the affinity of the receptors whilst reducing the sedative properties[17]. Simultaneously, chemically-modified sulfonamide-linked aryl scaffold-based 5-HT2A receptor antagonists were highly effective in hyperlocomotion, impulsivity and aggression suppression which are hallmarks in stress-induced and psychotic models. Notably, such studies also focus on functional selectivity or biased agonism, i.e., a point in which chemically distinct ligands can selectively engage a particular signaling pathway (e.g., the G-protein pathway over the 2=3 -arrestin pathways). With intelligent molecular engineering, medicinal chemists have shown that the side effects of signaling bias by ligand can be exploited to enhance therapeutic efficacy and reduce side effects, which provides a route to safer and more mechanism-specific treatment of mood and anxiety disorders.

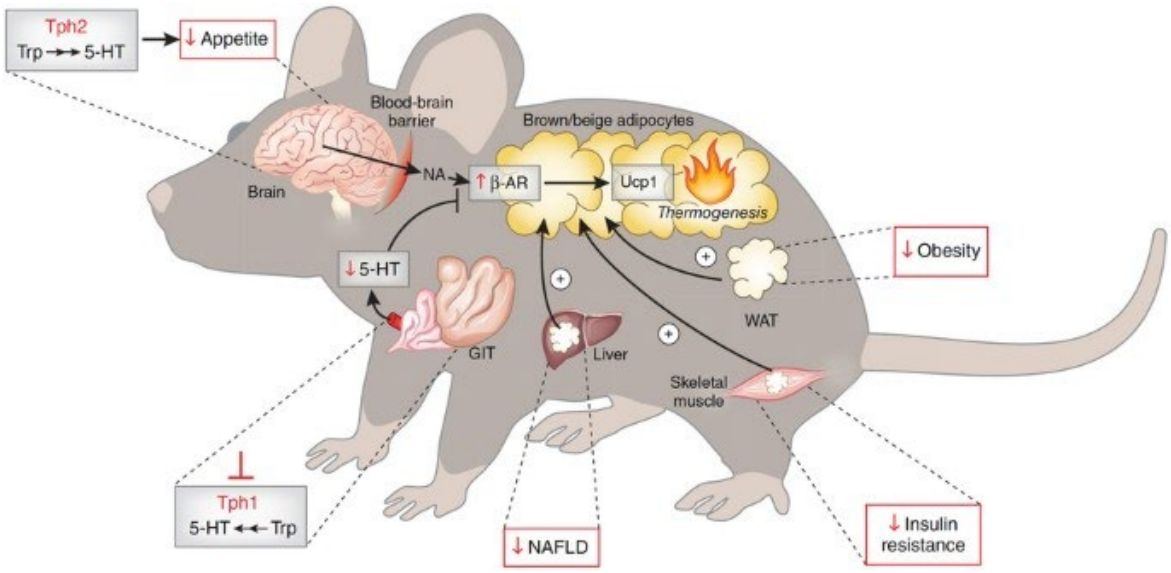

Figure 2: Systemic Role of Serotonin (5-HT) in Metabolic Regulation[18]

3.3.Glutamatergic GPCR Modulation in Cognitive Disorders

Amongst the receptors of these GPCRs, there are the metabotropic glutamate receptors (mGluRs) whose target has gained significant attention in dealing with cognitive and neurodegenerative diseases like Alzheimer and Schizophrenia. Most medicinal chemistry studies have focused on the synthesis of positive allosteric modulators (PAMs) incorporating benzoxazole and thiazole core structures, which have been engineered to increase the sensitivity of the receptor to endogenous glutamate but not to overstimulate it. These PAMs were observed to be very effective in enhancing spatial learning, memory retention, and synaptic plasticity in mouse models of APP/PS1 transgenic mouse models of Alzheimer disease[19]. The biochemical signs of improvement in behavior included higher rates of hippocampal levels of brain-derived neurotrophic factor (BDNF) and less deposits of amyloid-beta (A2). The presence of restored long-term potentiation (LTP) that is a demonstration of improved communication between synapses was confirmed by the electrophysiological recordings. Besides, there was decreased oxidative stress and neuronal apoptosis with repeated use of these modulators, which highlights their neuroprotective nature. Together, these observations depict the advanced function of medicinal chemistry in regulating mGluR subtypes using customized allosteric dynamics, to progress the development of specific, cognition-thought-provoking GPCR therapy of intricate brain diseases[20].

