


REVIEW

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# Advances in the molecular understanding of G protein-coupled receptors and their future therapeutic opportunities

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## Abstract

**Background:** Understanding the mechanisms, activated and inhibited pathways as well as other molecular targets involved in existing and emerging disease conditions provides useful insights into their proper diagnosis and treatment and aids drug discovery, development and production. G protein-coupled receptors (GPCRs) are one of the most important classes of targets for small-molecule drug discovery. Of all drug targets, GPCRs are the most studied, undoubtedly because of their pharmacological tractability and role in the pathophysiology as well as the pathogenesis of human diseases.

**Main body of the abstract:** GPCRs are regarded as the largest target class of the “druggable genome” representing approximately 19% of the currently available drug targets. They have long played a prominent role in drug discovery, such that as of this writing, 481 drugs (about 34% of all FDA-approved drugs) act on GPCRs. More than 320 therapeutic agents are currently under clinical trials, of which a significant percentage targets novel GPCRs. GPCRs are implicated in a wide variety of diseases including CNS disorders, inflammatory diseases such as rheumatoid arthritis and Crohn’s disease, as well as metabolic disease and cancer. The non-olfactory human GPCRs yet to be clinically explored or tried are endowed with perhaps a huge untapped potential drug discovery especially in the field of immunology and genetics.

**Short conclusion:** This review discusses the recent advances in the molecular pharmacology and future opportunities for targeting GPCRs with a view to drug development.

**Keywords:** G protein-coupled receptors, Receptor pharmacology, Computer-aided drug design, Drug targets, Drug discovery

## Background

Since medicine is an ever changing field, newer technologies when applied change our understanding and it is imperative that existing knowledge be updated. It is on this premise that this article is conceived. This review aims to provide an update on the receptor pharmacology, highlighting the untapped drug discovery potentials

of the G protein-coupled receptors (GPCRs). It considers and prioritizes recently (within the last decade) published articles on the advances on the structural biology of the human GPCRs as well as the application of different biotechnological approaches focusing on GPCRs as drug targets. These include recently introduced molecular docking algorithms, protein modelling, biased agonism and application of bioinformatics in computer-aided drug design. The review brings to fore the emerging trend and future therapeutic potentials of the orphan GPCRs.

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## Main text

G protein-coupled receptors (Fig. 1) are the most studied membrane receptors in humans as well as numerous other species [1]. As reported by Oprea and colleagues [2], there are more than 800 human GPCRs of which more than 400 are non-olfactory. They are not surprisingly the largest family of membrane receptors utilized as drug targets both for approved and novel drugs alike [3]. This is chiefly because of their ability to regulate numerous and diverse physiological processes [4] including regulation of appetite, taste, smell, inflammation amongst others. Additionally, GPCRs are endowed with immense druggable sites that are easily accessed by xenobiotics at the cell surface. Within the last two decades, there have been significant insights and understanding of G protein-coupled receptors [5]. Distortion in the signalling pathways or mutations in GPCRs have also been implicated in many diseases [6]. According to Hauser et al. [4], “recent advances in receptor pharmacology, breakthroughs in structural biology and innovations in biotechnology” have all potentiated newer avenues for GPCR drug discovery. Currently, numerous diseases involving the endocrine, cardiovascular, neural and immune systems have been effectively treated or managed through the pharmacological modulation of the GPCRs.