3.4.GPCR Allosteric and Biased Ligand Design

The development of allosteric and biased ligands represents a paradigm shift in GPCR-directed drugs discovery with medicinal chemistry developments. Allosteric modulators bind at topographical different binding sites as opposed to traditional orthosteric ligands which compete against endogenous neurotransmitters and it is possible to co-precisely regulate receptor conformation, selectivity, and signal bias. With the use of computational docking, molecular dynamics simulations, and fragment-based drug design most researchers have produced bitopic ligands, hybrid molecules that can bind to both orthosteric sites and allosteric sites concurrently.

This bipartite connection generates signaling responses that are highly fine-tuned with enhanced receptor subtype specificity and reduced undesired effects. It was experimentally confirmed in rat hippocampal slice models that mGluR2/3 positive allosteric modulators (PAMs) selective bisignaling of receptor to neuroprotective G-protein pathways facilitates the prevention of glutamate-induced excitotoxicity[21]. Reduced neuronal loss was confirmed by histological staining and normal excitatory transmission was observed by electrophysiological recording demonstrated the maintenance of synaptic integrity. These results confirm that allosteric and biased ligands represent a rationally designed family of GPCR modulators which can target signaling in advantageous pathways in a selective manner. That design of the medicinal chemical ligands thus introduces new lines of therapeutic neurological and psychiatric drug development that is safer and more effective.

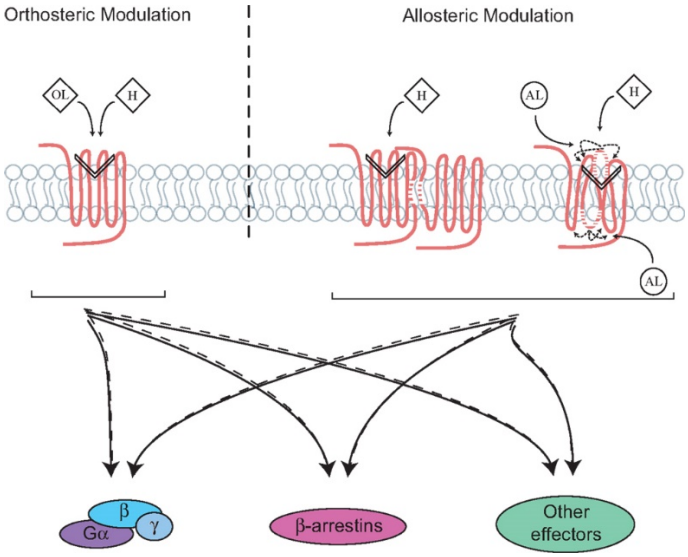

Figure 3: Allosteric and Biased Ligand Design[22]

4. MEDICINAL CHEMISTRY APPROACHES IN GPCR MODULATION

GPCR activity and signaling can be controlled with high precision with the help of medicinal chemistry methods such as SAR optimization, allosteric and bitopic ligand design, and computational design as well as ADMET tuning. Such strategies result in selective, stable, and brain-penetrant ligands that contribute to infections that improve therapeutic effects and safety even in neurological and psychiatric illnesses[23].

4.1.Structure–Activity Relationship (SAR) and Ligand Optimization

Modern GPCR-centered medicinal chemistry is still based on the structure-activity relationship (SAR), which allows rational design of drugs by generating systematic correlations between their molecular structure and biological activity. With the introduction of certain chemical alterations and the consideration of their pharmacological effects, it is possible to state important functional groups determining the receptor binding affinity, selectivity, and signaling bias.

Preclinical studies in electron-withdrawing fluorine or chlorine-modified D2/D3 agonist scaffolds suggested that incorporation of electron-withdrawing substituents, including the

fluorine theory group, made the binding of dopaminergic receptors in preclinical studies of 6-hydroxydopamine (6-OHDA)-lesioned rats much better, with improvement in locomotor recovery of the 6-hydroxydopamine lesion group (D2/D3). These replacements not only stabilized receptor-ligand interactions, but also lowered oxidative metabolism, augmenting half-life of compounds. Equally, the optimization of serotonergic ligands by the RA approximations showed that the exchange of the indole rings with either pyridine or quinoline groups in 5-HT1A agonists enhanced both lipophilicity and blood to brain barrier (BBB) permeations thereby augmenting the act of anxiolysis in the elevated plus maze paradigm[24].

Further, biased agonists, an unprecedented type of GPCR ligand, selected by SAR refinement have also been developed, and they selectively stimulate desirable intracellular signaling pathways. As an example, 5-HT2A biased agonists with carbazole backbones selectively promoted cortical serotonin signalling with antidepressant actions and avoided hallucinogens with 5-HT2A-driven, 2 -arrestin-mediated reactions. These findings demonstrate the potential of the directed, chemical fine-tuning of receptor conformation and functional bias to give safer and more specific neuropharmacology agents.

4.2.Allosteric and Bitopic Ligand Design

Allosteric modulators evolution has become a significant electrical break-through in GPCR drug discovery as it is now possible to regulate receptor activity via non-orthosteric binding points. In comparison with the traditional orthosteric ligands that compete with neurotransmitters that are produced by the body, allosteric modulators increase the response of the receptor, enhance its specificity to the subtype, and decrease subsorption. The mGluR5 and mGluR2 benzothiazole scaffolded and benzoxazole scaffolded positive allosteric modulators of mGluRs, have demonstrated outstanding neurocognitive improvements in rodent models of Alzheimer disease. They had no excitotoxic overstimulation, improved memory, density of synapses and survival of neurons[25].

Orthosteric and allosteric functions GPCR-targeted therapies have been further improved by parallel advancements in bitopic ligand design - hybridizing orthosteric and allosteric functions into one molecule. Bitopic mGluR1 modulators with benzylpiperidine linkers retained a longer hold on the receptor and induced neuroprotection via stabilization of G-protein-mediated signaling investigation in rat hippocampal slice assays. Electrophysiological evaluation proved that there is long-term potentiation (LTP) elicitation that is sustained and revealed that hybrid binding is both effective and stable. All these approaches are examples of how structural innovation in the ligand architecture can provide control over the receptors with improved therapeutic indices.

4.3.Computational and Fragment-Based Drug Design

Computational chemistry developments, molecular modeling and virtual screening under the direction of AI-guided virtual screening has changed the GPCR ligand discovery landscape. Homology modeling can be used to predict dynamics of the binding pockets and optimal ligand orientation predicted before synthesis by using high-resolution GPCR crystal structures. This hastens the process of drug development and lowering the costs and failure in the experiments[26].

Indicatively, the 5-HT7 receptor antagonists that emerged out of silico-designed based on quantitative structureactivity relationship (QSAR) modeling were optimized with strong hydrogen-bond acceptors and hydrophobic balance that produced molecules that performed highly in controlling mood and circadian rhythm in zebrafish and mouse models. On the same note, fragment-based drug design (FBDD) which consists of the construction of entire ligands using small pharmacophoric fragments has been used to potentiate high receptor selectivity with low toxicity. Taking a methodical assembly of these fragments in order to the planned binding interactions, medicinal chemists can generate low-molecular-weight GPCR modulators with preferred pharmacokinetic and pharmacodynamic plans. These computationally informed approaches are the union of the fields of structural biology, chemistry and informatics in the next generation GPCR drug discovery[27].