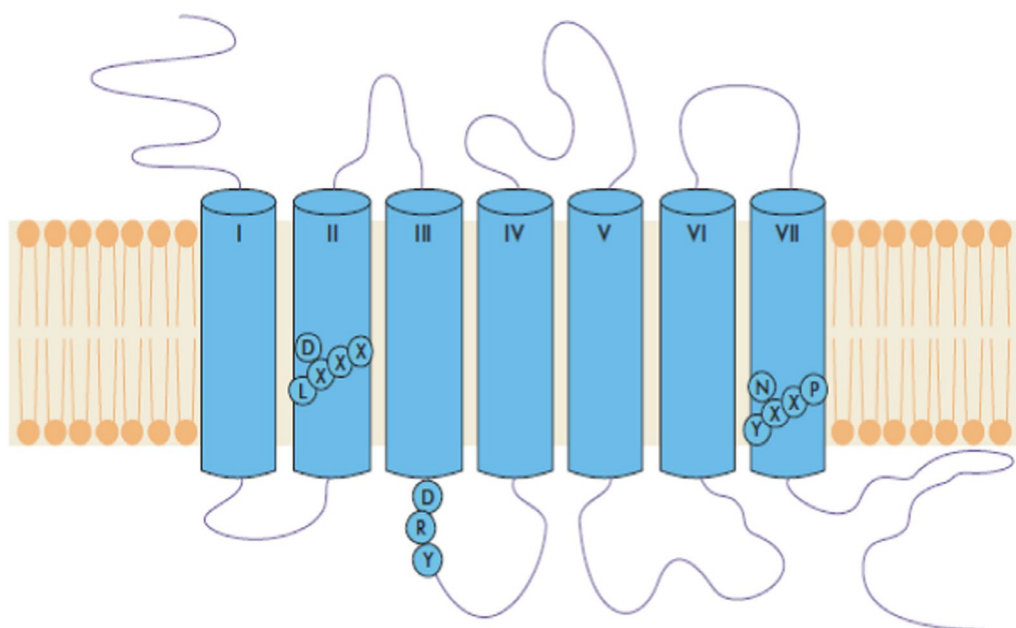
## Characteristic features of GPCRs

The G protein-coupled receptors are a large family of integral membrane proteins with seven transmembrane helices. Based on evolutionary homology the GPCR

superfamily has been divided into classes and families [7]. The GRAFS classification has five families namely: glutamate, rhodopsin, adhesion, frizzled and secretin [8]. The GPCRs are characterized by amino- or N-terminal domain linked to 7  $\alpha$ -helical transmembrane domains (TMDs) and carboxyl or C-terminal domain. The N-terminal segment and C-terminal segment are, respectively, located in the extracellular and intracellular spaces. When stimulated, an extracellular signal induces receptor conformational changes transmitting such signal to the cell interior and then to the intracellular messengers (G proteins, etc.) [9], arrestins [10] and others [11]. The transmembrane helical bundle (particularly the 3rd, 5th, 6th and 7th) are rearranged during receptor activation [12]. GPCRs interact with various intracellular partners including endogenous peptidergic ligands that trigger the downstream signalling cascade. These feats make them super promising category of drug targets to investigate [13].

## GPCRs as targets for computer-aided drug design

Molecular docking is a procedure often used in computer-aided drug design (CADD). Usually, it is applied at different stages of CADD so as to: “(1) predict the binding mode of already known ligands, (2) identify novel and potent ligands and (3) as a binding affinity predictive tool” [14]. Molecular docking is performed using a number of algorithms such as AutoDock [15], AutoDock Vina [16], Glide [17], GOLD [18], amongst others. This field has witnessed a number of improvements and innovative



**Fig. 1** Schematic Representation of GPCRs showing the 7 Helices, the connecting loops and some conserved amino acid motifs

applications such that molecular dynamics is now used as a docking tool [19]. Protein–protein docking has become an even more established method for predicting GPCR dimers. These innovative developments and improvements allow more sophisticated *in silico* studies with better understanding of the mechanisms involved as an outcome.

#### Recently introduced GPCR docking algorithms

Novel methods are usually ranked during dock competitions. As such, the CSAR 2014 Exercise included GPCR docking to a number of X-ray structures [20]. As reported by earlier studies [21, 22], recent breakthroughs such as X-ray crystallography and cryo-electron microscopy (cryo-EM) have been very pivotal to the determination of more than ten GPCR–G protein complex structures. However, many of the novel algorithms are yet to be ranked in any competition. One of such recently released algorithms though not tested on GPCRs is Yada [23]. It is a genetic algorithm designed to perform well in blind docking. Without a doubt, these new algorithms improve the quality of peptide docking.