4.4.Pharmacokinetic and ADMET Optimization

GPCR modulators need an elaborate optimization of ADMET (absorption, distribution, metabolism, excretion, and toxicity) to attain central nervous system (CNS) effect. To achieve the highest BBB penetration and minimal peripheral toxicity, medicinal chemists optimally balance molecular weight, lipophilicity (logP), polar surface area and hydrogen-bond donors/acceptors.

N-alkylated 5-HT1A agonists showed significantly better oral bioavailability and CNS concentrations compared to their parent analogs in preclinical models of depression, and induced behavioral effect with lower dosage. Likewise, modification of D3 receptor antagonists with fluoroalkyl group increased hepatic metabolism resistance, and thus increased half-life in Sprague Bible rats. These chemical optimization makes dosing less frequent and makes patients more compliant. Notably, refining of ADMET also includes metabolic stability screening by means of carrying out microsomal testing and in vivo biodistribution experimentation to guarantee a positive therapeutic window and safety profile of CNS-targeted GPCR drugs[28].

4.5.Scaffold Hopping and Hybrid Molecule Design

Scaffold hopping is a flexible medicinal chemistry methodology in which the backbone structure of a biologic active ligand is substituted with a new framework maintaining biologic activity without losing intellectual property and pharmacokinetics advantages. Dual 5-HT2A/D2 receptor antagonists that were prepared in animal models of schizophrenia through scaffold hopping of clozapine analogs could reduce hyperlocomotion and improve cognitive performance by much lower hepatotoxicity levels. This shows that scaffold redesign can be used to produce safer and more efficient polyfunctional ligands.

The hybrid molecule design is another innovative approach that combines two different pharmacophores into one compartment, and this approach allows modulating two or more GPCRs at the same time. Indicatively, dual D3/5-HT1A agonists in rat Parkinson disease models not only recovered motor coordination, but they also ameliorated the symptoms of depression as well which is a clear indication of dopaminergic as well as serotonergic malfunctions. These polypharmacological hybrid ligands depict the future of medicinal chemistry in the multifactorial disease of the nervous system by synergistic modulation of receptors[29].

4.6.Chemical Modulation of Receptor Signaling Pathways

The further development of medicinal chemistry is no longer limited to attaching to receptors but rather to the process of intracellular signaling dynamics. The activation of GPCRs can occur through a variety of pathways, including G alpha subunits, 2 -arrestin, and second messengers such as cAMP, and subtle chemical changes can promote activation of neuroprotective pathways[30].

Studies also demonstrated neurotrophic factor experimentalation (e.g. BDNF) encouraged and antagonized oxidative stress-induced apoptosis initiated by (R)-enantiomers of 2 -arrestin-biased D2 receptor ligands in preclinical studies of rat cortical neurons. These were stereochemically selective compounds that were more effective and safe in comparison to their racemic analogs. Tuned chirality, polarity, and substituent orientation can enable chemists to select advantageous G-protein or β-arrestin pathways, inhibit undesirable maladaptive signaling associated with desensitization or neurotoxicity. This specific modulation highlights the new function of chemical design in determining not only receptor activation, but also the quality and future response of the cellular results, giving a level of control over therapeutic signaling never tried before in any neurological and psychiatric drug therapy[31]

Table 1: GPCR Modulation and Neurotherapeutic Studies[32]

Author(s) & Year	Study Title / Description	Focus Area	Methodology	Key Findings
Wold et al. (2018)[33]	Allosteric modulation of Class A GPCRs: targets, agents, and emerging concepts	Allosteric modulation and therapeutic targeting of Class A GPCRs	Comprehensive review and analysis of allosteric modulators and receptor pharmacology	Highlighted the advantages of allosteric modulators for subtype selectivity and functional bias, promoting safer and more precise GPCR-targeted drugs
Ye et al. (2018)[34]	Orphan receptor GPR88 as an emerging neurotherapeutic target	Role of GPR88 in neurological and psychiatric disorders	Pharmacological and genetic studies on receptor function and signaling	Identified GPR88's role in motor control and emotional regulation; suggested its potential as a therapeutic target in Parkinson's, schizophrenia, and addiction
Ye et al. (2020)[35]	Small molecules selectively targeting sigma-1	Sigma-1 receptor (σ1R) modulation for	Design and synthesis of selective ligands	Demonstrated neuroprotective and neuromodulatory

	receptor for neurological diseases	neuroprotection and therapy	for σ1R with pharmacological evaluation	effects; established σ1R as a promising target for neurodegenerative and psychiatric disorders
Yu et al. (2019)[36]	Design and characterization of ogerin-based positive allosteric modulators for GPR68	Development of positive allosteric modulators (PAMs) for GPR68	Chemical synthesis, structural modeling, and functional assays	Developed PAMs that enhanced receptor signaling without direct activation; provided new insights into GPR68 modulation for therapeutic use
Zhang et al. (2024)[37]	Advances in GPCR structures, mechanisms, and drug discovery	Structural biology and mechanistic insights of GPCRs in drug design	Review of recent advances using cryo-electron microscopy and computational modeling	Highlighted breakthroughs enabling high-resolution visualization of GPCR dynamics; emphasized progress in developing biased agonists and allosteric modulators

5. DISCUSSION

Optimized ligand design because of research motivated by GPCRs has the potential to rectify motor, cognitive and emotional impairments in the nervous system altogether with the adoption of neurological diseases. Although the barrier of translational issues has been present, the promise of allosteric modulation, Artificial Intelligence-driven modeling, and targeted delivery systems offers more efficient and specific aerotherapeutics.

5.1.Interpretation and Analysis of Findings

The collective findings provided by the animal studies are that pharmaceutical chemistry has had a tremendous positive impact on the regulation of GPCR-based targets of neurological diseases. The role of rationally designed ligands in naturally designed ligands rationally designed ligands have been found to have succeeded in controlling dopaminergic, serotonergic, and glutamatergic pathways to rejuvenate motor, cognitive, and emotional abilities with the aid of the structure-activity relationship (SAR) analysis, allosteric modulation, and hybrid molecule synthesis. The chemically engineered compounds have enhanced behavioral results including; locomotor

recovery in Parkinsonian rat, reduction of anxiety in the Wistar models, and the increase in memory in the transgenic Alzheimer mice. Taken together, these findings support the claim that molecular-based chemical modifications are directly translated into neurobehavioral efficacy and these features selectivity of receptor affinity, subtype specificity and biased signaling determine therapeutic effects[38].

5.2.Implications and Significance

These results imply that medicinal chemistry is a foundation of contemporary neuropharmacology because it allows to strictly control the activity of GPCRs in their structure and functioning. The allosteric and bitopic ligands showed success in preclinical models and this indicates their potential in cancer therapy by attaining receptor subtype specificity, reduced desensitization and neuroprotective signaling. Better blood-brain barrier permeability and pharmacokinetic stability Computational modeling and pharmacophore-based design has further interposed the separation between chemical synthesis and pharmacological validation. Medical chemistry therefore can be involved in discovery of both new neuroactive molecules as well as providing or creating a mechanistic basis on which molecular design can be translated into relevant clinical therapeutic interventions of intricate ailments such as Parkinson, Alzheimer and depression[39].

5.3.Gaps and Future Research Directions

Regardless of its encouraging preclinical results, multiple gaps are still associated with GPCR-targeted drugs development. Animal limitations to the translation of animal data to human systems invariably lie in species-specific differences in receptor architecture and receptor signaling, and problems like receptor crosstalk, desensitization, and metabolic stability are significant. Future studies and directions are to combine AI-based molecular modeling in predictive ligand optimization, try allosteric ligand libraries or bitopic ligand libraries in underfiled GPCR subtypes, and utilize multi-omics and neuroimaging technologies in more effectively correlating chemical structure with functional phenotypes. Moreover, further improvements in nanocarrier-based CNS delivery systems and prodrug approach are also able to provide this system with higher therapeutic efficacy and safety. Conclusively, medicinal chemistry remains a flexible field to be used in GPCR drug discovery as it creates an environment ensuring the development of selective, brain-penetrant and functionally biased ligands have tremendous potential in future neurological therapeutics[40].