#### Bioinformatics of GPCR–G protein interactions

In recent years, better insight into the sequences, structures and signalling networks of GPCRs and G proteins is in the public domain. Useful bioinformatics and software tools for exploring GPCR–G protein interactions are available (Table 1). These include the protein data bank (PDB), the GPCRdb, gpDB and human gpDB. For instance, the GPCRdb database houses essential details about the structures, known mutations, homologues, ligands as well as phylogenetic relationships of GPCRs. Also, it identifies ligand binding sites as well as generates GPCR models for virtual screening. This explains why

GPCRdb is widely used for studying GPCRs. Certainly, the systematic analysis of data from the GPCRdb could give further insight into GPCRs and the interactions with their endogenous ligands (G proteins).

#### Antibodies as GPCR therapeutics

Prior to now, GPCRs were not drug targets for antibodies. This is so because GPCRs are predominantly targeted by small molecules. Additionally, the unique pharmacokinetic and pharmacodynamic profiles of antibodies made them compelling alternatives to small-molecule drugs. For instance, they do not readily gain entrance into the central nervous system, allowing for selective targeting of peripheral receptors. However, this has changed as current trends in drug discovery now produces therapeutic antibodies that targets GPCRs with large substrate-binding extracellular domains, with the extracellular domains functioning as binding site for the antibody [1]. The role of GPCRs in diverse physiological and pathophysiological processes has aided the identification of therapeutic areas in which GPCRs could be exploited as suitable as targets for antibody-based drugs (Fig. 2). Out of the more than 400 non-olfactory GPCRs, 88 have been strongly implicated in disease pathogenesis and as suitable targets for therapeutic antibodies.

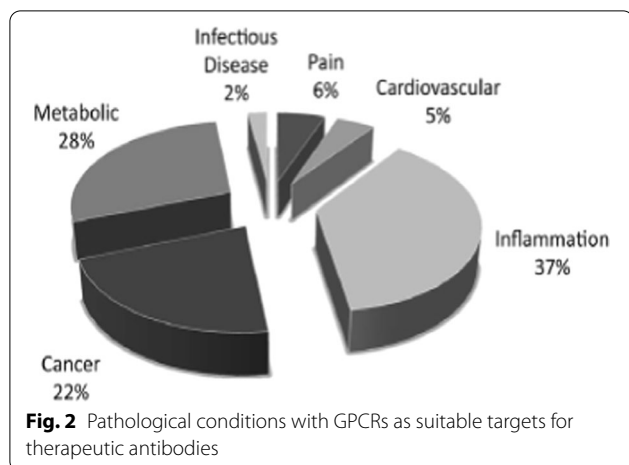
#### Biased agonism in the GPCR

This is a ligand-based signalling approach that is seen when multiple signal pathways coexist in a signalling process. From its inception in the field of biological science, the study of biased agonism focuses on the GPCRs, particularly the G protein and  $\beta$ -arrestin classical signal pathways [24] (Fig. 3).

Conventionally, if a receptor- and/or ligand-activated molecule has the inherent ability of interacting with

**Table 1** Databases and software tools for GPCR–G protein modelling

Database/software	Description
CHARMM-GUI	This is a web-based graphical user software that prepares biomolecular entities such as GPCRs and G proteins for dynamics/molecular simulations. <a href="http://www.charmm-gui.org/">http://www.charmm-gui.org/</a>
Human gpDB	This is a database with information about 36 human G proteins, 99 human effectors and 713 GPCRs. <a href="http://www.bioinformatics.biol.uoa.gr/human_gpdb/">http://www.bioinformatics.biol.uoa.gr/human_gpdb/</a>
OMP	It is a database with information about the structural classification of membrane proteins, spatial positions in the lipid bilayer and intracellular localization. <a href="http://www.opm.phar.umich.edu/">http://www.opm.phar.umich.edu/</a>
PDB	A repository that contains experimental dataset of structures of biological macromolecules. <a href="http://www.resb.org/">http://www.resb.org/</a>
gpPDB	This is a database that contains information about GPCRs, their effectors and known interactions. <a href="http://www.bioinformatics.biol.uoa.gr/gpDB/">http://www.bioinformatics.biol.uoa.gr/gpDB/</a>
GPCRdb	This database houses the structures, diagrams and web tools of GPCRs. <a href="http://www.gpcrdb.org/">http://www.gpcrdb.org/</a>



multiple downstream endogenous ligand [25] but directs the downstream signal based on biased ligand binding, only then is the concept of biased agonism applicable to such signalling pathways (Fig. 4). Using biased ligand agonism, many GPCRs-targeted drugs have been developed exploiting the templates provided by the crystal structures of 43 unique receptors and 196 ligand complexes [26].