6. CONCLUSION

The animal-based preclinical evidence clearly indicates that medicinal chemistry plays a pivotal role in the development of GPCR-targeted therapies to treat neurological disorders: with SAR-driven optimization, allosteric/bitopic and biased-ligand design, scaffold hopping and ADMET tuning, scientists have now made brain-penetrant compounds that repair motor functions, alleviate mood disorders and improve cognition in rodent, zebrafish, and primate models. These chemically engineered ligands have enhanced receptor affinity, subtype selectivity, signaling bias and pharmacokinetic, and molecular design translates into the meaningful neurobehavioral and neuroprotective. However, each of the species-finite receptor variations, receptor crosstalk,

and long-term physiological physiological dynamics of receptor signalling, and transport issues dampen direct clinical translation, demand cross-species validation, translational biomarkers, and better CNS delivery designs. To extrapolate in the future, the technological step that will be essential is the combination of AI-informed design, multi-omics readouts, and specific delivery platforms that will help to improve the quality of findings that have been successful in preclinical studies and translate them into clinical application. In sum, medicinal chemistry offers the mechanistic / practical repertoire to rationally tune-up GPCR signaling, giving a promising way out to safer, more selective, and effective neurotherapeutics.

REFERENCES

1. Adeoye, B. O., Akano, O. P., Awojebe, D. R., Ogunbiyi, B. T., Adeoye, A. D., Ukangwa, N. A., ... & Oyebanji, A. H. (2025). Nutraceutical regulations of G-protein coupled receptors in neurological, cardiovascular and endocrine disorders: a review. Phytochemistry Reviews, 1-18.
2. Azam, S., Haque, M. E., Jakaria, M., Jo, S. H., Kim, I. S., & Choi, D. K. (2020). G-protein-coupled receptors in CNS: a potential therapeutic target for intervention in neurodegenerative disorders and associated cognitive deficits. Cells, 9(2), 506.
3. Bassani, D., Pavan, M., Federico, S., Spalluto, G., Sturlese, M., & Moro, S. (2022). The multifaceted role of GPCRs in amyotrophic lateral sclerosis: a new therapeutic perspective? International Journal of Molecular Sciences, 23(9), 4504.
4. Bondarev, A. D., Attwood, M. M., Jonsson, J., Chubarev, V. N., Tarasov, V. V., & Schiöth, H. B. (2020). Opportunities and challenges for drug discovery in modulating Adhesion G protein-coupled receptor (GPCR) functions. Expert Opinion on Drug Discovery, 15(11), 1291-1307.
5. Brogi, S., Campiani, G., Brindisi, M., & Butini, S. (2019). Allosteric modulation of ionotropic glutamate receptors: an outlook on new therapeutic approaches to treat central nervous system disorders. ACS Medicinal Chemistry Letters, 10(3), 228-236.
6. Cheng, L., Xia, F., Li, Z., Shen, C., Yang, Z., Hou, H., ... & Shao, Z. (2023). Structure, function and drug discovery of GPCR signaling. Molecular Biomedicine, 4(1), 46.
7. Christopher, J. A., Orgován, Z., Congreve, M., Doré, A. S., Errey, J. C., Marshall, F. H., ... & Keserű, G. M. (2018). Structure-based optimization strategies for G protein-coupled receptor (GPCR) allosteric modulators: a case study from analyses of new metabotropic glutamate receptor 5 (mGlu5) X-ray structures. Journal of medicinal chemistry, 62(1), 207-222.
8. Coughlin, Q., Hopper, A. T., Blanco, M. J., Tirunagaru, V., Robichaud, A. J., & Doller, D. (2019). Allosteric modalities for membrane-bound receptors: insights from drug hunting for brain diseases. Journal of Medicinal Chemistry, 62(13), 5979-6002.

9. Crupi, R., Impellizzeri, D., & Cuzzocrea, S. (2019). Role of metabotropic glutamate receptors in neurological disorders. Frontiers in molecular neuroscience, 12, 20.

10. de Sena M Pinheiro, P., Rodrigues, D. A., do Couto Maia, R., Thota, S., & Fraga, C. A. (2019). The use of conformational restriction in medicinal chemistry. Current topics in medicinal chemistry, 19(19), 1712-1733.

11. Felder, C. C. (2019). GPCR drug discovery-moving beyond the orthosteric to the allosteric domain. Advances in pharmacology, 86, 1-20.

12. Han, B., Salituro, F. G., & Blanco, M. J. (2020). Impact of allosteric modulation in drug discovery: innovation in emerging chemical modalities. ACS Medicinal Chemistry Letters, 11(10), 1810-1819.

13. Haque, M. E., Kim, I. S., Jakaria, M., Akther, M., & Choi, D. K. (2018). Importance of GPCR-mediated microglial activation in Alzheimer's disease. Frontiers in cellular neuroscience, 12, 258.

14. Harris, S. S., & Urs, N. M. (2021). Targeting β-arrestins in the treatment of psychiatric and neurological disorders. CNS drugs, 35(3), 253-264.

15. Hatzipantelis, C. J., Langiu, M., Vandekolk, T. H., Pierce, T. L., Nithianantharajah, J., Stewart, G. D., & Langmead, C. J. (2020). Translation-focused approaches to GPCR drug discovery for cognitive impairments associated with schizophrenia. ACS Pharmacology & Translational Science, 3(6), 1042-1062.

16. Jacobson, K. A., Merighi, S., Varani, K., Borea, P. A., Baraldi, S., Aghazadeh Tabrizi, M., ... & Gessi, S. (2018). A3 adenosine receptors as modulators of inflammation: from medicinal chemistry to therapy. Medicinal research reviews, 38(4), 1031-1072.

17. Jankowska, A., Wesolowska, A., Pawlowski, M., & Chlon-Rzepa, G. (2018). Multi-target-directed ligands affecting serotonergic neurotransmission for Alzheimer's disease therapy: advances in chemical and biological research. Current Medicinal Chemistry, 25(17), 2045-2067.

18. Kaczor, A. A., Wróbel, T. M., & Bartuzi, D. (2022). Allosteric modulators of dopamine D2 receptors for fine-tuning of dopaminergic neurotransmission in cns diseases: overview, pharmacology, structural aspects and synthesis. Molecules, 28(1), 178.

19. Kamala, G. R. (2025). A Review on Therapeutic Advances and Challenges in Treating Neurological Disorders. Journal of Pharma Insights and Research, 3(4), 206-215.

20. Komatsu, H. (2021). Innovative therapeutic approaches for Huntington's disease: From nucleic acids to GPCR-targeting small molecules. Frontiers in Cellular Neuroscience, 15, 785703.

21. Liao, C., de Molliens, M. P., Schneebeli, S. T., Brewer, M., Song, G., Chatenet, D., ... & Li, J. (2019). Targeting the PAC1 receptor for neurological and metabolic disorders. Current topics in medicinal chemistry, 19(16), 1399-1417.

22. Lorente, J. S., Sokolov, A. V., Ferguson, G., Schiöth, H. B., Hauser, A. S., & Gloriam, D. E. (2025). GPCR drug discovery: new agents, targets and indications. Nature Reviews Drug Discovery, 1-22.

23. Lu, S., & Zhang, J. (2018). Small molecule allosteric modulators of G-protein-coupled receptors: drug–target interactions. Journal of medicinal chemistry, 62(1), 24-45.

24. Nieto, A., Bailey, T., Kaczanowska, K., & McDonald, P. (2021). GABAB receptor chemistry and pharmacology: Agonists, antagonists, and allosteric modulators. Behavioral Neurobiology of GABAB Receptor Function, 81-118.