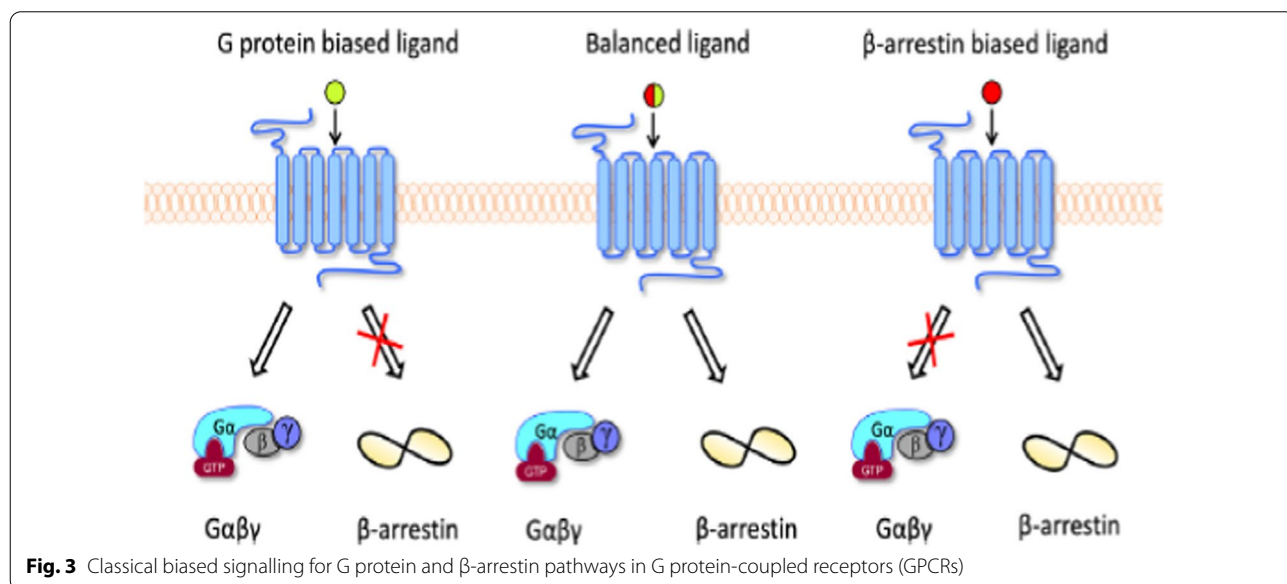
**Emerging trends and therapeutic opportunities for orphan GPCRs**