25. Rahman, M. M., Islam, M. R., Mim, S. A., Sultana, N., Chellappan, D. K., Dua, K., ... & Emran, T. B. (2022). Insights into the Promising Prospect of G Protein and GPCR-Mediated Signaling in Neuropathophysiology and Its Therapeutic Regulation. Oxidative Medicine and Cellular Longevity, 2022(1), 8425640.

26. Roth, B. L. (2019). Molecular pharmacology of metabotropic receptors targeted by neuropsychiatric drugs. Nature structural & molecular biology, 26(7), 535-544.

27. Saikia, S., Bordoloi, M., & Sarmah, R. (2019). Established and in-trial GPCR families in clinical trials: a review for target selection. Current drug targets, 20(5), 522-539.

28. Salmaso, V., & Jacobson, K. A. (2020). Purinergic signaling: impact of GPCR structures on rational drug design. ChemMedChem, 15(21), 1958-1973.

29. Shukla, R., Pahal, S., Gupta, A., Choudhary, P., Misra, K., & Singh, S. (2023). Modulation of GPCR receptors common to gut inflammatory diseases and neuronal disorders, Alzheimer's and Parkinson's diseases as druggable targets through Withania somnifera bioactives: an in silico study. Journal of Biomolecular Structure and Dynamics, 41(10), 4485-4503.

30. Slosky, L. M., Caron, M. G., & Barak, L. S. (2021). Biased allosteric modulators: new frontiers in GPCR drug discovery. Trends in pharmacological sciences, 42(4), 283-299.

31. Tan, L., Yan, W., McCorvy, J. D., & Cheng, J. (2018). Biased ligands of G protein-coupled receptors (GPCRs): Structure–functional selectivity relationships (SFSRs) and therapeutic potential. Journal of medicinal chemistry, 61(22), 9841-9878.

32. Wold, E. A., & Zhou, J. (2018). GPCR allosteric modulators: mechanistic advantages and therapeutic applications. Current topics in medicinal chemistry, 18(23), 2002.

33. Wold, E. A., Chen, J., Cunningham, K. A., & Zhou, J. (2018). Allosteric modulation of class A GPCRs: targets, agents, and emerging concepts. Journal of medicinal chemistry, 62(1), 88-127.

34. Ye, N., Li, B., Mao, Q., Wold, E. A., Tian, S., Allen, J. A., & Zhou, J. (2018). Orphan receptor GPR88 as an emerging neurotherapeutic target. ACS chemical neuroscience, 10(1), 190-200.

35. Ye, N., Qin, W., Tian, S., Xu, Q., Wold, E. A., Zhou, J., & Zhen, X. C. (2020). Small molecules selectively targeting sigma-1 receptor for the treatment of neurological diseases. Journal of medicinal chemistry, 63(24), 15187-15217.

36. Yu, X., Huang, X. P., Kenakin, T. P., Slocum, S. T., Chen, X., Martini, M. L., ... & Jin, J. (2019). Design, synthesis, and characterization of ogerin-based positive allosteric modulators for G protein-coupled receptor 68 (GPR68). Journal of medicinal chemistry, 62(16), 7557-7574.

37. Zhang, M., Chen, T., Lu, X., Lan, X., Chen, Z., & Lu, S. (2024). G protein-coupled receptors (GPCRs): advances in structures, mechanisms and drug discovery. Signal transduction and targeted therapy, 9(1), 88.

38. Zhang, Y., Tan, Y., Zhang, Z., Cheng, X., Duan, J., & Li, Y. (2024). Targeting Thyroid-Stimulating Hormone Receptor: a perspective on small-molecule modulators and their therapeutic potential. Journal of Medicinal Chemistry, 67(18), 16018-16034.

39. Zhang, Y., Wang, K., & Yu, Z. (2020). Drug development in channelopathies: Allosteric modulation of ligand-gated and voltage-gated ion channels. Journal of medicinal chemistry, 63(24), 15258-15278.

40. Zhou, J., & Wild, C. (2019). GPCR drug discovery: Emerging targets, novel approaches and future trends. Current topics in medicinal chemistry, 19(16), 1363.