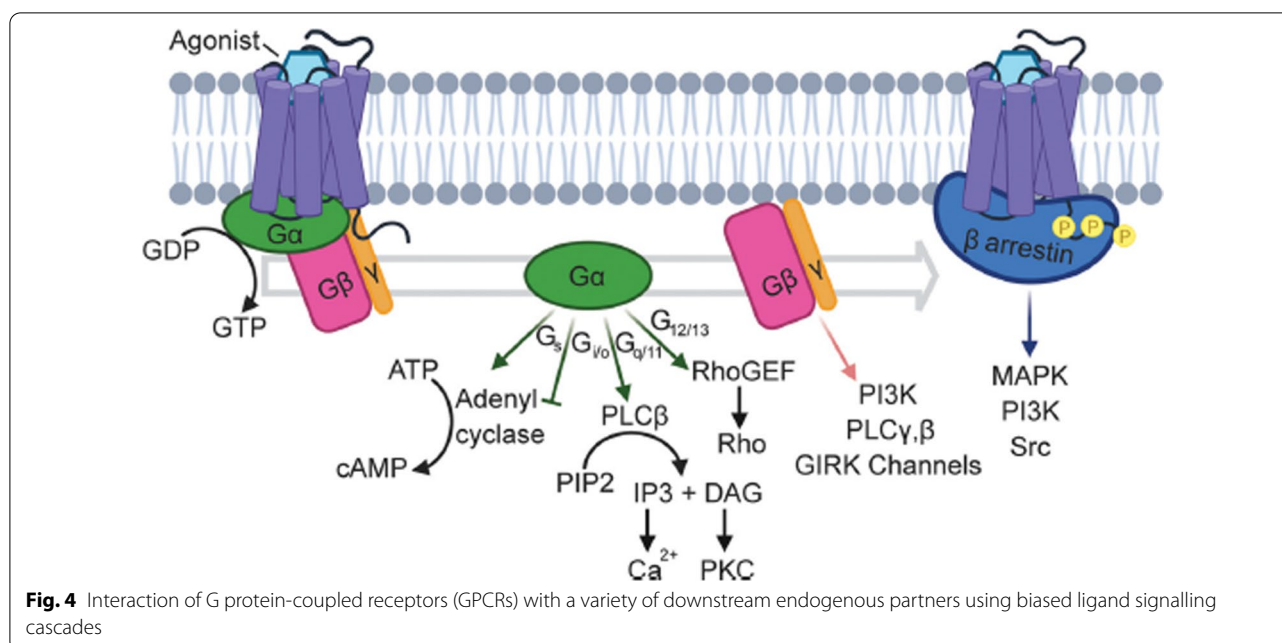
It has been estimated that more than half of the non-olfactory GPCRs encoded for the human genome have not been exploited as drug targets. Orphan GPCRs are GPCRs that were identified through their sequence but currently do not have an identified ligand. Efforts to identify the natural ligands for these orphan receptors

are without certain success. However, these receptors are potential drug targets and have been linked to many pathological conditions including metabolic disorders, inflammation, psychiatric disorders and cancers amongst others [4]. Development of therapeutic and functional antibodies should exploit these orphan receptors as such can provide useful insight into their role in pharmacotherapy of various diseases. In the field of metabolic disorder, especially diabetes and obesity, new GPCR-targeted drugs exploit the cell specificity of receptor expression to achieve activation of pancreatic beta cells, gut endocrine cells and neurons involved in the suppression of appetite. These drugs trick the body giving a false-positive response as though food was just consumed, thus stimulating the secretion of glucose-dependent insulin with a resultant inhibition of the hunger centres. The incretin receptors (GLP1R, GIPR) and bile acid receptor (GPBAR1) are amongst the widely exploited GPCRs in drug therapy for diabetes [27].

**Conclusions**

The G protein-coupled receptors are the extensively studied family of drug targets. These receptors interact selectively with various endogenous partners with different downstream signalling and pharmacological effects as an outcome. The recent advances in computational simulations and software have not only deepened our understanding of the GPCR activation process as well as specificity and tractability, but have overhaul structure-based drug discovery, and as a result, numerous GPCRs are now in clinical trials with interesting and promising outcomes.





#### Abbreviations

CADD: Computer-aided drug design; CNS: Central nervous system; cryo-EM: Cryo-electron microscopy; DNO: Daniel Nkereuwem Obot; GPCRs: G protein-coupled receptors; GRAFS: Glutamate, rhodopsin, adhesion, frizzled and secretin; PDB: Protein data bank; TMDs: Transmembrane domains; GJU: Godswill James Udom.

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#### Authors' contributions

This work was carried out in collaboration between all authors. Authors DNO and GJU conceived and planned the work. GJU prepared the article. All authors equally contributed to the vetting process and made significant financial contributions. All authors read and approved the final manuscript.

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#### Availability of data and materials

Datasets for the study will be made available upon a reasonable written request to the corresponding author.

#### Declarations

#### Ethical approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

The authors have declared that no competing interests exist.

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